UNIVERSITY OF MEDICINE AND HEALTH SCIENCES

Royal College of Surgeons in Ireland

repository@rcsi.com

Factors Associated with Retention in Opioid Agonist Treatment: A Mixed-Methods Approach

AUTHOR(S)

Aisling O'Connor

CITATION

O'Connor, Aisling (2022): Factors Associated with Retention in Opioid Agonist Treatment: A Mixed-Methods Approach. Royal College of Surgeons in Ireland. Thesis. https://doi.org/10.25419/rcsi.14528892.v1

DOI

10.25419/rcsi.14528892.v1

LICENCE

CC BY-NC-SA 4.0

This work is made available under the above open licence by RCSI and has been printed from https://repository.rcsi.com. For more information please contact repository@rcsi.com

URL

https://repository.rcsi.com/articles/thesis/Factors_Associated_with_Retention_in_Opioid_Agonist_Treatment_A_Mixed-Methods_Approach/14528892/1

Factors Associated with Retention in Opioid Agonist Treatment:

A Mixed-Methods Approach

A thesis submitted to the School of Postgraduate Studies, Faculty of Medicine and Health Sciences, Royal College of Surgeons in Ireland, in fulfilment of the degree of

Doctor of Philosophy (PhD) 2021

Aisling M. O' Connor BSc. MSc

RCSI School of Pharmacy and Biomolecular Sciences

Supervisors

Dr Gráinne Cousins, RCSI School of Pharmacy and Biomolecular Sciences, Ardilaun House, Dublin 2

Dr Fiona Boland, RCSI Data Science Centre, Beaux Lane House, Dublin 2

Prof. Joe Barry, Trinity College Dublin, University of Dublin, Public Health and Primary Care, Dublin 2

Candidate Thesis Declaration

I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree of Doctor of Philosophy is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

Signed: _____

Student number: _____

Date: _____

Contents

Candidate Thesis Declaration **2**

List of Acronyms and Abbreviations **9**

List of Figures **12**

List of Tables **12**

Summary **13**

Acknowledgements **15**

Chapter One: Introduction **16**

1.1 Opioid use disorder 17

1.1.1 DSM-IV vs. DSM-V 17

1.1.2 Global and national prevalence of opioid use disorder 20

1.1.3 Changes in profile of individuals with opioid use disorder 22

1.1.4 Harms associated with opioid use disorder 25

1.2 Harm risk reduction 28

1.2.1 Opioid Agonist Treatment (OAT) 29

1.2.2 Global availability of OAT 31

1.2.3 Harm reduction and OAT in an Irish context 32

1.3 Current OAT policy and procedures in Ireland 34

1.3.1 Central Treatment List 34

1.3.2 Methadone Treatment Protocol 35

1.3.3 OAT clinical guidelines 37

1.3.4 Service provision 38

1.4 Treatment Outcomes in OAT 39

1.4.1 Maudsley Addiction Profile (MAP) 40

1.4.2 Review of the MAP 41

1.4.3 Retention as a treatment outcome 41

1.5 Severe Acute Respiratory Syndrome Coronavirus 2 44

1.6 Aims and Objectives 45

Chapter Two: Retention of service users in opioid agonist treatment: A systematic review **47**

2.1 Introduction 48

2.2 Materials and methods 50

2.2.1 Protocol and registration 50
2.2.2 Eligibility criteria 50
2.2.3 Information sources and search 51
2.2.4 Study selection and data extraction 51
2.2.5 Risk of bias in individual studies 52
2.2.6 Summary measures and synthesis of results 52
2.3 Results 54
2.3.1 Study selection 54
2.4 Study characteristics 55
2.4.1 Country 55
2.4.2 Study design 56
2.4.3 Study setting and OAT 56
2.4.4 Participants 57
2.4.5 Primary outcome 57
2.4.6 Risk of bias within studies 58
2.5 Synthesis of results 59
2.5.1 Rates of retention and dropout 59
2.5.2 Factors associated with retention or dropout 61
2.6 Sensitivity analysis 77
2.7 Discussion 78
2.7.1 Statement of principal findings 78
2.7.2 Strengths and limitations 79
2.7.3 Clinical implications and areas for future research 80
2.8 Conclusion 81
Chapter Three: Factors associated with retention in opioid agonist treatment at six-months in a specialist treatment setting – a prospective cohort study 82
3.1 Introduction 83
3.2 Study design & methods 85
3.2.1 Study design 85
3.2.2 Setting 86
3.2.3 Inclusion criteria 87

3.2.4 Recruitment 88
3.3 Data collection 88
3.3.1 Data sources 88
3.3.2 Maudsley Addiction Profile (MAP) 89
3.3.3 Electronic Patient System (EPS) 90
3.4 Variables 90
3.4.1 Primary outcome 90
3.4.2 Secondary outcomes 91
3.4.3 Risk factors 92
3.5 Data management and protection 98
3.6 Study size 98
3.7 Statistical analysis 100
3.8 Results 102
3.8.1 Characteristics of the cohort 102
3.8.2 Primary outcome – time to discontinuation 104
3.8.3 Secondary outcome – dropout at 6 months 104
3.8.4 Sensitivity analysis 106
3.9 Discussion 106
3.9.1 Strengths and limitations 111
3.9.2 Conclusion 111
Chapter Four: Barriers and facilitators to retention in opioid agonist treatment from the perspective of service users and service providers 113
4.1 Introduction 114
4.2 Methods 118
4.2.1 Qualitative approach and research paradigm 118
4.2.2 Researcher characteristics and reflexivity 118
4.2.3 Context 119
4.2.4 Sample 119
4.3 Ethical issues pertaining to human subjects 120
4.3.1 Ethical approval 120
4.3.2 Data security 120

4.3.3 Potential risks and confidentiality 120
4.4 Data collection methods 121
4.4.1 Semi-structured interview 121
4.4.2 Data analysis 123
4.5 Results 123
4.5.1 Contextual information 124
4.5.2 Cyclical nature of OAT 125
4.5.3 Experiences that led to current OAT episode 125
4.5.4 Current life experiences 126
4.5.5 Treatment outcomes 128
4.6 Theme 1: Factors influencing retention in OAT 129
4.6.1 Sub-theme 1: Immediate barriers to retention 129
4.6.2 Sub-theme 2: Long term barriers to retention 132
4.6.3 Sub-theme 3: Facilitators to retention in OAT 135
4.7 Theme 2: Opportunities for improvement 136
4.7.1 Sub-theme 1: Therapeutic relationship 136
4.7.2 Sub-theme 2: Views of OAT 138
4.7.3 Sub-theme 3: Goals for treatment 139
4.8 Theme 3: The impact of COVID-19 on retention 141
4.8.1 Sub-theme 3: Take-home doses and community dispensing 141
4.8.2 Sub-theme 2: Communication with service users during COVID-19 142
4.8.3 Sub-theme 3: Cocooning services and extra provision of accommodation 143
4.9 Discussion 144
4.9.1 Summary of findings 144
4.9.2 Communication and the therapeutic relationship 145
4.9.3 Meaningful goal setting 147
4.9.4 Progression in treatment 149
4.9.5 Engagement in service evaluation 151
4.9.6 Implications for future research 153
4.9.7 Strengths and limitations 154
4.9.8 Conclusion 155

Chapter Five: Discussion **156**
5.1 Introduction 157
5.2 Summary of Findings 158
5.3 Results in the context of previous research 159
5.4 Strengths and limitations 166
5.5 Future research 168
5.6 Considering the impact of the thesis 170
5.6.1 Research-related impact 171
5.6.2 Impact on policy 172
5.6.3 Health service impact 172
5.6.4 Societal impact 173
5.7 Conclusion 174
References **175**
Appendices **191**
Appendix 1. Maudsley Addiction Profile 192
Appendix 2. Inclusion / exclusion criteria for systematic review 201
Appendix 3. Search strategy for systematic review 201
Appendix 4. Data extraction template for systematic review 205
Appendix 5. Newcastle-Ottawa Scale (NOS) template (adapted) 206
Appendix 6. Characteristics of studies included in systematic review 209
Appendix 7. Study results of the critical appraisal of included studies (NOS scores) 226
Appendix 8. Summary of results of included studies in systematic review; potential risk and protective factors explored 231
Appendix 9. Median retention rates of included studies in sensitivity analysis of systematic review (specialist treatment settings only). 312
Appendix 10. Synthesis of studies in specialist treatment settings 313
Appendix 11. RCSI Research Ethics Committee approval 319
Appendix 12. Health Services Executive Primary Care Research Committee approval 320
Appendix 13. Service user information sheet – prospective cohort study 321
Appendix 14. Service user consent – prospective cohort study 331
Appendix 15. Sensitivity analysis - prospective cohort study 334
Appendix 16. Service user information sheet – qualitative study 335

Appendix 17. Service user consent form – qualitative study 344
Appendix 18. Service provider information sheet – qualitative study 347
Appendix 19. Service provider consent form – qualitative study..... 351
Appendix 20. Service user interview schedule – qualitative study..... 352
Appendix 21. Service provider interview schedule – qualitative study..... 355

List of Acronyms and Abbreviations

AIDS: Acquired immunodeficiency syndrome

ASI: Addiction Severity Index

Bup: Buprenorphine

BZD: Benzodiazepine

CAMH: Centre for Addiction and Mental Health

CI: Confidence Interval

COVID-19: Coronavirus disease 2019

CTL: Central treatment list

DEA: Drug enforcement agency

DSM – V: Diagnostic and Statistical Manual of Mental Disorders V

EMCDDA: European Monitoring Centre for Drugs and Drug Addiction

EPS: Electronic patient system

GBD: Global Burden of Diseases, Injuries, and Risk Factors Study

GDPR: General Data Protection Regulations

GP: General Practitioner

HCV: Hepatitis C Virus

HIV: Human Immunodeficiency Virus

HSE: Health Service Executive

IDU: Intravenous drug use(r)

IV: Intravenous

IVU: Intravenous user

LAAM: Levo-alpha-acetylmethadol

LSD: Lysergic acid diethylamide

MAP: Maudsley Addiction Profile

MDMA: 3, 4-methylenedioxymethamphetamine

Mg(s): Milligram(s)

Ml(s): Millilitre(s)

MMT: Methadone Maintenance Treatment

N: Number of participants

Nal: Naloxone

Nalt: Naltrexone

NCEC: National Clinical Effectiveness Committee

NDRDI: National Drug-related Deaths Index

NDTC: National Drug Treatment Centre

NDTRS: National Drug Treatment Reporting System

NIDA: National Institute of Drug Abuse

NOS: Newcastle Ottawa Scale

OAT: Opioid antagonist treatment

OBOT: Office based opioid treatment

OECD: Organisation for Economic Co-operation and Development

OTP: Opiate treatment programs

OUD: Opioid use disorder

PPE: Personal protective equipment

PRSIMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCSI: Royal College of Surgeons in Ireland

RCT: Randomized control trial

ROSIE: Research outcome study in Ireland evaluating drug treatment effectiveness

SAMHSA: Substance Abuse and Mental Health Services Administration

SD: Standard Deviation

SU: Service user

TCD: Trinity College Dublin, University of Dublin

THD: Take home dose

TOP: Treatment outcome profile

UK: United Kingdom

UNODC: United Nations Office on Drugs and Crime

USA: United States of America

VA: Veteran's affairs

WHO: World Health Organization

List of Figures

Figure 1.1: Individual deaths from specific drugs in poisoning deaths in Ireland (2008 - 2017) . 27

Figure 1.2: OECD opioid-related deaths per million inhabitants 28

Figure 1.3: Central Treatment List Figures 2006 - 2019 34

Figure 2.1: Search strategy flowchart 55

Figure 3.1 : Recruitment of participants 99

List of Tables

Table 1.1: Recommendations from the review of the Methadone Treatment Protocol (2010) 36

Table 2.1: Variables suitable for inclusion by MAP 53

Table 2.2: Median retention rates across included studies 59

Table 2.3: Synthesis of results by risk factor; reporting total number of studies and number of studies reporting significant effects (direction of effects included) 62

Table 3.1: Risk factors according to the Maudsley Addiction Profile 93

Table 3.2: Demographic and treatment characteristics (n=117) 103

Table 3.3: Characteristics of those retained and those who dropped out at 6 months follow-up (n=112) 106

Table 3.4: Logistic Regression exploring factors associated with dropout 106

Table 4.1: Example of questions in each interview schedule 122

Summary

Background: The overall aim was to investigate factors associated with treatment retention and dropout in opioid antagonist treatment (OAT) through a mixed-methods approach.

Methods: This thesis consists of three studies; a systematic review to identify factors associated with retention/dropout in OAT according to the Maudsley Addiction Profile, followed by a six-month prospective cohort study in a specialist treatment setting in Ireland exploring factors associated with dropout, and finally a qualitative study with service users and providers exploring barriers and facilitators to retention.

Results: The systematic review included 67 articles across 21 countries with varying definitions of retention/dropout. The median retention rate was 57% at 12-months (n=37) and 38.4% at three years (n=8). Older age and higher doses were associated with increased retention in the majority of studies. Studies investigating substance use, negative attitudes to MMT, criminal activity and arrests/incarceration found them to be associated with reduced retention. Of 117 participants in the cohort study, excluding five lost to follow-up, 5% (n=6) had dropped out at six-months. Analysis was limited given the sample size and dropout rate, however, IV drug use showed evidence of an association with dropout (p=0.027). In the qualitative study, with data collected from 14 service users and eight service providers, social support, self-motivation and familial incentives were identified as facilitators to retention. Furthermore, areas for improvement in order to facilitate retention included the therapeutic relationship, views of OAT and a disparity in goals set.

Conclusion: Overall, this thesis adds to the body of evidence investigating factors associated with retention in OAT among adults. Principal findings of the systematic review highlighted heterogeneity in the definition and measurement of retention, making it difficult to compare studies. Despite this, younger age, substance use, lower doses of methadone, criminal activity/incarceration, and negative attitudes to MMT appeared to be associated with reduced retention. The cohort study identified a high retention rate at six-months with evidence of an

increase in IV drug use in those who dropped out. Finally, barriers to retention were identified, with some consensus between service users and providers regarding opportunities for improvement. Future research is required to develop a consensus on the definition of retention and further explore circumstances leading participants to dropout of OAT.

Acknowledgements

There are so many who have helped me to reach this milestone, and I will always be grateful to you all. Firstly, I would like to express my gratitude to my three supervisors Dr. Gráinne Cousins, Dr. Fiona Boland and Professor Joe Barry for their continued guidance, patience and support over the past four years. Thank you also to the StAR PhD Scholarship for funding my studies. I would also like to thank all the staff of the National Drug Treatment Centre, in particular Dr. Kevin Ducray, Dr. Mike Scully and Bill Ebbitt for their support in making this research possible. Thank you also to all the general attendants who helped with the recruitment process.

I would like to thank my friends from the department of psychiatry. Thank you for the coffee, chocolate, pints, chats and laughs throughout the years. To my friends Kitty and Ulla, I'm so grateful we were sat beside each other. You are both the best and I couldn't have done this without either of you. To Rosaleen my friend and mentor, thank you for helping me keep a level head and seeing the light at the end of the tunnel! To Trish, thank you for lending me your ear on so many occasions.

To Mam, Dad, Aodhán, Cormac and Tara. Thank you for your continued support and encouragement while I finished my "really long essay". To Mam and Dad, I promise you both I am done with school now! Thank you as well to Jean, Natalie and Sarah for making Sheriff Street feel like a second home.

To Christopher, you told me years ago while drunkenly walking home from a Kanye West gig that I could do this and I didn't believe you at the time. Thank you for believing in me then and continuing to do so throughout this process. I hate to say it, but you were right! I'm not able to put into words how grateful I am to you for your support.

Finally, thank you to the service users of the National Drug Treatment Centre, whom without their engagement, this would not have been possible.

Chapter One: Introduction

1.1 Opioid use disorder

Opioids are a class of drug that include opiates (derived from the poppy plant), semi-synthetic opiates (heroin derived from morphine) and synthetic opioids (1). Codeine, fentanyl, loperamide, methadone and morphine are opioids that are considered as essential medicines by the World Health Organization (WHO) (2) and are used for the treatment of acute pain, pain caused by cancer and opioid use disorder (3). Opioids work through binding to and activating mu-opioid receptors in the brain. This in turn activates the mesolimbic (midbrain) reward system. This system generates a signal which results in the release of dopamine, causing feelings of euphoria (4).

Opioid tolerance occurs when opioid receptors become less responsive to opioid stimulation due to prolonged use (4). As a result, more opioids are needed in order to stimulate the mesolimbic reward system and release dopamine. Once an individual has developed a tolerance to opioids, they are at risk of experiencing withdrawal symptoms if they discontinue their opioid use. This results in an opioid use disorder (OUD) as an individual will develop a problematic pattern of opioid use leading to problems or distress (5). Withdrawal symptoms are a result of changes to the locus ceruleus in the brain. The locus ceruleus produces noradrenaline which stimulates wakefulness, breathing, blood pressure, and general alertness (4). Opioid use suppresses the release of noradrenaline, however with repeated opioid use, locus ceruleus neurons adapt and increase in activity so that regular amounts of noradrenaline are released and an individual can function as normal. When the use of opioids stops, the increased activity in the locus cereuleus continues which causes withdrawal symptoms such as anxiety, muscle cramps, and diarrhoea (4). OUD is defined by the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) as a problematic pattern of opioid use leading to clinically significant impairment or distress (5).

1.1.1 DSM-IV vs. DSM-V

Three changes were made to the DSM-IV's definition and criteria of opioid dependence. In the DSM-V, opioid abuse and opioid dependence were combined into a single disorder (opioid use disorder) (5). The criteria for OUD differ from the criteria for opioid abuse or dependence. The

DSM-IV criteria for opioid abuse were met if individuals experienced one or more of 12 signs or symptoms. The criteria for opioid dependence were met if an individual experienced three or more of 12 signs or symptoms in the same 12-months. In the DSM-V, the criterion of experiencing legal difficulties was replaced by the criterion of experiencing cravings and a diagnosis of OUD is now made if an individual experiences at least two of the following 11 criteria in a 12-month period (5):

1. Taking larger amounts of opioids or over a longer period than was intended.
2. A persistent desire or unsuccessful efforts to cut down or control opioid use.
3. Spending large amounts of time on activities to obtain opioids, use, or recover from its effects.
4. Craving or experiencing urges to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations (at work, school, or at home).
6. Continuing opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Exhibits tolerance.
11. Exhibits withdrawal.

OUD also consists of cycles of abstinence and relapse over years or decades, which can include periods of treatment and/or incarceration (3). Several biological, psychological and social factors have been identified as risk factors for developing an OUD. The association between genetics and the development of an OUD have been extensively researched and indicate that certain genes

may increase the risk of developing an OUD (6-9). Experiencing pain and the subsequent prescribing of opioids has also been extensively researched and has also been identified as a potential risk factor in developing an OUD. A systematic review conducted in 2013 suggested that opioids for chronic pain conditions are not associated with a major risk for developing dependence (10). Conversely, more recent research has indicated that pain is significantly associated with prescription OUD (9, 11). A more up to date systematic review is required in order to consolidate recent and emerging findings.

In terms of psychological factors, Kilmas et al.'s systematic review highlighted that a history of other substance use disorders, certain mental health diagnoses, and concomitant prescription of certain psychiatric medications appeared to identify individuals at high risk of developing an OUD (12). However the studies in this review were noted as low in quality by the authors (12). Kaye et al. have also noted that mental illness appears to be associated with increased risk of developing an OUD, specifically with prescription opioids (9). Cragg et al.'s systematic review of risk factors for prescription OUD also highlighted that current or previous substance use and any mental health diagnoses appeared to be risk factors for developing an OUD. They also noted that being male and younger were also risk factors (13). Being younger in age was also highlighted as a risk factor in other systematic reviews of OUD predictors in the prescription of opioids for chronic pain (9) and outcomes associated with opioid use in the treatment of chronic non-cancer pain in older adults (9, 14). However, Cragg et al. noted that more than half of the studies included in their review were rated as having a high risk of bias (13).

In terms of social risk factors, Kaye et al. noted in their review of OUD predictors that being unmarried; unemployed, having a low income and having a lower education level were all associated with OUD (9). Other social risk factors for developing an OUD have been documented in grey literature and include a chaotic home environment during childhood, lack of a significant relationship with a caring adult, or a caregiver who abuses substances, suffers from mental illness, or engages in criminal behaviour (15, 16). However the evidence supporting these risk factors outlined in grey literature is unclear.

1.1.2 Global and national prevalence of opioid use disorder

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) estimated national, regional, and global prevalence of OUDs in 2017 of which the global age standardised prevalence was 510 people per 100 000 population (3, 17). The United Nations Office on Drugs and Crime (UNODC) Drug Report 2020 estimated that 57.8 million people had used opioids in 2018 (1.2% of the global population aged 15-64). Extra-medical opioid use (the use of illicit opioids and/or the use of pharmaceutical opioids either without a prescription or not as directed by a doctor), dependence, and harm are increasingly driven by ready supplies of illicit opioids globally and, in some countries, by overprescribing of opioids for non-cancer pain (3, 17). Higher than global average use of opioids in 2019 was reported in North America (3.6%), Australia (3.3%), New Zealand (3.3%), the Middle East and South-West Asia (2.6%) and South Asia (2%). The European Monitoring Centre for Drugs and Drug Addiction reported 1.3 million opioid users in 2018 (0.4% of the entire population)(18). Globally, an estimated 40·5 million people were dependent on opioids in 2017 (3).

Since the late-2000s, heroin supplies and transitions to heroin and Intra-Venous (IV) drug use has increased globally (3). From 2002 to 2019, the percentage of individuals with a past year heroin use disorder in the USA increased from 0.1 percent of the population (404,000 people) to 0.3 percent (745,000 people)(19). This figure has remained stable since 2009. In 2019, approximately 9.7 million people in the USA misused prescription opioids in the past year (3.7% of the population) (19). Of these figures, an estimated 404,000 people had misused both prescription opioids and heroin in the past year (0.1% of the population) (19). In Australia, almost four percent (3.7%) of the population reported the non-medical use of opioids (either pharmaceutical or heroin) in 2016 (20) . Pharmaceutical opioids accounted for 3.5% of this figure followed by heroin (0.1%) and methadone or buprenorphine (0.1%) (21). Heroin use disorder in the general population in Australia remains low from 0.2% in 2001 to less than 0.1% in 2019 (21). These figures have been consistently reported over time (22). The EMCDDA reported that in 2018 0.4%

of the EU adult population (1.3 million people) had an OUD. The United Kingdom reported 341,576 (0.5% of the national population) opioid users in 2015 (most recent figure) (23). In 2014, Ireland had approximately 18,988 opioid users (0.4% of the national population) (18).

The number of estimated individuals with an OUD in Ireland has fluctuated over time from 14,681 in 2001 to 20,790 in 2006 and 18,988 in 2014 (24). Data sources used for the 2014 study of estimating OUD in Ireland were the Irish Probation Service data, the National Drug Treatment Reporting System and the national opioid treatment register - the Central Treatment List (CTL). Although this method attempted to identify as many individuals with an OUD as possible across many settings, this report may have underestimated figures as it was unable to use data from the Hospital In-Patient Enquiry (HIPE) scheme and from An Garda Síochána (national police force) in the 2014 study which it had used in the previous study for 2001 and 2006 (24). It is also likely that there are many individuals with an OUD who have not interacted with any of the services mentioned above, and as such were not included in this estimation.

Synthetic Opioid Use

Over the past 20 years, there has been an increase in the misuse of pharmaceutical opioids particularly in North America where they are experiencing an opioid overdose crisis (17). There are an estimated 128 daily deaths in the USA as a result of synthetic opioids (17). In 2018, 9.9 million Americans reported the non-medical use of prescription opioids (17). In 2019, Sub-regions of Africa also reported high levels of the non-medical use of synthetic opioids, mainly tramadol. Australia has also seen a 21% increase in the proportion of people using synthethic opioids for illicit or non-medical purposes over their lifetime (from 2001 to 2013) (17).

According to the EMCDDA, synthetic opioids now account for 22% of all service users in treatment for an OUD in Europe (25). In 2018, treatment entrants for OUD in Europe reported misusing methadone, buprenorphine, fentanyl, codeine, morphine, tramadol and oxycodone (25). Although heroin accounts for the majority of OAT entrants in Ireland, the proportion has significantly decreased from 96.6% in 1996 to 88.5% in 2014 (26). Those in treatment for

prescription opioids has also increased over time (from 1.5% in 1996 to 8.6% in 2014) (26). These figures were calculated by conducting secondary analysis of annual reports of new persons entering opioid treatment over 19 years from the National Drug Treatment Reporting System (NDTRS) (26).

1.1.3 Changes in profile of individuals with opioid use disorder

There is currently an aging cohort of individuals with an OUD in Europe (27). The EMCDDA considers people who use drugs over the age of 40 as an "aging population" (28). In 2006, approximately one third of those with an OUD in Ireland were over 35 years of age, increasing to approximately two thirds in 2014 (18). In older opioid users the aging process is accelerated and they experience higher rates of degenerative disorders, circulatory and respiratory problems, pneumonia, breathlessness, diabetes, hepatitis and liver cirrhosis than their peers and younger people who use drugs. They may also be more susceptible to infection, overdose and suicide (28). Carew and Comiskey's analysis of the aging cohort of opioid users in Ireland indicated there has been an upward trend of opioid use among older adults, and a significant increase in the median age of those entering treatment (31 years and older) (26). This trend is expected to continue over the next two decades (29). Similar to Carew and Comiskey's findings, Cousins et al.'s study of the risk of mortality on and off MMT in primary care highlighted that 42.1% of their sample were 30 years of age or older (31.8% were aged 30-39 years and 10.3% were aged between 40-65 years)(30). Durand et al.'s. more recent study of the association between interruptions to the continuity of MMT and risk of drug-related poisoning deaths in a specialist treatment setting in Ireland also observed an aging population as the median age of their sample was 33.9 [IQR 30-38] years (31).

Poly-drug use

Poly-drug use is the use of more than one drug or type of drug, consumed at the same time or sequentially by an individual. These drugs include both legal and illegal substances (27). In the USA, 63% of opioid overdose deaths in the first half of 2018 also involved cocaine, methamphetamine, or benzodiazepines (32) . Between 2018 and 2019 poly-drug use in non-fatal

overdoses in the USA increased, with rates involving opioids, cocaine, and amphetamines increasing to 9.7%, 11.0%, and 18.3% from the previous year (33). Rates of non-fatal overdoses involving benzodiazepines decreased by three percent (33). As this data was derived from emergency department admissions for nonfatal overdoses in 29 states, these figures are likely an underrepresentation of poly-drug use across the USA.

Similarly, rates of poly-drug use deaths in Australia have increased, where four or more substances detected in these kind of deaths increasing 123% from 261 in 2014 to 582 in 2018 (34). The number of drug-induced deaths involving opioids have nearly trebled in the last 12 years, increasing from 338 in 2006 to 904 in 2017 (equating to 56.1% of all unintentional drug-induced deaths) (34). Deaths involving heroin increased by 434% (from 67 to 358 in 2017), deaths involving the chemical class 4,5-apoxymorphinian (oxycodone, morphine or codeine) (35) increased by 102% (from 170 to 344 in 2017) (34), and deaths involving the chemical class phenylpiperadine (fentanyl, pethidine or tramadol) (35) increased by over 1,000% (from 12 to 198 in 2017). Deaths involving methadone also increased by 122% (from 85 to 189 in 2017) (34).

From a European perspective, while opioids are implicated in 80% of drug poisoning deaths reported by the EMCDDA, post-mortem toxicology analyses of poisoning cases suggest that multiple drug toxicity is implicated in most cases (36). Poly-drug use deaths involving opioids in England and Wales were lower in 2019 than the 80% figure reported by the EMCDDA. Opiates (natural opioids such as heroin, morphine and codeine) were involved in just under half (49.2%) of drug poisonings registered in 2019, which has remained a consistent figure since 2006 (37). Since 2006, over half of all drug poisoning deaths in each year have involved an opiate. In 2018, a total of 2,208 drug poisoning deaths had an opiate mentioned on the death certificate (51% of all drug poisoning deaths). This figure is also similar to Scotland where heroin and/or morphine were implicated in 45% of all drug-related deaths in 2019 (n=537) (38). Of the 1,187 drug-related deaths in Scotland in 2018, there were 68 for which only one drug (and, perhaps, alcohol) was found to be present (38).

Poly-drug use in individuals with an OUD seeking treatment in Ireland has reduced from 74.5% in 1996 to 55% in 2019 (26, 39). However, drug poisoning deaths involving poly-drug use have increased with the National Drug-related Deaths Index reporting that in 2017, 58% of poisoning deaths in Ireland involved poly-drug use, an increase from 50% in 2008 (40). In addition to this, opioids were implicated in 51% of deaths where alcohol was implicated, 100% of deaths where diazepam was implicated and 100% of deaths where alprazolam was implicated following death as a result of poly-drug use (40). Benzodiazepines were also involved in 89% of deaths where methadone was implicated and 86% of deaths where heroin was implicated.

Homelessness

In Ireland, a substantial proportion of individuals accessing homeless services and/or accommodation also use drugs. Those who identified as homeless and active drug users increased from 23% in 2005 to 54% in 2013 (41). There are shared risk factors associated with both homelessness and drug use, and the relationship between both is regarded as complex. However, homelessness does not necessarily lead to drug use and vice-versa (41). Three separate cross-sectional assessments of the health status of the homeless population in Ireland were conducted in 1997, 2008 and 2013 (42-44). W

ithin these studies, there was an increase in lifetime drug use from 29% in 1997 to almost 80% in 2013 (41). Between 1998 and 2013 the percentage of those registered as homeless on the Central Treatment List (national register of individuals in receipt of OAT) increased from 1% to 7% (41). These three cross-sectional assessments were conducted using data from the CTL, the National Self-Harm Registry and the National Drug-related Index. These three databases do not take into account the total number of homeless individuals in Ireland. As a result, these registers should not be assumed to represent the proportionate increases in methadone use, self-harm or drug-related deaths in the homeless population as a whole (41).

1.1.4 Harms associated with opioid use disorder

OUD is associated with a reduction in quality of life, increased criminal activity, increased medical comorbidities, high rates of psychiatric morbidity, overdose, suicide, accidental injuries, and infectious diseases (HIV and HCV infection)(45). Globally, there are currently 130 million people infected with hepatitis C of which unsafe injecting practices accounts for an estimated 90% of new infections annually (3-4 million) (17). There is also evidence to suggest that OUD causes psychological harm to the families and children of individuals with an OUD as well as society through the costs of policing, courts, prisons, and prosecution and probation services (46, 47).

Individuals with an OUD also have a high risk of premature mortality, with mortality rates up to fifteen times that of the general population (48, 49). These increased mortality rates are primarily attributed to overdoses, violence, suicide, and smoking and alcohol-related causes (45). The aging population of individuals with an OUD and associated chronic illnesses also increase the risk of mortality amongst this population (50). Global deaths caused by drug use have increased by 25% within the past ten years with a 71% increase in deaths caused by OUDs (17). There is also an elevated risk of mortality from overdose during treatment initiation or discontinuation, or when tolerance is reduced after a period of abstinence and release from incarceration (3, 48). The increased risk during the first few weeks of OAT with methadone could be explained by an accumulation of methadone that exceeds opioid tolerance levels for an individual (48). The increased risk of mortality following treatment cessation may be explained by a reduced or loss of tolerance to opioids, should an individual return to drug use and potential poly-drug use during this time (48). Other factors that may contribute to mortality risk when an individual leaves treatment include the subsequent disruption in care and treatment for co-morbid conditions and lifestyle instability that may have caused the individual to leave treatment (51).

There are differing levels of risk for all-cause mortality and drug-related poisonings between methadone and buprenorphine throughout the various stages of treatment. Kimber et al. conducted a retrospective study of the mortality risk of OAT, comparing buprenorphine and MMT

using a cohort of all service users on OAT in New South Wales, Australia between 2001 and 2010 (52). Hickman et al. conducted a similar retrospective study in the UK, however they used a cohort of all service users on OAT in primary care from 1998 to 2014 (53). Kimber et al. stated that weak evidence suggested that all-cause mortality was lower for buprenorphine than methadone in the first four weeks of treatment (52). This was corroborated by Hickman et al who found service users on buprenorphine have lower all-cause mortality rates in the first four weeks of treatment initiation, the rest of the time in treatment and also the first four weeks of treatment cessation compared with service users on methadone (53). However, according to Kimber et al., drug-related mortality was lower for methadone compared to buprenorphine following treatment cessation (52) .

In Europe, opioids often in combination with other substances, were present in 82% of fatal overdoses reported in 2018 (54). In 2017, the National Drug-related Death Index reported that opioids was the main drug implicated in poisoning deaths in Ireland and has increased slightly from previous years (74 deaths in 2016 to 77 deaths in 2017)(see Figure 1.1) (55). Deaths where methadone was implicated decreased from 105 (2016) to 95 (2017), however it was also implicated in 25% of all poisoning deaths (55). Deaths where fentanyl was implicated remained unchanged (7 deaths in 2016 and 2017) in Ireland (55) (see Figure 1.1).

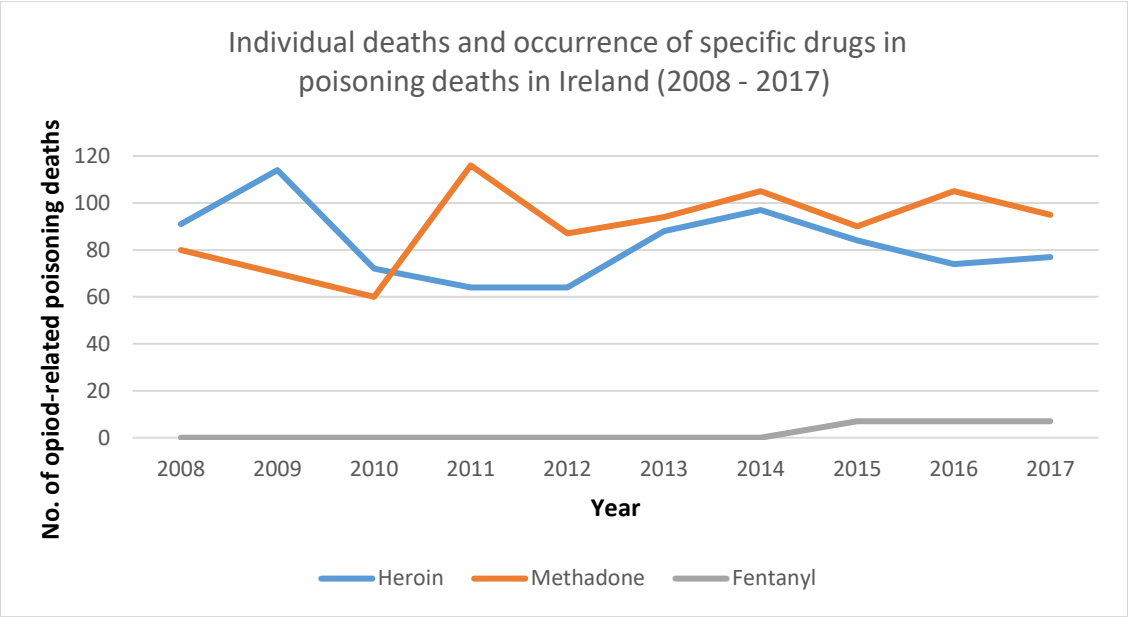

Figure 1.1: Individual deaths from specific drugs in poisoning deaths in Ireland (2008 - 2017)

The Organisation for Economic Co-operation and Development (OECD) compiled a report in 2019 in order to develop a comparative analysis of 25 countries' strategies to address, reduce and prevent opioid use. Data for this study was obtained from both the EMCDDA and additional OECD countries via responses from short questionnaires administered to them. According to the report, opioid-related death figures for Canada in 2011 were unavailable. In this report the average number of opioid-related deaths increased by 20% from 21.3 deaths per million inhabitants in 2011 to 25.8 deaths per million inhabitants in 2019 (or most recent data available) (see Figure 1.2) (56). Scotland was added to the table by AOC using data from Scottish drug-related death reports from 2011 and 2019 (57, 58). All individual countries reported an increase in deaths, however the European Union, Norway and Turkey reported a decrease in opioid-related deaths in 2018 from 14.5 to 12.3 deaths per million inhabitants (21, 59).

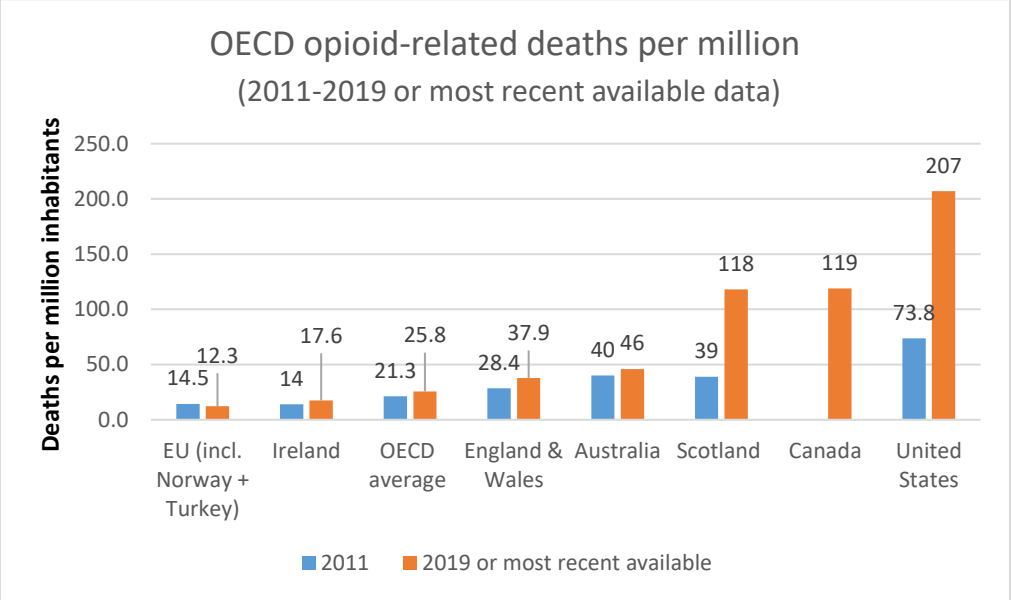

Figure 1.2: OECD opioid-related deaths per million inhabitants

1.2 Harm risk reduction

The WHO defines harm reduction as a set of policies, programmes, services and actions that aim to reduce the harm to individuals, communities and society related to drugs, including HIV infection (60). It is a public health approach that enables the safest way of using substances and provides necessary support in order to achieve the safest possible outcome for individuals using drugs (61). Supporters of harm reduction argue that for drug users who cannot or will not discontinue drug use, the best possible outcome may be for continued drug use under supervised and safer conditions (62). Up until the 1980s, drug services around the world were mainly concerned with curing addiction (63). Harm reduction strategies were then developed globally in response to the HIV and AIDs epidemic of the 1980s, however, they were often met with heavy opposition. The recent opioid epidemic in the US led to the partial lifting of the federal ban on spending on needle-exchange programs (63). However, harm reduction strategies in the US continue to be divisive with large political resistance and emphasis placed on abstinent based strategies to OUD (61).

In contrast, the Canadian Government officially adopted harm reduction as the framework for their National Drug Strategy in 1987 (64). They opened their first government funded needle and syringe exchange program in 1989 and by 2003 the first supervised injection facility was opened, with up to 200 visits per day (65). In Australia in the 1980s, harm reduction programmes such as needle exchange programs and safer sex education were developed in response to the risk of HIV and since 1995, harm reduction is the guiding principle of their National Drug Policy (66). Harm reduction strategies were also implemented across Europe in the 1980s. In 1984 the world's first government-funded needle exchange program began in the Netherlands. Following the Netherlands, Italy, Switzerland, Germany, and France also implemented programmes (67).

Needle exchange programmes were also introduced in the UK in response to the HIV and AIDs epidemic, however non-government organisations took the lead in co-ordinating programmes to support drug users from the 1980s onwards (68). From 2008 there has been a politically-driven recovery agenda focusing on abstinence which has led to restructuring of services around detoxification and abstinence, rather than OAT, in some parts of the UK (68). However, in more recent years many authors have advocated that recovery is not exclusively abstinence-based. Rather, it is a wider concept involving a process of both voluntary control of substance use plus working towards positive outcomes in a range of domains such as social capital (family and group relationships); human capital (health and well-being), physical capital (housing and money) and cultural capital (values, beliefs and attitudes)(69). The EMCDDA also considers reintegration as a part of recovery and states that it is dependent on three social pillars which are housing; education and training; and employment (69). The EMCDDA recommends that social re-integration includes all activities that aim to develop human, social, economic and institutional capital and activities that promote social integration should be integral to treatment (69).

1.2.1 Opioid Agonist Treatment (OAT)

Treatment for OUD focuses on pharmacological and psychosocial harm reduction interventions which aim to reduce or stop opioid use, prevent further associated harms and improve overall quality of life (45). In most cases, OUD treatment is long-term and similar to other long-term

treatment for chronic illnesses. Therefore, long-term treatment for an OUD should not be viewed as treatment failure, but as a cost-effective way of prolonging and improving quality of life (45). According to the Irish Clinical Guidelines for OUD, treating a person with OUD should aim to reduce drug use, risk-taking behaviours, morbidity, mortality and criminal activity. They should also promote stabilisation and onward progression, improve health and overall quality of life and encourage drug free lives for those who wish to stop their drug use (70).

Opioid agonist treatment (OAT), with either methadone or buprenorphine, is first line treatment for OUD (71, 72), and is classified as an essential medicine by the WHO (2, 3). OAT is considered to be the most effective treatment for OUD on the basis of evidence that it improves physical and mental health, reduces illicit drug use, criminal activity, the risk of HIV and Hepatitis C virus acquisition, and reduces mortality (3, 45). Due to its focus on reducing and preventing harms associated with OUD, OAT is considered a harm reduction approach in treating OUD (45). Despite this, global coverage of OAT is typically low and treatment quality is suboptimal even in higher income countries (3).

Methadone has the longest history of use for the treatment of an OUD, having been used globally since 1947 (73). Methadone is a full opioid-agonist. A full receptor agonist produces a maximum response (receptor activation) a system is capable of while occupying a relatively low percentage of the target protein receptors (74). Methadone binds to the mu-opioid receptors and activates them more steadily than other opioids, alleviating withdrawal symptoms and reducing cravings but does not produce feelings of euphoria. It has a half-life of approximately 24 hours in an opioid-tolerant person (73).

Buprenorphine is a synthetic partial opioid-agonist. A partial agonist has a lower efficacy and as such produces a sub-maximal response even when occupying a much higher percentage of the protein receptor population (74). This means the partial agonist will not produce a maximal response even if used at high concentrations, meaning that it will block opioid responses and

itself as doses increase (73). A partial opioid-agonist (such a naloxone) will also act as an antagonist in the presence of a full agonist which stops the binding of mu-opioid receptors and can prevent overdoses (73). Once consumed, buprenorphine has a half-life of up to 60 hours. This longer half-life helps maintain the drug at therapeutic opioid partial-agonist levels in the brain, again preferable to methadone's shorter half-life (75). The longer half-life is popular also with service users as less attendance to treatment settings is required (73).

At low doses, buprenorphine has effects like methadone but has a better safety profile as a result of its ceiling effect (45). Due to buprenorphine being a partial opioid-agonist, as the dose increases there is no further increase in drug action (45). As a result of this ceiling effect there is a reduced risk of overdose as it causes less respiratory depression compared to methadone (75). The pharmacokinetic safety profile of buprenorphine is offset by the fact that, as a sublingual tablet formulation it carries with it a greater risk of diversion and abuse potential via intravenous use in comparison to methadone (75-78). Buprenorphine in combination with naloxone (suboxone) reduces the risk of diversion and intravenous use as if injected, the naloxone component blocks the effect of the buprenorphine and prevents any feelings of euphoria (75).

There are several potential side effects of methadone, buprenorphine and buprenorphine/naloxone. These include arrhythmias, confusion, constipation, dizziness, drowsiness, dry mouth, euphoric mood, flushing, hallucination, headache, hyperhidrosis, hypotension, miosis, nausea, palpitations, respiratory depression, skin reactions, urinary retention, vertigo, visual impairment, vomiting and withdrawal syndrome (79).

1.2.2 Global availability of OAT

According to Larney et al., current global coverage rates of OAT for people who inject drugs remains low with 86 of 179 countries providing OAT for individuals who inject drugs (80). The WHO also considers OAT coverage to be low amongst most countries (45). Access to methadone is more restricted in the USA than anywhere else in the developed world (81). It can only be prescribed and dispensed through outpatient opiate treatment programmes (OTP) which are

regulated by the Drug Enforcement Agency (DEA), the Substance Abuse and Mental Health Services Administration (SAMHSA) and individual states (82). Access to buprenorphine is less restricted as medical doctors may prescribe it once they have obtained a federal waiver to do so (83). In 2013, less than 10% of people in the USA with an OUD were in receipt of OAT, however this figure may have increased with the introduction of the Affordable Care Act in 2010 (81). In 2019, 33% of all addiction treatment centres in the USA offered OAT (82).

OAT remains the most common treatment for OUD in the UK and is mainly offered through specialist outpatient drug services, often in shared care arrangements with GPs (23). In 2017, approximately 150,000 individuals received OAT in England and Wales with an estimated number of 341,576 high risk opioid users (23). OAT is also the main treatment for OUD in Australia with 69% of all drug treatment taking place in non-residential facilities. It is administered according to the laws of the relevant state or territory, and within a framework that includes medical, social and psychological treatment. The use of OAT versus withdrawal management in Australia has increased over a 10 year period and in 2017, 49,792 individuals were in receipt of OAT (20). Methadone and buprenorphine are the most commonly used forms of OAT in Europe with an estimated 50% of people with an OUD in Europe in receipt of some form of OAT. However, treatment coverage varies between countries in Europe (27). Results from modelling conducted by Degenhardt et al. have suggested that in a scenario with no OAT available, scaling OAT coverage to 40% within a community, increasing treatment duration to two years and dispensing OAT in all prisons would prevent between 7.7 to 25.9% of all deaths, between 34 – 57% of all deaths as a result of overdose and between 25 – 56% of all HIV-related deaths over a 20 year period (3).

1.2.3 Harm reduction and OAT in an Irish context

Methadone was first introduced for the treatment of heroin dependence in Ireland in 1971 by the Drug Treatment and Advisory Service (Jervis Street Centre) (84). The beginning of the 1980s saw a heroin epidemic in Dublin, and an increase in intravenous drug use as a result (85). In response to this growing epidemic, the Bradshaw Report was commissioned in 1983 in order to

ascertain the prevalence of heroin use in Dublin (85). This report led to the establishment of the Special Governmental Task Force on Drug Abuse who amended the Misuse of Drugs Act (1984) (86). This Act introduced an abstinence-based approach to drug use and harsher sentencing for drug offences. It also removed the requirement that justice should defer sentencing convicted drug offenders pending the completion of medical and social reports (85). Treatment services during this heroin epidemic were also abstinence based and were only available through the Jervis Street Centre and Coolmine Therapeutic Community (85).

In 1987, a harm reduction approach was implemented in Ireland as methadone maintenance treatment was offered to some of its heroin dependent service users in an attempt to deter IV drug use and reduce the spread of HIV (84). This approach was adopted as the previous abstinence based approach had not led to a reduction in drug use or the spread of HIV. Needle and syringe provision was first provided in 1989 by the AIDS Resource Centre at Baggot Street Hospital (85). In 1993 an expert group was established to develop a protocol for prescribing methadone. This group aimed to address difficulties in order to develop a protocol that would benefit patients and protect pharmacists, doctors and health workers involved in methadone therapy in the community (87). The 'Report of the Expert Group on the Establishment of a Protocol for the Prescribing of Methadone' was subsequently published in 1993. The protocol recommended methadone become available nationally and free of charge for those seeking treatment for an OUD (87). It also made recommendations on the type of methadone to be used and the roles of service providers. From the recommendations made in this report the Central Treatment List (CTL) was established (85), which is described in detail later in this chapter.

In Ireland, methadone is the most commonly used form of OAT, with 11,991 individuals in receipt of methadone in 2019 (18, 54). There are an estimated 18,988 individuals with an OUD in Ireland which indicates that there is a considerable number of people who use opioids not currently in treatment (24, 88). Buprenorphine as a form of OAT remains low in uptake in Ireland as it was added to the Misuse of Drugs (Supervision of Prescription and Supply of Methadone) regulations

in 2017 (89). The number of service users receiving OAT has increased year on year since 2006 with the proportion of service users aged 45 years or older increasing steadily (18, 24, 26) .

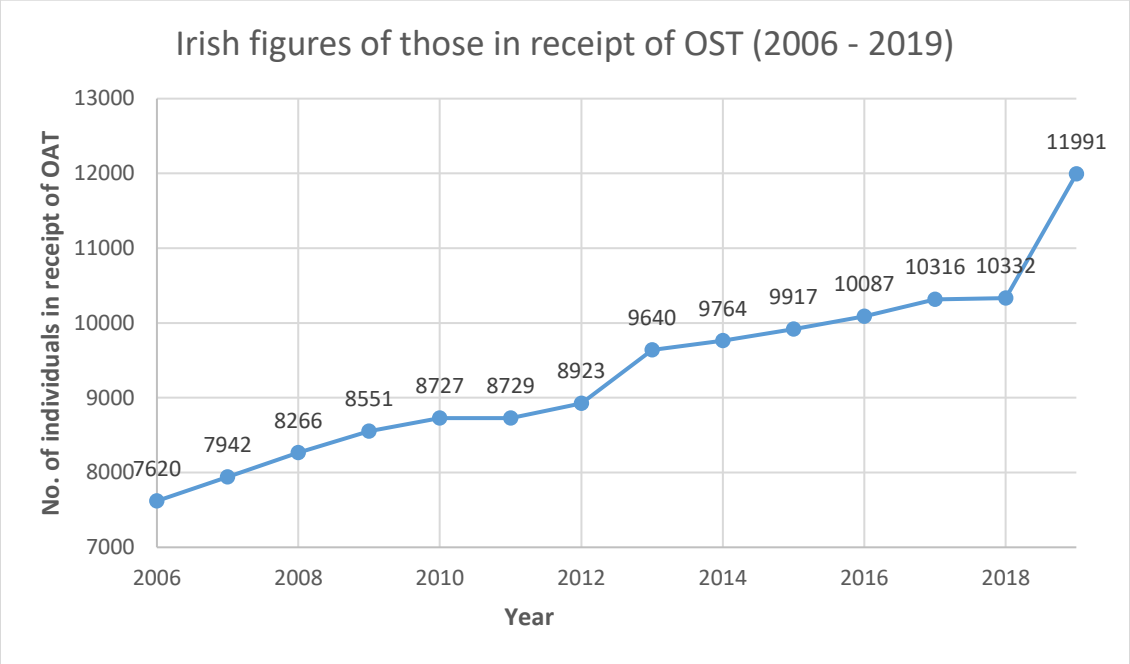

Figure 1.3: Central Treatment List Figures 2006 - 2019

1.3 Current OAT policy and procedures in Ireland

1.3.1 Central Treatment List

OAT in Ireland is provided in specialist outpatient addiction clinics, primary care settings and prisons, with approximately 60% of individuals receiving OAT in specialist addiction clinics and 40% receiving their OAT in primary care settings (Level 1 and 2 GPs) (84). Ninety percent of OAT services are based in Dublin (84). All individuals in receipt of OAT in Ireland are listed on the Central Treatment List (CTL), with each service user linked to one specific prescriber and a single dispensing site (84). The CTL is a complete register of all individuals receiving OAT for the treatment of an OUD and it is used to monitor treatment delivery and clinical governance. It is administered by the Drug Treatment Centre Board on behalf of the Health Service Executive (90).

The CTL holds the name, date of birth, gender, address, and date of entry on the CTL, date of exit and reason for exit for every service user registered. When a person is considered suitable for OAT, their doctor applies to the CTL for a place on the list and a unique number is allocated to the service user. This ensures that each individual can receive their OAT from one source. GPs have a statutory obligation to report initiation of treatment of OAT to the CTL, and as a result the list is considered a complete list of the individuals in receipt of OAT (90). Once on the CTL, treatment status can be tracked by transfer and exit records. A drug treatment card is used when service users are receiving their prescriptions in order to confirm their identity. Prescriptions cannot be prescribed to any person other than to whom a valid drug treatment card has been issued (91).

1.3.2 Methadone Treatment Protocol

The Misuse of Drugs (Supervision of Prescription and Supply of Methadone) regulations (2017) outlined the regulatory structures for treating OUD and also encouraged GPs to become involved in OAT (92). The regulations were amended in November 2017 to include the use of medicinal products containing buprenorphine authorised for OAT (92). The Methadone Treatment Protocol outlines procedures for prescribing, guidance and standards for patient management and care and protocols for clinical audit (84). A review of the protocol was commissioned by the HSE in 2010 and highlighted a list of recommendations in order to improve methadone services in Ireland. The recommendations from this review are outlined in Table 1.1 (93). This thesis will address the recommendations of: 1) maximising treatment provision and the efficacy of referral pathways and 2) data collection, collation and analysis. Specifically it will address the recommendations that consideration should be given to the broader utility of data monitoring with a view to some brief outcome monitoring process.

Table 1.1: Recommendations from the review of the Methadone Treatment Protocol (2010)

Recommendation	Main Areas Highlighted
1. Maximising treatment provision and the efficacy of referral pathways	¶ Support detoxification. ¶ Increase buprenorphine treatment. ¶ Improve multidisciplinary integrated services. ¶ Develop rural services/ services outside Dublin. ¶ Improve progression through referral pathways from treatment to rehabilitation and care planning. ¶ Improve electronic care planning and implement outcome monitoring.
2. Clinical governance and audit	¶ The lines of reporting and accountability in all services requires review so that all professionals have their within service reporting lines clarified. ¶ Audit processes should also be used to monitor treatment dropout. ¶ Auditing of the linkages to community services on discharge from prison and the use of the standard care planning electronic document should be used to assist in linking services together to improve overall patient outcomes
3. Enrolment of GPs, training of GPs, the criteria for level 1 and level 2 GPs and the GP co-ordinator role	¶ The cap on the number of patients with level 1 GPs should be abolished. Level 2 GPs cap should be increased from 35 patients to 50. ¶ There is need to expand the number of level 2 GPs. ¶ There should be a stated time limit for patients to be with level 2 GPs and they should ensure that the patient moves on to a level 1 GP within 12-months. There may be exceptional cases that require longer term management at level 2.
4. Urinalysis testing, its appropriateness and efficacy	¶ Frequent testing be stopped because it is not conducted often enough to be comprehensive and it mainly captures behaviour that is daily regular drug taking behaviour. ¶ Supervision of urine testing should be eliminated except where there is a legal requirement for supervision. ¶ Oral fluid testing should replace urinalysis testing

5. Methadone prescribing in Garda stations	¶ There is a need for a review of the procedures for medical assessment of people in custody. ¶ There is a need for clear and explicit guidelines for the management of opioid use disorder while in Garda custody. ¶ Doctors attending users in Garda stations should have access out of hours to the CTL.
6. Data collection, collation and analysis	¶ Consideration should be given to the broader utility of data monitoring with a view to some brief outcome monitoring process being built into this, where the status of an individual is systematically recorded on a once yearly basis. ¶ Enable wider data linkage through possible use of the PPS number that would enable ongoing mortality and other service utilisation analysis. ¶ Establishment of a group comprising the main data controllers so that maximum use can be made of data collected.

1.3.3 OAT clinical guidelines

Following these recommendations the clinical guidelines for OAT were created by the HSE, The Pharmacological Society of Ireland, the Irish College of General Practitioners (ICGP) and the College of Psychiatrists Ireland in 2016 (70). These guidelines were based on the principles that individuals with an OUD have the same entitlements as others provided services by the HSE and were developed to standardise and improve OAT care from an evidence-based perspective (70). The guidelines outline information on all stages of OAT from stabilisation and maintenance to detoxification and guidelines on working with vulnerable cohorts such as pregnant women, and adolescents (70). The guidelines stress the importance of retaining people in OAT on the basis that retention improves treatment outcomes (70). There are no recommendations within the guidelines regarding how long an individual should remain on OAT, however the WHO recommends that it should be continued as long as clinically indicated (45).

1.3.4 Service provision

OAT service provision is implemented under the National Drug Rehabilitation Framework which aims to ensure that individuals affected by drug misuse are offered a range of integrated options tailored to meet their needs and create individual rehabilitation pathways for them (88). OAT is facilitated through 314 specialist treatment centres, 82 low-threshold agencies, 356 specialised general practitioners and prison services (18). The National Drug Treatment Centre (NDTC) is the largest specialist addiction treatment centre in Ireland. Four consultant psychiatrists each lead a multidisciplinary team which includes clinical secretaries, social worker staff, nursing staff, psychiatrists, trainee psychiatrists, counsellors, key workers, child care workers and a clinical psychologist.

Service users in the NDTC are required to provide urine samples on a regular basis on the discretion of the medical staff. Samples are generally required on a weekly basis, but can become more frequent or infrequent depending on attendance and results of previous tests. Urine samples are required to be given onsite, however they are not supervised. Clinical guidelines recommend at least one random drug test per month and state that some clinical situations may require more testing in order to maintain stability (70).

In 2017, the Irish government launched the "Reducing Harm, Supporting Recovery" strategy that lays out the direction of government policy on drugs and alcohol use and misuse until 2025 (88). This strategy sets out five goals:

1. Promote and protect health and wellbeing.
2. Minimise the harms caused by the use and misuse of substances and promote rehabilitation and recovery.
3. Address the harms of drug markets and reduce access to drugs for harmful use.
4. Support participation of individuals, families and communities.
5. Develop sound and comprehensive evidence-informed policies and actions.

The strategy acknowledges the improvements that are required for OAT service provision including the need for more rural services to reduce waiting lists and travel times for service users (88). It stated that options will be explored to facilitate service provision in the community, specifically increasing level 1 and level 2 trained GPs and examining the feasibility of nurse led prescribing (88). Under the Methadone Treatment Protocol, all GPs who want to participate in OAT are required to take part in specialised training (level 1 or level 2). Following training, level 1 GPs can accept stabilised individuals on methadone from specialised treatment centres or level 2 GPs (94). Level 2 GPs can initiate opioid agonist treatment in their own practice following assessment from their local drug treatment service (94). However in 2019, 60% of OAT service users accessed treatment through specialist treatment centres (94).

The strategy had committed to providing other forms of OAT to those not clinically suited to methadone. As previously stated, the use of buprenorphine for OAT was introduced in 2017 following the amendment to the Misuse of Drug Regulations 2017 (89). Finally, the strategy also committed to reviewing the 2016 HSE clinical guidelines on OAT in line with National Clinical Effectiveness Committee (NCEC) processes. As of January 2020 the NCEC has not addressed this review, and has prioritised the development of 14 other national clinical guidelines (95).

1.4 Treatment Outcomes in OAT

Outcome evaluation in drug treatment settings focus on the consequences of treatment for service users, their families and the community (96). Outcomes can be measured against baseline pre-treatment status or pre-defined treatment goals, (96) and capture changes that service users may experience over time including treatment progression and reduction in drug use (97). Outcome measurements have historically used post-treatment abstinence from substances as a primary indictor of treatment success (97). In line with a shift to a harm reduction approach, this progressed to include reductions in health-risk behaviours, improvements in health problems and social functioning (97). According to Wiessing et al., there are a wide range of potential categories used for outcome evaluation in OAT due to the range of negative consequences associated with an OUD (98). As a result, there is substantial variation in the outcome variables

assessed in longitudinal observational studies of OAT (98). This variation and lack of comparability in indicators has been recognised in other areas of public health (98) and causes ambiguity and differences of expectations for treatment in OUD (98). The WHO recommends that best practice for OAT should include the intermittent or ongoing evaluation of the outcomes of treatment provided (45).

1.4.1 Maudsley Addiction Profile (MAP)

The Maudsley Addiction Profile (MAP) (Appendix one) (99) is an assessment tool that was developed for assessing treatment outcomes for individuals with alcohol and substance use disorders (100). It was developed in response to the recognition of the importance of focusing addiction services research on treatment outcomes (99, 100). In relation to OUD, this recognition came to fruition as OAT has proven to be effective in reducing cravings for opioids, but also needs to focus on optimising outcomes across a range of categories (70).

The MAP contains 60 items across four categories: substance use, health risk behaviour, health (both physical and mental) and social functioning which were informed by the Addiction Treatment Index, the Opiate Treatment Index and the Brief Symptom Inventory (99). All of the categories focus on questions related to a 30-day period before the administration of the tool. This time frame was chosen as a compromise between seven days (which was viewed as too short) and six-months which may have caused recall difficulties for participants. The MAP takes approximately 12 minutes to administer and is researcher led. It is also cost effective to use as it is in the public domain and can be used free of charge (with appropriate acknowledgements) (99).

During the testing of the MAP for validity, there was evidence of content related validity as a result of the use of the assessment tools which informed the development of the tool. Factorial validity suggested that all categories were statistically independent (99). A high level of concurrent validity was reported for substance use by comparing self-reported answers to urinalysis. Concurrent validity was also evident between the MAP in comparison to the Addiction Severity index and the Life Stressors and Social Resources Inventory as satisfactory correlations

were observed (r=0.74, p=.0001) (99, 100). Test re-test reliability was also investigated three days after the initial administration using intra-class correlation coefficients. Test re-test between interview groups (clinicians and researchers) was on average high (k=.084). Retest reliability was also high for all eight substances (average score of k=0.94). Re-test reliability coefficients for health risk behaviours, health, relationship conflict, employment and crime measures were also uniformly high (averaging k= 0.81). However, the short timeframe of reliability testing was acknowledged as a limitation in measuring for reliability (99).

1.4.2 Review of the MAP

The MAP has since been validated in Italy, Spain and Portugal with satisfactory scores reported for internal and test-retest reliability (101). The tool has also been used with psychiatric, comorbid and adolescent populations, however further research is needed on the reliability and validity of the instrument in these and other settings and with other populations (99). The predictive validity of the MAP also remains to be studied. A further limitation is that the MAP does not record demographic data and as such needs to be linked with other clinical data. The MAP was adapted to a shorter 20 item assessment tool in 2008 known as the Treatment Outcome Profile (TOP). The TOP covers four outcome categories: Substance use, injecting risk behaviour, crime and health and social function (combined) (102). It was decided that the TOP would not be used in this thesis as it did adequately address the categories that were of interest for the proposed prospective cohort study.

1.4.3 Retention as a treatment outcome

Retention in OAT is recognised as key indicator of treatment success (103). Retention in treatment reduces the risk of mortality associated with cessation and re-exposure to mortality risk during treatment (re)initiation, reduces harm across multiple health outcomes and helps to improve an individuals' overall quality of life (3, 104, 105). It is regarded as an important outcome measure, and should be incorporated with other outcome(s) measures (98, 106). Despite this, there is no clear consensus on what constitutes retention as it has a variety of definitions in treatment services and in research (106). Globally, retention rates across OAT are approximately

57% at 12-months and falls to 38.4% at 3 years (106). Continuity and retention in treatment is associated with better treatment outcomes (45). Observational studies also indicate that those who remain in long-term OAT are more likely to stay alive, and cessation of OAT is associated with a risk of relapse to opioid use. As such, the WHO recommends that OAT should be seen as long-term treatment that is continued as long as clinically indicated (45). Retention has been the primary outcome measure for many longitudinal studies focusing on OAT (106). These studies have mainly used data linkage of clinical files to assess retention rates and time to discontinuation over a variety of follow up periods (six-months to 24 years) (106) .

In an Irish context, retention in OAT has been investigated in four studies using different methodologies (103, 107-109). Mullen et al. investigated retention in OAT at 12-months in both primary care and specialist treatment centres by using a random sample of new treatment episodes from the CTL from 1999, 2001 and 2003 (103). This study found that 61% of the sample attended treatment for one continuous year, with gender (male), being younger, attending specialist treatment centre and an MMT dose of less than 60mg daily having a significant negative impact on retention. As this study used data from the CTL, it was unable to investigate the impact of contextual information on a service user's retention in OAT. This study acknowledged this limitation and also the limitation in the likely underreporting of poly-drug use (103). The study indicated that further research needs to be undertaken in order to ascertain what factors most contribute to an increase in retention in terms of both personal factors and treatment setting factors (103).

Cousins et al. conducted a study using data linkage (of the CTL, the Health Service Executive's Methadone Treatment Scheme and the General Medical Services pharmacy claims database) to examine the association between supervised consumption and retention in OAT primary care in Ireland over a six-year period (103, 107). This study highlighted that supervised methadone consumption (20-59% of scripts) increased retention, however supervision of 60% of scripts or more was associated with a faster time to discontinuation (107). It also highlighted that service users experiencing multiple treatment episodes stay in treatment for progressively longer

periods of time. Although this study was conducted using extensive data linkage, it was also unable to assess the impact of contextual information of a service users' life on retention. The study suggested further research should be conducted in order to determine how to optimally stratify service users' suitability for unsupervised dosing, in order to retain service users in treatment (107).

Darker et al. (108) conducted a cross-sectional study in the same specialist drug treatment centre where the data collection for this thesis was conducted. This study conducted structured face-to-face interviews with MMT service users (n=189, a response rate of 63%) to investigate retention and factoring influencing treatment breaks. The interview comprised of three categories: demographic factors, clinical factors and open-ended questions to determine service users' reasons for treatment breaks. In this study, 46% of participants self-reported a break in treatment. Older age, current methadone dose and prescription of antipsychotic medication were significant predictors of retention (108). Reasons for breaks in treatment ascertained from open ended questions included relapse into drug use, incarceration, weary of MMT, or problems at the clinic (108). Through the open ended question, participants also highlighted the following factors which enabled retention: wanting to get or stay clean, avoidance of withdrawal symptoms, methadone dependence and additional services provided (108). There were limitations in this study; retention was assessed by the self-reported presence and duration of breaks in treatment at any stage. No definition of a break in treatment was outlined in the study and was left for the service user to interpret. However a strength of this study was the open ended question to ascertain reasons for staying and leaving treatment (108).

Finally, Durand et al. conducted a cohort study investigating factors associated with dropout using data from 2,035 individuals attending specialist treatment centres in Ireland between 2010 and 2015 (109). Factors associated with dropout at three-months included low dose methadone (<60mg/day) and previous experiences of dropout. Dropout at 12-months was associated with low dose methadone, previous dropout, gender (male), benzodiazepines and number of comorbidities. Adherence was protective against dropout at both three and 12-months (109).

This study also acknowledged its limitations. This study had limited information regarding service users' contextual circumstances prior to dropout such as their social functioning, drug use or housing situation. Understanding service users' personal circumstances leading up to dropout particularly from their perspective, is important to address in future studies. Additional work is needed to explore service users' perceptions of OAT, and a detailed investigation exploring individual drug users' reasons for leaving or staying in treatment.

1.5 Severe Acute Respiratory Syndrome Coronavirus 2

In the final months of data collection for this thesis (February 2020 onwards), the COVID-19 pandemic reached Ireland. There were real concerns that disruption to care, particularly access to OAT and other prescribed medication would have detrimental consequences for people in treatment. As a result, changes to OAT provision were made in order to reduce the spread of the virus. These provisions resulted in the premature suspension of data collection from March 2020 in the NDTC. COVID-19 presented significant challenges to the provision of OAT services within the existing regulations and clinical guidelines, as OAT is heavily dependent on regular face-to-face health care delivery. In response to these concerns, the HSE National Social Inclusion Office created a contingency plan for the provision of OAT during the pandemic (110).

Inducting service users who were awaiting assessments in order to start OAT were highlighted as urgent and the assessment criteria were amended in order to speed up induction processes. OAT provision for service users who were self-isolating was also addressed. It was recommended that take-home doses (THDs) for the duration of self-isolation would be provided and delivered to the service user or else the provision of doses would be given to a family member following consent of the service user. Contingency plans were also documented for individuals with benzodiazepine or alcohol use disorders. In order to prevent withdrawals, GPs were advised to commence service users on a maximum dose of 30mg daily for benzodiazepine use disorder and benzodiazepines were recommended for those experiencing alcohol withdrawal in the community (110).

The NDTC are currently following these contingency plans while also maintaining social distancing between staff and service users through new policies and procedures. THDs have been clinically reviewed on a case-by-case basis and in some cases the amount of THDs have been increased for service users. Reviews, assessments and appointments are being conducted via telephone, video calls and within the clinic via a video conferencing system. Outreach staff are providing those who are self-isolating with their OAT doses. There has also been a reduction in the frequency of urine testing in order to minimise interactions between service users and staff as recommended by the COVID-19 contingency plan (110). In order to reduce the number of service users attending the clinic at any one time, times have been allotted for certain service users to attend.

The provision of remote care in response to COVID-19 increased the amount of THDs for service users and was deemed highly successful in maintaining OAT provision during the pandemic (111, 112). Initial reports regarding the contingency plan have highlighted that the move of drug treatment services to a remote model has been viewed as successful from the perspective of service providers (111, 112). On a European level, preliminary findings from the EMCDDA suggest that there was an initial decline in the provision of drug services in the first months of the pandemic. Initial difficulties cited by drug services included: "accessing sufficient personal protective equipment for staff, informing service users about COVID-19 risks; managing infected service users and concerns about staff vulnerability to infection and issues associated with enrolling new service users and managing the demand for OAT" (113).

1.6 Aims and Objectives

The overall aim of this thesis was to investigate factors associated with treatment retention in OAT in order to inform policy and practice which may aid in improving retention rates in specialist treatment settings in Ireland. A mixed methods study design was used to examine retention in OAT and identify protective and risk factors in a specialist treatment setting. To help achieve this aim, the primary objectives were as follows:

i) To conduct a systematic review to gather and assess the totality of evidence for protective factors supporting retention in OAT, with either methadone or buprenorphine, and risk factors for OAT dropout.

ii) To investigate factors associated with retention in OAT at six-months using a prospective cohort study of adults attending OAT, either methadone or buprenorphine, in a specialist treatment setting in Ireland using the Maudsley Addiction Profile and clinical data.

iii) To explore barriers and facilitators of retention in OAT, areas of service provision that work well and areas for improvement from the perspective of service users and service providers through the use of qualitative semi-structured interviews which were informed by the Maudsley Addiction Profile.

Chapter Two: Retention of service users in opioid agonist treatment: A systematic review

2.1 Introduction

Opioid use disorder is a serious public health problem, contributing substantially to the global disease burden. The number of people with an OUD worldwide increased from 18.2 million in 1990 to 26.8 million in 2016. Furthermore, the years of life lost attributable to OUD was estimated at 3.6 million in 2016 (114). Leading causes of death among people with an OUD include unintentional drug overdose, suicide, HIV, and Hepatitis C infection (49). North America is currently in the midst of an opioid crisis, with escalating opioid overdose deaths initially attributable to prescription opioid use, and more recently to the epidemic of illicit heroin use and illicitly manufactured fentanyl (115, 116). The opioid crisis represents an urgent challenge to reduce harms associated with opioids. Effective treatments are essential to address the emerging public health threats associated with OUD and opioid overdose.

Opioid agonist treatment (OAT), either with methadone or buprenorphine, is the first line treatment for OUD (71, 72), as it has been shown to be safe and effective in suppressing illicit opioid use (117, 118), improving mental and physical well-being (104, 119), and reducing mortality, especially overdose deaths (120). However, growing evidence suggests that mortality risk remains high during the first four weeks of treatment initiation and treatment cessation (52, 120-122). As a full opioid agonist, methadone can cause hazardous respiratory depression and is associated with an excess risk of death from overdose during the first four weeks of treatment initiation, relative to the remainder of time on treatment (48, 120-123). Buprenorphine, a partial opioid receptor agonist, is associated with a reduced risk of opioid overdose at treatment initiation when compared to methadone (52, 124). The mortality risk in the first four weeks following cessation of OAT, with either buprenorphine or methadone, is high (30, 52, 122, 123) and could exceed 30 deaths/1000 person years (48). While careful clinical assessment of opioid tolerance prior to induction onto methadone and continued monitoring during the induction phase may reduce the risk of mortality at treatment initiation, retaining service users in OAT,

either methadone or buprenorphine, will reduce the risk of exposure to mortality after cessation of OAT.

Previous systematic reviews of retention in OAT focused on drug dosing strategies (118, 125-127) with or without comparisons of medications (e.g. buprenorphine versus methadone) (118, 125-128). No systematic review to date has comprehensively investigated factors associated with both retention and cessation rates in OAT. One systematic review examined risk factors associated with dropout from addiction treatment, reporting on 122 studies which included an active psychosocial treatment between 1992 and 2013 (129). The most consistent risk factors for dropout across studies were cognitive deficits, low treatment alliance, personality disorder, and younger age. With the exception of younger age, demographic factors were not identified as consistent risk factors (129). As this review only included studies with an active psychosocial treatment, these findings may not be representative of OAT. Given that OAT is first-line treatment for OUD (71, 72), and retention in OAT is associated with substantial reductions in the risk for all-cause and overdose mortality (48), a comprehensive assessment of retention in OAT is warranted. Any such assessment needs to consider studies examining retention and studies examining dropout, as they are in-fact two sides of the same coin; staying in treatment versus dropping out of treatment.

A systematic review of retention rates in methadone maintenance treatment (MMT) in China, identified a number of non-treatment-related factors (socio-demographics, support system and social function, economic status and psychological status) and treatment-related factors (methadone dose, drug use, methadone use, MMT clinics, MMT participation, awareness of MMT and HIV sero-status) (130). Other systematic reviews on this topic were limited to specific factors associated with dropout and retention in MMT; specifically gender (131), drug use and sexual behaviours (132). In relation to the review by Bawor et al. on gender differences in outcomes of MMT, they pooled data from three studies and reported no evidence of gender differences in treatment retention across the three studies (131). The aim of this study was to

conduct a systematic review to identify both protective factors supporting retention in OAT, with either methadone or buprenorphine, and risk factors for OAT dropout.

2.2 Materials and methods

This systematic review was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (133).

2.2.1 Protocol and registration

A protocol was drafted by the reviewers in preparation for this review, and adhered to throughout; it was not published.

2.2.2 Eligibility criteria

RCTs and observational cohort studies with a minimum of six-months follow-up, investigating retention, or dropout, of OAT involving first-line pharmacological maintenance treatments for OUD (methadone, buprenorphine, or buprenorphine-naloxone combination) (71) were considered eligible for inclusion. RCTs comparing the effectiveness of different types of OAT were excluded. Non-randomized clinical trials, case-control studies, cross-sectional surveys, case reports, case series and qualitative research studies were also excluded. Any study that included the use of levo-alpha-acetylmethadol was excluded due to its wide discontinuation of use in the early 2000s. Levo-alpha-acetylmethadol was discontinued as a result of its links to increased risks of ventricular rhythm disorders (134). Studies that focused on OAT for use other than maintenance were excluded, for example, pain management and detoxification. Studies involving service users aged ≥ 18 years from primary care and specialist treatment settings were included. Samples representing subpopulations, such as HIV+ samples, prison populations, pregnant women and institutional settings such as hospitals and residential care were excluded. Treatment outcomes in these settings may be influenced by the environment and as such may be biased in reporting. We also excluded studies which reported on the same outcome (retention/dropout) for the same cohort, due to the risk of bias introduced through multiple testing. No further exclusion criteria were applied to the study samples to ensure that all articles were retrieved without restrictions on demographics of the samples.

The review was restricted to English language articles, published between January 2001 and October 2019. We chose 2001 as the opioid-agonist agent, levo-alpha-acetylmethadol (LAAM), was withdrawn from the European market in 2001, and was subsequently withdrawn from all markets (134). The primary outcomes were retention at a given time (dichotomous variable) or the time a service user was in treatment before dropout (if treatment ceased) or at the end of the study follow-up period (continuous variable). An overview of the exclusion/inclusion criteria are provided in appendix two.

2.2.3 Information sources and search

A comprehensive search was performed using MEDLINE, Embase, CINAHL, PsycInfo and Web of Science. The search strategy was developed with the assistance of a librarian. Initially, the main phrases and terms were identified; “opioid substitution treatment”, “treatment retention” and “dropout” and combined to create the search string. The search strategy for each database is available is presented in appendix three. The search, conducted in November 2017 and updated in October 2019, included title, abstracts and keywords in order to ensure that no relevant studies were omitted.

2.2.4 Study selection and data extraction

Titles and abstracts of identified studies were reviewed by one reviewer (AOC) to determine potential eligibility. Full text articles were then independently assessed by two reviewers (AOC/GC) for those articles considered eligible from title/abstract, or when it was unclear whether a study met the inclusion criteria from title and abstract. Any uncertainty in relation to study eligibility was resolved through discussion with other authors. The following data was independently extracted by two reviewers (AOC/GC) using a pre-piloted data extraction form (Appendix four): year of publication, country, treatment setting, sample size, study design, demographics (e.g. gender, age), data collection/follow-up period, outcome(s) (retention or dropout), definition of outcome(s), proportion retained in treatment at stated follow-up, reported risk/protective factor(s) investigated, analysis conducted and the associations reported.

Adjusted estimates were extracted from the studies where possible. A third author (LD) checked the extracted data.

2.2.5 Risk of bias in individual studies

Risk of bias was evaluated, by two reviewers, using an adapted form of the Newcastle Ottawa Scale (NOS) (appendix five) for observational studies, and the Cochrane Risk of Bias tool for RCTs. Within the NOS, a 'star system' was developed in which a study is assessed on three broad categories: 1) the selection of study groups; 2) the comparability of groups; and 3) the ascertainment of exposure and outcome. Three sections of the NOS assessment were amended to reflect the use of retention/dropout as the primary outcome. A maximum of 7 stars could be awarded to any one study. A maximum of three stars was awarded in the selection section; we added a star for studies that clearly defined retention/dropout. No star was given if a study failed to provide a clear definition of retention or treatment dropout. A maximum of one star was awarded in the comparability section. This was awarded if the study reported conducting multivariable analysis and stated what factors were included and adjusted for. The outcome section was unaltered, with a maximum of three possible stars. The Cochrane Risk of Bias Tool for RCTs, involved assessing random sequence generation, allocation concealment, selective reporting, blinding of participants, personnel and outcome assessor, and incomplete outcome data.

2.2.6 Summary measures and synthesis of results

Effect sizes reported in the included studies were reported in a variety of ways (i.e. hazard ratio, odds ratio, risk ratio) and as much information as possible was retrieved from studies. Where a study reported on multiple follow-ups, data on factors explored at all-time points (>six-months) were extracted. A narrative synthesis was conducted due to the heterogeneity of the studies included. The Economic and Social Research Council guidance on narrative synthesis was referred to when planning the synthesis (135). Specifically, a preliminary synthesis was developed by tabulating all studies to give an overview of study characteristics. Studies were then organised using categories from the Maudsley Addiction Profile. The categories were as follows:

demographics, substance use, treatment factors, health risk behaviours, health symptoms and social functioning. Variables suitable for inclusion in these categories are presented in Table 2.1. An 'other' category was included to capture additional variables investigated in included studies. The Maudsley Addiction Profile captures six of the eight outcome categories recommended by Wiessing et al. (98). Within the categories outlined above, where possible, relationships across studies were explored and similarities and differences highlighted.

Table 2.1: Variables suitable for inclusion by MAP

Category	Variables
Demographics	Age Gender Location Race
Substance use	Poly-drug use Cannabis use Benzodiazepine use Cocaine use Heroin use Alcohol use Amphetamines/ecstasy Drug use patterns
Treatment Factors	Medication type Dosage Previous treatments Year of treatment intake Treatment setting Treatment facilities

Health Risk Behaviour	Sexual behaviour Injecting Sharing needles
Health Symptoms	Non-fatal overdose Mental health (self-reported) Physical health (self-reported) HIV+/- Tuberculosis (TB) +/-
Social Functioning	Residence, work and training, relationships, illegal behaviours Marital Status Employment status Income Education Living status Social Support Legal issues

2.3 Results

2.3.1 Study selection

Of the 12,162 citations identified from this search strategy, 236 full text articles were assessed for eligibility, with 67 studies meeting the inclusion criteria (103, 136-201) (see Figure 2.1).

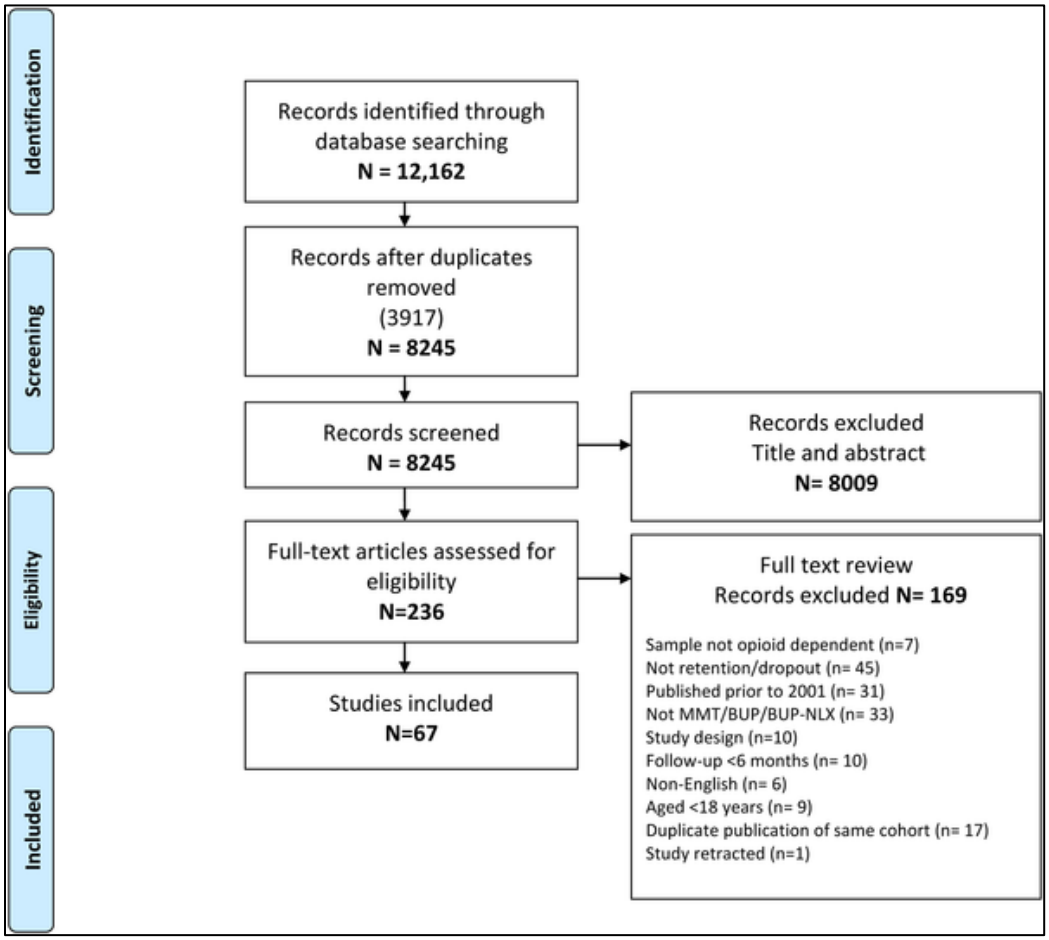

Figure 2.1: Search strategy flowchart

2.4 Study characteristics

The main characteristics of included studies are summarised below and presented in full detail in appendix six.

2.4.1 Country

Studies included in this review were conducted in 21 countries. The majority of studies were conducted in the USA (n = 25) (138, 139, 142, 144, 145, 152, 155, 159, 163, 166, 167, 169, 173-177, 179, 183, 186, 188, 190, 192, 197), China (n = 14) (136, 141, 150, 162, 170-172, 184, 194, 196, 198-201), Canada (n = 9) (147, 151, 157, 158, 178, 181, 182, 191, 193) and Europe (n = 9)

(103, 137, 143, 146, 148, 153, 156, 160, 164). The remaining studies were spread across Asia (n = 5) (165, 185, 187, 189, 195) Israel (n = 3) (140, 179, 180), India (n = 1) (154), Australia (n = 1) (149) and Africa (n = 1) (168).

2.4.2 Study design

Four of the included studies were randomised controlled trials (136-139). The majority of the observational studies involved a retrospective cohort study design (n = 37) (103, 142, 144, 147-149, 151, 154-159, 163, 164, 168, 169, 173-175, 177, 178, 180, 183-186, 188-191, 193-195, 197, 198, 201) with prospective cohort studies accounting for a further 23 studies (140, 141, 143, 145, 146, 150, 152, 153, 160, 162, 165-167, 170-172, 179, 181, 182, 187, 191, 192, 201). The remaining three studies involved an ambi-directional cohort study (199) and analyses of data collected as part of an RCT (161, 176).

2.4.3 Study setting and OAT

There was a large range of treatment settings, with OAT clinics accounting for the largest proportion of treatment settings at 56.7% (n = 38) (136, 138, 139, 141-144, 147, 150-156, 158, 160, 162, 165, 167, 169-172, 179-185, 187, 194, 196, 198-201). Other treatment settings included office based or primary care OAT (n = 8) (137, 145, 163, 186, 188, 191, 192, 197), hospital setting (n = 4) (166, 168, 189, 195), outpatient treatment programmes (n = 4) (159, 161, 176, 177) and mixed treatment settings (n = 3) (103, 146, 149). The remaining studies reported on national or regional registries, including health insurance databases (n = 10) (148, 157, 164, 174, 178, 190, 193) or Veteran Health Administration records in the US (173, 175).Two-thirds of the included studies focused on methadone maintenance treatment (MMT) (n = 45) (103, 136-144, 147, 150, 151, 153, 155, 159, 160, 162, 164-172, 178-185, 187, 189, 193-196, 198-201) with 21% focusing on Buprenorphine (n = 14) (145, 152, 154, 161, 163, 173-177, 186, 188, 192, 197). The remaining studies included mixed OAT (service users in study received either MMT or Buprenorphine) (n = 8) (146, 148, 149, 156-158, 190, 191).

2.4.4 Participants

There was a combined sample size of 294,592 participants (969 in RCTs and 293,623 in observational studies). Sample sizes ranged from 37 (136), to 107,740 (194). One study reported on the number of treatment episodes (n = 9,555) from a population-based treatment registry, rather than the number of participants (193). Most studies provided a gender breakdown for their sample, with a higher proportion of men in all but two studies (142, 155). The mean age of participants ranged from 22.4 years (154) to 47 years (145).

2.4.5 Primary outcome

All four RCTs reported on retention (136-139). While the majority of the observational studies reported on retention rates at various time points (n = 50), the primary outcome for most studies was treatment dropout (n = 39), followed by retention in treatment (n = 24). The most frequently used measure of dropout was time to discontinuation of OAT (n = 32), with varying thresholds applied to identify date of dropout. Almost half the studies reporting on time to discontinuation did not specify a threshold for identifying dropout (n = 13) (142, 145, 147, 148, 150, 161, 167, 170, 173, 174, 189, 195, 198) seven studies indicated that a service user was identified as having dropped out of OAT if they missed more than 30 consecutive days of treatment (158, 162, 165, 172, 178, 184, 196); six studies applied a threshold of seven days (149, 151, 154, 182, 200, 201), and the remaining studies applied a threshold of five days (187), ten days (156), 14 days (163, 171, 199), 21 days (168) and two months (164). The other six studies reporting on dropout used a binary measure, which identified service users as having dropped out of treatment after a specific period of follow-up (143, 153, 160, 166, 183, 192). The majority of studies measuring retention in treatment (n = 18) used a binary measure (103, 144, 146, 152, 155, 157, 159, 175-177, 179, 181, 185, 186, 188, 190, 193, 197), with six studies using a continuous measure of days in treatment (140, 141, 169, 180, 191, 194). The duration of follow-up varied across studies, ranging from six-months to 24 years.

2.4.6 Risk of bias within studies

The assessment of risk of bias for the included observational studies is detailed in appendix seven. The greatest risk of bias was selection bias, with 29 studies reporting on a select group (e.g. a single treatment site/clinic, veterans only) which may undermine the external validity (140-143, 145, 147, 151, 152, 154, 166-170, 173-177, 179-183, 189, 191, 192, 195, 197). In relation to internal validity, the risk of misclassifying the outcome was considered to be high or unclear for 17 studies (142, 145, 148, 160, 161, 164, 167, 170, 173, 174, 180, 185, 188, 189, 192, 195, 198).

As previously noted, many studies did not specify when dropout was ascertained, that is how many consecutive days without OAT were tolerated before a service user was considered to have left treatment. The potential risk of misclassification bias for exposure variables was identified as relatively low, with only four studies identified as having a high risk of misclassifying exposure (140, 169, 187, 189). Similarly, five studies did not clearly identify what covariates were adjusted for in their multivariable analyses (140, 153, 160, 161, 192). All studies were identified as having an appropriate duration of follow-up, with adequate follow-up of participants (complete follow-up or <20% attrition and description of loss provided). All four RCTs were considered to have a low risk of selection bias, as participants were randomised to groups (136-139).

Furthermore, intervention allocations could not have been foreseen in advance of or during enrolment for two trials (136, 139), this was unclear for Jaffray et al. and Marsch et al. (137, 138). The risk of selective outcome reporting was considered to be low for each study. However, the risk of performance bias was high in three of the trials due to a lack of blinding (136, 138, 139) While Jaffray et al. did not blind participants, they used a cluster trial design which controls for contamination between intervention and control participants (137). The risk of detection bias was considered to be unclear for three trials (136-138), with Schwartz et al. identified as high risk as the outcome assessor was unblinded at follow-up (139). Each of the trials was considered to have a low risk of attrition bias.

2.5 Synthesis of results

2.5.1 Rates of retention and dropout

All synthesized results are presented in appendix eight. As previously stated most studies reported on retention rates, even when the primary outcome analysed was dropout. Median retention rates for various time points and by type of OAT are reported in Table 2.2. Overall median retention rates were calculated using the reported retention rate for each study, for each reported follow-up period. Pooled data was not analysed chronologically due to the heterogeneity of the data. As expected, median retention rates decreased as duration of follow-up increased with overall median retention rates declining from 58% at six-months to 38.4% at 3 years. Median retention rates across type of OAT can be compared at six and 12-months follow-up. While retention was lower at 12-months for all types of OAT, median retention rates were highest in studies involving MMT at both time points. Median retention rates were lowest in mixed OAT studies. Consistent with these findings, reported dropout rates increased over time. For example, Sullivan et al. reported a dropout rate of 53% from MMT at six-months, which increased to 66% at 12-months and 77% at 24 months (194). With a longer duration of follow-up Zhang et al. reported a dropout rate of 46.3% from MMT at 12-months, which increased to 58.8% at 24 months and 87.6% at seven years (199).

Table 2.2: Median retention rates across included studies

	Retention six-months % (range)	**Retention 12-months % (range)**	**Retention 2 years % (range)**	**Retention 3 years % (range)**
MMT	67.0% (46.8% - 86.0%) [n=9]	60.7% (20.3% - 94.0%) [n=24] (103, 140-142, 151, 153, 159, 160,	49.8% (29.5% - 76.0%) [n=7]	54.0% (20.0% - 82.0%) [n=6] (142, 151, 164, 195, 196, 198)

	(168, 170, 171, 178, 179, 182, 183, 185, 187)	164-168, 170, 171, 178, 179, 181, 183, 185, 189, 195, 196, 198)	(147, 153, 168, 178, 193, 196, 198)	
BUP	56.8% (19.1% - 64.0%) [n=5] (154, 163, 175, 186, 192)	45.4% (11.7% - 61.6%) [n=6] (154, 173, 174, 177, 188, 197)	-	-
Mixed OAT	54.0% (52.6% -75.8%) [n=5] (149, 152, 156, 190, 191)	40.4% (33.0% - 65.8%) [n=7] (146, 149, 156-158, 190, 191)	-	-
Overall	58.0% (19.1% - 86.0%) [N=19] (149, 152, 154, 156, 163, 168, 170, 171, 175, 178, 179, 182, 183, 185-187, 190-192)	57.0% (11.7% - 94.0%) [N=37] (103, 140-142, 146, 149, 151, 153, 154, 156-160, 164-168, 170, 171, 173, 174, 177-179, 181, 183, 185, 188-191, 195-198)	49.8% (29.5% - 76.0%) [N=9] (147, 153, 156, 168, 177, 178, 193, 196, 198)	38.4% (13.7% - 82.0%) [N=8] (142, 151, 164, 173, 174, 195, 196, 198)

2.5.2 Factors associated with retention or dropout

As noted in appendix eight, the four included RCT's examined different interventions, including behavioural, drug and HIV risk reduction counselling (136), motivational interviewing for community pharmacists delivering OAT (137), a web-based behavioural intervention (138) and different levels of counselling in MMT (139). None of the four RCTs observed significant effects on service user retention. Results from the individual observational studies assessing the longitudinal association between risk or protective factors and retention are synthesized according to the Maudsley Addiction Profile (see Table 2.3).

The number of studies assessing individual factors are presented alongside the number of studies identifying a positive association or increased retention (which refers to a significant increase in retention or a reduction dropout) or a negative association or reduced retention (which refers to a significant decrease in retention or increase in dropout). The results are presented according to the type of OAT studied: MMT, buprenorphine or mixed OAT.

.

Table 2.3: Synthesis of results by risk factor; reporting total number of studies and number of studies reporting significant effects (direction of effects included)

	MMT			**Buprenorphine**			**Mixed OAT**		
Risk Factor	No. of studies	Ret+/ drop-	Ret- /drop+	No. of studies	Ret+/ drop-	Ret- /drop+	No. of studies	Ret+/ drop-	Ret- /drop+
Demographics									
Age (older)	31 (103, 142-144, 147, 155, 159, 164-168, 170, 171, 178-182, 184, 185, 187, 193, 195, 196, 198-201)	18 (142, 144, 148, 155, 159, 164, 168, 178-180, 184, 185, 187, 193, 196, 198, 199, 201)	0	12 (145, 161, 163, 174-177, 186, 188, 190, 192, 197)	8 (161, 163, 174, 175, 177, 186, 190, 197)	0	6 (146, 148, 149, 156, 158, 191)	4 (148, 149, 158, 191)	0
Gender (male)	24 (103, 142-144, 147, 155, 159, 164-168, 170, 171, 178, 181, 182,	1 (171)	7 (103, 144, 155, 168, 194, 196, 201)	9 (145, 161, 163, 176, 177, 186, 190, 192, 197)	1 (186)	3 (163, 177, 197)	6 (146, 148, 149, 156, 158, 191)	0	2 (149, 158)

	185, 189, 194, 196, 199-201)								
Race (Black/African American)	8 (144, 155, 159, 166, 167, 169, 170, 183)	0	3 (144, 155, 159)	4 (145, 173, 177, 197)	0	2 (173, 197)	0	-	-
Race (Hispanic)	2 (155, 166)	0	0	3 (145, 177, 197)	0	1 (197)	0	-	-
Area deprivation (most deprived)	1 (142)	0	1 (142)	0	-	-	0	-	-
Substance Use									
Cannabis	1 (183)	0	0	1 (192)	0	0	1 (191)	1 (191)	0
Benzodiazepine	6 (147, 172, 179, 180, 183, 190)	0	2 (179, 180)	5 (154, 177, 188, 192, 197)	0	0	1 (158)	0	1 (158)
Cocaine	10 (143-145, 147, 155,	0	6 (144, 147, 155,	6 (145, 161, 163, 176, 192, 197)	0	3 (161, 163, 176)	1(191)	0	0

	166, 167, 169, 182, 183)		169, 182, 183)						
Heroin/Opiates	8 (147, 159, 170, 179, 180, 183, 184, 187)	0	5 (159, 179, 180, 183, 184)	4 (145, 175, 192, 197)	0	2 (175, 192)	0	0	0
Alcohol	5 (155, 159, 166, 167, 172)	0	0	3 (177, 192, 197)	0	0	1 (191)	1 (191)	0
Amphetamine	7 (144, 155, 170, 172, 179, 183)	0	4 (144, 155, 172, 179)	1 (177)	0	0	0	0	0
Treatment Factors									
OAT Dosage (higher)	25 (103, 141-143, 150, 153, 164, 165, 167, 168, 170,	22 (103, 141, 142, 150, 153, 167, 168, 170, 171, 178-	0	3 (154, 161, 192)	1 (154)	1 (161)	1 (156)	1 (156)	0

	171, 178-181, 184, 187, 189, 194-196, 198, 199, 201)	181, 184, 187, 189, 194-196, 198, 199, 201)							
Treatment setting (specialist addiction clinic/prescriber)	1 (103)	0	1 (103)	1 (190)	0	1 (190)	1 (149)	0	1 (149)
Counselling	1 (167)	0	0	4 (145, 161, 163, 192)	1 (163)	0	0	0	0
Take-home OAT doses	3 (164, 187, 189)	2 (187, 189)	0	0	0	0	0	0	0
Previous OAT treatments	9 (155, 159, 164, 166, 178, 187, 193, 198, 201)	3 (164, 178, 201)	2 (193, 198)	3 (152, 176, 197)	1 (152)	0	0	0	0

Health Risk Behaviour									
Injection drug use	6 (103, 151, 155, 166, 169, 194)	0	1 (151)	2 (154, 161)	1 (154)	0	1(191)	0	1 (191)
Sharing needles	6 (182, 184, 196, 198, 200, 201)	2 (196, 201)	2 (184, 198)	0	0	0	0	0	0
Risky sexual behaviour	2 (168, 182)	0	0	0	0	0	0	0	0
Health Symptoms									
Mental health	10 (38, 42, 50, 54, 62, 65, 76, 77, 91, 96)	0	1 (180)	5 (163, 174, 177, 190, 197)	3 (163, 177, 197)	1 (174)	0	0	0
Poor physical health/ increasing comorbidities	7 (144, 159, 164, 167, 178, 195, 200)	2 (167, 178)	2 (144, 200)	2 (173, 190)	0	1 (173)	1 (146)	0	0
HIV +	5	1	0	1	0	0	2	0	0

	(165, 170, 171, 194, 195)	(165)		(192)			(156, 191)		
HCV+	6 (141, 169, 171, 179, 194, 195)	2 (141, 179)	1 (171)	2 (163, 197)	1 (163)	1 (197)	1 (156)	0	0
Tuberculosis +	1(170)	0	0	0	0	0	1(156)	0	0
Social Functioning									
Marital status (married/long term partner)	10 (155, 165, 166, 170-172, 183, 194, 199, 201)	4 (165, 172, 194, 201)	0	0	0	0	0	0	0
Employment status (employed/source of income)	14 (155, 159, 165, 167, 170, 171, 178, 182, 183, 189, 194-196, 201)	2 (189, 196)	1 (201)	2 (192, 197)	2 (192, 197)	0	0	0	0

Education (higher)	11 (143, 165, 166, 169-171, 178, 184, 194, 195, 199)	3 (184, 194, 199)	1 (178)	0	0	0	1 (191)	0	0
Homeless	3 (155, 164, 182)	0	1 (164)	0	0	0	1 (191)	0	0
Criminal activity/arrests	14 (144, 151, 155, 159, 164, 167, 170, 171, 181, 182, 187, 194, 195, 198)	0	9 (144, 151, 155, 167, 171, 181, 182, 194, 198)	0	0	0	3 (148, 149, 191)	0	2 (148, 149)
Family support (high)	4 (144, 170, 187, 198)	3 (144, 170, 198)	0	1 (154)	0	0	0	0	0
Contact with other drug users	3 (150, 198, 201)	0	2 (198, 201)	2 (154, 192)	0	1 (154)	0	0	0

Other									
Greater distance/time taken to reach OAT clinic	7 (142, 155, 165, 170, 171, 194, 201)	0	3 (171, 194, 201)	1 (186)	0	1 (186)	0	0	0
Attitudes to OAT (positive)	6 (166, 167, 170, 187, 198, 201)	5 (166, 167, 187, 198, 201)	0	0	0	0	0	0	0[1]

[1] Results relate to observational studies only**.** Ret+/drop- refers to positive effects such that the factor was associated with increased retention or reduced dropout; Ret-/drop+ refers to negative effects such that the factor associated with reduced retention or increased dropout. MMT (cohorts reporting on methadone maintenance treatment); BUP (cohorts reporting on buprenorphine or buprenorphine-naloxone combination); Mixed OAT). *****Pele et al. 2008 reported on two cohorts separately (Tel Aviv and Los Angeles) and Deck et al. 2005 reported on two cohorts separately (Oregon and Washington); each cohort is considered as a study in the analysis presented in this table.

Demographics

Age was the most frequently studied risk factor; of the 31 MMT studies examining age, 18 studies found increasing age to be associated with increased retention (142, 144, 148, 155, 159, 164, 168, 178-180, 184, 185, 187, 193, 196, 198, 199, 201). Similar patterns were observed for studies of buprenorphine, with eight of 12 included studies reporting increased retention with age (161, 163, 174, 175, 177, 186, 190, 197) and mixed OAT with four of the six included studies reporting consistent effects for age (148, 149, 158, 191). While gender was widely studied (n = 39), more than half the studies reported a non-significant association between gender and retention. However, where an association was observed, most studies identified men as having significantly lower retention (103, 144, 149, 155, 158, 163, 168, 177, 194, 196, 197, 201). Two studies reported opposite effects, one in relation to MMT (171) and the other buprenorphine (186).

Race and ethnicity was investigated across 16 studies (142, 144, 145, 155, 159, 164, 166, 167, 170, 177, 183, 188, 189, 191, 192, 197) with most studies reporting on Black or African American (n = 10) (144, 145, 155, 159, 166, 167, 169, 173, 177, 197), White (n = 12) (142, 144, 145, 155, 159, 166, 167, 170, 177, 191, 192, 197), Hispanic (n = 6) (142, 145, 155, 166, 177, 197) and Native American (n = 2) (144, 155) groups. Of the seven MMT studies reporting on Black or African Americans, five involved a comparison with white participants (144, 155, 159, 166, 167), with one study failing to report the comparison group (169). Of these seven studies, three reported reduced retention among African American service users relative to White (144, 155, 159). Similar results were observed in relation to buprenorphine, with two of the four studies reporting reduced retention among African Americans relative to White (197) or other races combined (White/Hispanic/Other) (173). None of the MMT cohorts reported effects for Hispanic race (155, 166), with only one (197) of the three Buprenorphine cohorts (145, 177, 197) reporting effects such that Hispanic race was associated with reduced retention relative to White. Three MMT cohorts examined Native American relative to White, with no evidence of an effect on retention (144, 155). Other assessments of race involved a comparison of Han v's Non-Han in a Chinese cohort, and Malay versus Non-Malay in a Malaysian cohort, with both studies reporting non-significant effects (194, 195). Only one study examined area deprivation, identifying a significant association between increasing deprivation and reduced retention in MMT (142).

Substance use

Thirty-six studies examined the effects of substance use on retention, however, measures of substance use varied greatly across studies ranging from type of drug(s) used, and patterns and frequency of drug use with different recall periods (e.g. lifetime use, last six-months or last 30 days). As outlined in Table 2.3, cocaine was most frequently assessed (n = 17), (143-145, 147, 155, 161, 163, 166, 167, 169, 176, 182, 183, 191, 192, 197) followed by benzodiazepines (n = 12) (147, 154, 158, 172, 177, 179, 180, 183, 188, 190, 192, 197) , heroin/opiates (n = 11) (145, 159, 170, 175, 179, 180, 183, 184, 187, 192, 197) and amphetamines (n = 6) (144, 155, 170, 172, 179, 183). Of the ten methadone cohorts reporting on cocaine, six found cocaine use to be associated with reduced retention (144, 147, 155, 169, 182, 183). Similarly, three of the six buprenorphine cohorts reported significant effects, with cocaine associated with reduced retention (161, 163, 176). A smaller number of studies reported significant effects for benzodiazepines; two (179, 180) of the six MMT cohorts reported illicit benzodiazepine use was associated with reduced retention. Similarly, baseline benzodiazepine use was associated with reduced retention in a mixed OAT sample (158). Benzodiazepines were not found to be associated with retention in the buprenorphine cohorts (154, 177, 188, 192, 197).

Amphetamine use was examined in eight methadone cohorts, with half the cohorts reporting a non-significant association (n = 4) (155, 170, 179, 183); the remaining four cohorts identified reduced retention with amphetamine use (144, 155, 172, 179). Twelve cohorts reported on heroin/opiate use, eight MMT (159, 170, 179, 180, 183, 184, 187) and four buprenorphine (145, 175, 192, 197) . Five of the MMT cohorts (159, 179, 180, 183, 184) and two of the buprenorphine cohorts (175, 192) reported a significant association, such that heroin/opiate use was associated with reduced retention. Methadone and buprenorphine cohorts reporting on alcohol consumption, all reported no association between alcohol and retention (155, 166, 167, 177, 191, 192, 197). In contrast, one cohort involving mixed OAT, found alcohol consumption to be associated with increased retention at six-months (191). Similarly, this cohort was the only study to identify a positive association between cannabis and retention. However, this study was identified as reporting on a select group with self-reported retention.

Treatment factors

Dosage was the most frequently studied treatment factor, studied across 26 methadone cohorts, (103, 141-143, 150, 153, 158, 164, 165, 167, 168, 170, 171, 178-181, 184, 187, 189, 194-196, 198, 199, 201) three buprenorphine cohorts (154, 161, 192) and one mixed OAT cohort (156). However, there was wide variability in measurement of dosage, ranging from average daily dose in categories (150, 165, 178) to dose at treatment initiation (168), or dose after 30 days (171) or at three-months (170). Twenty-two of the 25 methadone cohorts, reported that higher methadone doses were associated with increased retention (103, 141, 142, 150, 153, 167, 168, 170, 171, 178-181, 184, 187, 189, 194-196, 198, 199, 201). Only three of the buprenorphine cohorts reported on dose, with mixed results (154, 161, 192); one study found that increase in buprenorphine dose was associated with increased retention (154), with negative effects observed in another cohort (161). A mixed OAT cohort also reported improved retention among those receiving high and medium doses of OAT relative to low doses (156) .

Three studies reported on the potential effects of treatment setting or treatment provider on retention in MMT (103), buprenorphine (190), and mixed OAT (149). Each study observed a reduction in retention among those attending specialist addiction clinics or prescribers. Mullen et al. found that relative to those attending MMT in primary care, attendance at a specialist treatment centre was associated with reduced retention (103). Shcherbakova et al.'s buprenorphine cohort also found that being in the care of an addiction specialist was associated with reduced retention (190). A large Australian cohort of mixed OAT found that the effects of treatment setting may be time dependent. They observed that those attending correctional facilities, or community pharmacy, in the first nine months of treatment, had improved retention relative to those attending an OAT clinic. However, after the first nine months of treatment, those attending correctional facilities had reduced retention relative to those attending an OAT clinic, while attending community pharmacies remained protective (149).

Few studies examined counselling; one MMT cohort (167) and four buprenorphine cohorts (145, 161, 163, 192), with only one study reporting counselling as independently associated with retention (163). Access to take home doses of methadone was also observed to be associated with improved retention in two (187, 189) of the three MMT cohorts examining this factor (164, 187, 189). A number of studies also considered prior OAT experience (n = 12), with mixed results; of the 9 MMT cohorts, four reported non-significant effects (155, 159, 187), with three cohorts suggesting improved retention with prior OAT (164, 178, 201) and two cohorts suggesting reduced retention (193) (198). However, measures of prior treatment varied from prior treatment in the past two years (155), number of prior drug treatments (159, 178, 193), first treatment episode (y/n) (164) and re-enrolled in treatment (y/n) (198) (201). Only one of the three buprenorphine cohorts reported that those with prior buprenorphine experience has better treatment retention relative to buprenorphine-naïve participants (152).

Health risk behaviours

Eighteen studies investigated the association of health risk-taking behaviours on retention, 14 involved MMT cohorts (103, 151, 155, 166, 168, 169, 182, 184, 194-196, 198, 200, 201), two buprenorphine (154, 161) and one mixed OAT (191). As shown in Table 2.3, the most commonly assessed risk behaviour was injection drug use (six MMT cohorts (103, 151, 155, 166, 169, 194),two buprenorphine (154, 161) and one mixed OAT (191)), followed by use of unclean needles or needle sharing (five MMT cohorts (137, 182, 184, 196, 201)), and risky sexual behaviours (three MMT cohorts (168, 182, 195)). Studies reported various time frames of engaging in risk-taking behaviours, for example daily injecting (191) or currently injecting (151), injecting in the past 30 days (154, 155, 166), in the six-months prior to OAT (194) or lifetime injecting (ever inject) (103). There was no evidence of a relationship between injection drug use and retention in six of the seven MMT cohorts (103, 155, 166, 169, 194). In contrast, a Canadian cohort of service users in a MMT programme for dependence on opioid analgesics found that current injection drug use was associated with dropout (151). Socias et al. also found daily heroin injecting to be associated with reduced retention in mixed OAT at six-months (191). In contrast, a small buprenorphine cohort in India found past month injection use to be associated with reduced dropout at two years (154). Mixed results were also observed in relation to sharing

needles in MMT; two studies found no association (182, 200), with two studies reporting protective effects such that needle sharing experience was associated with reduced dropout (196, 201). In contrast, two additional studies identified needle sharing as risk factors for increased treatment dropout (184, 198). Two MMT cohorts examined risky sexual behaviour, one study assessed condom use (168), while the other assessed working in the sex trade (182). Both studies reported a non-significant effect. Current and previous legal issues were investigated in 17 studies (14 MMT cohorts (144, 151, 155, 159, 164, 167, 170, 171, 181, 182, 187, 194, 195, 198)) and three mixed OAT (148, 149, 191); with eleven studies consistently showing reduced retention associated with criminal activity and arrests/incarceration (144, 148, 149, 151, 155, 167, 171, 181, 194, 198) the remaining studies reported non-significant effects (159, 170, 182, 187, 191, 195). For example, history of arrests (lifetime) (198), arrested in the past two years (155), incarcerated during study period (149, 171) and increasing number of arrests or criminal charges (148, 151, 167, 181) were associated with reduced retention in treatment. Cox et al. also reported a significant reduction in retention with increasing days of serious conflict with others (excluding family) in the past month (151).

Health symptoms

Mental health status was the most frequently assessed health factor, examined in 11 MMT cohorts (143, 147, 155, 159, 167, 170, 180, 181, 195, 200), and five buprenorphine cohorts (163, 174, 177, 190, 197). The factors studied varied from psychiatric diagnosis (143, 174, 177, 190, 197) to the absence or presence of symptoms or severity of psychiatric symptoms (155, 159, 167, 170, 181, 195, 200), psychiatric treatment history (147) and prescribed psychiatric medications (163). Only one MMT study found significant effects, such that those with a DSM-IV Axis II diagnosis had reduced retention (180). Mixed results emerged in relation to buprenorphine, with four of the five buprenorphine cohorts reporting significant effects; three studies found mental health factors to be protective (163, 177, 197) with one study reporting the opposite (174). Haddad et al. found that individuals prescribed psychiatric medications had reduced dropout at 12-months (163), similarly Weinstein et al. found that individuals with any psychiatric diagnosis had greater retention at two years (197). Montalvo's US cohort also found that service users with depressive disorders and other mood disorders had increased retention at two years (177). In

contrast, Manhapra's nationwide US study of insured individuals found that service users with any psychiatric diagnosis had increased dropout at three years, however any psychotherapy was associated with reduced dropout during the same time period (174).

Ten studies reported on participants' physical health status, seven involved MMT cohorts (144, 159, 164, 167, 178, 195, 200), two buprenorphine (173, 190) and one mixed OAT (146). Mixed results were observed across the seven MMT cohorts; three studies reported no significant effects (159, 164, 195) two studies reported that service users with poorer health or greater comorbidities were found to have improved retention (167, 178), with two other studies reporting the opposite effect of reduced retention with poorer self-reported health (144, 200). Similarly, one buprenorphine cohort found a higher Charlson index (greater number of comorbidities) was independently associated with reduced retention (173). Variation observed across studies may be an artefact of measurement, as service users' physical health status was measured differently across studies. Some studies reported on comorbidity scores based on service users' drug dispensing records (173, 178, 190), while others used physical health scores such as the Addiction Severity Index (medical composite score) (159, 167) or the Short-Form 36 Health Survey (200). Of the eight studies that investigated HIV status, only one MMT cohort reported an independent association between being HIV + and reduced dropout (165), with all other studies reporting no evidence of an association (156, 170, 171, 191, 192, 194, 195). Mixed results were observed in relation to Hepatitis C status. Of the six MMT cohorts studying Hepatitis C, two reported that being HCV positive was associated with increased retention (141, 179) with one other study reporting reduced retention (171). Similarly, of the two buprenorphine cohorts examining HCV status, one study reported positive effects (increased retention) (163) and the other opposing effects (197).

Social functioning

Marital or relationship status was explored in ten studies, all involving MMT cohorts (155, 165, 166, 170-172, 194, 199, 201). Six studies reported no evidence of an association with retention (155, 166, 170, 171, 199, 200) . Three studies reported that being married, cohabiting or being in a long-term relationship was associated with increased retention (165, 194, 201). A Chinese study also found that being divorced, relative to being single, was associated with lower retention

(172). Employment was explored in fourteen MMT cohorts, (155, 159, 165, 167, 170, 171, 178, 189, 192, 194-197, 200, 201), and two buprenorphine (192, 197). Employment was generally assessed in terms of being employed versus unemployed (159, 165, 167, 170, 171, 178, 189, 192, 194-197, 201), with two studies reporting on whether participants had a stable source of income (155, 182). Five of the 16 studies found an association between employment and increased retention. A Malaysian study of MMT found that full-time employment was associated with reduced dropout compared to unemployment (189); similar effects were observed in a Chinese MMT cohort (196), with another large Chinese MMT cohort reporting opposing effects as employment was associated with increased dropout (201). The two buprenorphine cohorts reported consistent findings with employment associated with improved retention (192, 197).

Various levels of education were investigated across 11 MMT cohorts (165, 166, 169-171, 178, 184, 191, 194, 195, 199) and one mixed OAT (191). Three MMT cohorts found that higher levels of education were associated with greater retention (184, 194, 199), with one MMT cohort observing higher levels of education to be associated with increased dropout (178). However, it is important to note that the latter MMT cohort used ecological data (% of neighbourhood population at various levels of education) for education, not participants' actual level of education (178). Three MMT cohorts (155, 164, 182) and one mixed OAT (191) examined the effects of homelessness, with only one study observing a significant effect such that no fixed abode or living in an institution was associated with increased dropout (164). A number of studies would also suggest that living with family is protective; three MMT cohorts found that living with family relative to living with friends or alone was associated with increased retention (194, 196, 201). Two further studies identified that having children in the home was associated with increased retention (144, 179), an additional study did not provide evidence of this effect (192).

Current and previous legal issues were investigated in 17 studies (14 MMT cohorts (144, 151, 155, 159, 164, 167, 170, 171, 181, 182, 187, 194, 195, 198)) and three mixed OAT (148, 149, 191); with eleven studies consistently showing reduced retention associated with criminal activity and arrests/incarceration (144, 148, 149, 151, 155, 167, 171, 181, 194, 198) the remaining studies reported non-significant effects (159, 170, 182, 187, 191, 195). For example, history of arrests

(lifetime) (198), arrested in the past two years (155), incarcerated during study period (149, 171) and increasing number of arrests or criminal charges (148, 151, 167, 181) were associated with reduced retention in treatment. Cox et al. also reported a significant reduction in retention with increasing days of serious conflict with others (excluding family) in the past month (151) .Other social functioning factors considered across studies include family support and contact with other drug users. Four MMT cohorts (144, 170, 187, 198) and one buprenorphine (154) examined the role of family support, with three of the four MMT cohorts reporting increased retention with high family support (144, 170, 198). Consistent with these findings, Cao et al. also reported that service users who had relatives receiving MMT were more likely to remain in treatment (MMT) (150). In contrast, contact with other drug users was associated with reduced retention in two MMT cohorts (198, 201) and one buprenorphine cohort(154). In addition, a study of MMT in Indonesia found that perceived peer support increased the likelihood of dropout (187).

Other variables investigated in included studies

A number of studies reported on other variables, covering themes such as distance or time taken to reach OAT clinic (142, 155, 165, 170, 171, 186, 194, 201) and attitudes towards OAT (166, 167, 170, 187, 198, 201). Of the nine cohorts reporting on distance or time taken to reach OAT clinic, four studies (three MMT cohorts and one buprenorphine) reported significant effects, all suggesting that greater distances or travel time required to reach treatment was associated with reduced retention (171, 186, 194, 201). Consistent with these findings, Friedmann et al.'s study of 22 MMT clinics in the USA also reported that provision of transportation assistance was associated with increased retention (159). Attitudes to OAT were assessed in six MMT cohorts, with positive attitudes to MMT associated with increased retention in five of the six cohorts (166, 167, 187, 198, 201).

2.6 Sensitivity analysis

A sensitivity analysis of studies in specialist treatment settings was conducted. Median retention rates in specialist treatment settings decreased as duration of follow-up increased, with median rates declining from 61.3% at six-months to 46.5% at three years (see Appendix nine). These rates are similar to the overall median retention rates of all studies; 58% at six-months to 38.4% at 3 years. Similar to the main analysis of all treatment settings, MMT in specialist treatment settings

had higher rates of retention at six-months; 61.5% (range 46.8 – 86%) in comparison to buprenorphine and mixed OAT studies. However, in contrast to the main analysis, mixed OAT studies in specialist treatment settings had higher retention rates at 12-months; 65.8% (range 43.4 – 84%) in comparison to buprenorphine or MMT alone.

A synthesis of results for specialist treatment settings by risk factor is presented in appendix 10. Similar to the overall analysis, a large number of studies reported significant effects for age, such that older age was associated with increased retention in MMT and mixed OAT. Substance use was also found to have a negative impact on retention in MMT and mixed OAT. In contrast to all treatment settings, there was evidence to support that in addition to cocaine, heroin and amphetamine use, benzodiazepine use was also associated with increased risk of dropout in specialist treatment settings. Similar to the overall findings, higher OAT dose and positive attitudes to OAT were also found to be associated with increased retention in specialist treatment settings. Criminal activity, arrests and incarceration were also associated with reduced retention in this analysis. Of studies that explored marital status, being in a long term relationship was protective of retention as well as high family support which was also indicated in the overall findings. Finally, similar to the overall findings, contact with other drug users also appeared to be associated with reduced retention in studies that investigated this factor in specialist treatment settings.

2.7 Discussion

2.7.1 Statement of principal findings

Our systematic review identified 63 observational cohort studies examining factors associated with retention or dropout from OAT, and four RCTs assessing the effectiveness of different interventions in improving retention in OAT. Retention rates across the observational studies varied widely, with retention rates at 12-months varying from 11.7% (154) to 85.6% (140) across 37 studies. While the National Institute of Drug Abuse (NIDA) recommends a minimum of one year in OAT for best outcomes (202) the median retention rate across studies was approximately 57% at 12-months, which fell to 38.4% at three years. Furthermore, differences were observed by type of OAT, with methadone cohorts reporting a higher median retention rate at 12-months

compared to buprenorphine cohorts and mixed OAT cohorts. This finding is consistent with previous studies, suggesting that buprenorphine is associated with shorter duration of treatment relative to methadone (52, 53).

Studies included in this review were heterogeneous in nature with respect to treatment setting, type of OAT, risk factor assessment, ascertainment of outcome and duration of follow-up. While the presence of such methodological heterogeneity makes it difficult to synthesize results, there is limited evidence to support the influence of a number of factors on retention, including age, substance use, OAT drug dose, legal issues and attitudes to OAT. The majority of studies reported significant effects for age, such that older age was associated with increased retention in MMT, buprenorphine and mixed OAT. Substance use, particularly cocaine and heroin, were found to have a negative impact on retention in MMT and buprenorphine. Similarly, half the studies examining amphetamine use in MMT, reported reduced retention in treatment. Treatment-related factors were most commonly assessed in methadone cohorts. Despite wide variability in assessment of methadone dose, higher doses were consistently observed to be protective. Mixed results were observed in buprenorphine cohorts. Furthermore, two of the three MMT studies investigating take home doses, found that increased take home doses were associated with increased retention. This may be a marker of stability, and is consistent with the finding that increased family support and lower contact with other drug users was associated with increased retention in the majority of MMT studies assessing these factors. In contrast, and reflecting a more chaotic lifestyle, the majority of methadone and mixed OAT cohorts investigating legal issues found criminal activity and arrests/incarceration to be associated with reduced retention. Finally, positive attitudes to MMT were associated with increased retention in MMT.

2.7.2 Strengths and limitations

This review is the first to synthesize the totality of evidence in relation to factors associated with retention in OAT. We used robust and explicit methods to identify, select, appraise and synthesize the study findings. However, the findings of this review need to be considered in the context of the study limitations. Firstly, the study focused on adults aged ≥ 18 years, limiting generalizability of findings to younger cohorts. Secondly, studies had to have a minimum of six-

months follow-up to be included in this review, which excluded 10 studies examining early dropout. This was conducted in order to focus on retention following the initial induction period of treatment. However, growing evidence suggests that mortality risk is highest in the first four weeks following dropout, (30, 122, 123, 203) therefore understanding factors associated with early dropout is important, and could allow for the risk stratification of service users requiring more intensive engagement at the treatment initiation and stabilization stages. In addition, other risk factors not identified here, such as stress could be important risk factors for early dropout (204). Thirdly, the search was restricted to the English language, which may have resulted in us missing important studies published in other languages. Finally, we did not carry out a search of the grey literature which may have introduced a potential publication bias.

2.7.3 Clinical implications and areas for future research

OAT, with methadone or buprenorphine, has been shown to be safe and effective in suppressing illicit opioid use, improving physical and mental health, reducing mortality and transmission of HIV and hepatitis C virus, and drug-related crime (120, 126, 205-208). These protective features of OAT are unlikely to be sustained when a person drops out of treatment, particularly if they relapse. Therefore, identifying risk factors for treatment dropout is essential to inform future interventions targeted at retaining service users in treatment. While a large number of studies addressing this question were identified, the overall value of the evidence was diminished due to the lack of comparability across studies arising from variability in the definition of retention or dropout (98). There does not appear to be an accepted threshold for defining treatment dropout, studies apply various rules ranging from 30 consecutive days without a methadone or buprenorphine prescription, to 21 days, 14 days, 10 days, seven days, five days and up to two months. Furthermore, given the complexity of OAT and the fact that service users often cycle in and out of treatment (107, 209), the influence of different risk factors may vary over time, yet few studies consider risk factors as time varying covariates.

An international consensus project, using a Delphi methodology could be organised to reach consensus regarding the most clinically appropriate definition of retention. The Delphi methodology allows a consensus opinion to be reached among a panel of experts through an interactive process of questionnaires (210). A pooled analysis of individual level data from

multiple cohorts, particularly those using similar methods to ascertain outcome such as prescription refill data, could also be undertaken to inform an internationally agreed definition. This would allow studies to be replicated and promote scientific progress on this question (98). Furthermore, as noted by Brorson et al. (129) future studies should provide detail on the treatment process, particularly in relation to involuntary dropout. It is often unclear whether a service users' dropout was voluntary or involuntary, and while the outcome may be the same the risk factors are likely to be very different. Input from service users and treatment providers may also be beneficial in assessing what are the most pressing issues in retaining service users in treatment. Finally, it would be beneficial to update this review to include buprenorphine depots as an evolving form of OAT. Monthly dosing using this form of OAT by a healthcare professional could improve adherence and prevent service users discontinuing treatment for illicit opioid use (211).

2.8 Conclusion

Almost half the people in OAT are not retained in treatment at 12-months, and this rate reduces further with time. Younger age, substance use, lower doses of methadone, criminal activity/incarceration, and negative attitudes to MMT appear to be associated with reduced retention. A consensus definition of retention is required to allow for comparability across future studies.

Chapter Three: Factors associated with retention in opioid agonist treatment at six-months in a specialist treatment setting – a prospective cohort study

3.1 Introduction

As described in chapter two, retention rates vary widely across studies, with retention rates at six-months varying from 19.1 to 86%, and at 12-months varying from 11.7% to 94%. Studies of retention in specialist treatment settings reported a median retention rate of 61.3% (range: 19.1 – 86%) at six-months (149, 152, 154, 156, 170, 171, 179, 183, 185, 187, 194) and 60.3% at 12-months (range: 11.7 – 87%)(141, 142, 151, 153, 154, 156, 158, 160, 165, 167, 170, 171, 179, 181, 183, 185, 194, 196, 198). As noted, studies were heterogeneous with respect to treatment settings, risk factor assessment, and ascertainment of outcome and duration of follow-up. Meta-analysis was not possible, however there was some evidence to support the influence of a number of factors on retention in OAT, including methadone dose, age, substance misuse (particularly cocaine and heroin), criminal activity and attitudes to treatment (106).

Three studies presented in the systematic review in chapter two (103, 107, 108) have considered retention in an Irish context, two of which relied on data linkage (103, 107) and one collected data from participants but was cross-sectional in nature (108). As a result, they were unable to comprehensively assess the impact of contextual information of a service users' life on dropout. Mullen et al. found that 61% of their sample attended treatment for one continuous year, with being female, older and on an MMT dose greater than 60mg having a positive association with retention. Attending a specialist treatment centre, and receiving a MMT dose of less than 60mg daily was found to increase dropout at 12-months (103). Cousins et al. highlighted that supervised methadone consumption (20-59% of scripts) increased retention, however supervision of 60% of scripts or more was associated with a faster time to discontinuation (107). This finding corroborated qualitative research in relation to supervised consumption which found that while service users considered supervised consumption as acceptable in the short-term, moving away from supervision was important to them (212). Service users in receipt of take-home doses explained that they appreciated the trust and sense of reward that unsupervised treatment bought.

Darker et al. (108) reported 46% of participants self-reported a break in treatment, with age, current methadone dose and prescriptions for antipsychotic medication identified as significant predictors of less breaks in treatment (108).

A more recent study investigated retention in MMT at three and 12-months in specialist treatment setting in Ireland through the use of data linkage over five years (109). Within this study, almost 50% (49.7%, n=1353) of dropout events occurred within the first 90 days of treatment, 33% (n=902) of events occurred between 3 and 12-months, and 17% (n=469) of events occurred after 12-months (109). Factors associated with dropout at three-months were low dose MMT and experiences of previous dropout (109). Dropout at 12-months was associated with low dose methadone, previous dropout, being male, prescribed benzodiazepines and number of comorbidities. Adherence to treatment was protective against dropout at both three and 12-months (109). However it is important to note that this study had a clear limitation in being unable to report contextual information and service users' personal circumstances and perspectives leading up to dropout (109).

There is substantial variation in outcome variables used in observational studies investigating OUD treatment due to the range of negative consequences associated with OUD (98). This variation and lack of comparability has been recognised in other areas of public health and causes ambiguity and differences of expectations for treatment outcomes (98). In the context of dropout, chapter two highlighted the difficulty in comparing studies due to the heterogeneity in definitions of retention, risk factor assessment, and ascertainment of outcome and duration of follow-up. Wiessing et al. conducted a systematic review of measurements to assess outcomes of OUD treatment in longitudinal observational studies (98). In this review they noted that the use of a comprehensive framework for reporting at least seven out of eight domains (drug use, crime, health, treatment-related, social functioning, harms, mortality, and economic use which can be excluded if necessary) would improve consensus and comparability in research and treatment for OUD (98).

In order to comprehensively assess factors associated with dropout at six-months the Maudsley Addiction Profile (MAP)(99) will be used to collect self-reported data in this study. The MAP

covers five of the eight domains noted by Wiessing et al. (drug use, harms, health, social functioning and crime) (98, 99). The average number of MAP categories reported in the 44 studies based in specialist treatment settings in chapter two was 3.2 out of a possible six. In Wiessing et al.'s systematic review the average number of domains reported out of a possible eight was 3.7 (98). This further highlights the heterogeneity in longitudinal studies investigating OAT and the need to comprehensively assess risk factors. The MAP has been used both internationally (213-215) and in Ireland (216-219) to investigate outcomes for individuals with an OUD on OAT. However, few studies have applied MAP to the study of dropout. The MAP is a validated questionnaire used for treatment outcome research (99) and has been validated for use in four countries: the United Kingdom, Italy, Spain and Portugal (101). The MAP asks participants to answer questions in relation to the exposures listed over the 30 days prior to the date of the assessment (99).

Retention in OAT is associated with reductions in risk for all-cause and overdose mortality in people with OUD (48). The time immediately after leaving OAT is also a period of increased mortality risk (48). This is the first time that the MAP which encompasses six of the eight domains highlighted by Wiessing et al.'s to investigate retention with an adult population in a specialist treatment setting. It will therefore help provide new insights into what factors are associated with retention. Sixty percent of OAT users in Ireland currently receive treatment from specialist treatment settings and 40% in primary care settings (Level 1 and 2 GPs)(84). In Europe, most treatment for OUD is also provided on an outpatient basis, most commonly in specialist drug services (27). For this reason, the study was conducted in a specialist treatment setting in order to capture a representative sample of individuals on OAT. As such the aim of this study is to ascertain what factors, based on the MAP, are associated with dropout in OAT at six-months among adults attending a specialist addiction treatment centre.

3.2 Study design & methods

Study design

The study was a prospective cohort study investigating factors associated with dropout from OAT at six-months follow-up. While NIDA recommends a minimum of 12 months in OAT for best

outcomes, dropout rates from OAT are high within the first three-months of initiation (109, 132). Retention rates at six-months varied from 19.1% to 86% in the systematic review presented in chapter two. Hence, for this study, we focused on dropout at six-months. In following the structure of the MAP within chapter two, the MAP was also used for data collection in this study. It was reported using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (220). Ethical approval was obtained from the Royal College of Surgeons in Ireland's Research Ethics Committee (REC 1596) March 2019 (Appendix 11). Approval was also obtained from the HSE Primary Care Research Committee in April 2019 (Appendix 12).

3.2.2 Setting

In 2019, 11,991 individuals with OUD were in receipt of OAT treatment in Ireland. The National Drug Treatment Centre (NDTC) is the largest OAT specialist treatment centre in Ireland with 759 service users in attendance in 2019, accounting for 10.5% of service users attending a specialist treatment setting for OAT in Ireland (94).

The NDTC receives referrals from a variety of settings, including General Practitioners (GPs), hospitals, prisons, drug support services, homeless support services and other drug treatment centres. They are also known to accept referrals of service users with complex and challenging needs and service users who need to be transferred from other clinics due to safety concerns. All service users sign a treatment contract when they initiate treatment in the NDTC, which advises that they may be invited to participate in research studies. The model of care is psychiatry led with four psychiatrists each leading a multidisciplinary team that includes a clinical secretary, social workers, nurses, psychiatrists, trainee psychiatrists, counsellors, key workers, child care workers and a clinical psychologist. General attendants within the NDTC are responsible for the supervision and management of both dispensing floors and interact with service users throughout the entire day.

The centre also has childcare facilities, counselling and meeting rooms. Recruitment and baseline data collection was conducted between June 2019 and March 2020 with a 6-month follow-up period (December 2019 – September 2020).

3.2.3 Inclusion criteria

A new-user design was planned for this study. A new-user design identifies all individuals in a defined population who start a course of treatment (or restart depending on the clinical context), thereby purposefully excluding prevalent users (221). The new-user design allows for the study of the full time course of outcome risk after treatment initiation, with representation of early and late events (221, 222). It also ensures appropriate temporal ordering of baseline confounders, exposures, and outcomes. However, a new-user design may over represent poor compliers to medications who may be recommencing treatment (222). Despite the strengths of new-user designs, the implementation is not always feasible in practice as exclusion of prevalent users often reduces follow-up time, sample size and study power (221, 222).

In line with a new-user design, the initial inclusion criteria were as follows; adults aged ≥18 years, with OUD initiating an OAT treatment episode in the NDTC during the study observation period. The following exclusion criteria were considered: service users commencing detoxification; transfers from prisons, hospitals and other clinics (as they were considered to be prevalent users); and at the request of treating consultants, service users attending a challenging behaviour treatment group due to safety and lone working policies. However, it became apparent that it would not be possible to recruit the desired sample size of 140 participants during the study period using a new-user design because of the time constraints of the study and a lack of new service users attending the clinic in the required time frame. Therefore the inclusion criteria were revised to include service users transferring from prisons, hospitals and other clinics to the NDTC. While this represents a new treatment episode in the NDTC, such transfers involve the continuation of an OAT episode commenced elsewhere. As a result, the study design was changed to include specific prevalent users; those who had been released from prison, discharged from hospital, or transferred from other treatment settings and those who had started treatment for the first time, or recommenced treatment following dropout, up to 4 months prior to the commencement of data collection which began in June 2019. This 4-month time-period was used in order to facilitate the recruitment of a sufficient sample size.

3.2.4 Recruitment

Clinical secretaries with responsibility for each of the four consultants' service user lists, acted as gatekeepers, identifying service users who had commenced a new treatment episode within the specific time period. These lists were reviewed by AOC to ensure that the potential participants met the inclusion criteria. The list was also monitored to check if potential participants who had not attended treatment for up to 28 days had returned to treatment. Once the service user lists had been reviewed and potential participants identified, appointments were entered into the Electronic Patient System (EPS). Collaboration with the general attendants ensured that when potential participants arrived for their treatment AOC was contacted. This recruitment strategy was approved by the treatment centre General Manager.

All eligible participants were approached by AOC and invited to participate in this study. The study was explained to them and an information sheet was also provided. The information sheet was written in consultation with the National Adult Literacy Agency in order to ensure that the sheet was in plain English and accessible for all potential participants (see Appendix 13). This information leaflet explained the purpose of the study, what informed consent is, what participants would be required to do, the benefits and risks of participation, the information that would be obtained (with their consent), data protection and privacy rights under the General Data Protection Regulations (GDPR) and contact details of AOC and her supervisory team. Potential participants were given approximately two weeks to consider their willingness to participate. They were asked to contact AOC via the general attendants if they decided to take part in the study. Once service users agreed to participate, their consent was obtained (see Appendix 14).

3.3 Data collection

3.3.1 Data sources

The following two data sources were used: the Maudsley Addiction Profile in a face-to-face interview which was linked to service users' clinical records using the EPS.

3.3.2 Maudsley Addiction Profile (MAP)

While the MAP is used in the NDTC as part of the clinical assessment process when a new service user start their treatment, it was repeated with the participants by AOC once they had been recruited. It is a self-reported assessment that was completed with AOC present.

Data collection using the MAP took approximately ten to fifteen minutes to administer depending on the literacy and comprehension skills of the participant. Additional time was also allocated for questions the participant had regarding the study. The assessment was administered using pen and paper in meeting rooms on the treatment floors of the NDTC. Following completion of data collection, the data was inputted onsite to a protected electronic file and the paper document was locked in a filing cabinet of collaborator KD in the NDTC. A small financial token in the form of a convenience store voucher (€10) was given to participants as a token of gratitude for their involvement in the study. These vouchers could be exchanged for any products excluding cigarettes, alcohol or gambling products. In addition to the baseline interview, further baseline data and treatment-related factors were extracted from participants' clinical file on the EPS. This brought the total number of Wiessing et al.'s domains covered from five (collected at baseline interview), to six with the inclusion of treatment-related factors that were extracted from the EPS.

It was decided that ascertaining the economic estimates of drug use was not feasible due to the way in which participants described their drug use and the variability in street costs and as such it was not included in the study. Wiessing et al. (98) suggest that this can be excluded if it is not feasible to collect the data. The domain of mortality within Wiessing's framework was also excluded. This was excluded as deaths of NDTC service users are only recorded in case notes if the centre is notified by external organisations or family members.

Table 3.1 outlines the six categories of the MAP used in the face-to-face interviews, drug use, injecting and sexual behaviour, health symptoms, social functioning and treatment-related factors. The tool was piloted on 16 participants and following this, additional questions were added regarding age at first drug use, IV use and OAT use. Participants recruited in the pilot stage were also included in the study. Consequently, the additional questions are missing for the first

16 participants. In line with the procedure of conducting the MAP, all participants were asked to answer the questions in relation to what they had experienced in the 30 days prior to the baseline interview.

3.3.3 Electronic Patient System (EPS)

The EPS is the internal system used for the management of clinical records for all service users attending the NDTC. Upon commencing treatment, each service user is assigned a unique identifier. This number does not link to any other database. All information regarding service users' treatment is recorded on this system including medication dispensing records, attendance records, urine drug testing, referrals to external agencies, care plans and progress notes. All staff and members of the multi-disciplinary team have access to the EPS. For this study, AOC was given access to the EPS in order to arrange appointments with potential participants and to extract all data required upon consent from participants.

Onsite unsupervised urine testing is regularly conducted for cocaine, opioids and benzodiazepines in the NDTC and at the discretion of medical staff. Less frequent tests are also conducted for cannabis and amphetamines. Samples are required on a weekly basis but can become more frequent or infrequent depending on the service users' attendance and results of previous tests. Alcohol is tested through breathalyser equipment by a nurse onsite if there is a suspicion that a service user is intoxicated. Irish clinical guidelines recommend at least one random drug test per month and state that some clinical situations may require more testing in order to maintain stability (70). Participants' date of birth, OAT type, median dose, take home doses and urine analysis for cocaine, opioids and benzodiazepines and clinical diagnoses were all extracted from the EPS.

3.4 Variables

3.4.1 Primary outcome

The primary outcome for this study was dropout (time to discontinuation) at six-months follow-up. If participants were recorded as inactive on the EPS, their date of dropout was considered the last date of coverage from their last OAT prescription. For the remaining participants, who were recorded as active on the EPS, their attendance in the previous 28 days was examined. If a

participant was classified as 'active' but had not received methadone or buprenorphine in the previous 28 days, they were classified as having dropped out for this study, and the last day of their OAT prescription coverage was recorded as date of dropout. For those who had dropped out of treatment, the duration of their treatment episode was calculated by subtracting the end date of coverage from their last OAT prescription from their study start date.

If a participant transferred to another treatment setting, time to discontinuation could not be calculated and as a result they were censored from the study. Although they remained on OAT, AOC was unable to extract information on where they were transferred to and their subsequent treatment in the new setting. The focus here was on time to discontinuation following treatment initiation, hence, participants who had dropped out, regardless of subsequently returning to treatment, were considered as having dropped out from the treatment episode and their time to discontinuation calculated. As a result, the last coverage date from their last OAT prescription before dropout was considered the date of time to discontinuation. Service users' status on the CTL remains active for up to 28 days from their first day of non-attendance. During this time, outreach support from the NDTC attempt to contact the service user in order to encourage them to return to treatment. If no contact is made, and the service user does not attend the centre for 28 days, exit forms are sent to the central treatment list and they are discharged as a service user from the NDTC.

3.4.2 Secondary outcomes

The secondary outcome was a categorical variable of dropout (yes/no) at six-months. Dropout was ascertained by checking if service users were still active on the EPS system at follow-up. If the participant was still active, but had not attended the clinic in the 28 days prior to the 6 month follow-up period, they were considered to have dropped out of treatment. Reasons for dropout were also recorded where available on the EPS. If a participant had transferred to a different OAT provider including primary care, prison or inpatient detoxification during the follow-up period, they were classified as retained in treatment. Participants who dropped out of treatment and subsequently returned before the six-month follow-up period ended were also considered to be retained in treatment.

3.4.3 Risk factors

Risk factors were assessed according to the MAP (see Table 3.1) during the face-to-face interviews and information regarding treatment factors and substance abuse (urinalysis) was obtained from the service users clinical records. Table 3.1 describes what sources were used to obtain data.

Table 3.1: Risk factors according to the Maudsley Addiction Profile

Basic demographics	**Drug use past 30 days**	**Injecting and sexual behaviour past 30 days**	**Health Symptoms past 30 days**	**Social functioning past 30 days**	**Social functioning (illegal activities) past 30 days**
MAP Gender Ethnicity Country of birth **EPS** Age at assessment **Additional information** Age at first OAT Age at first drug use Age at first drug IV use	**MAP** Frequency (days) of use Route of use for the following: Alcohol Heroin Opioids Illicit benzodiazepines Cocaine HCL Crack cocaine Amphetamines	**MAP** IV drug use Frequency (days) sharing needles Did the participant share a syringe How often does the participant use a new syringe Penetrative sex in the past month Penetrative sex in the past month without a condom	**MAP** Experience specific physical symptoms (see Appendix one). Experience specific psychological symptoms (see Appendix one) **EPS** Clinical diagnoses (Y/N)	**MAP** Accommodation types accessed (see Appendix one) Number of accommodation types accessed Number of months spent in current address In paid employment in the past month Days employed Absent from paid employment	**MAP** Did the participant conduct the following illegal activity: Selling drugs Committing fraud Stealing from a property Stealing from a person Shoplifting Stealing from a vehicle Stealing a vehicle Other theft

	Non-fatal overdose **Additional information from the EPS** OAT type Baseline dose Dispensing arrangements Take home doses Dates of urine tests (for duration of study period) Drugs tested for: Alcohol Opioids Benzodiazepine Cocaine	Number of people with whom they engaged in unprotected sexual intercourse Frequency of unprotected sexual intercourse		Days absent from employment In a voluntary position Days volunteering In education or training Days in education or training Looking after dependents Days looking after dependents Unemployed in the past month Days unemployed in the past month In a romantic relationship in the past month Days contact with partner	Criminal damage Public order offence Soliciting Committing any other crime Days (frequency) committing crime Times committing crime in one day Total number of crimes committed

				Days of conflict with partner Days contact with children (U18) Days conflict with children (U18) Days contact with friends Days conflict with friends	

Substance use

Substance use was identified objectively using data from urinalysis recorded on the EPS. A participant was considered to have used a substance if they had at least one positive urine test for cocaine, opioids or benzodiazepines during the study period. The number of positive urine tests during the six-months follow-up were also recorded. However, for those service users participating in the study during the COVID-19 pandemic, the number of urine tests requested reduced due to changes in clinical practices to mitigate the risks of transmission of COVID-19. Participants also reported on whether they experienced a non-fatal overdose and number of non-fatal overdoses in the 30 days prior baseline interview.

Treatment factors

Type of OAT drug (methadone or buprenorphine/buprenorphine combinations), take home doses (THDs) and OAT dose was recorded from EPS. The median methadone and buprenorphine dose over the study period was recorded to account for variability over time. For example, several missed doses often prompts a review of a service users' dose due to a loss of tolerance for opioids. The NDTC requires that service users recommence induction after 5 missed doses. Service users engaging in MMT are generally recommenced on 20mg (in line with clinical guidelines of 10-40mg depending on service user assessment) (70). Buprenorphine/naloxone service users are recommenced on between 4-8mg in line with clinical guidelines (70).

In accordance with prescribing recommendations from the WHO (45) and HSE clinical guidelines for OAT (70), median methadone dosage was further categorised as below (<60mg/day) and within (60-120mg/day) the recommended methadone maintenance range of 60-120mg/day (70). A category for more than 120mg/day was also created, however this was subsequently removed as no participants in receipt of MMT were within this range. No categories were created for buprenorphine due to the small sample size (n=7). Prescribing recommendations for buprenorphine/naloxone state that doses between 16-24mg daily are usually required for stabilisation, although some service users may require higher doses. The recommended dose for buprenorphine alone is 32mg daily (70). For each participant, the median number of daily THDs over the 6-month study period was calculated from prescription data in the EPS.

Access to THDs is determined by service user and community safety and on clinical stability of the service user, and varies over the course of OAT (70). Daily supervised consumption occurs during in the induction phase, with no more than 6 days THD during the stabilisation and

maintenance phase. However, for those service users participating in the study during the COVID-19 pandemic, access to THDs was increased to support service users who were vulnerable, cocooning or unable to travel.

Health risk behaviours

Health risk behaviour data was collected using the MAP. Sexual risk-taking behaviour was defined as self-reporting penetrative sex in the past 30 days without using a condom and self-reporting the number of partners that participants had unprotected penetrative sex with. Intravenous drug use was defined as injecting drugs at least once in the 30 days prior to baseline interview. Risk-taking injecting practices were defined as self-reporting the use of shared needles in the 30 days prior to baseline interview.

Health

A Likert scale (never, rarely, sometimes, often, always) was used to describe the severity in which participants experienced ten physical and nine psychological health symptoms in the 30 days prior to baseline interview. These symptoms were derived from the anxiety and depression sub-scales of the Brief Symptom Inventory and the Opiate Treatment Index for use in the MAP (99). Any comorbidities, medical or psychiatric, diagnosed by treating doctors in the NDTC are recorded on service users' clinical record in the EPS. In some cases these are recorded from service users self-reporting during their initial assessment which is then confirmed with external agencies. The presence of a medical and/or psychiatric diagnosis was extracted from participants' clinical records to create two binary variables; medical diagnosis and psychiatric diagnoses.

Social functioning

A categorical variable was created to capture those who were experiencing homelessness in the month prior to baseline interview. Participants who reported at least one day sleeping rough or sleeping in homeless accommodation were considered to be experiencing homelessness. Participants also reported the amount of time (months) they had spent in their current address. Categorical variables were created to ascertain if participants were engaged in employment, either full time or part time in the 30 days prior to baseline interview. Participants were considered to be employed if they reported at least one day of involvement in the 30 days prior to baseline interview. Continuous variables were created to determine how many days of contact and serious conflict in the 30 days prior to baseline interview each participant had with their partner, friends or children less than 18 year of age (if applicable).

Illegal activities

Participants reported on illegal activities in the 30 days prior to baseline interview. A list of 12 common crimes is recorded in the MAP (see Table 3.1: social functioning – illegal activities). Participants were considered to have taken part in illegal activities if they self-reported at least one activity. The number of crimes committed was also calculated in the 30 days prior to the baseline interview.

3.5 Data management and protection

All clinical data is maintained by the NDTC under the HSE. All data required for this study (the MAP and extraction from clinical records) was collected by AOC. Data collected was stored on a password-protected computer within the NDTC. Hard copies of consent forms and data collected were stored in a locked filing cabinet in the office of the study collaborator within the NDTC. Data was pseudonymised and a unique identifier was created for each service user, which could link back to the person, to facilitate the follow-up data collection. The file linking study identifier to a participant did not leave the NDTC and AOC was the only researcher capable of accessing the study identifiers. All study data was stored in a secure password protected folder on the RCSI v-drive. The data will be retained for a maximum of five years, or a period of one year after publication/submission of the final report.

3.6 Study size

Assuming a population standard deviation of approximately 46 days, a sample size of 140 would allow the mean time to discontinuation to be estimated with 95% confidence and a precision of approximately 8 days, in addition to exploring potentially associated risks factors. The standard deviation was estimated based on the time period of the study (i.e. 6 months). Dividing the range of possible values (0 days to approximately 183 days) by 4 usually gives a rough standard deviation, in this case approximately 46 days. Based on previous work in a primary care setting, the mean retention (length of time in treatment) was 168 days per treatment episode (standard deviation of 91.25 days)(223). It was recognised early in recruitment that this figure of 140 would be difficult to attain due to the limited new service users attending the clinic and the chaotic attendance that some potential participants demonstrated. A total of 209 potential participants entering treatment from 15th March 2019 to 28th January 2020 were identified by gatekeepers as eligible for inclusion. The recruitment and data collection period was due to end on April 1st 2020 in order to allow for six-months follow-up data collection in September 2020. However, following the World Health Organisation's formal declaration of a

global pandemic on March 11th (224) and the Irish Government's announcement on March 12th in relation to COVID-19 (225), recruitment was suspended and ultimately ceased prematurely. This suspension of recruitment was implemented by the general manager of the NDTC in order to adhere to emerging COVID-19 policies. During the recruitment period, potential participants were excluded on the following grounds (Figure 3.1):

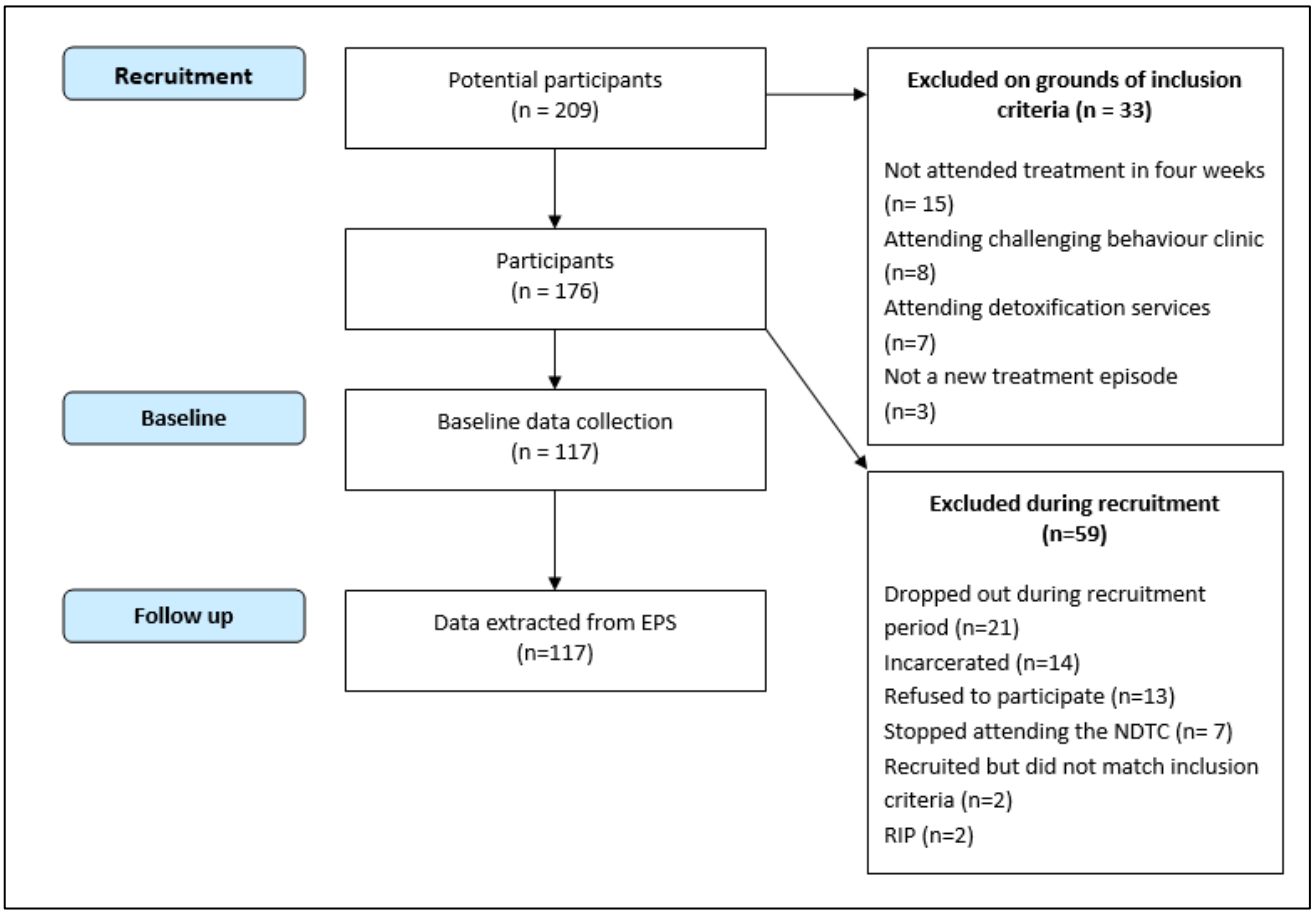

Figure 3.1 : Recruitment of participants

One hundred and seventeen participants were recruited for the study, a response rate of 66.5%. AOC had sole responsibility for the recruitment and completion of baseline interviews for all participants. Approximately 10 appointments per day were arranged with potential participants to discuss recruitment and complete the baseline interview upon consent. This number was chosen in order to mitigate for multiple potential participants attending at the same time, as the NDTC operates as a walk-in clinic. Of the 10 appointments made daily, recruitment of participants and completion of the baseline interview would vary widely from zero to six. Of those recruited, some participants would complete the baseline interview immediately

following their consent to participate, whereas others would ask to complete the baseline interview on a different date.

AOC often met with potential participants several times before finalising a date and time for interview. Participants also reported having busy lives and the interviews would often have to be rearranged as a result of time constraints, child care issues or clashing appointments. On rare occasions, participants appeared under the influence of a substance and AOC suggested a different day to complete the baseline interview. Consequently, the median time between the start of treatment episodes and completion of the baseline interview was 88 [IQR 45-203] days. Due to the challenges experienced in recruitment, face-to-face interviews for 34 participants (29%) took place after six-months in treatment, therefore this has implications for data obtained from the MAP. However this did not affect data that was collected from the EPS. Due to the different times that baseline interviews were conducted, it is important to take this into consideration when interpreting the results of this study.

3.7 Statistical analysis

Descriptive statistics (e.g. means and standard deviations or medians and interquartile ranges for continuous variables, frequency and percentages for categorical variables) were used to describe the basic demographics of the sample. Participants were also profiled in line with MAP, under the following categories: substance use, treatment factors, injecting and risk-taking behaviours, health, and social functioning.

The primary outcome of interest was time to dropout within a six-month period. The secondary outcome of interest was a categorical variable at six-months: dropout (yes/no). A survival analysis of discontinuation of treatment was planned as well as a multivariable logistic regression analysis of factors associated with dropout but unfortunately was not possible as outlined in the results section.

For the secondary outcome, dropout (yes/no), between-group comparisons of continuous variables were made using the Mann Whitney U test at follow-up. A non-parametric test was selected due to the skewed nature of the data. Chi Square tests were used to compare categorical variables. Specific variables selected for univariable analysis were informed by previous literature and by each domain of the MAP. At least one variable from each domain of the MAP was selected. Chapter two highlighted that younger age, substance use (particularly

cocaine and heroin use), OAT dose, and criminal activity appear to be associated with dropout and as a result were explored in this study.

The variables selected were also informed by the current HSE OAT guidelines which outline criteria for assessing stability in service users in order to provide THDs. These clinical stability indictors are defined as: adherence with treatment directives, no recent problematic substance use, stable housing, a stable OAT dose and emotional stability (70). The following variables that were tested were informed by these criteria for stability: in employment (social function), accessing homeless accommodation (social functioning), and co-morbidities (health). The final variable tested was to investigate if there was a relation between treatment episodes occurring during the COVID-19 pandemic and dropout.

The treatment dropout rule according to treatment provider of 28 days may have misclassified participants on treatment. In order to migitate for this potential bias, a sensitivity analysis was also conducted in order to investigate dropout at 14 days. This analysis classified a participant as having dropped out of treatment if they had not attended the clinic within 14 days from date of last prescription.Following the results of the initial sensitivity analysis, a further analysis on the primary outcome was conducted. This sensitivity analysis compared characteristics and risk factors of those who were retained and those who dropped out. Where analysis resulted in less than five participants, the results were referred to as less than or equal to five, in line with GDPR regulations, and to ensure anonymity.

3.8 Results

3.8.1 Characteristics of the cohort

Service user and treatment characteristics are presented in Table 3.2. A total of 117 participants were recruited, 74.4% male (n=87), with a median age 37.5 years [IQR 32 – 42.5]. The median age at first drug use and first IV drug use was 22 [IQR 18-28] years. Median age entering OAT was 25 [IQR 19-31] years. Almost 85% (n=99) of participants self-reported substance use at baseline and the median number of substances self-reported was 2 [IQR1-3]. Of the 108 participants who tested positive for benzodiazepines at least once, 27 were also in receipt of a benzodiazepine prescription from the NDTC. Seventeen percent of participants (n=20) reported injecting drugs in the 30 days prior to baseline interview with the median number of days for IV drug use being 4 (IQR2-21). More than one-third of participants were returning to treatment following a dropout period of at least 28 days (38.5%, n=45). While 55% (n=60) of service users on MMT were prescribed 60-120 mgs daily, 45% (n=50) were in receipt of less than 60 mg of MMT and the median treatment dose for those in receipt of buprenorphine/naloxone was 8 [IQR 4-8] mg.

Fourteen percent of participants (n=17) reported accessing two or more types of accommodation with 48% (48.7%, n=57) reporting experiences of homelessness in the month prior to baseline interview. Thirty percent of all participants (n=36) reported that they had cared for dependents (children or elderly parents) while forty-seven percent (n=55) stated that they were in an intimate relationship at the time of data collection. Fifty-four percent (n=63) also reported having friends, however 15.8% (n=10) reported that they did not have contact with their friends in the 30 days prior to baseline interview.

Fifty four percent (n=63) of participants reported having children under the age of 18, of which 36.5% (n=23) reported that they had no contact with them in the 30 days prior to baseline interview. Median days of contact in the previous 30 days between participants and their partners was 30 [IQR 15 – 30] days, with friends was 30 [IQR 8-30] days and with children under 18 years of age was 4 [IQR 0-30] days. All participants reported at least one day of social contact with their friend(s), partner or child/children. Twenty eight percent (n=33) of participants reported taking part in an illegal activity in the 30 days prior to baseline interview and the most frequently committed crimes included shoplifting, selling drugs and public order

Table 3.2: Demographic and treatment characteristics (n=117)

Demographics	**N (%)** [1]
Male	87 (74.3%)
Median age at study start (years)	37.5 [IQR 32-42.5]
Substance Use[2] N (%)	
Illicit Benzodiazepines	108 (92.3%)
Heroin	98 (83.8%)
Cocaine (HCL/crack)	86 (73.5%)
Alcohol	19 (16.2%)
Treatment Factors	
In receipt of MMT	110 (94%)
In receipt of Buprenorphine	7 (6%)
Median MMT dose:	
≤ 60 mg	50 (45.5%)
61 to 120 mg	60 (54.5%)
Median Buprenorphine dose	8 [IQR 4-8]
Median Take Home Dose (MMT)	
0	85 (77.2%)
1-2	11 (10%)
≥2	14 (12.7%)
Median Take Home Dose (BUP)	
0	≤5
1	≤5
Treatment episode type	
Returning to treatment	45 (38.5%)
Transfer from prison	36 (30.8%)
Transfer from hospital/inpatient detoxification	19 (16.2%)
First treatment episode	17 (14.5%)
Injecting and risk-taking behavior N (%)	
IV drug use	20 (17%)
Always injects with a new needle[3]	15 (75%)
Often injects with a new needle	≤5
Sometimes/rarely injects with a new needle	≤5
Health N (%)	
Diagnosis of physical illness/condition	28 (24%)
Diagnosis of mental illness/condition	30 (25%)
Social functioning N (%)	
Experienced homelessness	57 (48.7%)
In employment	8 (6.8%)
Committed crime(s)	32 (27%)
Treatment episode occurred during implementation of COIVD – 19 contingency plan	
Yes	64 (54.7%)

MMT = Methadone Maintenance Treatment; BUP = Buprenorphine

[1] Unless stated otherwise

[2] At least 1 positive urine result during participants' treatment episode(s) throughout study period

[3] Missing data (n=1)

offences (namely begging). The median number of crimes committed by participants was 2 [IQR 1-9] in the 30 days prior to baseline interview.

3.8.2 Primary outcome – time to discontinuation

Five participants were transferred from the NDTC to another treatment service during the study follow-up period. It was not possible to determine if they were retained in the treatment service they transferred to during the follow-up period, leaving a sample of 112 participants in which time to discontinuation could be calculated. Of the 112 participants, 16 participants dropped out at some point during the study period. The median days in treatment before dropout for these 16 participants was 80 [IQR 25.6- 92.3] days. Of these 16 participants, ten participants returned to treatment at some point in the study follow-up period. The median days in treatment before dropout for this group was 63.5 [IQR 15.8 – 91.2] days. Although these ten participants returned to treatment following dropout, they were considered to have dropped out of treatment in line with the primary outcome. Due to the small number of events (n=16), the study lacked power to conduct a survival analysis or logistic regression.

3.8.3 Secondary outcome – dropout at 6 months

At the end of the six month study period, 95% (94.6%, n=106) of participants were retained and five percent (n=6) of participants had dropped out. "Of those retained, an additional 10 (9.4%) participants left the NDTC during the study period, but returned after at least 28 days of absence. Due to COVID-19 restrictions it could not be ascertained via clinical records if these 10 participants dropped out from OAT or were transferred to another setting during their absence from NDTC. This was not possible as access to the clinic for AOC was prohibited (during lockdown restrictions) and non-HSE staff are not permitted remote access to the EPS"

The characteristics for those retained (n=106) and those who dropped out (n=6), in addition to univariable analysis are presented in Table 3.3. The median age, although not statistically significant (p=.051), was 38 [IQR 32 – 43] years for those retained in comparison to 33 [IQR 26-35] years for those who dropped out. Opioid use was similar for those retained and those who dropped out. All participants who dropped out of treatment tested positive for cocaine use at least once in their study period in comparison to 72% of those retained, although this was not statistically significant. However, there was evidence of a statistically significant difference in IV drug use ($p<0.05$), with a higher percent of participants who dropped out reporting IV drug use. In terms of illegal activities, the median number of crimes committed was higher for those who

dropped out (3[IQR 1-25]) in comparison to those who were retained (2 [IQR1-8]). Shoplifting remained the most frequently reported illegal activity by both those retained (15%, n=11) and those who dropped out (less than or equal to five).

Characteristics	Retained (n=106)	Dropped out (n=6)	P value[1]
Gender (male)	80 (75.8%)	3 (50%)	0.166
Median age at baseline (years)	38 [IQR32 – 43]	33 [IQR26 – 35]	0.051
Substance Use[2] N (%)			
Illicit Benzodiazepines[3]	98 (92.5%)	6 (100%)	0.485
Heroin	89 (84%)	≤5	>0.05
Cocaine (HCL/crack)	77 (72.6%)	6 (100%)	0.137
Alcohol	19 (17%)	≤5	>0.05
Treatment episode characteristics N (%)			
Median MMT dose for treatment episode			
≤ 60 mg	45 (45.5%)	≤5	
61 to 120 mg	54 (54.5%)	≤5	>0.05
Median Buprenorphine dose	8 [IQR 4-8]	-	
Median Take Home Dose (MMT)			
0	75 (75.8%)	6 (100%)	
1-2	10 (10%)	-	
≥2	14 (14.2%)	-	0.390
Median Take Home Dose (BUP)			
0	≤5	-	-
1	≤5	-	-
Treatment episode during COVID – 19	55	≤5	>0.05
Injecting and risk-taking behaviour N (%)			
IV drug use (self-reported)	16 (14%)	≤5	<0.05
Health N (%)			
Diagnosis of physical illness/condition	26 (24.5%)	≤5	>0.05
Diagnosis of mental illness/condition	26 (24.5%)	≤5	>0.05
Social functioning N (%)			
Experienced homelessness	49 (46%)	≤5	>0.05
In employment	8 (7.5%)	≤5	>0.05
Crime(s) committed	27 (25.5%)	≤5	>0.05

[1] Univariate analysis
[2] Any positive urine result during participants' treatment episode(s) throughout study period
[3] 26 retained participants were in receipt of a BZD prescription, 1 participant who dropped out was in receipt of a BZD prescription

Table 3.3: Characteristics of those retained and those who dropped out at 6 months follow-up (n=112)

Associations between dropout and risk factors

Although there was a very small number of participants who dropped out, a logistic regression model was explored with age and median MMT dose as these variables have been widely reported as being associated with reduced dropout in OAT (106). Unsurprisingly given the small sample size, there was no evidence of an association between these variables and dropout in this study (see Table 3.4).

Table 3.4: Logistic Regression exploring factors associated with dropout

Variable	Unadjusted Odds Ratio	95% C.I.	P-Value
Age at baseline	1.114	0.983-1.262	0.090
Median MMT dose	1.830	0.002 – 12.92	0.418

3.8.4 Sensitivity analysis

The treatment dropout rule of 28 days may have misclassified participants on treatment. Hence, a sensitivity analysis was performed using a gap of 14 days from date of last prescription to classify a participant as dropped out. This increased the number of participants who dropped out of treatment from 5% (n=6) to 11.6% (n=13). Any individual who left their treatment within the NDTC and subsequently returned throughout the study period amongst those retained also increased to 40.4% (n=40). A limitation of the study is that it was not possible to ascertain if these participants dropped out from treatment or were transferred to another setting. This was due to COVID-19 restrictions which meant that AOC was unable to access data in the NDTC. As a result of this, further analysis could not be conducted.

3.9 Discussion

This study investigated the time to dropout in a six-month period, the number of participants retained at six-months, and explored potential risk factors associated with dropout among Irish adults attending a specialist addiction treatment centre. During the six-month period, 16 (14.3%) participants dropped out of treatment and the median time to dropout was 80 [IQR 25.6- 92.3] days. At six-months, 10 of the participants who had dropped out had returned to treatment and 95% (n=106) of all participants were in treatment. The observed level of

retention in this study is higher than rates reported in previous studies in both specialist treatment and primary care settings; the median retention rate at six-months across 38 studies in specialist treatment settings was 61.3% (range: 19.1 – 86%) (149, 152, 154, 156, 170, 171, 179, 183, 185, 187, 194) and 60.3% (range: 11.7 – 87%) at 12- months (141, 142, 151, 153, 154, 156, 158, 160, 165, 167, 170, 171, 179, 181, 183, 185, 194, 196, 198). In comparison, overall median retention rates of studies in primary care settings was 54.7% (41 – 58%) at six-months (163, 186, 191, 192) and 40% (38.5 - 45.7%) at 12-months (188, 191, 197).

There are four tentative hypotheses for the low dropout rate in this study. First, the rate may be as a result of the high standards and quality of care provided by the NDTC to their service users. Positive opinions of MMT service have been associated with retention (166, 167, 187, 198, 201), however service users' attitudes toward treatment were not sought in this study. A further in-depth study of service users' opinion of OAT and attitude towards their treatment would be warranted in order to ascertain how they perceive treatment and their levels of satisfaction. The NDTC is the largest specialist treatment centre in Ireland, and in addition to medical treatment it offers psychological and social support through clinical psychologists, counsellors and social workers. However, a Cochrane review conducted in 2011 stated that adding psychosocial support to OAT is not associated with improved retention rates (226). This review requires updating in order to include any research conducted in this area in the past ten years.

The second hypothesis concerns the number of participants who were returning to treatment or transferring from a different setting (85.5%, n=100). Studies investigating retention in primary care (107) and across all settings (178) have shown that service users experiencing multiple treatment episodes tended to stay in treatment for progressively longer periods in later episodes. The number of previous treatment episodes for these 100 participants was not ascertained and this may have influenced their retention in this treatment episode (107). In contrast, Durand et al. have recently highlighted previous dropouts from treatment is associated with dropout from OAT at three and 12-months (109). Thirdly, the low dropout rate in this study may have been influenced by the COVID-19 OAT contingency plan and a lack of access to illicit drugs. According to the EMCDDA and Europol, a consistent evaluation of heroin distribution at the consumer level had not emerged as of May 2020, but at the time there did not appear to have been a significant impact on supply at the local level (227). However, qualitative evidence from Scotland and Bristol have suggested that there have been some drug

shortages with less variety, reduced quality and some price increases (228, 229). Preliminary findings across Europe have suggested an overall decline in drug use during the first three-months of the pandemic. Localised shortages of heroin were reported which may be associated with the increase in attempts to access OAT and the reduction of high risk opioid use in Ireland (230, 231). Thirty three percent of Irish respondents to the EMCCDA mini-European Web Survey on the impact of COVID-19 reported less drug use since the beginning of the pandemic, however 22% reported more use and 14% reported the same amount of drug use (230, 231).

Fifty five percent (n=64) of participants' treatment episodes occurred during the timeframe of COVID-19. As a result, there may be bias in this rate due to the contingency plans put in place to alleviate the impact of the pandemic. The contingency plan for OAT service users throughout the pandemic has allowed for less frequent urine testing, more take home doses (and less travel to the clinic as a result), delivery of doses to those cocooning, benzodiazepine maintenance for those in self-isolation, community dispensing for service users travelling long distances and access to appropriate accommodation for service users who were experiencing homelessness (112). These procedures may have facilitated a reduction in dropout, but would require a specific investigation to be conducted in order to ascertain this. Finally, the difficulties experienced during the recruitment process resulted in 21 potential participants dropping out of treatment before AOC could approach them. This may have led to selection bias as these potential participants were not recruited to the study. Selection bias affects observational studies and is produced when the sample gathered does not represent the population. This can lead to the subjective assessment of outcomes as those with certain characteristics can be over or under represented (232). In this case, participants who were retained may be overly represented in the sample. This may have been caused by survival bias (233).

Survival bias occurs in studies that assess the effect of a treatment on survival or "failure time" (234). Bias may have been introduced as those several participants (n=21, as seen in Figure 3.1) dropped out of treatment prior to recruitment. These participants did not have an opportunity to become exposed to treatment during the study period and were unexposed by definition. This introduced a biased survival advantage with the exposed participants as analysis did not account for those 21 participants who were classified as unexposed when they may have been exposed and subsequent dropouts if they were reached on time (234). If these 21 service users were recruited and dropped out during the study period, the retention rate for would have reduced to 80.3% (retained n=106, dropped out n=27).

In terms of the participants' characteristics, a recent systematic review highlighted that characteristics of OAT service users are changing globally (29). In this study the median age of participants recruited was 37.5 [IQR 32-42.5] years. Approximately 13 years ago (2007), the National Drug Treatment Research Outcome Study in Ireland (ROSIE), reported that 68% of those entering a new MMT treatment episode in Ireland (n=215) were male with a mean age of 28 (SD6.6) (235). The ROSIE study was the first national prospective, longitudinal drug treatment outcome study with the aim of evaluating the effectiveness of treatment and intervention strategies for opiate use in Ireland (235). The ROSIE study recruited 404 participants who were followed up over a three year period, and self-reported data collected was based on the UK's National Treatment Outcome Research Study and the MAP (219). In 2012, Mullen et al. conducted a prospective cohort study investigating retention rates and associated factors in a specialist treatment centre for OAT users using data linkage (103). This study reported a mean age of 26, with 75% of the cohort under the age of 30 (103). Across Europe, there is an aging cohort of OAT service users with 35 being the mean age of those entering treatment for an OUD (54).

Carew and Comiskey's analysis of the aging cohort of opioid users in Ireland in all forms of OUD treatment indicated that individuals are initiating their opioid use at an older age and are waiting longer intervals of time between the first use of opioids and seeking treatment (26). The median age that individuals commenced illicit drug use was 15 years and remained unchanged from 1996 to 2014 (26). These figures are similar to the age that participants in this study commenced illicit drug use (15 [IQR 13-19] years). The median age entering treatment increased significantly (by 11 years) from age 20 in 1996 to age 31 in 2014 (26). Again these figures are similar to the age of first OAT use reported by participants in this study (25 [IQR18-31] years). However it must be noted that Carew and Comiskey refer to all forms of OUD treatment in their study, and not exclusively OAT. Finally Carew and Comiskey reported that the median age commencing injecting increased significantly by three years from 19 years (1996) to 22 years (2014) (26). This also corresponds with the age of first IV drug use reported by participants in this study (22[IQR 18-28]).

In comparison to the ROSIE study, this study also saw an increased use in the amount of benzodiazepines (92.3% vs 45%) and cocaine (73.5% vs 40%) (235) and an increase in drug use in comparison to Mullen et al.'s study (103) . This is also consistent with the observed increase in drug-related deaths where benzodiazepines were

implicated in 63 poisoning deaths in 2017, an increase of 34%, from 47 deaths in 2016. Cocaine poisoning deaths also increased by 26% from 42 deaths in 2016 to 53 in 2017 (40). However, both the ROSIE study and Mullen's study relied on self-reported data for drug use which is often underreported. Despite this increase in drug use, methods of drug consumption are changing as IV drug use appears to be decreasing among those with an OUD. Mullen's study reported that 74% of service users entering MMT had injected drugs in the 30 days prior to treatment (103). In contrast, seventeen percent of service users in this study reporting injecting drug use. However, in this study baseline interviews were completed at different time points in treatment, hence, participants could have stabilised on their OAT dose and no longer be using heroin intravenously to prevent cravings and withdrawal.

This study did not find any evidence of factors associated with dropout, except IV drug use, and this should be interpreted with caution, primarily as a result of the unusually low number of participants dropping out and insufficient power for statistical analysis. However older age in OAT has consistently been reported as a protective factor against dropout (106, 129) and while there was no the evidence of a significant age effect in this study, those who were retained had a median age of 38 [IQR 32-43] and those who dropped out had a median age of 33[IQR26-35] (p=0.051). In this study we saw that a significantly higher percent of participants who dropped out reported IV drug use (p=0.027). Injecting drug use has not been extensively investigated as a predictor of dropout in OAT. Chapter two highlighted that ten of 67 studies investigated IV drug use. Two of these studies identified IV drug use as a risk factor for dropout, and one identified IV use as a protective factor for retention. However, these studies reported different timeframes for engaging in IV use (daily, current or in the past 30 days) (106) across different settings and OAT types.

It would be beneficial to repeat this study on a larger scale in order to address the power issue and potential biases that were introduced. This would involve a larger sample size from more than one specialist treatment setting. An additional researcher would be required in order to approach potential participants before they drop out of treatment as experienced in the data collection for this study. Two researchers would allow recruitment to be conducted in a timelier manner and also would reduce the time that the researcher spent recruiting individual participants in this study. A further bias of the study is the potential impact of the COVID-19 contingency plan for service users during the follow-up period. The implementation of outreach support and home delivery of OAT with increased THDs and reduced drug screening has been

recommended during COVID-19 (110, 236). The impact of these changes to services should be studied prospectively in order to investigate what influence (if any) these changes are having on treatment retention. A need for research to evaluate changes to services due to COVID-19 have already been urgently called for (236).

3.9.1 Strengths and limitations

To date, no longitudinal study has been conducted in Ireland investigating dropout in OAT users in an adult population in specialist clinics that used both clinical data (including urinalysis) and data relating to the contextual factors of an individual's life circumstances. However, when interpreting the results of this study, the following limitations should be considered. Due to the unexpected dropout rate, the study lacked power to conduct a survival analysis or multivariable logistic regression to explore factors potentially associated with dropout. There may also be prevalent user bias in the study due to the change in inclusion criteria from a new-user design to including certain prevalent users, as well as selection bias and subsequent ascertainment bias. The study may also have been influenced by the contingency plan implemented to address COVID-19 public health policy. This plan reduced the frequency of urine testing, while increasing take home doses and offering delivery services for those cocooning.

The issues in recruitment and data collection experienced in this study could be used to inform future studies on how to address these potential difficulties when recruiting and collecting data from similar populations. Finally, due to the variation in the timing of when baseline interviews were conducted (including 34 which were conducted after the follow-up end date), it is important to be cautious when interpreting the self-reported results of this study.

3.9.2 Conclusion

This study had a 5% dropout rate at the 6-month follow-period. Although a lack of power resulted in limited analysis, there appeared to be a difference in IV drug use between those retained and those who dropped out. Furthermore, consistent with previous literature, it seemed that those retained were generally slightly older. Retention in treatment is vital as it reduces the risk of mortality associated with treatment cessation and treatment re-initiation, reduces harm across multiple health outcomes and helps to improve an individuals' overall quality of life (3, 104, 105). It is therefore regarded as an important outcome measure, and should be incorporated into OAT outcome measure studies (98). The use of the MAP can facilitate the monitoring of this outcome and associated risk factors in a structured manner,

incorporating six of the eight categories noted by Wiessing et al. (98). A larger study is required in order to ascertain factors associated with dropout in Irish OAT settings. It would also be beneficial to conduct a study investigating the impact of COVID-19 OAT policy on dropout in order to inform future changes to policy and practice.

Chapter Four: Barriers and facilitators to retention in opioid agonist treatment from the perspective of service users and service providers

4.1 Introduction

Qualitative research in relation to OAT has primarily focused on service users in order to gain their perspectives. In a recent systematic review of service provider and users' perspectives of OAT, 101 studies focused on service users' perspectives and 65 focused on service provider perspectives (237). Although the major themes for studies identified in this review were attitudes and beliefs, studies focusing on service providers have also explored the experiences of providing and facilitating OAT (238-241). Studies that have focused on service users have also focused on their experiences of treatment services (241, 242), barriers to accessing OAT (239, 243-245), perceptions of OAT following release from prison (246, 247), experiences of progressing through OAT treatment (248), stigma in treatment (249-252) and involvement in their own treatment planning (253-258). Very few studies have focused specifically on retention in treatment from the perspective of either service users or providers (259, 260).

A dislike of service providers and clinical procedures by service users is a common barrier to retention in OAT identified across different treatment settings and countries (239, 243-245, 261, 262). Barriers to retention in an Irish context were described in Mayock et al.'s qualitative study which recruited 25 service users from both primary care and specialist treatment clinics (261). This study aimed to examine service user perspectives' on MMT, focusing on the lived experience of methadone treatment, participants' social relationships and their health and social care needs. Several topics were targeted for discussion in this study which included social functioning, drug use, health (both physical and mental) and risk-taking or harmful behaviours. Service users reported that frequent urine testing and attendance to the clinic resulted in feeling undermined and dismissed by staff in specilaist treatment centres. Service users attending community pharmacies also felt dehumanised by staff as they felt they were treated differently to other customers (261). Service users attending primary care were not obliged to provide frequent urines samples or recevied additional THDs and stated that they were more in control of their treatment and had better relationships with service providers as a result (261).

Deering et al.'s study (239) of 85 service users and clinical managers of each specialist treatment clinic (n=18) in New Zealand reported similar barriers identified by Mayock et al. (261). Both service users and providers described how some procedures conducted in their clinic were viewed as barriers to retention. Restricted takeaways, waiting lists, being tied to one clinic,

being required to attend a chemist every/almost every day, random urine screenings, concerns about confidentiality, requirements to attend counselling, interacting with other drug users, and a requirement to be assessed for treatment were all listed as concerns (239). A further study conducted in China explored (262) factors associated with the decline of service user attendance in MMT from the perspectives of service users and providers. The qualitative component of this study consisted of service user focus groups which addressed the following topics: treatment-related factors, attitudes and experiences of MMT and reasons for leaving treatment (262). The reasons for the decline were similar to Mayock (261) and Deering et al. (239) in that the inconvenience of being in the clinic and poor service provision were highlighted as barriers (262).

Kermode et al. offered other factors that can contribute to dropout from a specialist treatment setting in India (263). They conducted a mixed methods study of which the qualitative component explored the health, social and behavioural impacts of OAT and factors that led to dropout from the perspective of service users and providers. The semi –structured interviews were guided by a tailored theme list, however the study did not describe what these themes were. Factors identified by service users and providers as contributing to dropout included: drug use, negative interactions with peers, inconvenient hours of the clinic, misinformation about methadone and stigma in the form of pressure from family members to end treatment prematurely (263). Truong et al. (264) also explored factors influencing dropout from a community based buprenorphine progamme in Baltimore. A semi-structured interview guide was used to collect data, but the study did not outline what informed the guide (264). This study highlighted some challenges that were not identified in other studies which included: struggles with active OUDs, comorbid mental health issues, criminal justice system involvement, stigma, and conflicts in beliefs on how clinics should operate.

Poor communication between stakeholders and service users has also been identified as a barrier to treatment retention and success across various countries and settings. Van Hout and Bingham (260) interviewed 16 level one and level two GPs involved in OAT provision in Ireland in order to explore experiences of methadone prescribing, therapeutic alliance and methadone treatment pathways. These GPs discussed issues relating to long term maintenance and retention which included the chronic nature of relapse, co-occurring psychiatric and physical illness and difficulties in treating poly-drug use, especially alcohol (260). Service providers in this study stated that their relationships with service users were largely positive and that service

users' treatment goals were facilitated in a client-centered manner. These reports of positive communication between service users and providers may be related to the stability in seeing the same clinician on a consistent basis which is possible in primary care but not always so in specialist treatment settings.

Hayashi et al. (259) reported communication as a barrier in accessing OAT and subsequent retention to MMT in Bangkok, Thailand through a mixed methods study. Sixteen service users of MMT from ten clinics were interviewed for the qualitative component of this study. Attitudes to MMT, as well as social, structural and environmental drivers of drug-related harm were addressed in the semi-structured interviews (259). Service users highlighted that they were discouraged from availing of MMT by service providers and stigmatized for doing so as it was seen as a Western medicine. Service users also stated that it was difficult to negotiate higher doses of methadone, and that doses were often reduced abruptly without consultation (259). Poor communication between service users and providers was also described in Lin and Detel's study exploring low-dose OAT and premature dropout from the perspective of 28 service providers in Chinese MMT clinics (265). It is unclear how the semi-structured interviews in this study were structured.

Service providers explained that breakdowns in communication between service users and service providers about dosage adjustment was common as many service providers stated that they had been intimidated into prescribing whatever dosage was demanded by the service users. Although communication in relation to dosing has also been highlighted in Ireland, service users were requesting lowers dose of OAT (261) in comparison to service users in China and Thailand who were requesting higher doses (259, 265) . This is likely due to the differing clinical guidelines in both countries for OAT dosing and also the various stages of treatment that these service users were in. This may also be as a result of the disparity in goal setting between service users and providers.

A disparity in goal setting between service providers and users was evident in McKeganey et al.'s study of 1001 service users entering a new treatment episode in 33 agencies across Scotland (266). A structured questionnaire was used to collect information on drug use, treatment-related factors, social functioning and any involvement in criminal activity. Upon entering treatment, 42.5% of participants commencing MMT hoped to achieve abstinence alone, 35.2% hoped to achieve a combination of abstinence and harm reduction and 22.3%

hoped to avail of harm reduction only (266). However a limitation of this study is that social desirability bias may have been introduced which was acknowledged. Participants' definitions of abstinence was also not sought which may mean different things for different individuals (266). Despite these limitations, it is clear that service users' goals may differ greatly from service providers' goals for treatment.

A focus on harm reduction practices to improve retention was explored by Strike et al. by interviewing 46 service users and 24 service providers. The semi-structured interview used focused primarily on treatment-related factors and drug use (267). The use of harm reduction practices to help retention caused unease amongst some of the service providers as they felt that accepting poly-drug use during treatment was a contradiction of their obligation to help service users (267). Treatment goals for service users in this study were self-defined (harm reduction or abstinence). However this also led to issues for service providers as some service users found it difficult to attend a clinic with other individuals with an active OUD (267). One clinic had started to transfer service users to other services in an attempt to respond to this issue. As the views of service users is one of many relevant factors that should be considered when developing and delivering drug-treatment services (266), understanding their perspective on what influences their decisions to stay or leave is also important.

While previous quantitative studies have examined factors associated with treatment dropout, using data linkage studies or service user surveys, and qualitative studies have focused on service users' experiences of treatment services, few qualitative studies have considered factors specifically influencing treatment retention. As outlined in chapter two, Wiessing et al. (98) have noted the importance of considering the use of eight categories in future studies investigating OAT. Although this referred to observational cohort studies, this structure could also be used to guide semi-structured interviews in qualitative research. Of the studies reviewed in preparation for this study, very few provided information on the issues or themes that semi-structured interviews focused on and of those that did, none reported exploring all eight themes. This may be as a result of the process of qualitative research which is often inductive rather than deductive in nature (268).

In-depth qualitative interviews with service users are important in order to ascertain personal, treatment, and contextual factors related to treatment retention. It is also valuable to ascertain the perspectives of service providers in order to see where agreements and disparities lie between service users and providers. This information would aid in highlighting areas of service provision that could be progressed in order to improve and facilitate the retention of service users. The aim of this study was to explore barriers and facilitators to retention in OAT, and to identify areas of service provision that work well and areas for improvement from the perspective of both service users and service providers, using qualitative semi-structured interviews informed by the Maudsley Addiction Profile.

4.2 Methods

4.2.1 Qualitative approach and research paradigm

In line with the overall mixed methods approach of this thesis, this study adopted a qualitative research design using a pragmatic research paradigm. Pragmatism posits that there is no way that any human action can ever be separated from past experiences and the beliefs that have arisen from these experiences (269). As such, all knowledge is based on experience. Pragmatism was adopted for this study as it focuses on combining the different strengths of both quantitative and qualitative research (269). A qualitative inductive approach was adopted for this study as it is the best method to explore the unique experiences of service users, service providers and their perspectives on retention in OAT.

4.2.2 Researcher characteristics and reflexivity

It must be acknowledged that the researcher's characteristics and previous experiences may influence the process of data collection where a dialogue is open between the researcher and participant. The researcher has previous professional experience working in a homeless accommodation service for six years. Many of the service users in this accommodation used drugs and were engaged in OAT. As a result, the researcher had some working knowledge of OAT and the NDTC. Before conducting the study, consideration was given to the possibility that the researcher would recognise service users from the accommodation service in the NDTC and vice versa. This was acknowledged in the ethical application for the study and the general manager of the NDTC was also made aware of this. There was also a possibility that the researcher had previous working relationships with service providers through interactions with

drug treatment services in a professional capacity. It transpired that the researcher had a prior working relationship with only one service provider recruited.

4.2.3 Context

As stated in chapter one, the NDTC is the largest provider of OAT services in Dublin, Ireland with 537 service users in attendance. The NDTC provides both methadone and buprenorphine/naloxone as forms of OAT. This treatment centre receives service users on a daily basis (Monday to Friday) between 9.00am – 12.30pm and 2.15pm to 4.30pm, and operates limited hours at the weekend (10.00am – 12.30pm). Service users receiving OAT can attend for their dose at any time between these hours. If service users receive THDs they are obliged to attend the centre before 11.30am or 3.30pm. Service users receive THD on public holidays as the clinic is closed. All qualitative interviews with service users were undertaken concurrently with the face-to-face structured interviews that were conducted in chapter three. Once a service user had consented to take part in the structured interviews, they were asked to participate in this study. If they agreed, a date was agreed to meet. Qualitative interviews with service providers were also conducted concurrently with the baseline interviews in chapter three.

4.2.4 Sample

Within qualitative researcher, the researcher does not seek "generalisability" or "representativeness" and therefore focuses less on sample size and more on sample adequacy. Sample size is important only as it relates to judging the extent to which issues of data saturation have been carefully considered (270). It was felt that a sample size of between 15 to 20 service users and eight to ten service providers would be adequate in order to reach data saturation.

A subset of participants from the prospective cohort study who agreed to participate in this study was recruited. Within this subset, purposive sampling was used to ensure that there was a representation of men and women, service users prescribed methadone and buprenorphine, service users returning to treatment following dropout, service users starting treatment for the first time and service users transferring their treatment from prison following release.

Service providers were initially recruited from staff within the NDTC. Purposive sampling was also used in order to recruit both medical staff (doctors) and other team members (non-medical staff). Following the restriction measures implemented as a result of COVID-19, four additional

interviews were conducted. One of these interviews was conducted with a service provider of the NDTC who was interviewed prior to COVID-19 and was re-interviewed. The additional three service providers were recruited using purposive sampling to target providers who were involved in the provision of OAT and implementation of the OAT contingency plan put in place for COVID-19 outside of the NDTC.

4.3 Ethical issues pertaining to human subjects

4.3.1 Ethical approval

Ethical approval was received from the Royal College of Surgeons in Ireland's Research Ethics Committee in May 2019 (REC no: 1596bb) (see Appendix 11). The study protocol was also reviewed by the general manager and the four consultants in the NDTC.

4.3.2 Data security

All interviews were conducted by AOC. Following each interview, an electronic recording was transferred from a Dictaphone to a secure folder of the RCSI V-drive on the researcher's encrypted and password-protected laptop. Once the recording was secure on the V-drive it was deleted from the Dictaphone. A professional transcription service was used to transcribe the interviews. Both the researcher and the transcription service signed a non-disclosure agreement before the audio files were transferred. All transcripts were pseudonymised by removing any information that would make the participants identifiable and each transcription was assigned a unique identification number. After pseudonymisation, the data collected was made available to the researcher's supervision team. All study data was stored in a secure folder of the RCSI v-drive. The data will be retained for a maximum of five years, or a period of one year after publication/submission of the final report.

4.3.3 Potential risks and confidentiality

The outline of the study, including the limitations of confidentiality were summarised to both service users and providers in an information sheet provided and in person (see appendices 16 and 17). All participants were also made aware that the audio recording would be transcribed by a professional service. Service users were advised prior to the interview, that confidentiality would be broken in certain circumstances i.e. where there was serious threat placed on the well-being of the participant, a child, or another individual. They were advised that there would be no risk to their physical health if they consented to taking part in the study. No potential risks to service providers was envisaged. Service users were also advised that there was a small

chance of becoming emotional during the interview due to the nature of discussing sensitive topics. Participants were then asked to sign a consent form (see appendices 18 and 19). As the researcher has professional experience in working with this service user group it was felt that any situation where participants became emotionally upset or angry would be dealt with appropriately due to her experience. However, no participants became visibly upset or asked to withdraw from the interview.

4.4 Data collection methods

4.4.1 Semi-structured interview

Semi-structured interviews using an interview schedule were chosen as the data collection method for this study. The interview schedule was structured according to the four main sections of the MAP (substance use, injecting and sexual behaviour, health (physical + psychological) and social functioning (99) in relation retention in OAT (see Table 4.1). Contextual questions were also asked in relation to service users' personal lived experiences in each domain. Interviews with service users and providers were conducted in parallel with each other, and interview schedules were amended slightly throughout the process in order to ask more in-depth questions about emerging topics. The interview schedule for service users was shortened as initial participants often stated that they did not have time for an in-depth conversation or appeared to struggle with the nature of the questions (see Appendix 20). An additional section in relation to COVID-19 was also added to the schedule for four service providers following the decision to explore the pandemic's potential impact on study results (see Appendix 21).

Table 4.1: Example of questions in each interview schedule

Maudsley Domain	**Qualitative question for service user**	**Qualitative question for service provider**
Drug use	- Do you think your current substance use (if any) affects your treatment? In what ways? - Have there been times in the past when your drug use stopped you taking OAT? Why do you think this happened?	- What kind of impact does continued drug use by service users have on their treatment and retention in treatment?
Injecting and sexual Behavior	- Do you carry out any behaviours/actions that you think are "risky" to your health? - Do you think these actions influence your treatment? How?	- Do you feel these behaviours impacts on their retention in treatment? In what way? - Do you think service users would agree that these behaviours are having such an impact?
Health (physical + psychological)	- Do you think your health impacts your treatment (positively or negatively)? In what way? - Are you linked in with any other services for your health? Do you think this helps or hinders you coming here?	- What are the biggest physical health/mental health issues affecting service users' treatment and retention? - How aware are service users about the impact of their health needs on their treatment?
Social functioning	- What do you think most helps and hinders you in coming here for treatment (in terms of social life)? - What in the past has helped and hindered your treatment?	- What are the biggest obstacles you see in terms of social functioning for service users staying in treatment? Do you think they would agree with your assessment?

Fourteen interviews were conducted with service users and each lasted approximately 20 minutes. Similarly, when service providers consented to taking part in the study, a time and date was arranged to meet and conduct the interview within the NDTC. Eight interviews were conducted with service providers; four face-to-face, and four over telephone (one service user took part in both the face-to-face and telephone interview). These interviews lasted between 30 to 60 minutes as service providers stated they had the time to participate in the interview and were familiar with engaging in qualitative research.

4.4.2 Data analysis

All transcripts were checked against the recordings to ensure accuracy. Data management and analysis was conducted using Nvivo12 software. Thematic analysis using an inductive approach was chosen for analysis. This was used as it provides flexibility in that it is not tied to one theoretical framework (268). Thematic analysis using an inductive approach also allows categories to evolve from the data without trying to adjust data into a pre-existing model. As this thesis was conducted through a mixed-methods approach, it was appropriate to use an inductive approach where the themes identified would link to the data generated (268). Thematic analysis consists of six stages: familiarisation with the data, generating initial codes, searching for themes, reviewing themes, defining and naming themes, and producing the report (268). Familiarisation of the data was carried out by reading all transcripts between three to four times while listening to the audio recording of each transcript. Initial codes were generated using the line-by-line coding technique which is an inductive form of coding (270). Forty-nine codes were generated which initially generated eight themes. These themes were then defined, named and further refined to three themes with each theme containing three subthemes. Theme one and two included perspectives from both service users and services providers, however theme three focused solely on the perspective of service providers' views of retention in the context of COVID-19.

4.5 Results

The following section offers an overview of the study's sample. Demographic details are provided for the sample of service users which includes basic demographics, education and employment and housing status.

Fourteen service users were recruited, all prior to the COVID-19 pandemic. Eight of the participants were male (57%) and 6 were female (43%). Age of participants ranged from 21 to

47 years, with a mean age of 38 years. Ten of the participants were in receipt of MMT (71%) and four were in receipt of buprenorphine (29%). Eight participants reported that they were returning to treatment following a period of dropout (57%), four were attending the clinic following release from prison (29%) and two were attending for their first treatment episode in the NDTC for OAT (14%). Fifteen years (15.6) was the median age for leaving school reported by service users. Less than five service users were currently in part-time employment or in education. Six service users reported that they cared for dependents on a full time basis (children or elderly parents).

Six service users reported living in their own home (owned or rented) (43%), five reported that they lived with parents or relatives on a full time basis (36%), and less than five reported that they were accessing homeless services and/or rough sleeping. Seven service providers were recruited in total: four prior to COVID-19 and three after. Five of the service providers were staff members of the NDTC, with the remaining two involved in the provision of OAT in Dublin (one within homeless accommodation and one within a primary care service for the homeless population). The professional roles of the service providers are as follows; medical doctor (n=2), senior management (n=2), child-care worker (n=1), clinical psychologist (n=1) and addiction counsellor (n=1).

4.5.1 Contextual information

Service users discussed their first experience of illicit drug use, with age of first use ranging from 11 to 19 years. Illicit substances that were initially tried by service users varied from weed (cannabis) to club drugs such as MDMA and LSD, or heroin. Some service users explained that their heroin use first started in order to “come down” from club drugs. The other primary reason that service users reported first trying heroin was in order to self-medicate for pain after sustaining traumatic injuries or undergoing surgery. Some service users also described engaging in illegal activities from a young age. These service users explained that engaging in illegal activities and subsequently serving custodial sentences were often intertwined with consuming drugs. Service users also described their current experiences with incarceration, outlining that it had been a regular occurrence from their teenage years into adulthood. Less than five service users reported that they were either currently homeless or accessing homeless services. However, many other service users reported past experiences of sleeping rough and/or accessing homeless services.

4.5.2 Cyclical nature of OAT

The majority of service users had experiences of dropping out and recommencing treatment on a regular basis over a long period of time.

"I've been on and off methadone, I could
time (SU8)."

"This is my fifth or sixth time on methadone. I've been here... this is my third time coming
back here [to the NDTC]" (SU3)

Long periods of abstinence from illicit substances and off OAT were also experienced by some.

"I think I stay was 14 or 15 and then came off treatment a few years
later and then I'd be clean since up until (SU13).

"The first time was 1997, and I did it fo
[residential] treatment" (SU1).

Both medical doctors interviewed acknowledged that cycling in and out of treatment was something that many of the service users experienced, sometimes over long periods of time and due to many complex life circumstances.

"I think that some [service users] drop out of treatment know re
anyway depending on the circumstances of their lives and other factors. Some have an
established history" (SP6)

"I have folks who come and who stay. I have folks who come back and dropout again. I'
thinking of one female patient who I met a c
being out of treatment, prison drug treatment and occasionally back here. So it will vary from
person to person (SP4)".

4.5.3 Experiences that led to current OAT episode

Traumatic experiences precipitating a relapse were cited as the predominant reason why service users decided to return to OAT. Service users did not necessarily describe the traumatic event, but focused on how they were feeling, which seemed to motivate their return to treatment.

"I knew I was going to do something stupi you are only going to start getting strung o smoked heroin in fucking nine years, until last year and I started again and I was like what am I even doing like?" (SU4)

"I just hit rock bottom. I was seeking out going to kill myself. So, I decided to get h (SU6).

Other service users cited external influences such as children and instructions from health care practitioners as the reason they returned to OAT:

"I need my treatment. I need to get bette (SU13).

"I had to go into hospital... and the ysht could dm'et I walking really. I had to get, I think, four blood transfusions. It was that which started me off into the recovery again" (SU7).

While service users identified key moments which prompted them to enter into treatment, service providers noted these key moments can also result in treatment dropout.

"We have trauma here that is so massive... somebody delve into that trauma, if it's ac service users do [SP3]. you know?"

4.5.4 Current life experiences

As well as offering a description of their past experiences, service users were asked how they felt their life was at present. They were free to describe their daily lives and discuss any topic they felt was currently infringing on their treatment. Homelessness and unstable accommodation was identified as an important issue:

"It just feels like it's at a still. I do like I'm trying to find a new place. The landlord is hol back. So, I can't even look for a place until I have that deposit" (SU13).

"I have been living in so many people's h this one six-months and it is getting toxic as well (SU4)."

"There's an issue I don't get to see my k
want me in the house taking drugs. That's wh (SU3)

Participants gave a variety of reasons as to why they had or were currently experiencing homelessness. Service user three had been accessing homeless services at the time of the interview for three years due to the breakdown of a relationship with their partner.

"I was down there [location] the last year in a hostel. It's good. Well it was
like this, I was after being on the stre
splitting up from [expartner]" (SU3)

Both service users and providers raised homelessness as a significant barrier to retention. Service provider two discussed the impact of homelessness on service users' treatment progression.

"I think more than half of our clients ar
which don's' t liwkoer ki.n oIrtd'er to get a house you
you need to have stability and security and the, the structure of your own home in order to get
mental well" (SP2).

Service provider six also reiterated the importance of having a stable home in order to engage and remain in treatment.

"Having a roof over your heads and adequa
being able to do anything else and if you'r
population, particularly those who are not in long-term or supported placement, the folks over
in the hostels and in different hostels, "o
stabilise any aspect of their functioning, let alone if you know are a problematic
relationship with alcohol or opioids" (SP6).

Drug use was also discussed by some service users when describing their current experiences. Unlike their housing situations, their current drug use was described positively, and from a harm reduction perspective.

"So, where I used to be smoking an eighth
to smoking a bag to two bags a week" (SU6).

"I don't smoke hash every day anymore. I now maybe once or twice a week or something. Or even (SU14).

4.5.5 Treatment outcomes

Service providers described a shift in the approaches of treating addiction from abstinence based to harm reduction over the past two decades.

"I think maybe 15 to 20 years ago there moved away ... most agencies would-based model to a moved harm reduction model" (SP2).

This change was reflected in how they now treat service users and the treatment outcomes that are focused on in the NDTC.

"We [NDTC], I suppose, aligned with the been a realisation, the folks in treatment, treatment as conventionally defined and I suppose we measures to multidimensional and are looking at other health outcomes, criminal justice outcomes, work relationships and so on and s (SP4).

Service providers viewed opioid agonist treatment as a component of a harm reduction strategy.

"Over the years I suppose working with cl I'd see it is that... So, the methadone is par in there" (SP3).

This shift in treatment approaches has also influenced how service providers view treatment outcomes and which outcomes they prioritise with service users. This has resulted in the inclusion of many treatment outcomes when determining how successful OAT is.

"So, the outcomes are not only about dr psychological wellness, relationships, educa for people to either kind of reduce or cease problematic drug use... that has (SP2).

Service provider four also highlighted that other treatment categories such as socio-

demographic factors often influenced a clients' ability to remain in treatment.

"We know people dropping out of treatmen sometimes happens, tends to be associated with much worse outcomes across the range of medical and socio-demographic categories and mortality is much higher for people who are out of treatment.. But we, I suppose, aligned w from unidimensional outcome measures to multidimensional and are looking at other health outcomes, criminal justice outcomes, work relationships and so on and so on. (SP4). th"

Despite this shift to a harm reduction approach, there appeared to be a conflict between abstinence based goals among service users and harm reduction based goals among service providers which is described in detail in Sections 4.7.2 and 4.7.3. Service providers were aware of differences in service users' treatment goals, however, they stated that many factors must be taken into account when planning treatment goals, particularly clinical safety. They were also aware of the frustrations that this caused some service users, but believed that communication in this area had improved.

4.6 Theme 1: Factors influencing retention in OAT

4.6.1 Sub-theme 1: Immediate barriers to retention

ά w Ŝ Ř Ŧ ť l· Ǝ ă ɛ́ ƛ Ř Ŝ ƴ ǘ ƛ Ŧ ƛ Ŝ Ř ō è LJ l· NJ ǘ ƛ Ŏ ƛ LJ l· ƴ ǘ ă

Service users identified their own individual "red flags" when barriers to retention in OAT were discussed. These "red flags" for dropping out of treatment appeared to be emotional responses to stressful scenarios that they experienced:

"All it takes is me to have a bad day, an a someone I know and next (SU2). thing I know I'm on

"My girlfriend had a baby and all over there and I was going to church and all that and just [w that (SU8)".

Other service users identified more subtle changes to their thoughts regarding their OAT as "red flags". These changes appeared to be gradual and subconscious at the time.

"As I said, just, I don't know, I mustn't ha party at the time. Then I'd start drinking, chasing women and I just relapsed." (SU3).

"A (242) just gradually started using what I thought were okay kind of medications. But it was just the pattern of use again. Just one thing led to another. Within six months to a year I was back using strong painkillers" (SU7).

Difficulties travelling to clinic

Practical issues were also identified by service users as immediate barriers to remaining on OAT. Many service users were spending considerable amounts of time on public transport or arranging transport with friends and family. Some were travelling long distances up to four times a week.

"I do have to throw my sister fifteen qui if I'm doing that four times a week—that is sixty quid. I can't even afford to buy a packet of smokes for myself in the week, you know." (SU2).

Although many service users had a government issued travel pass, many felt the need to rely on friends and family for transport to the clinic due to poor public transport services in their areas.

"I come down from the country and there a impossible for me to get here. So, I have to get a bus from A to B, which is a thirty-five minute drive away [from participants' homes]. ck just a it (SU6).

Service providers were aware the challenges that travelling from long distances posed to their service users, citing the financial implications of accessing daily public transport.

"[Service users] joy for the train fare or the bus fare so, they would have been caught repeatedly on the train without a ticket. So, they have to adopt very

elaborate ways of getting on and off the train without getting caught, so it can be very, very difficult" (SP3)

Service providers also appeared frustrated by this barrier, however it appeared that some progression had been made in the region that this study took place in.

"It's quite an ask to ask people who don't transport and catch lifts from that [long] distance that except argue and advocate for treatment centres to be made available locally and within [CHO] seven we've been doing that's, [laughing] some limited as it is" (SP4)

Physical and mental illness

A further barrier identified by service users were the difficulties in maintaining their physical and mental health while on OAT. Many described how their illness affected their retention to treatment on a daily basis.

"I have a very low immune system from the sk colds, flus and because I am on public transport, I pick them up even more. So, every second day I am down with something else" (SU6)

Some service users felt that their illness was negatively affecting their retention and progression in their treatment.

"I'm also ill at the moment so that's kind o (SU2)

"I suffer very very bad with OCD, like I have tissues in my bag, to wipe the soles of my runners, I keep washing my hands and my house, if I see a piece of hair on the floor I panic. I do be by myself in the chair [and I] don't (SU10)

4.6.2 Sub-theme 2: Long term barriers to retention

Stigma

Stigma and the fear of stigma were also identified by service users as a barrier to remaining in OAT. Two forms of stigma were highlighted: stigma from service users' social environment such as friends and employers, and also self-imposed stigma from attending the clinic. This self-imposed stigma originated from larger society and subsequently transferred to service users attending the clinic.

One service user explained how although they kept their addiction secret for years, they had lost many lifelong friends as a result of a relapse and dropping out of treatment.

"I hid my addiction from all my friends for the most painful thing I've ever gone throug stopped ringing me, stopped taking my calls, (SU1).

Another participant described how they were reluctant to return to work full-time due to the potential added stress they may experience. However they felt unable to discuss this with their employers due to the fear of stigma.

"I suppose with work, I met. Hely did not't meet blacktheuml lw every week. I told them I am attending a specialist. They did ask me once or twice and waite for a deeper answer, but I just didn't give (SU7).

These forms of stigma from social environments and larger society resulted in service users internalising this stigma when attending the clinic for their OAT. Feelings of shame and degradation were highlighted as daily barriers to attending treatment.

"I was ignoring them first [other service us anyway. Like some of them don't care, some of them don't care. Like some of them will hang around and talk but I'd be a bit embarrassed (SU8).

Service users were aware that this self-imposed stigma was a societal issue due to addiction being perceived as a criminal issue.

"There's the stigma about addiction. It s is issue." (SU2).

Despite their awareness of the origin of this stigma, service users still described experiencing it on a regular basis.

"In the beginning. It is still a sort of degrading feeling having to do it. At first, I was ashamed I was doing it, but I knew that I would be more ashamed being on heroin than getting methadone" (SU6).

Personal struggles with addiction

Service users articulated how difficult it was to manage their addiction while attending the clinic. One described their addiction as all-consuming and conveyed a sense of fear as to how much influence their addiction had over them

"I realised, I actually, this addiction wants me using. And it will use [and use] everything in my life to get me out the door, to tell me, I have to use. And really, deep down, the minute I am out, I will crack, I'll be on my wanting me to pick up. So that's the biggest (SU1).

Another service user described how they were prioritising their addiction over treatment at present. They explained that they found it difficult to attend the clinic on a regular basis due to this.

"Yeah, it's just trying to come in. I just c kind of the point where I'm going buying gear because I can't be arsed coming here to get my methadone" (SU12).

Another service user described their constant desire for consuming illicit drugs and how they needed very little reason to use.

"I just love drugs. Just going around off my need an excuse. You're making excuses anyway, you know. I mean I'd [sic] a love affair with drugs" (SU2).

In contrast to this, one service user described their active effort on a weekly basis to reduce their drug use.

"Yesterday I gave a urine... I think now to be honest; I always take tablets. But with crack and heroin, because I've been trying to stay away (SU5).

from them. So, I want to see was it clean yesterday, I haven't touched them now in about five or six days" (SU7).

Service providers acknowledged current drug use as a barrier to retention. However their view of drug use as a barrier focused on the consumption of drugs rather than daily psychological struggle that service users articulated. Service provider two expressed concerns regarding the increasing number of service users engaging in poly-drug use and the impact that consuming benzodiazepines and pregabalin was having.

"Particularly kind of drugs like Lyrica (SP2). I would be concerned look at the drugs implicated in overdose, u methadone, benzos and Lyrica. Lyrica seems to be the drug that has been involved in the biggest increase... it's the drug that's in an increas

Service provider eight described the difficulties in retaining service users in OAT who were actively using heroin.

"My biggest issue is that people, in my exp coming off heroin, that first of all it is hard enough coming off heroin and secondly, prior to getting established accommodation, that ther (SP8).

Negative interactions with other service users

A final long-term barrier highlighted by service users was negative interactions with other service users. These interactions often involved service users being asked if they would like to buy illicit substances before entering the clinic.

"Yeah, just dealing with each end of the lan you're getting asked do you want all sorts, you know" (SU13).

These negative interactions combined with service users' personal struggle with their own addiction resulted in a regular occurrence of feeling tempted to relapse into drug use and a dislike of attending the clinic which affected their motivation to attend.

"It's... you're seeing people you don't want t be asked. Like it could be your last 20 euro in your pocket and you're thinking will I, won't I, will I, won't I?" (SU11).

"I see a driung going on up the lane and the ga of that shit. I hate coming in here every week. But do you know what, it is the only place that I could find that took me in straight away. I c (SU4).

4.6.3 Sub-theme 3: Facilitators to retention in OAT

Social support

Social support from family and partners was identified as a protective factor for retention by service users. One described the wrap around social support they experienced from both public services and their family and how it has helped them remain in treatment.

"The courts are saying to me, you have to be family, everyone. So, I'm actually doing it before" (SU1).

Other service users described the immense amount of support they received from their partners and family and how it continues to motivate them.

"Without [partner] I wouldn't have done this for this. Well the clinic as well but [partn (SU10).

"The support from my partner for one. My nephew living in the house too. I think the world of him, and he thinks the world of me" (SU6).

Self-motivation and familial incentives

Self-motivation and the sources of that motivation were described by service users as another facilitator to retention in treatment. Service users described how their motivation came from a variety of sources that included a need to maintain physical health, maintain their housing or to improve and maintain social contact with their families. One older service user described how a sense of exhaustion from their drug addiction has now motivated them to stay in treatment.

"I'm too old now. I'm tired now. I'm worn life with my grandkids n (SU10).

This sense of exhaustion was also highlighted by another who described their desire to stay in treatment.

"Just sick of being sick. Wake up sick every morning" (SU3).

Other service users highlighted more tangible incentives that aided them staying in treatment.

"This time I'll actually try to stay out of reason. Just to stop me using and to stop me from robbing and doing all that. That's the only thing" (SU8).

"Well I know if I don't [stay in treatment] can't take that chance again. It's so hard (SU11).

4.7 Theme 2: Opportunities for improvement

4.7.1 Sub-theme 1: Therapeutic relationship

Service users' relationships and communication with service providers appeared to comprise of positive interactions with non-medical staff, and negative perceptions of and interactions with medical staff. Service users described their interactions with floor staff as personable and mostly positive.

"Yeah, you can talk to them and they understand (SU3)"

"They are lovely. I never had an issue at (SU7).

Some service users also spoke in high regard for the wider medical staff and how it positively impacts their treatment.

"They treat you like a human being. And they care, you get treated like a human being, they see... I'll tell you what's really good and it's not a big deal to the staff, and it's why I stand this" (SU1).

"No, I get on great with all the staff, like, I get on great with all the staff the

and have a buzz with them... me, you know what I mean. Doctor Like he saved my life" (SU9).

However, many service users also voiced their frustrations in efforts to communicate with medical staff which resulted in reduced engagement with staff and negative perceptions of treatment.

*"I am now but no one is actually hearing what I am saying. It is frustrating like. I f**king hate methadone but if you do say to tell you no, you are wrong, it's body. I know, I bother engaging with anything else in here"* (SU4).

One service user felt that medical staff should be allowed more autonomy and was frustrated that their consultant made all clinical decisions regarding treatment.

"Doctors what they find it very hard to be able to change anything on the computer because... We all understand that, th of it but when the boss has not got his feet on the floor and there's a problem or there's an issu and they're [medical staff] on the same page as me, they should have the authority to be able to do that, you know. Where's the doctor? If they're a doctor they should have the authority to be able to change the scrip it, it is poured on" t b (SU2).

Finally, although service users were aware that doctors and medical staff were often overworked, one service user felt that these staff should be more personable in their communication.

"Every time you come for it, you get the same bays n behaviour. Just from my impressions, from what I have seen, some doctors kind of look down on you when you come into see them and they don I know that they work with a lot of people every day, but they have no connection with any of these people. Once they hear their name, five minutes later they forget their name because they are seeing that many people" (SU6).

Service providers also had similar views as to how they saw their relationships with service users. One service provider described the difficulties in working with service users who can be demanding which impacts on the therapeutic relationship.

"Characteristically folks sometimes ignored immediately and to tre
I suppose while that would be nice, that doe
doesn't work for us" (SP4).

Another service provider described how it is important to acknowledge that breakdowns in therapeutic relationships are often the responsibility of both service users and service providers combined.

"Well, I suppose it can be up and down. G
on and you see clients with a crear pt paoi mt ,p r tahc et ri et 'i
And I suppose then the place where difficulties can arise is, well, one, if a client comes in and
they're annoyed about something or they're a
how we deal with that, how we manage that. And the reality of
the best place to manage stuff either, so
everyone's human and the staff sometimes get
to me there's kind of a balance in that that we ha
where the client will get the blame over stu
but that's the reality of what was a staff member who down
didn't respond well in the fifty-fifty" (SP3).

Service provider two highlighted that therapeutic relationships improve once it is recognised that service users attend OAT by choice and should be active participants in their treatment plans.

"I think it's increasingly improving [the
better and better and better when there's an
have capacity... they have the right to choose or n
in addiction really should meet people where

4.7.2 Sub-theme 2: Views of OAT

There was a sense of ambivalence when service users were asked what their opinion of OAT was. One service user felt that more individuals should be offered buprenorphine rather than methadone.

"I think the people genuinely should just go on to suboxone [buprenorphine] because the methado (SU13).

Another service user struggled with societal views that OAT simply replaces one addiction for another.

*"I always feel myself at a [narcotics anonymous] meeting, for some stupid reason. It is purely because somebody might start off the meeting saying something negative about being on methadone. Saying, I was getting free drugs every week. I do give a ****, you know. So, I don't see it as a free drug* (SU7). *If I w*

However his view was not reiterated by other service users who did feel that OAT was another drug that should not be offered as a form of long-term treatment.

"Methadone is a drug I believe. It should be only short-term. I will come off this, I'm going to see the doctor here to ask them to (SU8)

"It does serve its purpose but is it just just another addiction? (SU4).

"Everyone that starts methadone can tell it [heroin], go through the sickness with Xanax or something or go on methadone? Just say stay away from that methadone, it should been never invented" (SU5).

4.7.3 Sub-theme 3: Goals for treatment

Similar to the different views on OAT, service users' goals for their treatment greatly varied from no goals identified, a desire to detox immediately or a structured plan with a timeframe on detoxing from OAT. Those who wanted to detox from OAT were willing to do this unsupervised and against medical advice through the use of pregabalin.

"My goal is to go completely off this" (SU2).

"I want to come off it. I want to, I don't really care about the tape but my plan was to come (SU11).

"Like I literally just want to detox and again. I'm trying to detox as quick as I can (SU13)

Other service users appeared willing to stabilise on their OAT before detoxing through residential detox services or through the clinic.

"Well I want to stay on it for a year and to treatment just to come off them" (SU10)

"I want a year on methadone, I want to s coming off it" (SU1)

Finally, some service users were unsure of their long term goals beyond stabilizing on their treatment.

"I have thought about long term yet. I don't know. hospital did say to me if I was finding it hard to get off it, they would certainly help me out. At the moment I am okay" (SU7)

Service providers were aware of the difference in service users' goals, however they stated that many factors must be taken into account when planning treatment goals, especially clinical safety.

"You're trying to hold the balance and I sup that are holding the balance on that and trying to clinical safety of it and that's the thing t (SP3)

Service providers were also aware of the frustrations that some service users experienced in relation to their treatment goals, but believed that communication in this area had improved.

"People do get frustrated but they don't alw really frustrated and would have left or whatever. Yeah, and I think, I do that many, I don't think the kind of treatme (SP2)

Finally, one service provider questioned the current process of reviewing treatment plans and the need to include service users more meaningfully in therapeutic collaboration and goal setting.

"Are we asking the right questions and are w simply reviewing people and then reviewing, thinking, would be, you know, wondering are we asking the clients the right question or are we just, you know, on a continuum here. So, I think there are challenges to the model within here that need to be looked at going forward" (SP5).

4.8 Theme 3: The impact of COVID-19 on retention

The following theme focused solely on the perspective of service providers views of retention in the context of COVID-19 and as a result, it should be noted that the views of service users in relation to this theme are unknown.

4.8.1 Sub-theme 3: Take-home doses and community dispensing

A successful outcome of the contingency planning for OAT provision during COVID-19 was the increased provision of THDs in order to reduce the amount of footfall in the community and in specialist treatment clinics. Service providers explained that THDs were increased as opposed to community dispensing in order to protect pharmacies from increased footfall, and also to protect service users' confidentiality.

"The other arthuinndg cionfjiudsentiality. In other anybody in. You don't want somebody queuing everybody else. That's just not particularly of confidentiality" (SP6).

However, consultants were granted permission to write dispensing scripts for their service users who were travelling long distances for their weekly THDs. According to service providers, this had been received positively by service users.

"So, now they [NDTC consultants] can writ Limerick and they're relatively stable they don't have to come back up here now for their dispensing...that's been a benefit to a lot of (SP5).

This implementation of increased THDs and some community dispensing would have certainly reduced the amount of travelling required of service users, which was identified as a barrier to

retention. Service users also highlighted negative interactions with other service users and stigma attached to attending the clinic as a barrier to retention. The extra provision of THDs and community dispensing would also have reduced the amount of interactions service users had with other service users and the stigma attached to attending the NDTC. Service providers stated that they would like to see this increase in THDs and community dispensing continue in the future post COVID-19.

"There's something in that that is a week you ca take-aways during COVID-19, why can't you do that in the norm? That type of practice now needs to continue as well, you know..." (SP5).

This move to increasing THDs and community dispensing was seen as a positive progression for OAT specialist services, however service providers also highlighted that this increase in service provision would require increased resources and facilities.

"The biggest challenge is now going back to n It's -19 OAT Contingency plan] created opportun think the difficulty is at the moment, we've treatment that fits them will need augmentation and increased resources, particularly maintain services for folks we've taken in" (SP7).

4.8.2 Sub-theme 2: Communication with service users during COVID-19

Service providers stated that extra efforts were made during the COVID-19 lockdown restrictions to continue communicating and engaging with service users. This involved changing the structure of clinical procedures to ensure social distancing was maintained. There was an increase in outreach to service users through phone calls to ensure that their well-being was being monitored.

"What we're trying to do is either on the least check in with some of those folks and ensure they're not compl and that from a clinical point of view, that doing OK" (SP6).

Service providers felt that this increase in communication with service users was generally well received as service users were receptive to the precautions put in place. Many service users highlighted that their physical and mental health and struggle with addiction had an impact on their retention in treatment on an almost daily basis. An increased level of communication and outreach with service users introduced during COVID-19 pandemic may improve relationships between service users and providers. This improvement in the therapeutic relationship could also aid service users to address and manage their daily struggles with their health and addiction issues. Service providers acknowledged that the increase in communication with both service users and other service providers had been a successful outcome of service provision during COVID-19. Service providers stated that increased communication with both service users and other service providers should continue post COVD-19.

"We should be able to look how we provid services. So, that there is a greater network there. And one of the things I've seen during COVID is that there has been a greater engagement with local services around the country and ourselves to provide levels of support that (SP5)

4.8.3 Sub-theme 3: Cocooning services and extra provision of accommodation

In response to COVID-19, cocooning services were required for vulnerable OAT service users and those who tested positive for COVID-19. Outreach OAT and benzodiazepine maintenance were also provided for those in isolation and cocooning.

"we would deliver the methadone to them outreach worker through the Ana Liffey Drug Treatment Project. So, we basically got four beds in one of the isolation units which is a remarkable support, and we were able to start them on methadone immediately. So, while they were in isolation, we rapidly increase the methadone and we'd nursing supervision, also we provid go out, we gave high dose benzodiazepine, high dose I mean up to 30 milligrams of diazepam" ... (SP8)

In order to assess priority for cocooning a medical score was devised and extra accommodation facilities were obtained from Dublin City Council and the Health Service Executive. This rapid creation of assessment and extra facilities allowed for vulnerable service users to be immediately cocooned.

"So, we got 450 units extra for both iso
created a medical score with [league], which I applied to everybody. That if you were aged 40-50 you got one point, aged 50-60 two points, 60-70 three points, and over 70, four points. If you had a medical morbidity, cardiac or respiratory you got one point, if you had diabetes you got two points, if you had controlled HIV, two points, if you had uncontrolled HIV that gives a person four points. We applied that to everyone, then we actually created a list of around 350 people who we then... basically, and we were able to HSE contact the DCC (Dublin City Council) and the DRHE (Dublin Region Homeless Executive) and we were able to basically cocoon them" (SP8).

These cocooning and outreach services were facilitated by inter-agency collaborations between statutory agencies and non-government organisations that worked together to ensure that all vulnerable service users received their OAT. These provisions as a result of COVID-19 also addressed many barriers to retention that service users highlighted. According to service providers, service users' health outcomes improved as a result of this increased provision. Service users had described how their health status caused them difficulties in engaging in OAT that were now being alleviated as a result of improved accommodation for those who were homeless and considered to have compromised health. Service providers are now trying to ensure that this level of service provision will be maintained post COVID-19.

"I think the impact... better impact, because if people are in better accommodation, so they're more likely to be (SP8).

"One of the plus-ends, if there is a plus, is the homeless services have been able to get most of our homeless patients into better quality accommodation. So, the numbers of people who are definitely sleeping rough or sleeping on the streets seems to have dropped" (SP6).

4.9 Discussion

4.9.1 Summary of findings

This study explored factors influencing retention in OAT from the perspective of service users and providers. Both service users and service providers highlighted key barriers and facilitators

to retention in OAT. Barriers identified and classified as red flags by participants included stressful life events, difficulties travelling to the clinic, physical and mental illness, the stigma associated with attending the clinic, personal struggles with addiction and negative interactions with service users. In contrast, social support, self-motivation and familial incentives were identified as facilitators to retention. Both service users and providers highlighted three areas of treatment as areas for improvement: the therapeutic relationship, views of OAT held by service users and a disparity in goals set by service users and providers.

The contingency plan that was created in response to COVID-19 addressed many barriers that service users reported by increasing THDs and community dispensing, increasing communication between service users, providers and other services and by cocooning vulnerable service users and sourcing better accommodation for those service users who were homeless. THDs, telephone consultations, rapid induction for new treatment episodes, community dispensing and the introduction of buprenorphine prolonged-release injection to suitable service users have been introduced in many countries across Europe (231, 271, 272), and Australia (273). Audio-only communication for buprenorphine induction and increased THDs for stable service users has also been introduced in the USA (274, 275). Findings from this chapter will now be discussed in the context of current literature and emerging findings of the impact of COVID-19 on OAT provision.

4.9.2 Communication and the therapeutic relationship

Clinical guidelines for OAT in Ireland highlight that forming a therapeutic alliance is a consistent predictor of engagement and retention of service users in drug treatment (70). These guidelines also state that good communication between service users and providers is crucial in providing optimal treatment (70). The therapeutic relationship was described by both service users and providers as an area that could be improved in order to facilitate retention in OAT. This finding is consistent with studies conducted in primary care and community settings which found that functional relationships and good communication between all parties facilitated OAT service provision (276, 277).

There appeared to be a difference in the relationships that service users reported having with medical and non-medical staff. Service users reported a more strained relationship with medical staff due to feelings of frustration, not feeling heard and a lack of continuity of care as a result of not seeing the same doctor consistently throughout treatment. In a study exploring the

experiences of doctors prescribing MMT, Van Hout and Bingham reported that issues relating to mistrust, control and sanctioning (in some instances) were observed by GPs to form the basis for strained therapeutic relationships (260).

A complex dynamic between service users and service providers was evident as service users generally described having better relationships with non-medical staff who did not have influence on their OAT care plan and were also long term employees of the treatment centre. Service users felt that communication with their doctors was brief and focused purely on medication. This was also evident in Mayock et al.'s study where participants felt that their treatment and interactions with medical staff were primarily focused on their OAT medication and dosing. Service users in this study stated that medical staff did not incorporate discussing any personal or social challenges that may have been impacting on their treatment (261). However, service users may have unrealistic expectations as to what level of support their doctors and clinical staff can provide under the constraints of resources available. Andersson and Johnson's conducted a study of service users' views and experiences of choice in which 33 service users were interviewed across six OAT clinics in Sweden (253). In 2014 service users' in Sweden were granted a choice in deciding which clinic they could use to access their OAT. Service users in this study highlighted that poor communication and a strained therapeutic relationship was a reason that many chose to transfer to another clinic (253). As this choice is not available to service users' in Ireland, poor communication may result in service users dropping out of treatment.

Service providers acknowledged the difficulties in maintaining positive therapeutic relationships. One service provider stated that it was important to acknowledge that both service users and providers are responsible for therapeutic relationships and their breakdown. It is evident that there is a need for more, but also better, communication throughout the service in order to facilitate retention. This has been emphasised in previous research (256), with Damon et al. stating that lack of communication in the MMT therapeutic relationships eroded trust and limited service users' participation in treatment decisions (254). Al-Tayyib et al. (252) also highlighted that service users' perceptions of staff not caring about them also appeared to be a barrier to retention in OAT. Poor communication in the therapeutic relationship can also lead to negative attitudes towards OAT, which has been found to be a predictor of dropout (106). Many service users reported negative attitudes towards OAT stating

that they believed it was a “replacement for another addiction” and that they wanted to “come off the drug completely”.

Service providers reported an increase in the levels of communication between service users, and other agencies as a result of the COVID-19 contingency plan for OAT provision (110, 278). This increase in communication was to ensure the clinical safety of service users who were receiving more THDs or being dispensed doses in the community. In Ireland, the move of drug treatment services to a remote model particularly in contacting service users was seen as successful from the perspective of service providers (111, 112). The EMCDDA has also reported that service providers across Europe believe that the use of telemedicine as an adjunct to face-to-face services should be continued post-COVID-19 (271).

In Bristol, the LUCID-B (Living under Coronavirus and Injecting Drugs in Bristol) study is a rapid qualitative study examining how people who inject drugs are being affected by the COVID-19 pandemic. In the fourth interim report published, participants who were experiencing homelessness reported difficulties with access to reliable internet access which impacted their ability to avail of their support services (228). Almost 50% (48.7%, n=57) of study participants in chapter three had experienced accessing homeless services in the month prior to baseline interviews. Basic amenities such as access to mobile phones, ability to charge them and credit to make phone calls must also be considered when engaging remotely with service users who are experiencing homelessness.

The LUCID-B study also reported mixed opinions in relation to appointments moving to the telephone with some missing face-to-face interaction and others finding it more convenient (228). These differing views were also held by 208 service users in Wales who took part in a peer led study of how COVID-19 was impacting their access to services (279). Service users interviewed for this study highlighted that their relationships with non-medical staff members were often better than relationships with medical staff. These non-medical staff could be used to improve communication with service users and medical staff. However, it was evident during this study that many participants only engaged with certain general attendant staff and their medical supports.

4.9.3 Meaningful goal setting

Communication and the therapeutic relationships also impacted on how service users perceived their goals for treatment and collaboration with service providers. There appeared to be a

disparity between service users' goals for treatment and what service providers assessed as clinically safe and appropriate. Many service users reported that their goal was to eventually detox from OAT and become abstinent. This disparity in goal setting has been previously reported in literature as Mayock et al. described how a large number of participants in their study entered MMT with the expectation that they would attempt to detox at some stage in their treatment but learned that this goal was strongly discouraged (261).

Despite service users being discouraged from detoxification and an emphasis on a harm reduction approach, McKearney et al.'s study of 1001 service users entering a new treatment episode in 33 agencies across Scotland (266) highlighted that 42.5% of participants commencing MMT hoped to achieve abstinence alone, 35.2% hoped to achieve a combination of abstinence and harm reduction and 22.3% hoped to avail of harm reduction only (266). Participants definitions of abstinence was not sought which may mean different things for different individuals (266). It is evident from this study and Mayock et al.'s that detoxification and abstinence may be a prominent goal for service users in OAT.

However, as also noted by McKeganey et al., although abstinence is aspirational, it may not be a realistic goal for some service users (266). This raises the question of what persistent attempts at abstinence would do to a service users' motivation and clinically what is safer and more appropriate; attempt(s) at detoxification or long term harm reduction measures (266). While it is imperative that service providers consider their duty of care, current OAT clinical guidelines state that care plans should clearly document the service users' aims and goals for treatment and outline the range of treatments required to achieve the user's goals with regular formal plan reviews involving both service users and providers (70).

This disparity in goal setting also frustrated participants when their request for a reduction in dose was denied. Negotiating treatment dose has been reported as a contentious issue in previous literature with reductions in dosages being denied in Ireland (261), but also requests for higher doses in other countries being denied due to service providers' fears of fatalities (259) or stigma associated with OAT (280). Clinical safety was discussed as an important component of treatment by service providers in this study. There also appeared to be a disconnect in the information shared with service users by providers (an emphasis on harm reduction) and the service users' expectations for their own for treatment plans (progression to detoxification) (266).

Despite the information shared with service users on the dangers of detoxing or reducing doses unsupervised, some explained that they were willing to do this and had already done so in the past. Due to the clinical risks of withdrawal symptoms associated with opioid detoxification it is recommended that this should be planned in conjunction with ongoing treatment (45). It was also unclear if service users were aware of the repercussions of unsupervised detoxification or aware that detoxification is not as effective a treatment as OAT due to the high rates of relapse (45, 70). It appeared that a perceived breakdown in communication or feelings of frustrations in relation to goal setting was a reason that had caused service users to leave OAT in the past. Improving collaboration between service users and providers is needed, most particularly with regard to goal setting and involvement in care planning. The balance of goal setting and clinical safety needs to be communicated in an accessible manner to service users in order to resolve the disparity in goal setting. Service providers must also acknowledge that the goal for some service users is to become opioid free and develop realistic and clinically safe goals in relation to this (70, 93) .

4.9.4 Progression in treatment

Many service users were motivated to progress in their treatment by being granted more THDs or by being transferred to primary care. This goal is common for service users in specialist treatment centres and is often viewed as a milestone in treatment (261). Clinical guidelines stipulate that clear communication and collaboration is required between service users and providers for progression in treatment or transfers of care (70).

Durand et al.'s retrospective study of 2,899 people prescribed and dispensed methadone in specialist addiction services in Ireland between January 2010 and December 2015 highlighted that only 19% of transitions between services involved transfers from specialist settings to primary care with 10% of transfers being from primary care to specialist treatment settings. The most frequent transitions involved transfers from prison to addiction services (35%) followed by addiction services to prison (32%) (31). The review of the Opioid Protocol previously made a recommendation to ensure progression through treatment ten years ago (93). This review highlighted that the shortage of appropriately trained GPs was as a significant barrier to treatment progression (93). An increase in level 1 and level 2 GPs (Section 1.3.4) would aid in integrating OAT into general healthcare and reduce stigma. This would also reduce time spent

attending clinics and negative interactions which service users highlighted as a barrier to retention.

The increase in THDs, community dispensing and move to longer-acting OAT medications implemented as a result of COVID-19 also has the capability to address barriers to retention and treatment progression that service users described in this study (112, 228, 231, 271, 279, 281). Service users experienced stigma and articulated feelings of shame as a result of their OAT. Reducing stigma has been reported as a key step in increasing retention to MMT (249, 250). Woo expanded on this in their study and stated that the self and interpersonal stigma surrounding MMT led to some service users lowering their dose prematurely which resulted in withdrawal and dropout (249).

An increase in THDs or community dispensing would also aid in integrating OAT into the community with other forms of healthcare provision. This would contribute to a shift in the public perception of OAT. As noted by Mayock et al., specialist addiction services in Ireland have become an indication of the reluctance of OAT being accepted by established branches of medicine such as primary care and to normalise addiction as a medical condition (261). In 2019, approximately 60% of those in receipt of MMT were service users of specialist addiction clinics rather than GP surgeries (84). There is a need to investigate why treatment progression to primary care services remains low at less than 20% (31).

An increase in THDs and community dispensing would also aid in reducing the hours spent by some service users travelling to the clinic on a nearly daily basis. Some service users reported time spent travelling and poor public transport services were barriers to remaining on their OAT. Travel distance to OAT clinics has been explored in both quantitative and qualitative studies, with results indicating that longer periods of time spent travelling to clinics predicts dropout (171, 201, 241) . Although these studies were all conducted with MMT service users in China, this barrier appears widespread in OAT settings.

Consideration needs to be given to the clinical implications of providing increased THDs as a result of the COVID-19 contingency plan. Increasing THDs may result in an increase in the diversion of OAT. Although the diversion of OAT medications has been described as a growing problem in recent years, there has been little systematic monitoring or data collection able to quantify the magnitude of the problem (282). Previous research has outlined that diversion of OAT is conducted in order to supplement income by “dealing” or in order to support friends or

peers in opioid withdrawal and is carried out by accessing several doctors at the same time ("doctor-shopping") or buying doses from other service users (283) (284).

Supervised consumption of OAT doses and regular urinalysis has been used to monitor treatment progression and also reduce the risk of diversion (280). Despite this, Saulle et al.'s cochrane review of the effectiveness of supervised dosing of OAT found that at three or more month's follow-up, there was no evidence of supervised dosing being associated with increased retention. The review called for further research as it was unable to make any conclusion on the effectiveness of supervised dosing compared to dispensing of THD, in the context of retention in OAT (285). Following this review, through a cohort study of persons experiencing ≥1 MMT treatment episodes in primary care over six years in Ireland, Cousins et al. found that having between 20 and 60% of methadone scripts supervised (compared to >20%) was associated with reduced time to discontinuation (280). In this study they also noted that reducing the supervised consumption of doses with the aim of retaining a service user needs to be balanced against the risk of diversion and the increased availability of OAT through more THDs which may increase the risk of OAT-related deaths in the community (280). This study called for more work in order to determine how to stratify service users' suitability for unsupervised dosing, while retaining service users but also simultaneously reducing diversion and injecting (280). This proposal for further research is particularly important now in light of the COVID-19 contingency plan for OAT and what elements of the plan service users and providers hope to continue post-pandemic.

4.9.5 Engagement in service evaluation

Clinical guidelines for OAT stipulate that:

"Service users should be fully involved in the development of their care plans, setting appropriate treatment goals and reviewing their progress in treatment. It is also good practice to involve service users in the design, planning, development and evaluation of services, and in advocacy and support groups linked to local drug treatment" (pp.11) (70).

This view is held in all other general healthcare settings and also healthcare research through public-patient involvement (286). Despite this, many service users expressed that their goals for treatment were dismissed and they felt they were not listened to. There was a sense that assumptions were made on behalf of the service users and as a result they felt they had little autonomy over their treatment. In previous research, Fischer and Neale (287) explored service

providers' explanation for lack of service user involvement in treatment. Service providers articulated that service user involvement was not always feasible due to service users acting exploitatively or having unrealistic treatment expectations. This in turn led to service users viewing service providers in a negative light (287).

Service users' lack of involvement in treatment planning and service evaluation has been previously explored in Ireland (257, 258, 277). These studies have outlined that service user involvement is progressive and desirable (257) and that shared care treatment approaches in Ireland are essential (277). Despite this, King noted that both service users and providers in her study described service users as passive and "symbolic" players in planning, developing, evaluating and delivering the services they received (257).

Van Hout et al. suggested that reasons behind these low levels of involvement was the stigma related to drug use which made service users reluctant to meaningfully engage in treatment planning (258). The power dynamic between service users and providers in all stages of treatment implementation and evaluation was also noted as a reason for low levels of involvement (258). Service providers in this study also questioned the level of capacity and training required for service users to meaningfully engage in service provision and evaluation (258).

These studies suggested that there is a need for transparency from service providers so that service users are aware of the extent to which policy makers and service providers can respond to their views and act on their recommendations (258). Education and training for both service users and providers involved in treatment services was also recommended in order to progress the meaningful involvement of service users in service provision and evaluation (257, 258, 277).

Although these studies were conducted in Ireland, all forms of drug treatment services (including MMT) were included and both service users and providers were recruited. From these findings and the findings outlined in theme two, it needs to be stressed that a lack of autonomy for service users in their treatment and service provision can often impact on their motivation to stay in treatment. In line with clinical guidelines for OAT (70) and previous recommendations made (93), service users need to be included in meaningful evaluations of service provision in order to evaluate and assess how to facilitate retention in their treatment.

4.9.6 Implications for future research

This study identified the therapeutic relationship, views of OAT held by service users and a disparity in goals set by service users and providers as barriers and facilitators to dropout. Despite these insights, this study has generated further questions to be addressed with both service users and service providers of OAT in terms of both clinical practice and policy.There is a need to investigate what the goals of service users are upon starting OAT in order to inform treatment plans and facilitate retention in treatment. McKeganey et al. highlighted that the goals of service users in Scotland were mainly concerned with achieving abstinence (266). Many participants in this study also stated goals of detoxification from OAT, however this cannot be generalised due to the nature of qualitative research. It would be beneficial to understand service users' goals upon entering treatment in terms of harm reduction versus abstinence, but also to ascertain what service users consider abstinence as this term can have various meanings to individuals (266). It would also be beneficial to assess service users' understanding of why some goals in treatment may be unrealistic due to clinical safety.

Difficulties in communication between service users and providers was highlighted by service users in this study as a significant issue in practice. HSE clinical guidelines state that good communication between service users and providers is crucial in providing optimal treatment (70). Despite this, some service users in this study felt communication with medical staff was brief and at times dismissive which has also been reflected in other studies (253, 261). Service users also highlighted positive relationships with non-medical staff (such as general attendants, social workers and counsellors), however as psychosocial treatment was not explored in this study it would be beneficial to explore how much psychosocial services are availed of, the communication between service users these staff members and its impact on retention. Engaging with individuals who dropped out of OAT and exploring circumstances which led them to dropping out of OAT could help gain a sense of what this unexplored cohort experience and could aid in maintaining individuals in treatment in the future. It could also facilitate changes to practice that may encourage individuals to return to treatment if they wish to do so.

In terms of treatment progression, Durand et al.'s retrospective study of 2899 individuals in specialist addiction services highlighted that only 19% of service users transferred from specialist settings to primary care between January 2010 and December 2015 (31). The

Reducing Harm, Supporting Recovery health-led response to drug and alcohol use in Ireland 2017-2025 policy (88) outlined the Department of Health's commitment to examining potential mechanisms to increase access to OAT such as the expansion of GP prescribing, nurse-led prescribing and the provision of OAT in community-based settings and homeless services. Before examining potential mechanisms to increase access and capacity of OAT in primary care settings, it is important to first assess why so few individuals who may be suitable for primary care are progressing from specialist treatment settings.

There may be several clinical reasons for this lack of progression including capacity of services and service users who may be unsuitable for primary care. However policy reasons such as the markers of stability for increased THDs may also be unnecessarily impeding progression (70). For example, the marker of living in stable accommodation could be beyond the remit of service users who may be demonstrating stability in all other aspects of their lives. As approximately 60% of OAT in Ireland is provided through specialist treatment settings it is important to engage with service users and providers in order to assess the lack of progression. Finally, at present all COVID-19 related studies have been rapidly conducted cross-sectional surveys or rapidly conducted literature reviews. In order to progress the understanding of the impact of COVID-19 contingency plans on retention in OAT, multi-method collaborations incorporating ethnography and qualitative research will need to be conducted in order to enhance the strength of evidence of COVID-19 contingency plans' impact on OAT and retention from the perspective of providers, but also more importantly service users (288).

4.9.7 Strengths and limitations

This study generated insights into the factors influencing retention in OAT from the perspective of service users and providers. This study was the first to explore the views and opinions of both service users and service providers concurrently from an Irish perspective. This study adds to the growing body of literature related to the importance of communication and the therapeutic relationship in OAT, and emphasises the importance of these components in facilitating retention in treatment. This study also adds to emerging findings regarding the disparity in goal setting between service users and providers, taking into account both perspectives. Furthermore, this study offered insight into how service provision of OAT changed in the initial weeks of COVID-19 restrictions in Ireland. This research piece was conducted within the NDTC and as such there are some aspects to the study that could be viewed as limitations.

Firstly, as this study was conducted in a single clinic only service users currently engaged in treatment were recruited and the insights provided by the service users and providers are unique to the NDTC. As a result, the study did not recruit individuals who had dropped out of treatment and were not in treatment at the time of the study. However many of these participants had experienced dropping out of treatment in the past. Secondly, recruitment and data collection was suspended prematurely due to the implementation of national restrictions and as a result data saturation was not met. However, this presented an opportunity to recruit additional service providers involved in the service provision or care of OAT service users. A final limitation of the study is that it did not focus on psychosocial services and as such it is unclear if these could help with improving therapeutic relationships and communication between service users and medical staff.

4.9.8 Conclusion

This study aimed to explore the factors influencing retention in OAT from the perspective of service users and providers. Data was collected from 14 service users and eight service providers through semi-structured interviews using purposive sampling. Data was analysed using thematic analysis. The findings revealed that service users and providers have complex relationships that influence how service users perceive their treatment. Service users highlighted stigma, negative interactions with service users, time spent travelling to the clinic, illness, experiencing stress and their personal struggles with addiction as barriers to retention. They highlighted social support, self-motivation and familial incentives as facilitators. There appeared to be a disparity in goal setting between service users and providers as service users were motivated to detox from OAT, while clinical staff were concerned with clinical safety. The COVID-19 contingency plan for OAT service users was deemed a success by service providers in the initial weeks of its implementation. The increase in THDs reduced time spent by service users' interaction with other service users and time spent travelling to the clinic. The contingency plan also increased communication between service users and providers and also aided in placing homeless service users in better accommodation.

Future research needs to engage with individuals who dropped out of OAT and exploring circumstances which led them to dropping out of OAT could aid in maintaining individuals in treatment in the future. It would also be beneficial to investigate what the goals of service users

are upon starting OAT in order to inform treatment plans and facilitate retention in treatment and also assess why so few individuals who may be suitable for primary care are not progressing from specialist treatment settings. Finally, research is also needed to explore how much psychosocial services are availed of and their impact on communication between service users and medical staff.

Chapter Five: Discussion

5.1 Introduction

The overall aim of this thesis was to investigate factors associated with retention in OAT in order inform future policies and service provision to facilitate the improvement of retention rates in Ireland. In this chapter, the overall findings are summarized in the context of previous research. This is followed by the strengths and limitations of this thesis, implications for future research,

the overall research impact in terms of research-related impacts, policy impacts, service impacts, societal impacts (289) and finally, an overall conclusion.

5.2 Summary of Findings

The first objective was to examine the totality of evidence for risk factors and protective factors associated with retention in OAT. The systematic review in chapter two highlighted that while the NIDA recommends a minimum of one year in OAT for best outcomes (202), the median retention rate across observational studies was approximately 57% at 12-months, which fell to 38.4% at three years. Studies included were heterogeneous in nature with respect to treatment setting, type of OAT, risk factor assessment, ascertainment of outcome and duration of follow-up. While the presence of such methodological heterogeneity made it difficult to synthesise results, there was limited evidence to support the influence of a number of factors on retention, including age, substance use, OAT drug dose, legal issues, and attitudes to OAT. Younger age, substance use (particularly cocaine and heroin use), lower doses of methadone, criminal activity/incarceration and negative attitudes to MMT appeared to be associated with reduced retention in OAT. Furthermore, differences were observed by type of OAT, with methadone cohorts reporting a higher retention rates at 12-months compared to buprenorphine cohorts.

Median retention rates in specialist treatment settings decreased as duration of follow-up increased, with median rates declining from 61.3% at six-months to 46.5% at three years. These rates are similar to the overall median retention rates of all studies included in the review. MMT in specialist treatment settings had higher rates of retention at six-months; 61.5% (range 46.8 – 86%) in comparison to buprenorphine and mixed OAT studies. However, mixed OAT studies in specialist treatment settings had higher retention rates at 12-months; 65.8% (range 43.4 – 84%) in comparison to buprenorphine or MMT alone. Similar to the overall analysis, younger age, substance use (cocaine, heroin, amphetamine and benzodiazepine use), contact with other drug users and criminal activity was also found to have a negative impact on retention in MMT and mixed OAT in specialist treatment settings. Higher OAT dose and positive attitudes to OAT were also found to be associated with increased retention in specialist treatment settings.

Following completion of the systematic review, a prospective cohort study with OAT service users in a specialist treatment setting in Ireland was conducted to investigate retention rates and factors associated with retention in OAT at six-months using both self-reported and clinical data. Time to discontinuation for those who dropped out (n=16) was 83.9 [IQR 29.4- 95.9] days.

For the secondary outcome (retention at 6 months, a binary variable), the study had a 95% rate of retention at the 6-months follow-up and there was evidence that engaging in IV drug use was univariately associated with an increased risk in dropout at 6-months. Although age at the beginning of treatment episode did not reach statistical significance, a trend was observed which has clinical significance, in that older individuals were more likely to be retained at six-months. Finally, the sample in this study appeared to be injecting less, but using more drugs than previous Irish studies conducted in similar settings (103, 235), however these previous studies relied on self-reported data whereas urinalysis was used in this study.

Finally, in order to further explore contextual information from the perspective of service users and providers, the third objective was to explore the barriers and facilitators of retention in OAT using qualitative semi-structured interviews which were informed by the MAP. The findings revealed that service users and providers have complex relationships that influence how service users perceive their treatment. Service users highlighted stigma, negative interactions with service users, time spent travelling to the clinic, illness, experiencing stress and their personal struggles with addiction as barriers to retention. They highlighted social support, self-motivation and familial incentives as facilitators. Both service users and providers highlighted three areas of treatment as areas of improvement: the therapeutic relationship, views of OAT held by service users and a disparity in goals set by service users and providers

The contingency plan that was created in response to COVID-19 addressed many barriers that service users reported by increasing THDs and community dispensing, increasing communication between service users, providers and other services and by cocooning vulnerable service users and sourcing better accommodation for those service users who were homeless.The COVID-19 contingency plan for OAT service users was deemed a success by service providers in the initial weeks of its implementation, however the perspective of service users is needed in order to comprehensively evaluate the contingency plan.

5.3 Results in the context of previous research

The findings outlined in chapter two highlighted that younger age, drug use (particularly cocaine and heroin use), lower doses of MMT, criminal attitudes and negative attitudes towards OAT appear to be associated with increased dropout. Despite the importance placed on treatment outcomes for monitoring treatment progress in OAT, there was significant heterogeneity across the included studies, particularly in relation to the definition of retention and outcome

measures used to monitor it (106). This experience of heterogeneity was not unique to the review presented in chapter two as it has been raised as an issue in several previous systematic reviews investigating OAT and factors associated with retention.

Brorson et al. reported that heterogeneity was evident across study designs, samples and measurement methods in their systematic review of 122 studies in order to investigate factors associated with dropout (129). They called for future studies to include more thorough descriptions of designs, procedures and reporting effect sizes that allow for comparison in order to facilitate meta-analysis, and for researchers to agree on definitions of dropout (129). Korownyk et al. also highlighted that that heterogeneity was high in RCTs included in their systematic review investigating the treatment of OUD in primary care settings (290) and as a result they stated that their findings could not be generalised to other settings. Finally, Zhang et al. reported that heterogeneity created issues in conducting their meta-analysis of factors associated with retention in MMT in china (132). Wiessing et al. have suggested that heterogeneity across studies diminishes the overall value of evidence as comparability issues can create ambiguity in treatment expectations, outcome measurement and evaluation (98). Developing a consensus on the definition of retention, specifically in relation to defining the duration of time a person is without treatment before being categorised as having dropped out and how to measure treatment outcomes would allow studies to be replicated and facilitate scientific and clinical progress in this area (98, 129).

Despite this heterogeneity, these systematic reviews were able to demonstrate evidence to support certain risk and protective factors similar to those presented in chapter two. Korownyk et al.'s (290) systematic review of 39 systematic reviews and 26 RCTs investigating the treatment of OUD in primary care settings stated that the addition of standard counselling to OAT is associated with increased retention in comparison to no or minimal counselling. They also reported that higher service user satisfaction in primary care is also associated with increased retention (290). This is consistent with findings presented in chapter two that stated that negative attitudes towards OAT appears to be associated with dropout (290). Conversely, although Brorson et al.'s review highlighted younger age as a risk factor for dropout, they reported unique factors associated with dropout in comparison to the findings in chapter two. Studies in Brorson et al.'s review included an active psychosocial component to OAT which may have influenced review's findings. They reported that cognitive deficits, low treatment alliance and personality disorder appeared to be associated with dropout (129). Brorson et al. also

noted that little is known about the potential risk factors related to treatment programs and to the treatment processes.

Zhang et al. also reported some similar findings to those presented in chapter two in their systematic review of factors associated with retention in MMT in china. A total of 74 studies representing 43,263 individuals were included in the analysis (132). This review noted that 30% of participants dropped out of treatment within the first three-months of MMT. In comparison, a recent Irish study of MMT service users found that almost 50% (49.7%) of dropouts occurred during the first 90 days (109). Reasons for dropout in Zhang et al.'s review were cited as: arrested by police and sent to detention centres due to relapse in drug use (22%), voluntary dropout (19%), relocating outside the coverage of the clinic (13%), illness or death (6%) and unregistered by the MMT clinics (6%). Similar to the findings presented in chapter two, criminal activity (7.6%) and dosing issues (0.1%) were also cited as factors contributing to dropout (132). This review noted limitations in that 13% of studies that met inclusion criteria which reported high dropout rates did not indicate the reasons for dropout. As noted in the findings in chapter two it was often unclear whether service users' dropout was voluntary or involuntary, and while the outcome may be the same the risk factors are likely to be very different. Finally Zhang et al. highlighted that MMT doses for Chinese service users is substantially lower than the recommended dose of between 60-120mg which may have a strong effect on retention rates (132).

Lower doses of MMT as a risk factor for dropout was also highlighted in the findings of chapter two. Faggiano et al.'s Cochrane review of MMT at different doses stated that MMT doses ranging from 60 to 100 mg/day are more effective than lower dosages (less than 60mg/day) in retaining individuals in treatment (291). This was later corroborated by Amato et al.'s overview of systematic reviews which stated that MMT is more effective at retaining individuals in treatment than buprenorphine maintenance treatment, methadone detoxification or no treatment, with higher doses more effective than medium or lower doses (126). Two further systematic reviews have investigated OAT medications, but focused on prison settings and retention post-incarceration (292, 293). These reviews suggested that individuals who are exposed to OAT in prison are likely to be retained in OAT post-release. MMT was found to be associated with higher retention post-incarceration in comparison to buprenorphine and buprenorphine/naloxone (292).

Timko et al.'s systematic of OAT medications associated with increased retention stated further research is needed to investigate the association between behavioural therapies and retention as studies in the review that focused on behavioural therapies may have lacked statistical power as no differences were detected between intervention and control conditions when investigating supervised consumption of dose, additional counselling and education, or support (125). Contingency management (such as increased THDs) was noted to show promise in increasing retention.

The cohort study presented in chapter three had a high retention rate at six-months follow-up (95%, n=106). This represents a substantially higher retention rate compared to previous observational studies reported in the systematic review in Chapter two, with retention rates ranging between 19.1 – 86% across studies in specialist addiction setting (149, 154, 156, 170, 171, 182, 183, 185, 187). Of the studies included in the sensitivity analysis that reported retention rates of 70% or higher (n=4) (156, 171, 181, 185), three reported an aging sample with mean age of their study participants 36.4 (156), 36.6 (171) and 40.4 years (185) respectively. Participants in all four of these studies were mainly male (mean percentage 84.6% (75-97.2%)) (156, 171, 181, 185). Seventy five percent of participants in the cohort study presented in chapter three were male with a mean age of 37.6 (21-54) years. The similarity in demographics across these studies is consistent with global reports of an aging and predominately male cohort seeking treatment for OUD (17, 54). As these studies with older cohorts showed higher rates of retention (of 70% or more), this could explain, in part, the high retention rate observed in chapter three.

Injecting drug use was associated with increased dropout The four other studies with retention rates above 70% reported a variety of factors associated with retention: medium (156) to high doses of OAT (156, 182), being tested for TB and testing positive for HIV or TB (156) and being older (185). They also reported that being female, a history of imprisonment, travelling longer distances to the clinic, having a lower methadone dose after 30 days, being HCV positive, clinic location, criminal charges (171), and low self-esteem (182) predicted dropout.

Chapter four explored the perspective of service users in relation to retention and the barriers and facilitators to remaining in treatment. There was a sense of ambivalence from service users when asked what their opinion of OAT was, and if they planned to remain in treatment on a long-term basis. Goals for treatment greatly, from no goals identified, to a desire to detox

immediately or a structured plan with a timeframe on detoxing from OAT. Conversely, the WHO recommends that OAT should be seen as long-term treatment that is continued as long as clinically indicated (45). However one of the main criticism of OAT and harm reduction philosophy is that individuals often feel stuck on treatment for years against their wishes.

Mayock and Butler observed this in their study exploring pathways to recovery and social reintegration in long term service users of MMT (294). Their study found that although gaining stability was a primary perceived benefit of MMT, service users perceived an absence of treatment progression with a large number articulating a sense of being 'stuck' or trapped in a cycle that did not lead to progress or change (294). Of the service users who stated that their goal was to reduce their MMT dose or become drug free, they said that they were not assisted in striving towards these goals and were not permitted to discuss these goals with their doctors (294). According to Harris and McElrath, this lack of progress in treatment disempowers service users, whereas recovery requires empowerment (295). Recovery from OUD is now considered a process, however the perceived "clean versus dirty" dichotomy of recovery and subsequent stigma has restricted service users' ability to progress in their recovery and contributed to dropout (295).

A previous study conducted by McKeganey et al. indicated that 42.5% of MMT service users stated their goal for treatment was complete abstinence, with over one-third reporting their goal for treatment was to initially reduce the harm associated with their drug use with a view to becoming abstinent and 22.3% reported that their goal for OAT was only to reduce the harms associated with their drug use (266). Although abstinence was highlighted as a goal for treatment by 77.2% of the MMT service users interviewed, it is not always a realistic goal for those who aspire to it (266).

This study offered insight into what service users may wish to achieve from treatment. Service providers interviewed in chapter four were aware of the difference in service users' goals, however they stated that many factors must be taken into account when planning treatment goals, especially clinical safety. These differences in treatment goals and the time spent in treatment placed a strain on the therapeutic relationship. A similar observation was made in a previous qualitative study in the US, with feelings of resentment and distrust towards service providers expressed by service users (296). Previous systematic reviews have ascertained that MMT is more effective in comparison to methadone detoxification, no treatment,

buprenorphine maintenance and heroin plus methadone in retaining service users in treatment (125, 126). The systematic review presented in chapter two suggests that low doses are associated with reduced retention (106). Within the findings of chapter three, although a lack of power resulted in limited analysis, those who injected drugs were more likely to have dropped out of treatment at six-months. Overall, this cohort also appeared to be injecting less, but using more drugs than previous studies (103, 235), however previous studies have relied on self-reported data whereas urinalysis was used in this study.

The findings of chapter four outlined that facilitators to retention described by service users was social support they received from family and friends, self-motivation to remain in treatment and familial incentives such as seeing their children and being able to remain welcome in their homes. Low social support has been reported to be associated with dropout in MMT (170) and family support has been reported as associated with retention in MMT (198). There is also limited qualitative research exploring facilitators to retention in buprenorphine treatment. One qualitative study explored retention in a randomised control trial investigating the effectiveness of buprenorphine. Facilitators to retention cited by the service users were satisfaction with the treatment, personal determination and support from staff (297). Service users interviewed in chapter four identified immediate barriers to retention in OAT as red flags, difficulties travelling to the clinic and managing physical and mental illness. Long-term barriers identified were the stigma associated with OAT, personal struggles with addiction and negative interactions with other service users in the clinic. Areas for improvement acknowledged by both service users and service providers was the therapeutic relationship, meaningful goal setting and involving service users in service evaluation.

Qualitative research in relation to OAT has primarily focused on service users in order to gain their perspectives. Of the studies that have focused on some aspect of what affects retention in OAT, a lack of communication between stakeholders and service users and a dislike of clinic procedures by service users were highlighted in studies across different settings and countries (239, 259, 276). Poor communication between service users and providers was also described in Lin and Detel's study exploring Low-dose OAT and premature dropout in China (265).

Barriers to retention in an Irish context were described in Mayock et al.'s qualitative study which recruited 25 service users from both primary care and specialist treatment clinics (261). In this study, service users reported that frequent urine testing and attendance to the clinic resulted

in feeling undermined and dismissed by staff in specilaist treatment centres. Service users attending community pharmacies also felt dehumanised by staff as the felt they were treated differently to other customers (261). Service users who attended primary care, were not obliged to provide frequent urines or recevied additional THDs and stated that they were more in control of their treatment and had better relationships with service providers as a result (261).

Deering et al.'s study (239) of 85 service users and clinical managers of each specialist treatment clinic (n=18) in New Zealand reported similar barriers to Mayock et al. (261). Both service users and providers described how some procedures conducted in their clinic were viewed as barriers to retention. Restricted takeaways, waiting lists, being tied to one clinic, being required to attend a chemist every/almost every day, random urine screenings, concerns about confidentiality, requirements to attend counselling, interacting with other drug users, and a requirement to be assessed for treatment were all listed as concerns (239). A further study conducted in China explored (262) the factors associated with the decline of service user attendance in MMT from the perspectives of service users and providers. The reasons for the decline in attendance were also similar to Mayock (261) and Deering et al. (239) in that, the inconvenience of being in the clinic and poor service provision were highlighted as barriers (262).

Although the studies outlined above were conducted in different countries and settings, many of the recommendations to improve services were similar from the perspectives of both service users and providers presented in chapter four. Studies recommended that training and education for service users, providers and the general public would aid in improving services (262, 265, 276), improve communication between service users, providers and stakeholders (248, 276) and reduce stigma associated with OAT (248, 259, 276). The COVID-19 contingency plan was deemed successful by two service providers in the initial weeks of implementation. Respondents in the EMCDDA trendspotter briefing on the impact of COVID-19 on drug services stated that the use of telemedicine as an adjunct to face-to-face services should be continued, regulations should continue to allow greater numbers of service users availing of OAT and reductions in urine testing, daily visits and the need for supervised consumption should also continue reduced (271). Limited research from the perspective of service users in relation to the implementation of contingency plans, specifically community dispensing, increased THDs and rapid induction to OAT have also been generally positive (228, 279).

5.4 Strengths and limitations

Key strengths

In this thesis, the systematic review presented in chapter two was the first to synthesise the totality of evidence in relation to factors associated with retention in OAT. Robust and explicit methods were used to identify, select, appraise and synthesise the study findings. This review highlighted the lack of consensus in the definition of what timeframe off treatment is considered as dropout and subsequent difficulties in comparing studies of factors associated with dropout in OAT. This variation and lack of comparability has been recognised in other areas of public health and causes ambiguity and differences of expectations for treatment outcomes (98). Chapter three presented a prospective cohort study using the MAP which covered six of the eight domains recommended for use in OUD observational studies recommended by Wiessing et al. (98). Additionally before this thesis, no longitudinal study had been conducted in Ireland investigating dropout in OAT users in an adult population that used both clinical data (including urinalysis) and self-reported data relating to the contextual factors of an individual's life circumstances.

While previous qualitative studies have focused on service users' experiences of treatment services, few qualitative studies have considered factors specifically influencing treatment retention. Of the studies reviewed in preparation for this study (239, 259-267), very few provided information on the issues or themes that informed the semi-structured interviews of those that did, none reported exploring all eight domains highlighted by Wiessing et al. (98). The qualitative study presented in chapter four also used the MAP in order to structure the categories for questions in the semi-structured interviews, however this structure was not exhaustive in that service users and providers could speak about other topics if they chose to. This structure was used in order to discuss as many contextual factors as possible that may have influenced service users' treatment. It also offered some insight into how service provision of OAT was conducted in the initial weeks of COVID-19 restrictions in Ireland and its potential impact on treatment retention.

Key limitations

The following limitations should be considered when interpreting findings of this thesis. Firstly, the inclusion criteria for the systematic review in chapter two focused on adults (>18 years), limiting generalisability of findings to adult cohorts. The inclusion criteria also required that

studies had to have a minimum of six-months follow-up which excluded studies of early dropout. Durand et al. highlighted in their retrospective study of service users in a specialist treatment centre between 2010 and 2015 that 49.7% of dropout events occurred within the first 90 days of the study period (109), therefore understanding factors associated with early dropout is important, and could allow for the risk stratification of service users requiring more intensive engagement at the treatment initiation and stabilisation stages. In addition, other risk factors not identified in the systematic review, such as stress could be important risk factors for early dropout (204). The search was also limited to the English language and published studies which may have resulted in missing important non-English studies and an introduction of potential publication bias.

In terms of the cohort study presented in chapter three, the difficulties experienced with the recruitment process may have introduced several forms of bias. Prevalent user bias may have been introduced when the inclusion criteria was changed to include those transferring from other settings. Twenty-one potential participants dropped out of treatment before there was an opportunity to approach them. As a result, this may have caused the high retention rate of the study due to ascertainment and survival bias (232, 233). The high retention rate, which may have been influenced by the contingency plans introduced to address COVID-19 public health policy, also limited the exploration of factors associated with retention and dropout.It was not possible to ascertain who received increased amounts of support following the lockdown restrictions at the time of the study. In addition to this, due to variation of when baseline interviews were conducted (including 34 which were conducted after the follow-up end date), it is important to be cautious when interpreting the self-reported results of this study. Although the systematic review identified that most studies do not take account of the fact that individuals transition in and out of treatment (accounting for re-occurring events and time dependent covariates), this was not addressed in the cohort study presented in chapter three which presents a further limitation. However the systematic review informed Durand et al.'s (109) retrospective cohort study investigating factors associated with early and later dropout from methadone maintenance treatment in specialist addiction clinics which addressed this limitation.

Finally, the qualitative study presented in chapter four was conducted within the NDTC and as with all qualitative research, the insights provided by the service users and providers cannot be

generalised to the overall population of those in receipt of OAT in Ireland. Purposive sampling for this study excluded those who were not currently in treatment which may have introduced bias as those only in active treatment were spoken to. Recruitment and data collection was also suspended prematurely due to the implementation of national restrictions and as a result data saturation was not met. However, this presented an opportunity to recruit additional service providers involved in the service provision or care of OAT service users during the initial weeks of the COVID-19 contingency plan. A final limitation of the study is that it did not focus on psychosocial services and as such it is unclear if these could help with improving therapeutic relationships and communication between service users and medical staff.

5.5 Future research

The findings of this thesis have shed light on potential directions for future research. Firstly, it is evident that an international consensus on what constitutes retention in OAT is needed, specifically how much time off treatment is considered a dropout. The systematic review presented in chapter two highlighted that studies differed in their definition of dropout as anywhere from five days (187) to two months without OAT (164). Heterogeneity in studies investigating retention in OAT has been highlighted in four (106, 129, 293, 298) systematic reviews including the review presented in chapter two. The value of research and evidence diminishes when there is a lack of comparability across studies (98).

Some studies have acknowledged the potential bias in defining retention in terms of accepted timeframes for time to discontinuation and have conducted sensitivity analyses in order to address this. The cohort study presented in chapter two defined dropout as 28 days off treatment from the last date of coverage from the last prescription. This was done in line with the timeframes used within the NDTC. A sensitivity analysis was conducted defining dropout as 14 days off treatment from the last date of coverage from the last prescription. This increased the number of participants who dropped out of treatment from 5% (n=6) to 11.6% (n=13). Any absences and subsequent returns throughout the study period amongst those retained also increased from 9.4% (n=10) to 40.4% (n=40). A limitation of the study is that it was not possible to ascertain if these participants dropped out from treatment or were transferred to another setting due to COVID-19 restrictions.

Durand et al. conducted a sensitivity analysis when examining the risk of mortality associated with interruptions to the continuity of MMT. They used a seven day rule to classify time on and

off treatment, but repeated analyses extending the tolerance level to 14 days in order to address potential bias in the seven day classification (31). This sensitivity analysis did not alter the overall findings for all-cause mortality, however the risk of drug-related poisoning deaths during the first month following treatment initiation after a period out of treatment was weakened and did not remain significant in multivariable analysis (31). Durand et al. also performed a sensitivity analysis from a seven day dropout rule to a 28 day dropout rule in their study investigating factors associated with early and later dropout from MMT in specialist addiction clinics (109). This sensitivity analysis gave comparable results to the main analysis (109).

Conducting a Delphi consensus would facilitate the development of an international agreement on the definition of retention in terms of duration of time without treatment before being categorised as having dropped out of OAT in specialist treatment settings. The Delphi technique is a widely used and accepted method for gathering data from expert opinions. It is a group communication process which aims to reach a consensus of opinion on a specific issue (299). The process of developing a consensus could begin on a European level through recruiting an expert representative and a service user representative from each of the focal points under the European Monitoring Centre for Drugs and Drug Addiction. The EMCDDA currently has representative focal points in 30 European countries which are required to provide national information on an annual basis. As collaboration across these countries is already established under the EMCDDA, an addition of this type of project could be feasible.

Secondly, it would be beneficial to repeat the prospective cohort study on a larger scale in order to address the power issue and potential biases that were introduced. This would involve a larger sample size from more than one specialist treatment setting. An additional researcher would also be required in order to approach potential participants before they dropped out of treatment as experienced in the data collection for this thesis. A further approach to address the issues experienced would be to identify potential participants on the waiting list to enter treatment. A follow-up period at 12-months in addition to six-months would also be beneficial to facilitate comparability with other studies. This was not possible due to the time constraints of the thesis. Prospective studies focusing on treatment factors and treatment process factors rather than basic demographics have also been called for (129). Attitudes to treatment and treatment satisfaction would be useful to include in studies focusing on treatment factors due to the previous studies that have indicated their influence on retention (106).

A further bias of the study presented in chapter three is the potential impact of the COVID-19 contingency plan for service users during the follow-up period. The implementation of outreach support and home delivery of OAT with increased THDs and reduced drug screening was recommended during COVID-19 (110, 236). The impact of these changes to services should be studied prospectively in order to investigate what influence (if any) these changes are having on treatment retention. A need for research to evaluate changes to services due to COVID-19 have already been urgently called for (236). There is also a need to monitor the retention rates of the 650 new OAT service users in Ireland who were rapidly inducted between March and June 2020. This should be done in order to investigate if those who were rapidly initiated are retained over time. There is also a need to gain the perspectives of service users in Ireland in relation to the impact of the COVID-19 contingency plan on their ability to stay in treatment.

Although risk factors for dropout were discussed with service users in chapter four, these participants were in treatment at the time which poses the risk of survival bias. Some of these participants had experienced dropout in the past but did not divulge if this dropout was voluntary or involuntary. However this cohort is still important as previous dropouts have been shown to be associated with future dropout (109). It is often unclear when a service user's dropout is voluntary or involuntary, and while the outcome may be the same the risk factors are likely to be very different. This was also noted as a limitation of the systematic review presented in chapter two. It would be beneficial to conduct a further qualitative study with individuals who have dropped out of treatment and not yet returned to explore whether these dropouts were voluntary or involuntary. This would also offer insight into why individuals currently not in treatment are uninterested or reluctant to engage with services. Finally, HSE clinical guidelines stipulate that it is good practice to involve service users in the design, planning, development, and evaluation of services (70). There is a need to consider how to facilitate more active and meaningful engagement of service users in both conducting research and service evaluation.

5.6 Considering the impact of the thesis

Four core categories of the impact of health research were identified by Kuruvilla et al. when they developed the Research Impact Framework (289). These categories are: research-related, policy, health and societal impacts (289) and will structure the following section of discussion.

5.6.1 Research-related impact

This thesis has contributed evidence to research investigating factors associated with retention in OAT. The synthesis and findings of the systematic review in chapter two established the heterogeneity evident in observational studies investigating factors associated with retention. This heterogeneity was as a result of differences in the definition of retention between studies and also the methods in which exposure variables were investigated (clinical data versus self-reported and a variety of assessment tools used). This systematic review informed a six year cohort study investigating factors associated with early and later dropout from MMT in specialist addiction clinics (109). This cohort study addressed the limitation identified in the systematic review in that most studies do not take account of the fact that individuals transition in and out of treatment (accounting for re-occurring events and time dependent covariates). Finally, this review recommended the need for consensus in a definition of retention, specifically in relation what amount of time a person should be off treatment before being considered dropped out.

The cohort study presented in chapter three implemented a potential solution to this heterogeneity by using the MAP and clinical data to collect and report data on six of eight categories highlighted as important in future studies investigating OAT. (98). Finally, the qualitative study offered insight into the barriers and facilitators of retention in OAT from the perspective of service users and offered some insight into the early stages of implementing the COVID-19 contingency plan for people who use drugs. To date, this thesis has produced the publication of the systematic review in a peer reviewed journal and has been cited in five studies related to OAT (109, 300-303).

Finally, this thesis strengthened the collaborative relationship between the School of Pharmacy and Bimolecular Sciences in Royal College of Surgeons in Ireland (RCSI) and the NDTC. The NDTC was a collaborator in both the cohort and qualitative study from the early stages of ethical application right through to the end of data collection. Three staff members of the NDTC were in regular contact with AOC in order to facilitate the research process (general manager, consultant psychiatrist and clinical psychologist). The successful completion of this thesis and the positive professional relationships developed may facilitate further studies by RCSI that require access to the service users of the NDTC.

5.6.2 Impact on policy

The results of this thesis may be beneficial to policymakers on a national level. The review of the opioid protocol and subsequent recommendations led to the introduction of clinical guidelines for opioid agonist treatment in Ireland in 2016 (93). The results from this thesis substantiates the importance of communication and collaboration in the therapeutic relationship between service user and provider in order to encourage retention in treatment (70). These guidelines outline clinical markers of stability in OAT that determine appropriateness for take-home doses (70). However, there is no indication in the guidelines as to what are the risk and protective factors for retention.

The importance of retention in treatment and factors associated with retention should be explicitly outlined in these guidelines in order to inform risk stratification in OAT. However, as previously stated the evidence regarding factors associated with dropout is not clear due to substantial heterogeneity in study methods, outcome measurement tools used and also the timeframes used to define treatment dropout. A consensus of timeframes and measurement tools used to assess factors associated with dropout is needed before risk stratification can be included in policy documents to identify service users who require more intensive engagement in treatment (204).

The Reducing Harm, Supporting Recovery strategy (88) also needs to fulfil its aim to examine potential mechanisms to increase access to OATs such as the expansion of primary care prescribing and the provision of OATs in community-based settings. Service users articulated that they were motivated to progress in their treatment and felt frustrated as they perceived that their goals for treatment were not being acknowledged. Service users also highlighted that negative interactions with other service users in the NDTC and time spent travelling to the clinic were barriers to retention. Effort should be made to increase access to primary care and transition to primary care for those service users who are suitable as was recommended in 2010 review of the methadone treatment protocol (93). This may help in alleviate these barriers and improve retention.

5.6.3 Health service impact

As previously stated, the inclusion of the importance of retention, and associated factors, in the clinical guidelines for OAT in Ireland would inform risk stratification, contribute to evidence-based clinical practice and strengthen the current quality of care. However in order to do this,

there needs to be a clear evidence base for the risk factors associated with dropout. The systematic review presented in chapter two highlighted significant heterogeneity in terms of the timeframes off treatment before being considered dropped out of treatment and also how risk factors were assessed (e.g. lifetime IV drug use versus IV drug use in the past 30 days).

In order to address this heterogeneity, conducting a Delphi consensus (299) would facilitate the development of an international agreement on the definition of retention in terms of duration of time without treatment before being categorised as a dropout in OAT in specialist treatment settings. This would also need to be conducted in order to agree upon which standardized outcome measurement tools to use when investigating factors associated with dropout. A standardization of this could allow for the risk stratification of service users requiring more intensive engagement at the treatment initiation, stabilization stages and also those who may experience repeated episodes (204).

A standardised assessment tool such as the MAP that is validated and reliable and already used in clinical settings should be used across all settings in OAT provision to facilitate service evaluation and further research. This would ensure that at least six of Wiessing et al.'s eight recommended categories (98) could be monitored. The COVID-19 contingency plan for people who use drugs (110) has demonstrated potential strategies to address some of the barriers to retention highlighted by service users in chapter four. The increase in provision of THDs and community dispensing may have alleviated travelling times to the NDTC and reduced negative interactions with other service users. The access to better accommodation for service users experiencing homelessness may also have addressed health issues which were also identified as a barrier. Initial reports from the implementation of the COVID-19 management plan have been successful (112) and have offered some insights as to how service users would self-manage an increase in THDs and community dispensing. However research in this area is required in order to investigate the long-term effects of this contingency plan on retention in treatment.

5.6.4 Societal impact

The findings and recommendations of this thesis may affect the attitudes of the general public towards those on OAT. An increase in service provision through primary care and community dispensing would uphold the principle that individuals with an OUD have the same entitlements as others provided services by the HSE as stated in the clinical guidelines for the provision of

OAT (70). As OAT is long-term and similar to other long-term treatments for chronic illnesses (45), progression to treatment in a community setting would reduce the stigma experienced by service users from the general public and subsequent negative attitudes towards OAT. The research in this thesis focused explicitly on the needs of disadvantaged and vulnerable populations. This is a potential opportunity to improve the health equity and health status of this population by implementing additional interventions to those identified as being at risk of dropping out of treatment (younger service users, those with a criminal history, IV drug users).

5.7 Conclusion

Overall, this thesis adds to the body of evidence investigating factors associated with retention in OAT among adults. Principal findings from this thesis highlight that there is heterogeneity in how retention is defined and measured, which needs to be addressed. There was a high retention rate observed amongst an aging population with an increase in IV drug use, benzodiazepine use, heroin use and cocaine use in comparison to other studies. However, this study may have been influenced by survival and ascertainment bias. Finally, facilitators and barriers to retention were identified by service users, with some consensus between service users and providers regrading opportunities for improvement in OAT.

Future research is needed to develop a consensus on retention and outcome measurement in OAT. The cohort study in chapter three should be conducted on a larger scale to remove potential bias and ascertain if retention rates are as high as reported. A further prospective cohort study is also required to investigate the impact of the COVID-19 contingency plan on retention in OAT. Finally, future research should engage with individuals who have dropped out of treatment and not returned in order to explore their hesitancy to return to treatment.

References

1. National Institute on Drug Abuse. Opioids: National Institute on Drug Abuse 2020 [
2. World Health Organization. Model List of Essential Medicines. Geneva: World Health Organisation; 2019.
3. Degenhardt L, Grebely J, Stone J, Hickman M, Vickerman P, Marshall BDL, et al. Global patterns of opioid use and dependence: Harms to populations, interventions, and future action. The Lancet. 2019;394(10208):1560-79.
4. Kosten TR, George TP. The neurobiology of opioid dependence: implications for treatment. Science & practice perspectives. 2002;1(1):13-20.
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). 5th ed. America: American Psychiatric Association, ; 2013.
6. Berrettini W. A brief review of the genetics and pharmacogenetics of opioid use disorders. Dialogues in clinical neuroscience. 2017;19(3):229-36.
7. Kendler KS, Jacobson KC, Prescott CA, Neale MC. Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. The American Journal of Psychiatry. 2003;160(4):687-96.
8. Gelernter J, Kranzler HR, Sherva R, Koesterer R, Almasy L, Zhao H, et al. Genome-wide association study of opioid dependence: Multiple associations mapped to calcium and potassium pathways. Biological Psychiatry. 2014;76(1):66-74.
9. Kaye AD, Jones MR, Kaye AM, Ripoll JG, Galan V, Beakley BD, et al. Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse: Part 1. Pain Physician. 2017;20:S93-S109.
10. Minozzi S, Amato L, Davoli M. Development of dependence following treatment with opioid analgesics for pain relief: a systematic review. Addiction (Abingdon, England). 2013;108(4):688-98.
11. Blanco C, Wall MM, Okuda M, Wang S, Iza M, Olfson M. Pain as a predictor of opioid use disorder in a nationally representative sample. The American Journal of Psychiatry. 2016;173(12):1189-95.
12. Klimas J, Gorfinkel L, Fairbairn N, Amato L, Ahamad K, Nolan S, et al. Strategies to Identify Patient Risks of Prescription Opioid Addiction When Initiating Opioids for Pain: A Systematic Review. JAMA Network Open. 2019:e193365-e.
13. Cragg A, Hau JP, Woo SA, Kitchen SA, Liu C, Doyle-Waters MM, et al. Risk Factors for Misuse of Prescribed Opioids: A Systematic Review and Meta-Analysis. Annals of Emergency Medicine. 2019;74(5):634-46.

14. Papaleontiou M, Henderson CR, Jr., Turner BJ, Moore AA, Olkhovskaya Y, Amanfo L, et al. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: a systematic review and meta-analysis. Journal of the American Geriatrics Society. 2010;58(7):1353-69.
15. Conroy E, Degenhardt L, Mattick RP, Nelson EC. Child maltreatment as a risk factor for opioid dependence: Comparison of family characteristics and type and severity of child maltreatment with a matched control group. Child Abuse & Neglect. 2009;33(6):343-52.
16. NIDA issues research-based guide to youth prevention. John Wiley & Sons, Inc.; 1997. p. 4.
17. United Nations Office on Drugs and Crime. World Drug Report. Drug Use and Health Consequences: United Nations,; 2020.
18. Health Research Board. Ireland Country Drug Report 2019. Dublin 2019.
19. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2019 National Survey on Drug Use and Health. Rockville, : Center for Behavioral Health Statistics and Quality Substance Abuse and Mental Health Services Administration, ; 2019.
20. Australian Institute of Health and Welfare. Opioid harm in Australia and comparisons between Australia and Canada. Canberra: Australian Institute of Health and Welfare,; 2018
21. Australian Institute of Health and Welfare. Alcohol, tobacco & other drugs in Australia Australia: Australian Institute of Health and Welfare, ; 2020 [Available from: https://www.aihw.gov.au/reports/alcohol/alcohol-tobacco-other-drugs-australia/contents/introduction.
22. Australian Institute of Health and Welfare. Non-medical use of pharmaceuticals Trends, harms, and treatment 2006–07 to 2015–16. In: Welfare AIoHa, editor. Canberra: Australian Institute of Health and Welfare; 2017.
23. European Monintoring Centre for Drugs and Drug Addiction. United Kingdom Country Drug Report 2019. Lisbon: European Monitoring Centre for Drugs and Drug Addiction, ; 2020
24. Hay G, Jaddoa, A., Oyston, J., Webster, J., Van Hout, M., Rael dos Santos, A., . Estimating the prevalence of problematic opiate use in Ireland using indirect statistical methods. Dublin National Advisory Committee on Drugs and Alcohol. ; 2017.
25. European Monintoring Centre for Drugs and Drug Addiction. European Drug Report 2019: Trends and Developments. Lisbon; 2019.
26. Carew AM, Comiskey C. Rising incidence of ageing opioid users within the EU wide treatment demand indicator; The Irish opioid epidemic from 1996 to 2014. Drug and Alcohol Dependence. 2018;192:329-37.
27. European Monintoring Centre for Drugs and Drug Addiction. Health and Social Responses to Drug Problems: A European Guide. In: European Monintoring Centre for Drugs and Drug Addiction, editor. Lisbon: European Monitoring Centre for Drugs and Drug Addiction,; 2017.
28. European Monintoring Centre for Drugs and Drug Addiction. Treatment and Care for Older Drug Users. Lisbon: European Monitoring Centre for Drugs and Drug Addiction, ; 2010.
29. Carew AM, Comiskey C. Treatment for opioid use and outcomes in older adults: A systematic literature review. Drug and Alcohol Dependence. 2018;182:48-57.
30. Cousins G, Boland F, Courtney B, Barry J, Lyons S, Fahey T. Risk of mortality on and off methadone substitution treatment in primary care: a national cohort study. Addiction. 2016;111(1):73-82.
31. Durand L, O'Driscoll D, Boland F, Keenan E, Ryan BK, Barry J, et al. Do interruptions to the continuity of methadone maintenance treatment in specialist addiction settings increase the risk of drug-related poisoning deaths? A retrospective cohort study. Addiction (Abingdon, England). 2020.
32. Gladden RM, O'Donnell J, Mattson CL, Seth P. Changes in Opioid-Involved Overdose Deaths by Opioid Type and Presence of Benzodiazepines, Cocaine, and Methamphetamine - 25 States, July-December 2017 to January-June 2018. MMWR Morbidity and mortality weekly report. 2019;68(34):737-44.
33. Liu S, Scholl L, Hoots B, Seth P. Nonfatal Drug and Polydrug Overdoses Treated in Emergency Departments - 29 States, 2018-2019. MMWR: Morbidity & Mortality Weekly Report. 2020;69(34):1149-55.

34. Penington Institute. Australia's Annual Overdose Report 2019. Melbourne: Penington Institute,; 2019.
35. Drewes AM, Jensen RD, Nielsen LM, Droney J, Christrup LL, Arendt-Nielsen L, et al. Differences between opioids: pharmacological, experimental, clinical and economical perspectives. British journal of clinical pharmacology. 2013;75(1):60-78.
36. EMCDDA. European Drug Report 2020: Trends and Developments Lisbon: EMCDDA; 2020 [Available from: https://www.emcdda.europa.eu/publications/edr/trends-developments/2020_en.
37. Office for National Statistics. Deaths related to drug poisoning in England and Wales: 2019 registrations. Office for National Statistics, ; 2020
38. National Records of Scotland. Drug-related deaths in Scotland in 2018. National Records of Scotland, ; 2019
39. O' Neill D, Carew AM., Lyons, S., . National Drug Treatment Reporting System 2013 – 2019 Drug Data. Dublin 2020
40. Health Research Board. National Drug-Related Deaths Index 2008 to 2017 data. Dublin 2019.
41. Glynn RW, Lynn E, Griffin E, Fitzgerald M, Ward M. Self-Harm, Methadone Use and Drug-Related Deaths amongst Those Registered As Being of No Fixed Abode or Homeless in Ireland. Irish Medical Journal. 2017;110(9):93-101.
42. Holohan TW. Health and homelessness in Dublin. Irish medical journal. 2000;93(2):41-3.
43. O'Carroll A, O'Reilly F. Health of the homeless in Dublin: has anything changed in the context of Ireland's economic boom? European journal of public health. 2008;18(5):448-53.
44. Keogh C, O'Brien KK, Hoban A, O'Carroll A, Fahey T. Health and use of health services of people who are homeless and at risk of homelessness who receive free primary health care in Dublin. BMC health services research. 2015;15:58.
45. World Health Organization. Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence. 2009.
46. Disley E, Mulcahy AW, Pardal M, Rubin J, Ruggeri K. Development of a Framework to Estimate the Cost of Opioid Dependence. Rand health quarterly. 2014;3(4):2.
47. Ruetsch C. Empirical view of opioid dependence. Journal of managed care pharmacy : JMCP. 2010;16(1 Suppl B):S9-S13.
48. Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ (Clinical Research Ed). 2017;357:j1550-j.
49. Degenhardt L, Bucello C, Mathers B, Briegleb C, Ali H, Hickman M, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction. 2011;106(1):32-51.
50. Bech AB, Clausen T, Waal H, Šaltytė Benth J, Skeie I. Mortality and causes of death among patients with opioid use disorder receiving opioid agonist treatment: a national register study. BMC health services research. 2019;19(1):440.
51. Pearce LA, Min JE, Piske M, Zhou H, Homayra F, Slaunwhite A, et al. Opioid agonist treatment and risk of mortality during opioid overdose public health emergency: Population based retrospective cohort study. BMJ: British Medical Journal. 2020;368.
52. Kimber J, Larney S, Hickman M, Randall D, Degenhardt L. Mortality risk of opioid substitution therapy with methadone versus buprenorphine: a retrospective cohort study. Lancet Psychiatry. 2015;2(10):901-8.
53. Hickman M, Steer C, Tilling K, Lim AG, Marsden J, Millar T, et al. The impact of buprenorphine and methadone on mortality: a primary care cohort study in the United Kingdom. Addiction. 2018;113(8):1461-76.
54. European Monintoring Centre for Drugs and Drug Addiction. European Drug Report 2020: Trends and Developments

Lisbon: European Monintoring Centre for Drugs and Drug Addiction,

; 2020.

55. Health Research Board. National Drug-Related Deaths Index 2008 – 2017 Data Dublin Health Research Board, ; 2017.
56. OECD. Addressing Problematic Opioid Use in OECD Countries2019.
57. National Records of Scotland. Drug-related deaths in Scotland Scotland National Records of Scotland; 2019
58. National Records of Scotland. Drug-related deaths in Scotland in 2011. Scotland: National Records of Scotland, ; 2011
59. European Monintoring Centre for Drugs and Drug Addiction. Health and social responses to drug problems: a European guide. Lisbon: European Monitoring Centre for Drugs and Drug Addiction, ; 2017.
60. World Health Organization. Harm Reduction Denmark: World Health Organization, ; 2020 [Available from: https://www.euro.who.int/en/health-topics/communicable-diseases/hivaids/policy/policy-guidance-for-areas-of-intervention/harm-reduction#:~:text=Harm%20reduction%20is%20a%20set,PWIDs)%20and%20their%20sexual%20partners.
61. Wodak A, McLeod L. The role of harm reduction in controlling HIV among injecting drug users. AIDS. 2008;22(Suppl2):S81-S92.
62. National Advisory Committee on Drugs. A Review of Harm Reduction Approaches in Ireland and Evidence from the International Literature. Dublin National Advisory Committee on Drugs, ; 2003.
63. Des Jarlais DC. Harm reduction in the USA: The research perspective and an archive to David Purchase. Harm Reduction Journal. 2017;14.
64. Riley D. The Harm Reduction Model: Pragmatic Approaches to Drug Use from the Area Between Intolerance and Neglect. Ottawa: Canadian Centre on Substance Abuse; 1994.
65. Kerr T, Mitra S, Kennedy MC, McNeil R. Supervised injection facilities in Canada: past, present, and future. Harm reduction journal. 2017;14(1):28.
66. Wellbourne-Wood D. Harm reduction in Australia: Some problems putting policy into practice. International Journal of Drug Policy. 1999;10(5):403-13.
67. National Advisory Committee on Drugs. Needle Exchange Provisionin Ireland: The Context, Current Levels of Service Provision and Recommendations. Dublin National Advisory Committee on Drugs, ; 2008.
68. Kalk NJ, Robertson JR, Kidd B, Day E, Kelleher MJ, Gilvarry E, et al. Treatment and Intervention for Opiate Dependence in the United Kingdom: Lessons from Triumph and Failure. European Journal on Criminal Policy and Research. 2018;24(2):183-200.
69. Dale-Perera A. Recovery, reintegration, abstinence, harm reduction: the role of different goals within drug treatment in the European context. In: European Monintoring Centre for Drugs and Drug Addiction, editor. Lisbon: European Monitoring Centre for Drugs and Drug Addiction, ; 2017
70. Health Service Executive. Clinical guidelines for opioid substitution treatment. In: Department of Health, editor. Dublin Health Service Executive, ; 2016.
71. Stotts AL, Dodrill CL, Kosten TR. Opioid dependence treatment: options in pharmacotherapy. Expert Opin Pharmacother. 2009;10(11):1727-40.
72. Jordan CJ, Cao J, Newman AH, Xi Z-X. Progress in agonist therapy for substance use disorders: Lessons learned from methadone and buprenorphine. Neuropharmacology. 2019;158.
73. National Institute on Drug Abuse. Medications to Treat Opioid Use Disorder Research Report. Baltimore; 2018.
74. Berg KA, Clarke WP. Making sense of pharmacology: Inverse agonism and functional selectivity. International Journal of Neuropsychopharmacology. 2018;21(10):962-77.
75. Whelan PJ, Remski K. Buprenorphine vs methadone treatment: A review of evidence in both developed and developing worlds. Journal of neurosciences in rural practice. 2012;3(1):45-50.
76. Johnson B, Richert T. Diversion of methadone and buprenorphine by patients in opioid substitution treatment in Sweden: prevalence estimates and risk factors. The International journal on drug policy. 2015;26(2):183-90.

77. Winstock AR, Lea T, Sheridan J. Prevalence of diversion and injection of methadone and buprenorphine among clients receiving opioid treatment at community pharmacies in New South Wales, Australia. International Journal of Drug Policy. 2008;19(6):450-8.
78. Launonen E, Alho H, Kotovirta E, Wallace I, Simojoki K. Diversion of opioid maintenance treatment medications and predictors for diversion among Finnish maintenance treatment patients. International Journal of Drug Policy. 2015;26(9):875-82.
79. Joint Formulary Committee. British National Formulary. London British Medical Association and Royal Pharmaceutical Society of Great Britain; 2020.
80. Larney S, Peacock A, Leung J, Colledge S, Hickman M, Vickerman P, et al. Global, regional, and country-level coverage of interventions to prevent and manage HIV and hepatitis C among people who inject drugs: a systematic review. The Lancet Global Health. 2017;5(12):e1208-e20.
81. Nosyk B, Douglas Anglin M, Brissette S, Kerr T, Marsh DC, Schackman BR, et al. A call for evidence-based medical treatment of opioid dependence in the united states and Canada. Health Affairs. 2013;32(8):1462-9.
82. Substance Abuse and Mental Health Services Administration. National Survey of Substance Abuse Treatment Services (N-SSATS): 2019 Data on Substance Abuse Treatment Facilities. Rockville, Maryland Substance Abuse and Mental Health Services Administration, ; 2020.
83. Davis CS, Samuels EA. Continuing increased access to buprenorphine in the United States via telemedicine after COVID-19. The International journal on drug policy. 2020:102905.
84. Delargy I, Crowley D, Hout MC. Twenty years of the methadone treatment protocol in Ireland: Reflections on the role of general practice. Harm Reduction Journal. 2019;16.
85. Butler S. Drug problems and drug policies in Ireland: A quarter of a century reviewed. Administration 1991;39(3):210 - 35.
86. Misuse of Drugs Act, (1984).
87. Department of Health. Report of the Expert Group on the Establishment of a PROTOCOL for the PRESCRIBING OF METHADONE Dublin Department of Health, ; 1993.
88. Deptarment of Health. Reducing Harm, Supporting Recovery: A health-led response to drug and alcohol use in Ireland 2017-2025. In: Deptarment of Health, editor. Dublin 2017.
89. Misuse of Drugs (Supervision of Prescription and Supply of Methadone and Medicinal Products containing Buprenorphine authorised for Opioid Substitution Treatment) Regulations 2017, 522/2017 (2017).
90. Long J. Recording drug treatment in Ireland. Drugnet Ireland. 2005 (15):11-2.
91. Department of Health and Children. Review of the METHADONE TREATMENT Protocol. Dublin Deptarment of Health and Children, ; 1998.
92. Misuse of Drugs (Supervision of Prescription and Supply of Methadone) Regulations, Stat. 225/1998 (1998).
93. Michael Farrell JB. The Introduction of the Opioid Treatment Protocol. In: Health Do, editor. Dublin Health Services Executive 2010.
94. Health Research Board. Focal Point Ireland: national report for 2019 - treatment. . Dublin: Health Research Board, ; 2020.
95. National Clinical Effectiveness Committee. NCEC Clinical Guidelines in Development. In: Department of Health, editor. Dublin 2020
96. European Monintoring Centre for Drugs and Drug Addiction. Guidelines for the evaluation of treatment in the fi eld of problem drug use: a manual for researchers and professionals Lisbon: European Monitoring Centre for Drugs and Drug Addiction, ; 2007.
97. Marsden J, Ogbourne A, Farrell CM, Rush B. International guidelines for the evaluation of treatment services and systems psychoactive substance use disorder. In: Organization WH, editor. Geneva: World Health Organization; 2000.
98. Wiessing Lucas MF, Shane Darke, Simon Roland, Paul Griffiths,. Large variation in measures used to assess outcomes of opioid dependence treatment: A systematic review of longitudinal observational studies. Drug And Alcohol Review. 2018;37 Suppl 1:S323-S38.
99. Marsden J, Gossop M , Stewart D, Best D, Farrell M, J S. The Maudsley Addiction Profile: A brief instrument for treatment outcome research – development and user manual London; 1998.

100. Deady M. A Review of Screening, Assessment and Outcome Measures for Drug and Alcohol Settings. New South Wales: NSW Health Department, ; 2009
101. Marsden J, Nizzoli U, Corbelli C, Margaron H, Torres M, Prada De Castro I, et al. New European instruments for treatment outcome research: reliability of the maudsley addiction profile and treatment perceptions questionnaire in Italy, Spain and Portugal. European addiction research. 2000;6(3):115-22.
102. Marsden J, Farrell M, Bradbury C, Dale-Perera A, Eastwood B, Roxburgh M, et al. Development of the Treatment Outcomes Profile. Addiction. 2008;103(9):1450-60.
103. Mullen L, Barry J, Long J, Keenan E, Mulholland D, Grogan L, et al. A national study of the retention of Irish opiate users in methadone substitution treatment. The American Journal Of Drug And Alcohol Abuse. 2012;38(6):551-8.
104. Ward J, Hall W, Mattick RP. Role of maintenance treatment in opioid dependence. Lancet (London, England). 1999;353(9148):221-6.
105. Margaret Curtin, Lucy Dillon, Brian Galvin, Ciara Guiney, Suzi Lyons, Millar S. Focal Point Ireland: national report for 2016 - Drug policy Ireland. Dublin Health Research Board; 2016.
106. O'Connor AM, Cousins G, Durand L, Barry J, Boland F. Retention of patients in opioid substitution treatment: A systematic review. PloS one. 2020;15(5):e0232086.
107. Cousins G, Boland F, Barry J, Lyons S, Keenan E, O'Driscoll D, et al. J-shaped relationship between supervised methadone consumption and retention in methadone maintenance treatment (MMT) in primary care: National cohort study. Drug & Alcohol Dependence. 2017;173:126-31.
108. Darker CD, Ho J, Kelly G, Whiston L, Barry J. Demographic and clinical factors predicting retention in methadone maintenance: results from an Irish cohort. Irish Journal Of Medical Science. 2016;185(2):433-41.
109. Durand L, Boland F, O'Driscoll D, Bennett K, Barry J, Keenan E, et al. Factors associated with early and later dropout from methadone maintenance treatment in specialist addiction clinics: a six-year cohort study using proportional hazards frailty models for recurrent treatment episodes. Drug and Alcohol Dependence. 2020:108466.
110. Office of Social Inclusion. Guidance on Contingency Planning for People who use Drugs and COVID-19 In: Inclusion OfS, editor. Dublin Health Service Executive 2020.
111. Crowley D, Delargy I. A national model of remote care for assessing and providing opioid agonist treatment during the COVID-19 pandemic: a report. Harm reduction journal. 2020;17(1):49.
112. O Carroll A, Duffin, T., Collins, J. . Saving Lives in the time of COVID-19 Case Study of Harm Reduction, Homelessness and Drug Use in Dublin, Ireland. London: The London School of Economics and Political Science 2020.
113. European Monintoring Centre for Drugs and Drug Addiction. EMCDDA update on the implications of COVID-19 for people who use drugs and drug service providers. Lisbon: European Monitoring Centre for Drugs and Drug Addiction 2020.
114. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. The lancet Psychiatry. 2018;5(12):987-1012.
115. Bell J, Strang J. Medication Treatment of Opioid Use Disorder. Biological psychiatry. 2020;87(1):82-8.
116. Drew L. Opioids by the Numbers Nature. 2020.
117. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. The Cochrane database of systematic reviews. 2009(3):CD002209.
118. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014(2):Cd002207.
119. Lawrinson P, Ali R, Buavirat A, Chiamwongpaet S, Dvoryak S, Habrat B, et al. Key findings from the WHO collaborative study on substitution therapy for opioid dependence and HIV/AIDS. Addiction. 2008;103(9):1484-92.

120. Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: Risk factors and lives saved. Drug and Alcohol Dependence. 2009;105(1-2):9-15.
121. Cousins G, Teljeur C, Motterlini N, McCowan C, Dimitrov BD, Fahey T. Risk of drug-related mortality during periods of transition in methadone maintenance treatment: a cohort study. J Subst Abuse Treat. 2011;41(3):252-60.
122. Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: Prospective observational study in UK General Practice Research Database. BMJ: British Medical Journal. 2010;341(7779):1-8.
123. Evans E, Li L, Min J, Huang D, Urada D, Liu L, et al. Mortality among individuals accessing pharmacological treatment for opioid dependence in California, 2006-10. Addiction. 2015;110(6):996-1005.
124. Kress HG. Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. European Journal of Pain. 2009;13(3):219-30.
125. Timko C, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: A systematic review. Journal Of Addictive Diseases. 2016;35(1):22-35.
126. Amato L, Davoli M, Perucci CA, Ferri M, Faggiano F, Mattick RP. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: Available evidence to inform clinical practice and research. Journal of Substance Abuse Treatment. 2005;28(4):321-9.
127. Sung S, Conry JM. Role of buprenorphine in the management of heroin addiction. The Annals Of Pharmacotherapy. 2006;40(3):501-5.
128. Rahimi-Movaghar A, Amin-Esmaeili M, Hefazi M, Yousefi-Nooraie R. Pharmacological therapies for maintenance treatments of opium dependence. The Cochrane Database Of Systematic Reviews. 2013(1):CD007775.
129. Brorson HH, Arnevik EA, Rand-Hendriksen K, Duckert F. Drop-out from addiction treatment: A systematic review of risk factors. Clinical Psychology Review. 2013;33(8):1010-24.
130. Zhou KN, Zhuang GH. Retention in methadone maintenance treatment in mainland China, 2004-2012: A literature review. Addictive Behaviors. 2014;39(1):22-9.
131. Bawor M, Dennis BB, Bhalerao A, Plater C, Worster A, Varenbut M, et al. Sex differences in outcomes of methadone maintenance treatment for opioid use disorder: a systematic review and meta-analysis. CMAJ Open. 2015;3(3):E344-E51.
132. Zhang L, Chow EPF, Zhuang X, Liang Y, Wang Y, Tang C, et al. Methadone maintenance treatment participant retention and behavioural effectiveness in China: a systematic review and meta-analysis. Plos One. 2013;8(7):e68906-e.
133. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. BMJ. 2009;339.
134. Nielsen S, Larance B, Degenhardt L, Gowing L, Kehler C, Lintzeris N. Opioid agonist treatment for pharmaceutical opioid dependent people. Cochrane Database Syst Rev. 2016(5):Cd011117.
135. Popay J, Roberts H, Sowden AJ, Petticrew M, Arai L, Rodgers M, et al. Guidance on the conduct of narrative synthesis in systematic Reviews. A Product from the ESRC Methods Programme. Version 1. Lancaster University: Lancaster uinversity 2006.
136. Chawarski MC, Zhou W, Schottenfeld RS. Behavioral drug and HIV risk reduction counseling (BDRC) in MMT programs in Wuhan, China: a pilot randomized clinical trial. Drug Alcohol Depend. 2011;115(3):237-9.
137. Jaffray M, Matheson C, Bond CM, Lee AJ, McLernon DJ, Johnstone A, et al. Does training in motivational interviewing for community pharmacists improve outcomes for methadone patients? A cluster randomised controlled trial. Int J Pharm Pract. 2014;22(1):4-12.
138. Marsch LA, Guarino H, Acosta M, Aponte-Melendez Y, Cleland C, Grabinski M, et al. Web-based behavioral treatment for substance use disorders as a partial replacement of standard methadone maintenance treatment. Journal of Substance Abuse Treatment. 2014;46(1):43-51.

139. Schwartz RP, Kelly SM, O'Grady KE, Gandhi D, Jaffe JH. Randomized trial of standard methadone treatment compared to initiating methadone without counseling: 12-month findings. Addiction. 2012;107(5):943-52.
140. Abramsohn Y, Peles E, Potik D, Schreiber S, Adelson M. Sense of coherence as a stable predictor for methadone maintenance treatment (MMT) outcome. J Psychoactive Drugs. 2009;41(3):249-53.
141. Adelson M, Wilson HW, Celeste VY, Linzy S, Kreek MJ, Peles E. Methadone maintenance treatment experience in Macao--prospective follow-up for initial 4.5 years. J Psychoactive Drugs. 2013;45(4):313-21.
142. Amiri S, Hirchak K, Lutz R, McDonell MG, McPherson SM, Roll JM, et al. Three-year retention in methadone opioid agonist treatment: A survival analysis of clients by dose, area deprivation, and availability of alcohol and cannabis outlets. Drug Alcohol Depend. 2018;193:63-8.
143. Astals M, Diaz L, Domingo-Salvany A, Martin-Santos R, Bulbena A, Torrens M. Impact of co-occurring psychiatric disorders on retention in a methadone maintenance program: an 18-month follow-up study. Int J Environ Res Public Health. 2009;6(11):2822-32.
144. Banta-Green CJ, Maynard C, Koepsell TD, Wells EA, Donovan DM. Retention in methadone maintenance drug treatment for prescription-type opioid primary users compared to heroin users. Addiction. 2009;104(5):775-83.
145. Bhatraju EPG, E.: Tofighi, B.: McNeely, J.: DiRocco, D.: Flannery, M.: Garment, A.: Goldfeld, K.: Gourevitch, M. N.: Lee, J. D. Public sector low threshold office-based buprenorphine treatment: outcomes at year 7. Addict Sci Clin Pract. 2017;12(1):7.
146. Bounes V, Palmaro A, Lapeyre-Mestre M, Roussin A. Long-term Consequences of Acute Pain for Patients under Methadone or Buprenorphine Maintenance Treatment. Pain Physician. 2013;16(6):E739-47.
147. Brands B, Blake J, Marsh DC, Sproule B, Jeyapalan R, Li S. The impact of benzodiazepine use on methadone maintenance treatment outcomes. J Addict Dis. 2008;27(3):37-48.
148. Bukten AS, S.: Waal, H.: Clausen, T. Factors associated with dropout among patients in opioid maintenance treatment (OMT) and predictors of re-entry. A national registry-based study. Addict Behav. 2014;39(10):1504-9.
149. Burns L, Randall D, Hall WD, Law M, Butler T, Bell J, et al. Opioid agonist pharmacotherapy in New South Wales from 1985 to 2006: patient characteristics and patterns and predictors of treatment retention. Addiction. 2009;104(8):1363-72.
150. Cao XW, Z.: Rou, K.: Li, L.: Lin, C.: Wang, C.: Luo, W.: Pang, L.: Yin, W.: Li, J. Retention and its predictors among methadone maintenance treatment clients in China: a six-year cohort study. Drug Alcohol Depend. 2014;145:87-93.
151. Cox JA, R.: Maurais, E.: Haley, N.: Small, C. Predictors of methadone program non-retention for opioid analgesic dependent patients. J Subst Abuse Treat. 2013;44(1):52-60.
152. Cunningham C, Roose R, Starrels JL, Giovanniello AG, Sohler N. Prior buprenorphine experience is associated with office-based buprenorphine treatment outcomes. Journal of General Internal Medicine. 2012;27:S288.
153. Davstad I, Stenbacka M, Leifman A, Beck O, Korkmaz S, Romelsjo A. Patterns of illicit drug use and retention in a methadone program: a longitudinal study. J Opioid Manag. 2007;3(1):27-34.
154. Dayal P, Balhara YPS. A naturalistic study of predictors of retention in treatment among emerging adults entering first buprenorphine maintenance treatment for opioid use disorders. J Subst Abuse Treat. 2017;80:1-5.
155. Deck D, Carlson MJ. Retention in publicly funded methadone maintenance treatment in two Western States. J Behav Health Serv Res. 2005;32(1):43-60.
156. Dumchev K, Dvoryak S, Chernova O, Morozova O, Altice FL. Retention in medication-assisted treatment programs in Ukraine-Identifying factors contributing to a continuing HIV epidemic. Int J Drug Policy. 2017;48:44-53.
157. Eibl JK, Gomes T, Martins D, Camacho X, Juurlink DN, Mamdani MM, et al. Evaluating the Effectiveness of First-Time Methadone Maintenance Therapy Across Northern, Rural, and Urban Regions of Ontario, Canada. J Addict Med. 2015;9(6):440-6.

158. Franklyn AME, J. K.: Gauthier, G.: Pellegrini, D.: Lightfoot, N. E.: Marsh, D. C. The impact of benzodiazepine use in patients enrolled in opioid agonist therapy in Northern and rural Ontario. Harm Reduct J. 2017;14(1):6.
159. Friedmann PD, Lemon SC, Stein MD. Transportation and retention in outpatient drug abuse treatment programs. J Subst Abuse Treat. 2001;21(2):97-103.
160. Gerra G, Saenz E, Busse A, Maremmani I, Ciccocioppo R, Zaimovic A, et al. Supervised daily consumption, contingent take-home incentive and non-contingent take-home in methadone maintenance. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35(2):483-9.
161. Gryczynski J, Mitchell SG, Jaffe JH, O'Grady KE, Olsen YK, Schwartz RP. Leaving buprenorphine treatment: patients' reasons for cessation of care. J Subst Abuse Treat. 2014;46(3):356-61.
162. Gu JX, Huifang: Lau, Joseph T. F.: Hao, Yuantao: Zhong, Ying: Fan, Lirui: Zhao, Yuteng: Hao, Chun: Ling, Wenhua. Misconceptions predict dropout and poor adherence prospectively among newly admitted first-time methadone maintenance treatment clients in Guangzhou, China. Addiction. 2012;107(9):1641-9.
163. Haddad MS, Zelenev A, Altice FL. Integrating buprenorphine maintenance therapy into federally qualified health centers: real-world substance abuse treatment outcomes. Drug Alcohol Depend. 2013;131(1-2):127-35.
164. Huissoud T, Rousson V, Dubois-Arber F. Methadone treatments in a Swiss region, 2001-2008: a registry-based analysis. BMC Psychiatry. 2012;12:238.
165. Johns B, Chau LB, Hanh KH, Manh PD, Do HM, Duong AT, et al. Association Between User Fees and Dropout from Methadone Maintenance Therapy: Results of a Cohort Study in Vietnam. Health Systems & Reform. 2018;4(2):101-13.
166. Kayman DJ, Goldstein MF, Deren S, Rosenblum A. Predicting treatment retention with a brief "Opinions About Methadone" scale. J Psychoactive Drugs. 2006;38(1):93-100.
167. Kelly SM, O'Grady KE, Mitchell SG, Brown BS, Schwartz RP. Predictors of methadone treatment retention from a multi-site study: a survival analysis. Drug Alcohol Depend. 2011;117(2-3):170-5.
168. Lambdin BH, Masao F, Chang O, Kaduri P, Mbwambo J, Magimba A, et al. Methadone treatment for HIV prevention-feasibility, retention, and predictors of attrition in Dar es Salaam, Tanzania: a retrospective cohort study. Clin Infect Dis. 2014;59(5):735-42.
169. Ledgerwood DM, Lister JJ, LaLiberte B, Lundahl LH, Greenwald MK. Injection opioid use as a predictor of treatment outcomes among methadone-maintained opioid-dependent patients. Addictive behaviors. 2019;90:191-5.
170. Lin H-C, Chen K-Y, Wang P-W, Yen C-F, Wu H-C, Yen C-N, et al. Predictors for dropping-out from methadone maintenance therapy programs among heroin users in southern Taiwan. Substance Use & Misuse. 2013;48(1-2):181-91.
171. Lin CKH, C. C.: Peng, C. Y.: Chao, E.: Lee, T. S. H. Factors associated with methadone treatment duration: A Cox regression analysis. PLoS One. 2015;10(4).
172. Liu D, Gu J, Xu HF, Hao C, Jiao MX, Zhang X, et al. Club drugs and alcohol abuse predicted dropout and poor adherence among methadone maintenance treatment patients in Guangzhou, China. Aids Care-Psychological and Socio-Medical Aspects of Aids/Hiv. 2017;29(4):458-63.
173. Manhapra A, Petrakis I, Rosenheck R. Three-year retention in buprenorphine treatment for opioid use disorder nationally in the Veterans Health Administration. Am J Addict. 2017;26(6):572-80.
174. Manhapra A, Agbese E, Leslie DL, Rosenheck RA. Three-Year Retention in Buprenorphine Treatment for Opioid Use Disorder Among Privately Insured Adults. Psychiatr Serv. 2018;69(7):768-76.
175. Meshberg-Cohen S, Black AC, DeViva JC, Petrakis IL, Rosen MI. Trauma treatment for veterans in buprenorphine maintenance treatment for opioid use disorder. Addictive Behaviors. 2019;89:29-34.
176. Monico LBM, S. G.: Gryczynski, J.: Schwartz, R. P.: O'Grady, K. E.: Olsen, Y. K.: Jaffe, J. H. Prior Experience with Non-Prescribed Buprenorphine: Role in Treatment Entry and Retention. J Subst Abuse Treat. 2015;57:57-62.
177. Montalvo C, Stankiewicz B, Brochier A, Henderson DC, Borba CPC. Long-Term Retention in an Outpatient Behavioral Health Clinic With Buprenorphine. American Journal on Addictions. 2019;28(5):339-46.

178. Nosyk B, MacNab YC, Sun H, Fischer B, Marsh DC, Schechter MT, et al. Proportional hazards frailty models for recurrent methadone maintenance treatment. Am J Epidemiol. 2009;170(6):783-92.
179. Peles EL, Shirley: Kreek, Mary Jeanne: Adelson, Miriam. One-year and cumulative retention as predictors of success in methadone maintenance treatment: A comparison of two clinics in the United States and Israel. J Addict Dis. 2008;27(4):11-25.
180. Peles E, Schreiber S, Sason A, Adelson M. Similarities and changes between 15- and 24-year survival and retention rates of patients in a large medical-affiliated methadone maintenance treatment (MMT) center. Drug Alcohol Depend. 2018;185:112-9.
181. Perreault M, Julien D, White ND, Rabouin D, Lauzon P, Milton D. Psychological predictors of retention in a low-threshold methadone maintenance treatment for opioid addicts: a 1-year follow-up study. Subst Use Misuse. 2015;50(1):24-31.
182. Perreault M, Rousseau M, Lauzon P, Mercier C, Tremblay I, Héroux M. Determinants of retention in a Canadian low-threshold Methadone Maintenance Program. Journal of Maintenance in the Addictions. 2005;3(2-4):37-51.
183. Proctor SLC, A. L.: Kopak, A. M.: Hoffmann, N. G.: Herschman, P. L.: Polukhina, N. Predictors of patient retention in methadone maintenance treatment. Psychol Addict Behav. 2015;29(4):906-17.
184. Ren JN, Zhen: Asche, Carl V.: Zhuang, Minghua: Kirkness, Carmen S.: Ye, Xiangyang: Fu, Jie: Pan, Qichao. Trends and predictors in methadone maintenance treatment dropout in Shanghai, China: 2005–2011. Curr Med Res Opin. 2013;29(7):731-8.
185. Ruadze ET, K. Retention in Georgia opioid substitution therapy program and associated factors. Harm Reduct J. 2016;13(1):35.
186. Saloner BD, M.: Caleb Alexander, G. Patterns of Buprenorphine-Naloxone Treatment for Opioid Use Disorder in a Multistate Population. Med Care. 2017;55(7):669-76.
187. Sarasvita RT, A.: Utomo, B.: Ali, R. Predictive factors for treatment retention in methadone programs in Indonesia. J Subst Abuse Treat. 2012;42(3):239-46.
188. Schuman-Olivier ZH, B. B.: Weiss, R. D.: Borodovsky, J.: Shaffer, H. J.: Albanese, M. J. Benzodiazepine use during buprenorphine treatment for opioid dependence: clinical and safety outcomes. Drug Alcohol Depend. 2013;132(3):580-6.
189. Shakira RHW, Sarimah A, Norsa'adah B. Factor Predictive of 1-Year Retention on Methadone Maintenance Therapy Program: A Survival Analysis Study. Addictive Disorders & Their Treatment. 2017;16(2):64-9.
190. Shcherbakova N, Tereso G, Spain J, Roose RJ. Treatment Persistence Among Insured Patients Newly Starting Buprenorphine/Naloxone for Opioid Use Disorder. Ann Pharmacother. 2018;52(5):405-14.
191. Socías ME, Wood E, Lake S, Nolan S, Fairbairn N, Hayashi K, et al. High-intensity cannabis use is associated with retention in opioid agonist treatment: a longitudinal analysis. Addiction. 2018;113(12):2250-8.
192. Stein MDC, P.: Friedmann, P. D. Buprenorphine retention in primary care. J Gen Intern Med. 2005;20(11):1038-41.
193. Strike CJG, W.: Urbanoski, K.: Fischer, B.: Marsh, D. C.: Millson, M. Factors predicting 2-year retention in methadone maintenance treatment for opioid dependence. Addict Behav. 2005;30(5):1025-8.
194. Sullivan SG, Wu Z, Detels R. Time to first treatment interruption in the Chinese methadone maintenance treatment programme. Drug Alcohol Depend. 2013;133(2):427-32.
195. Teoh J, Yee A, Danaee M. Predictors of retention and mortality among patients on methadone maintenance therapy. Heroin Addiction and Related Clinical Problems. 2018;20(4):19-28.
196. Wei XW, L.: Wang, X.: Li, J.: Li, H.: Jia, W. A study of 6-year retention in methadone maintenance treatment among opioid-dependent patients in Xi'an. J Addict Med. 2013;7(5):342-8.
197. Weinstein ZMK, Hyunjoong W.: Cheng, Debbie M.: Quinn, Emily: Hui, David: Labelle, Colleen T.: Drainoni, Mari-Lynn: Bachman, Sara S.: Samet, Jeffrey H. Long-term retention in Office Based Opioid Treatment with buprenorphine. J Subst Abuse Treat. 2017;74:65-70.
198. Yang FL, P.: Li, Y.: He, Q.: Long, Q.: Fu, X.: Luo, Y. Predictors of retention in community-based methadone maintenance treatment program in Pearl River Delta, China. Harm Reduct J. 2013;10:3.

199. Zhang LZ, X.: Zhang, D.: Li, X.: Zhao, P.: Ling, L. Investigation of Repeat Client Drop-Out and Re-Enrolment Cycles in Fourteen Methadone Maintenance Treatment Clinics in Guangdong, China. PLoS One. 2015;10(10):e0139942.
200. Zhou KW, D.: Li, H.: Wei, X.: Yin, J.: Liang, P.: Kou, L.: Hao, M.: You, L.: Li, X.: Zhuang, G. Bidirectional relationships between retention and health-related quality of life in Chinese mainland patients receiving methadone maintenance treatment. PLoS One. 2017;12(6):e0179009.
201. Zhou KNL, H. X.: Wei, X. L.: Li, X. M.: Zhuang, G. H. Medication Adherence in Patients Undergoing Methadone Maintenance Treatment in Xi'an, China. J Addict Med. 2017;11(1):28-33.
202. Blanken P, Hendriks VM, van Ree JM, van den Brink W. Outcome of long-term heroin-assisted treatment offered to chronic, treatment-resistant heroin addicts in the Netherlands. Addiction. 2010;105(2):300-8.
203. Kimber J, Copeland L, Hickman M, Macleod J, McKenzie J, De Angelis D, et al. Survival and cessation in injecting drug users: prospective observational study of outcomes and effect of opiate substitution treatment. BMJ: British Medical Journal (Overseas & Retired Doctors Edition). 2010;341(7764):c3172-c.
204. Panlilio LV, Stull SW, Kowalczyk WJ, Phillips KA, Schroeder JR, Bertz JW, et al. Stress, craving and mood as predictors of early dropout from opioid agonist therapy. Drug and Alcohol Dependence. 2019;202:200-8.
205. Platt L, Minozzi S, Reed J, Vickerman P, Hagan H, French C, et al. Needle and syringe programmes and opioid substitution therapy for preventing HCV transmission among people who inject drugs: findings from a Cochrane Review and meta-analysis. Addiction (Abingdon, England). 2018;113(3):545-63.
206. Nosyk B, Min JE, Evans E, Li L, Liu L, Lima VD, et al. The Effects of Opioid Substitution Treatment and Highly Active Antiretroviral Therapy on the Cause-Specific Risk of Mortality Among HIV-Positive People Who Inject Drugs. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015;61(7):1157-65.
207. Mathers BM, Degenhardt L, Ali H, Wiessing L, Hickman M, Mattick RP, et al. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. Lancet (London, England). 2010;375(9719):1014-28.
208. MacArthur GJ, Minozzi S, Martin N, Vickerman P, Deren S, Bruneau J, et al. Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis. BMJ (Clinical research ed). 2012;345:e5945.
209. Bell J, Burrell T, Indig D, Gilmour S. Cycling in and out of treatment; participation in methadone treatment in NSW, 1990-2002. Drug Alcohol Depend. 2006;81(1):55-61.
210. Holton AE, Gallagher PJ, Ryan C, Fahey T, Cousins G. Consensus validation of the POSAMINO (POtentially Serious Alcohol-Medication INteractions in Older adults) criteria. BMJ open. 2017;7(11):e017453.
211. Haight BR, Learned SM, Laffont CM, Fudala PJ, Zhao Y, Garofalo AS, et al. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2019;393(10173):778-90.
212. Notley C, Holland R, Maskrey V, Nagar J, Kouimtsidis C. Regaining control: The patient experience of supervised compared with unsupervised consumption in opiate substitution treatment. Drug and Alcohol Review. 2014;33(1):64-70.
213. van Reekum EA, Rosic T, Hudson J, Sanger N, Marsh DC, Worster A, et al. Social functioning outcomes in men and women receiving medication-assisted treatment for opioid use disorder. Biology of sex differences. 2020;11(1):20.
214. Oviedo-Joekes E, Nosyk B, Brissette S, Chettiar J, Schneeberger P, Marsh DC, et al. The North American Opiate Medication Initiative (NAOMI): profile of participants in North America's first trial of heroin-assisted treatment. Journal of urban health : bulletin of the New York Academy of Medicine. 2008;85(6):812-25.
215. Rosic T, Worster A, Thabane L, Marsh DC, Samaan Z. Exploring psychological symptoms and associated factors in patients receiving medication-assisted treatment for opioid-use disorder. BJPsych open. 2020;6(1):e8.

216. Comiskey CM. A 3 year national longitudinal study comparing drug treatment outcomes for opioid users with and without children in their custodial care at intake. Journal of Substance Abuse Treatment. 2013;44(1):90-6.
217. Ducray K, Darker C, Smyth BP. Situational and psycho-social factors associated with relapse following residential detoxification in a population of Irish opioid dependent patients. Irish Journal of Psychological Medicine. 2012;29(2):72-9.
218. Collins R, Boggs B, Taggart N, Kelly M, Drillington A, Swanton I, et al. Efficacy of treatment in an opioid -dependent population group using the Maudsley Addiction Profile (MAP) tool. The Ulster medical journal. 2009;78(1):21-5.
219. Comiskey C, Kelly, P., Leckey, Y., McCullouch, L.,O Duill, B., Stapleton, R., White, E., . The ROSIE Study: Drug Treatment Outcomes in Ireland. Dublin: National Advisory Committee on Drugs and Alcohol, ; 2009.
220. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Journal of clinical epidemiology. 2008;61(4):344-9.
221. Luijken K, Spekreijse, J., Van Smeden, M., Gardarsdottir, H. . The Use of Incident and Prevelent-User Designs in Pharmacoepidemology: A systematic Review of the Literature. Leiden University Medical Centre2020.
222. Ray WA. Evaluating Medication Effects Outside of Clinical Trials: New-User Designs. American Journal of Epidemiology. 2003;158(9):915-20.
223. Cousins G, Boland F, Barry J, Lyons S, Bennett K, Fahey T. Retention in Methadone Maintenance Treatment (MMT) in primary care: National cohort study using proportional hazards frailty model for recurrent MMT episodes. Pharmacoepidemiology and Drug Safety. 2016;25:228.
224. WHO announces COVID-19 outbreak a pandemic [press release]. Denmark World Health Organization Regional Office for Europe

2020.
225. Irish Government News Service. Statement by An Taoiseach Leo Varadkar On measures to tackle Covid-19 Washington, 12 March 2020. In: Government Information Service, editor. 2020.
226. Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. Cochrane Database of Systematic Reviews. 2011:N.PAG-N.PAG.
227. European Monintoring Centre for Drugs and Drug Addiction. E. EU Drug Markets: Impact of COVID-19. Lisbon European Monitoring Centre for Drugs and Drug Addiction; 2020
228. Hines L, Kesten, J., Holland, A., Family, H., Scott, J., Linton, M., Ayres, R., Hussey, D., Telfer, M., Wilkinson, M., Horwood, J. . LUCID-B Study: Interim Report 4. Bristol University of Bristol 2020
229. Crew. Covid-19 Drug Market Survey Summary Month 1 April 2020 Edinburgh: Crew 2020
230. Addiction EMCfDaD. EMCDDA trendspotter briefing - June 2020: Impact of COVID-19 on patterns of drug use and drugrelated harms in Europe. Lisbon: European Monitoring Centre for Drugs and Drug Addiction 2020
231. Mongan D, Galvin, B., Farragher, L., Dunne, M., Nelson, M. . Impact of COVID-19 on drug services in four countries : An evidence brief. Dublin Health Research Board 2020
232. Bell T, Watson M, Sharp D, Lyons I, Lewis G. Factors associated with being a false positive on the General Health Questionnaire. Social Psychiatry and Psychiatric Epidemiology: The International Journal for Research in Social and Genetic Epidemiology and Mental Health Services. 2005;40(5):402-7.
233. Delgado-Rodríguez M, Llorca J. Bias. Journal of Epidemiology & Community Health. 2004;58(8):635-41.
234. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. American Journal of Epidemiology. 2005;162(10):1016-23.
235. Cox G, Comiskey C. Characteristics of opiate users presenting for a new treatment episode: Baseline data from the national drug treatment outcome study in Ireland (ROSIE). Drugs: Education, Prevention & Policy. 2007;14(3):217-30.

236. Wilkinson R, Hines L, Holland A, Mandal S, Phipps E. Rapid evidence review of harm reduction interventions and messaging for people who inject drugs during pandemic events: implications for the ongoing COVID-19 response. Harm reduction journal. 2020;17(1):95.
237. Cioe K, Biondi BE, Easly R, Simard A, Zheng X, Springer SA. A systematic review of patients' and providers' perspectives of medications for treatment of opioid use disorder. Journal of substance abuse treatment. 2020;119:108146.
238. Fonseca J, Chang A, Chang F. Perceived Barriers and Facilitators to Providing Methadone Maintenance Treatment Among Rural Community Pharmacists in Southwestern Ontario. The Journal of rural health : official journal of the American Rural Health Association and the National Rural Health Care Association. 2018;34(1):23-30.
239. Deering DEA, Sheridan J, Sellman JD, Adamson SJ, Pooley S, Robertson R, et al. Consumer and treatment provider perspectives on reducing barriers to opioid substitution treatment and improving treatment attractiveness. Addictive Behaviors. 2011;36(6):636-42.
240. Holliday S, Magin P, Oldmeadow C, Attia J, Dunbabin J, Henry JM, et al. An examination of the influences on New South Wales general practitioners regarding the provision of opioid substitution therapy. Drug Alcohol Rev. 2013;32(5):495-503.
241. Wu F, Peng C-Y, Jiang H, Zhang R, Zhao M, Li J, et al. Methadone maintenance treatment in China: perceived challenges from the perspectives of service providers and patients. Journal of public health (Oxford, England). 2013;35(2):206-12.
242. Sohler NL, Weiss L, Egan JE, Lopez CM, Favaro J, Cordero R, et al. Consumer attitudes about opioid addiction treatment: a focus group study in New York City. J Opioid Manag. 2013;9(2):111-9.
243. Jeske CP, O'Byrne P. Perceptions and Experiences of Methadone Maintenance Treatment: A Qualitative Descriptive Research Study. Journal of addictions nursing. 2019;30(4):248-53.
244. Philbin MM, Zhang F. Exploring stakeholder perceptions of facilitators and barriers to accessing methadone maintenance clinics in Yunnan Province, China. AIDS care. 2010;22(5):623-9.
245. Tofighi B, Williams AR, Chemi C, Suhail-Sindhu S, Dickson V, Lee JD. Patient Barriers and Facilitators to Medications for Opioid Use Disorder in Primary Care. Substance Use & Misuse. 2019;54(14):2409-19.
246. Velasquez M, Flannery M, Badolato R, Vittitow A, McDonald RD, Tofighi B, et al. Perceptions of extended-release naltrexone, methadone, and buprenorphine treatments following release from jail. Addiction science & clinical practice. 2019;14(1):37.
247. Fox AD, Maradiaga J, Weiss L, Sanchez J, Starrels JL, Cunningham CO. Release from incarceration, relapse to opioid use and the potential for buprenorphine maintenance treatment: a qualitative study of the perceptions of former inmates with opioid use disorder. Addict Sci Clin Pract. 2015;10:2.
248. Moran L, Keenan E, Elmusharaf K. Barriers to progressing through a methadone maintenance treatment programme: perspectives of the clients in the Mid-West of Ireland's drug and alcohol services. BMC health services research. 2018;18(1):911.
249. Woo J, Bhalerao A, Bawor M, Bhatt M, Dennis B, Mouravska N, et al. "Don't Judge a Book by Its Cover": A Qualitative Study of Methadone Patients' Experiences of Stigma. Substance Abuse: Research & Treatment. 2017(11):1-12.
250. Conner KO, Rosen D. 'You're nothing but a junkie': Multiple experiences of stigma in an aging methadone maintenance population. Journal of Social Work Practice in the Addictions. 2008;8(2):244-64.
251. Conner KO, Rosen D, Wexler S, Brown C. 'It's like night and day He's White I'm Black': Shared stigmas between counselors and older adult methadone clients. Best Practices in Mental Health: An International Journal. 2010;6(1):17-32.
252. Al-Tayyib AA, Koester S. Injection drug users' experience with and attitudes toward methadone clinics in Denver, CO. J Subst Abuse Treat. 2011;41(1):30-6.
253. Andersson L, Johnson B. Patient choice as a means of empowerment in opioid substitution treatment: a case from Sweden. Drugs: Education, Prevention & Policy. 2020;27(2):105-17.

254. Damon W, Small W, Anderson S, Maher L, Wood E, Kerr T, et al. 'Crisis' and 'everyday' initiators: A qualitative study of coercion and agency in the context of methadone maintenance treatment initiation. Drug Alcohol Rev. 2017;36(2):253-60.
255. Fischer J, Neale J, Bloor M, Jenkins N. Conflict and user involvement in drug misuse treatment decision-making: A qualitative study. Substance Abuse Treatment, Prevention, and Policy. 2008;3.
256. Yarborough BJ, Stumbo SP, McCarty D, Mertens J, Weisner C, Green CA. Methadone, buprenorphine and preferences for opioid agonist treatment: A qualitative analysis. Drug Alcohol Depend. 2016;160:112-8.
257. King A. Service user involvement in methadone maintenance programmes: The 'philosophy, the ideal and the reality'. Drugs: Education, Prevention & Policy. 2011;18(4):276-84.
258. Van Hout MC, McElrath K. Service user involvement in drug treatment programmes: Barriers to implementation and potential benefits for client recovery. Drugs: Education, Prevention & Policy. 2012;19(6):474-83.
259. Hayashi K, Ti L, Ayutthaya PPN, Suwannawong P, Kaplan K, Small W, et al. Barriers to retention in methadone maintenance therapy among people who inject drugs in Bangkok, Thailand: A mixed-methods study. Harm Reduct J. 2017;14.
260. Van Hout MC, Bingham T. A qualitative study of prescribing doctor experiences of methadone maintenance treatment. International Journal of Mental Health and Addiction. 2014;12(3):227-42.
261. Mayock P, Butler, S., Hoey, D. . “Just Maintaining the Status Quo”? The experiences of long-term participants in methadone maintenance treatment. Dun Laoghaire Rathdown Drug and Alcohol Task Froce, ; 2018.
262. Zhang L, Bao JY, Harrington A, Fan XD, Ning Z, Zhang JY, et al. Mixed methods to explore factors associated with the decline of patients in the methadone maintenance treatment program in Shanghai, China. Harm Reduction Journal. 2019;16.
263. Kermode M, Choudhurimayum RS, Rajkumar LS, Haregu T, Armstrong G. Retention and outcomes for clients attending a methadone clinic in a resource-constrained setting: a mixed methods prospective cohort study in Imphal, Northeast India. Harm reduction journal. 2020;17(1):68.
264. Truong C, Krawczyk N, Dejman M, Marshall-Shah S, Tormohlen K, Agus D, et al. Challenges on the road to recovery: Exploring attitudes and experiences of clients in a community-based buprenorphine program in Baltimore City. Addictive Behaviors. 2019;93:14-9.
265. Lin C, Detels R. A qualitative study exploring the reason for low dosage of methadone prescribed in the MMT clinics in China. Drug Alcohol Depend. 2011;117(1):45-9.
266. McKeganey N, Morris Z, Neale J, Robertson M. What are drug users looking for when they contact drug services: Abstinence or harm reduction? Drugs: Education, Prevention & Policy. 2004;11(5):423-35.
267. Strike C, Millson M, Hopkins S, Smith C. What is low threshold methadone maintenance treatment? Int J Drug Policy. 2013;24(6):e51-6.
268. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006;3(2):77-101.
269. Morgan D. Integrating Qualitative and Quantitative Methods: A Pragmatic Approach. California: Sage; 2014.
270. Charmaz K. Constructing Grounded Theory. 2nd ed. London: Sage; 2014.
271. European Monintoring Centre for Drugs and Drug Addiction. EMCDDA Trendspotting Briefing: Impact of COVID-19 on Drug Services and Help-Seeking in Europe. Lisbon: EMCDDA; 2020.
272. Deptatrment of Health. Guidance for Alcohol and Drug services in Northern Ireland to best deliver treatment and care during the COVID-19 pandemic. In: Deptartment of Health, editor. Belfast United Kingdom Government 2020.
273. Lintzeris N, Hayes, V., Arunogiri, S. . Interim guidance for the delivery of medication assisted treatment of opioid dependence in response to COVID-19: a national response. New South Wales, Australia: University of Sydney 2020.
274. Samuels EA, Clark SA, Wunsch C, Jordison Keeler LA, Reddy N, Vanjani R, et al. Innovation During COVID-19: Improving Addiction Treatment Access. Journal of addiction medicine. 2020;14(4):e8-e9.

275. Substance Abuse and Mental Health Services Administration. Considerations for the Care and Treatment of Mental and Substance Use Disorders in the COVID-19 Epidemic: March 20, 2020 In: Administration SAaMHS, editor. Rockville, Maryland Substance Abuse and Mental Health Services Administration

2020
276. Chaar BB, Wang H, Day CA, Hanrahan JR, Winstock AR, Fois R. Factors influencing pharmacy services in opioid substitution treatment. Drug and alcohol review. 2013;32(4):426-34.
277. Van Hout MC, Bingham T. Prescribing Doctor attitudes, experiences and perspectives on the provision of methadone maintenance treatment in Dublin. . Dublin: Dublin North East Drugs Task Force; 2011.
278. Department of the Taoiseach. Report on the Social Implications of COVID-19 in Ireland In: Department of the Taoiseach, editor. Dublin Government of Ireland, ; 2020.
279. Kaleidoscope Project. Peer-led COVID-19 Impact Survey: A review of the Impact of COVID-19 on drug and alcohol users in Wales. Wales: Kaleidoscope Project,

; 2020
280. Cousins G, Boland F, Barry J, Lyons S, Keenan E, O'Driscoll D, et al. J-shaped relationship between supervised methadone consumption and retention in methadone maintenance treatment (MMT) in primary care: National cohort study. Drug Alcohol Depend. 2017;173:126-31.
281. McNeill I. Rapid Internal Process Evaluation of Covid-19 Contingency Planning - Opioid Substitution Treatment (OST) in Prisons. In: Directorate CPH, editor. Scotland Covid Public Health Directorate 2020
282. European Monintoring Centre for Drugs and Drug Addiction. Strategies to prevent diversion of opioid substitution treatment medications. Lisbon: European Monitoring Centre for Drugs and Drug Addiction 2016
283. Cicero TJ, Kurtz SP, Surratt HL, Ibanez GE, Ellis MS, Levi-Minzi MA, et al. Multiple Determinants of Specific Modes of Prescription Opioid Diversion. Journal of drug issues. 2011;41(2):283-304.
284. Havnes IA, Clausen T, Middelthon A-L. 'Diversion' of methadone or buprenorphine: 'Harm' versus 'helping'. Harm Reduction Journal. 2013;10.
285. Saulle R, Vecchi S, Gowing L. Supervised dosing with a long-acting opioid medication in the management of opioid dependence. The Cochrane Database Of Systematic Reviews. 2017;4:CD011983.
286. National Screening Service. Patient and Public Partnership Strategy 2019-2023 Dublin Natoinal Screening Service, ; 2019
287. Fischer J, Neale J. Involving drug users in treatment decisions: An exploration of potential problems. Drugs: Education, Prevention & Policy. 2008;15(2):161-75.
288. Grebely J, Cerdá M, Rhodes T. COVID-19 and the health of people who use drugs: What is and what could be? The International journal on drug policy. 2020;83:102958.
289. Kuruvilla S, Mays N, Pleasant A, Walt G. Describing the impact of health research: a Research Impact Framework. BMC health services research. 2006;6:134.
290. Korownyk C, Perry D, Ton J, Kolber MR, Garrison S, Thomas B, et al. Opioid use disorder in primary care: PEER umbrella systematic review of systematic reviews. Canadian family physician Medecin de famille canadien. 2019;65(5):e194-e206.
291. Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. Cochrane Database Syst Rev. 2003(3):Cd002208.
292. Malta M, Varatharajan T, Russell C, Pang M, Bonato S, Fischer B. Opioid-related treatment, interventions, and outcomes among incarcerated persons: A systematic review. PLoS medicine. 2019;16(12):e1003002.
293. Hedrich D, Alves P, Farrell M, Stover H, Moller L, Mayet S. The effectiveness of opioid maintenance treatment in prison settings: a systematic review. Addiction. 2012;107(3):501-17.

294. Mayock P, Butler S. Pathways to 'recovery' and social reintegration: The experiences of long-term clients of methadone maintenance treatment in an Irish drug treatment setting. The International journal on drug policy. 2021;90:103092.
295. Harris J, McElrath K. Methadone as social control: Institutionalized stigma and the prospect of recovery. Qualitative Health Research. 2012;22(6):810-24.
296. Sohler NL, Weiss L, Egan JE, López CM, Favaro J, Cordero R, et al. Consumer attitudes about opioid addiction treatment: a focus group study in New York City. Journal of opioid management. 2013;9(2):111-9.
297. Teruya C, Schwartz RP, Mitchell SG, Hasson AL, Thomas C, Buoncristiani SH, et al. Patient perspectives on buprenorphine/naloxone: a qualitative study of retention during the starting treatment with agonist replacement therapies (START) study. J Psychoactive Drugs. 2014;46(5):412-26.
298. Feelemyer J, Des Jarlais D, Arasteh K, Abdul-Quader AS, Hagan H. Retention of participants in medication-assisted programs in low- and middle-income countries: an international systematic review. Addiction (Abingdon, England). 2014;109(1):20-32.
299. Hsu CHS, A; . The Delphi Technique: Making Sense of Consensus Practical Assessment, Research and Evaluation. 2007;12(10).
300. Dong H, Hayashi K, Fairbairn N, Milloy MJ, DeBeck K, Wood E, et al. Long term pre-treatment opioid use trajectories in relation to opioid agonist therapy outcomes among people who use drugs in a Canadian setting. Addictive behaviors. 2021;112:106655.
301. Khan A, Khan Q, Kolb E. Supportive alternate site provision of buprenorphine: Overcoming barriers and improving patient outcomes. Journal of Substance Abuse Treatment. 2021;123:108256.
302. Palis H, Guh D, MacDonald S, Harrison S, Brissette S, Marsh DC, et al. Longitudinal patterns of cocaine use among patients receiving injectable hydromorphone or diacetylmorphine for the treatment of opioid use disorder: A growth curve modeling approach. Drug and Alcohol Dependence. 2020.
303. MacLean RR, Spinola S, Garcia-Vassallo G, Sofuoglu M. The Impact of Chronic Pain on Opioid Use Disorder Treatment Outcomes. Current Addiction Reports. 2021.

Appendices

Appendix 1. Maudsley Addiction Profile

Maudsley Addiction Profile

Client details

Initial of first name: ☐ ***initial of family name:*** ☐

Sex: M/F ☐ ***Age***: ☐

Interviewer - complete if appropriate for country or skip

Observe and code ethnic group White ☐ Black ☐ Asian ☐ Other ☐

Ask client: ñ How would you describe your ethnic grou

record verbatim ☐

Ask client: ñ What was your country of birth? ☐

Interviewer details

Name ☐ ***Team/clinic*** ☐

Date

Day ☐☐ ☐☐ ☐☐ ☐☐

Record interviewer type

Clinician ☐ ***Researcher*** ☐

Case ☐☐☐

© J.Marsden, M. Gossop, C. Edwards, D. Best, D. Stewart & P. Lehmann; National Addiction Centre, London, UK (1996) MAP v1.0 (12/96)

[*Interviewer read out*] "We're going to begin by looking at your use of different substances in the past month. By the last month I mean the last 30 days."

1. For each drug, ask if client has used in past month, and record X (yes) or leave blank (no).
2. If Yes, show *Card1* and ask client to recall the total number of days used in pastmonth.
3. Ask client to recall typical amount consumed across a day of this drugtype.
4. Ask client to indicate main route of administration in past month and enter number(s).

Main route(s)
oral
snort/sniff
smoke/chase
inject

Drug type	Used past month? [or blank]	Days used in past month	Amount consumed on a typical day in past month [record verbatim]	Main route(s)
A1 Alcohol				
A2 Heroin				
A3 Problem opioids 1.				
2.				
A4 Problem benzos. 1.				
2.				
A5 Cocaine - *hydrocholoride*				
A6 Cocaine - *crack/base*				

A8"In the past month, have you had a drugs overdose?" No Yes *If Yes, how many times?* [ ]

Section B: Injecting and sexual behaviour

B1. [Interviewer] "Can I just check, at any time in the past month, did you inject drugs?"

Interviewer- show Card 1

Yes If Yes: "On how many days did you inject?

No *if No, skip to interviewer prompt before B4*

B3. "In the past month, did you ever use a needle or syringe which had been used by someone else?"

Yes If Yes: "How many times in total did you do this?" times ☐

B4. "How often did you inject with a new, unused needle and syringe?"

Never	Rarely	Some-times	Often	Always
4	3	2	1	0

Interviewer- "I'm now going to ask you a couple of questions about your sexual behaviour during the past month."

B5. "Have you had *penetrative sex* (ie. vaginal or anal) in the past month?" Yes

No *if No, skip to Section C*

B6. "In the past month, have you had *penetrative sex* without using a condom at any time?"

Yes If Yes: "How many people have you had sex with, when not using a condom?"

total people

No ***if No, skip to Section C***

B7. ñ In the past month, how many ***times*** have you had penetrative sex without using a condom?

Section C: Health

Physical health

Interviewer - show Card 2

ñWeôre now going to look at your physical hea
you had the following problems?ò

[Card 2]	Never	Rarely	Sometimes	Often	Always
	0	1	2	3	4
	0	1	2	3	4
a. Poor appetite	0	1	2	3	4
b. Tiredness/fatigue	0	1	2	3	4
c. Nausea	0	1	2	3	4
d. Stomach pains	0	1	2	3	4
e. Difficulty breathing	0	1	2	3	4
f. Chest pains	0	1	2	3	4
g. Joint / bone pains	0	1	2	3	4
h. Muscle pains	0	1	2	3	4

Psychological health

Interviewer - show card 2

ñIôm now going to ask you to think about how you
month, how often have you had the following exper

[Card 2]	Never	Rarely	Sometimes	Often	Always
a. Feeling tense	0	1	2	3	4
b. Suddenly scared for no reason . .	0	1	2	3	4
c. Feeling fearful	0	1	2	3	4
d. Nervousness or shakiness inside	0	1	2	3	4
e. Spells of terror or panic	0	1	2	3	4
f. Feeling hopeless about the future	0	1	2	3	4
g. Feelings of worthlessness	0	1	2	3	4
h. Feeling no interest in things . . .	0	1	2	3	4
i. Feeling lonely	0	1	2	3	4

Section D: Social functioning

Interviewer - ñ I ô m n o w g o i n g t o a s k y o u s o m e g e n e r a l q u e s
m o n t ***Show*** ò ***Card 3.***

D1. ñ I n t h e p a s t ***nights*** m o n t h , h o w m a n y n i g h t s y o u s p e n t a t t h e f o l l o w i n

[Card 3]	*Nights* **[0-30]**
Own or rented home	
Relatives'/Partner's/Friends'/others' home	
Hostel/other temporary accommodation On the street (homeless)	
Prison/other detention/police station	
Hospital/residential treatment	
Other (*specify)*	

[***interviewer - check sum of nights spent in one or more places = 30***]

D2. ñ H o w l o n g h a v e y o u l i v e d a t y o u r c u r r e n t a d d r e

Work and training

D3. ñ A t a n y t i m e i n t h e p a s t m o n t h , d i d y o u h a
w o r k) ? ò

Yes If Y e s : ñ h o w m a n y d a y s d i d y o u h a v e a j o b ? ò

No ***if No, skip to D5***

D4. ñ I n p a s t m o n t h , did you miss any days due to sickness or unauthorised
a b s e n c e ? ò

Yes I f Y e s : ñ h o w m a n y d a y s d i d y o u m i s s ? ò

No

D5. ñ A t a n y t i m e i n t h e p a s t m o n t h , d i d y o u h a
j o b ? ò

Yes If Yes: ñ how many hids a? yòs did you do

D6. ñ In the past month, did you have a place o

Yes If Yes: ñ how did you a td ta ey ns d ? ò

No

D7. ñ I the past month, were you looking after dependents and/or the h o m e ? ò

Yes If Yes: ñ how many you doing y t shi w e? ròe

No

D8. ñ At any time in the unpeas t l o y o n d t? hò, were you

Yes If Yes: ñ how many you udnaeyns p l w oe y r eed ? ò

No

Relationships

D9. ñ I the past month, have you been in a relationship with a partner, either for some or all of the t i m e ? ò ***Interviewer - use Card 1***

Yes No if no, complete D10 (a) and (b) for relatives and friends

D10. ñ I n t h e p a s t m o n t h , o n h o w m a n y d a y s : w e r e y o u children

(a) did you have serious conflict with [ ] [ ] [ ]

Illegal activities

D11. ***Interviewer -*** ñ This section concerns only things that past month which are illegalò

Show Card 4

Remind client of confidentiality

[Card 4]	In past month?		Days committed [1-30]		Number of times on typical
Selling drugs		*if yes ...*		*and...*	
Fraud/forgery		*if yes ...*		*and...*	
Theft from a property		*if yes ...*		*and...*	
Theft from a person		*if yes ...*		*and...*	
Shoplifting		*if yes ...*		*and...*	
Theft from a vehicle		*if yes ...*		*and...*	
Theft of a vehicle		*if yes ...*		*and...*	
Other theft (specify)		*if yes ...*		*and...*	
Criminal damage		*if yes ...*		*and...*	
Public order offence		*if yes ...*		*and...*	

END OF MAP INTERVIEW

Interviewer enter time completed [ ][ ]

Appendix 2. Inclusion / exclusion criteria for systematic review

	Inclusion	**Exclusion**
Population	Adults aged ≥18 years in receipt of opioid agonist treatment for opioid dependence	Pregnant women, HIV service users only
Intervention and OAT	Opioid agonist treatment, with methadone, buprenorphine, or Buprenorphine-naloxone combination	Opioid agonist therapy for pain management or detox or LAAM
Setting	Primary Care, Specialist Treatment	Inpatients, prison, residential care settings
Study Type	Cohort studies, RCTs	Non-randomized clinical trials, case-control studies, cross-sectional surveys, case reports, case series and qualitative research studies, commentary, editorials and responses; duplicate publication of the same cohort
Study Outcome	Retention or cessation / dropout	
Follow-up period	at least six-months follow-up	less than six-months follow-up
Protective or risk factors	Any factor explored in relation to retention or cessation/dropout	

Appendix 3. Search strategy for systematic review

Pubmed

S1	"Opioid-Related Disorders"[Mesh] OR "Opiate Agonist Treatment"[Mesh]
S2	(Opioid* OR Opiate* OR methadone OR buprenorphine)
S3	"Buprenorphine"[Mesh] OR "Buprenorphine, Naloxone Drug Combination"[Mesh]
S4	"Methadone"[Mesh]
S5	((("Opioid-Related Disorders"[Mesh] OR "Opiate Agonist Treatment"[Mesh])) OR ((Opioid* OR Opiate* OR methadone OR buprenorphine))) OR ("Buprenorphine"[Mesh] OR "Buprenorphine, Naloxone Drug Combination"[Mesh])) OR "Methadone"[Mesh] (S1 OR S2 OR S3 OR S4)
S6	"Patient Compliance"[Mesh]
S7	complian* OR adherence OR retention OR persisten*
S8	("Patient Compliance"[Mesh]) OR (complian* OR adherence OR retention OR persisten*) (S6 OR S7)
S9	(((((("Opioid-Related Disorders"[Mesh] OR "Opiate Agonist Treatment"[Mesh])) OR ((Opioid* OR Opiate* OR methadone OR buprenorphine))) OR ("Buprenorphine"[Mesh] OR "Buprenorphine, Naloxone Drug Combination"[Mesh])) OR "Methadone"[Mesh])) AND (("Patient Compliance"[Mesh]) OR (complian* OR adherence OR retention OR persisten*)) (S8 AND S5)
	Filters: Species – Humans

Psycinfo

S1	opioid* OR opiate* OR methadone OR buprenorphine
S2	DE" naloxone" OR DE "Buprenorphine"
S3	DE "methadone" OR DE "methadone maintenance"
S4	DE "opiates" OR DE "substance use disorder" OR DE "maintenance therapy"
S5	S1 OR S2 OR S3 OR S4
S6	complian* OR adherence OR retention OR persisten*
S7	S6 OR S7

S8	S5 AND S8
S9	Search Options : Population Group - Human

Web of Science

	Query
1	opiate addiction
2	"opiate addiction"
3	opioid addiction
4	"opioid addiction"
5	opiate agonist
6	"opiate agonist"
7	opioid agonist
8	"opioid agonist"
9	buprenorphine
10	opioid maintenance
11	opioid replacement
12	methadone
13	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12
14	Patient adher*
15	patient complia*
16	"treatment refusal"
17	patient retention
18	treatment dropout
19	"treatment cessation"
20	medication adherence
21	"patient dropout"
22	S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21
23	S13 AND S22 *no option to screen for human only studies

Embase

S1	‘opiate addiction'/exp OR 'opiate agonist treatment'/exp
S2	‘buprenorphine'
S3	‘methadone'
S4	S1 OR S2 OR S3
S5	'patient compliance'/exp OR 'patient compliance'
S6	patient retention
S7	‘patient retention’/exp
S8	‘treatment refusal'/exp
S9	‘patient dropout’/exp' or 'patient dropout'
S10	S5 OR S6 OR S7 OR S8 OR S9
S11	S4 AND S10
S12	Study type: Human

CINHAL

S1	"Opioid-Related Disorders"[Mesh] OR "Opiate Agonist Treatment"[Mesh]
S2	Search (Opioid* OR Opiate* OR methadone OR buprenorphine)s
S3	Search "Buprenorphine"[Mesh] OR "Buprenorphine, Naloxone Drug Combination"[Mesh]
S4	Search "Methadone"[Mesh]
S5	((("Opioid-Related Disorders"[Mesh] OR "Opiate Agonist Treatment"[Mesh])) OR ((Opioid* OR Opiate* OR methadone OR buprenorphine))) OR ("Buprenorphine"[Mesh] OR "Buprenorphine, Naloxone Drug Combination"[Mesh])) OR "Methadone"[Mesh] (S1 OR S2 OR S3 OR S4)
S6	Search "Patient Compliance"[Mesh]
S7	Search complian* OR adherence OR retention OR persisten*
S8	Search ("Patient Compliance"[Mesh]) OR (complian* OR adherence OR retention OR persisten*) (S6 OR S7)

S9	Search (((((("Opioid-Related Disorders"[Mesh] OR "Opiate Agonist Treatment"[Mesh])) OR ((Opioid* OR Opiate* OR methadone OR buprenorphine))) OR ("Buprenorphine"[Mesh] OR "Buprenorphine, Naloxone Drug Combination"[Mesh])) OR "Methadone"[Mesh])) AND (("Patient Compliance"[Mesh]) OR (complian* OR adherence OR retention OR persisten*)) (S8 AND S5)
	Search Options: Human

Appendix 4. Data extraction template for systematic review

Reference (authors, year, title, journal): _____

Setting (country and treatment setting): _____

OAT Type: _____

Study Design (RCT/cohort study): _____

Participants

N: _____

Sex: _____

Mean age (±SD): _____

Age range: _____

Study Outcome definition(s): _____

Duration of follow-up (data collection periods): _____

Outcome(s) of interest (retention/cessation/dropout): _____

Time points: _____

Proportion(s) of sample retained in treatment: _____

Proportion(s) of sample ceasing treatment (dropout): _____

Analysis conducted: _____

Reported risk/protective factors explored and associations reported: _____

Appendix 5. Newcastle-Ottawa Scale (NOS) template (adapted)

Please note that within each section a maximum of one star can be given for each numbered item. Hence, a maximum of 3 stars can be awarded for the selection and outcome sections and a maximum of 1 star for the comparability section.

Selection

1) Representativeness of the exposed cohort (Include a small description of the sample) ★

a) Truly representative of the average OAT user in the community (random sample from dataset/medical records)

b) Somewhat representative ★ of the average OAT user in the community (non-random sample from dataset e.g. inclusion/exclusion criteria in place)

c) Selected group of users e.g. OAT users from one specific treatment centre, HIV only, veterans only

d) No description of the derivation of the cohort

2) Ascertainment of exposure (to factors investigated in the studies)

a) Secure record (e.g. surgical ★ records) ★

b) Structured interview

c) Written self-report

d) No description

3) Demonstration that retention/cessation (outcome of interest) is clearly defined

a) Yes ★

b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis (list factors adjusted for)

a) Multivariate analysis and factors adjusted for stated ★

b) Multivariate analysis, no statement on factors adjusted for

c) Univariate analysis

d) Other analysis

Outcome

1) Assessment of outcome

a) Independent blind assessment

b) Record linkage

c) Self-report

d) No description

2) Was follow-up long enough for outcomes to occur (list timeframe of **follow-up**)

a) Yes (>six-months)

b) No (<six-months)

3) Adequacy of follow up of cohorts

a) Complete follow up - all subjects accounted for/ databases used

b) Subjects lost to follow-up unlikely to introduce bias - small number lost (<20%) and description provided of those lost)

c) Follow-up rate < 80% and no description of those lost

d) No statement

Appendix 6. Characteristics of studies included in systematic review

Author	Country and Treatment Setting	Participants: N Sex Mean age (±SD) Age Range	OAT type*	Intervention	Follow-up period	Primary outcome assessed	Study outcome(s) definitions	Treatment effects
Chawarski 2011(136)	2 MMT Clinics China	N=37 81% men 36.7 years (7.2)	MMT	RCT: MMT only vs. MMT plus weekly individual drug and HIV counselling	six-months	Retention	Retention defined as continuing to receive MMT at six-months	No difference in retention: 83.3% retention in MMT only vs. 76.2% in MMT plus weekly counselling
Jaffray 2014 (137)	76 Community pharmacies, Scotland	N=542 64% men 32 years	MMT	Cluster RCT: Pharmacists randomised to intervention (Motivational interviewing training + resource pack); control (usual care)	six-months	Retention	A service user was considered retained if they were still receiving treatment from the same or another pharmacy or clinic.	No difference in retention : 88% retention in MMT in intervention group vs 81% in usual care
Marsch 2014(138)	Large MMT clinic, urban North-eastern USA	N=160 75% men 40.7 years (9.8)	MMT New entries to MMT	RCT: MMT + counselling vs MMT +reduced counselling + web-based therapeutic education	12-months	Retention	Retention calculated as the number of days each participant actively participated in study	No difference in retention: HR 0.94, p=0.74

Schwartz 2012 (139)	Two methadone programmes in Baltimore, USA	N=230 70% men 43.2 years (8.0)	MMT New entries to MMT	RCT: Interim methadone (IM) (supervised methadone with emergency counselling); standard methadone (SM) (usual MMT with routine counselling); Restored methadone (RM) (routine counselling with smaller caseloads)	12-months	Retention	Retention in treatment at 12-months	55.2% retained at 12-months; no differences between the 3 groups in rates of retention (60.6% IM; 54.8% SM; 37% RM)

Author	Country and Treatment Setting	Participants: N Sex Mean age (±SD) Age Range	OST type*	Study Design	Data collection / Follow-up period	Primary outcome assessed	Study outcome(s) definitions
Abramsohn 2009 (35)	Israel, Tel Aviv MMT clinic	N=90 73.3% men 39.8(±9.9) years NR	MMT	Prospective cohort study	September 2003 -April 2006	Retention	Duration in treatment from admission until the patient withdrew or until the end of follow-up (July 2007) was used for calculating cumulative retention in treatment.
Adelson 2013 (36)	Macao (Special Administrative Region of the People's Republic of China) MMT clinic	N=163 81% men 39.5 (±10.2) years Range: 20.4–71.8	MMT	Prospective cohort study	October 2005 - March 2010	Retention	One-year treatment retention defined as patient staying in treatment for a period of at least 1 year. Duration of treatment defined as starting at the time of patients' initial admission and ending when patient either left treatment or until study end. Long term retention (4.5 years)
Amiri 2018 (37)	USA, Washington State funded opioid treatment program (clinic)	N = 851 49% men 36.3 (± 11.7) years (NR)	MMT	Retrospective cohort study	February 2015 – December 2017	Dropout	Dropout: time based on number of days in treatment from the first dose date until the client dropped out of treatment or the closure of the study on 31st December 2017; and status indicator to distinguish between those who dropped out or were censored. Clients who discontinued their treatment were coded as dropped out of treatment.
Astals 2009 (38)	Spain, Barcelona 1 MMT clinic	N=189 77% male 34(±7.5) years NR	MMT	Prospective cohort study	NR	Dropout	Retention in the MMT at 18 months: remaining in the same MMT program and stable doses
Banta-Green 2009 (39)	USA, Washington State 11 MMT clinics	N=2308 51.6% men 40.6(±10.3) years NR	MMT	Retrospective cohort study	January 2004 – December 2005	Retention	12 month retention: remaining in treatment at day 366 following admission to MMT.
Bhatraju 2017 (40)	USA, New York City Primary Care Centre, Office	N=485 83% men 47 (SD NR) years Range: 23–73	BUP.	Prospective cohort study	August 2006 -June 2013	Dropout	Treatment retention: continuous variable (weeks) consisting of the time between the initial and last week of the last

	based buprenorphine treatment in a large urban-public hospital						active buprenorphine maintenance or taper prescription. Dropout defined as time to dropout
Bounes 2013 (41)	Mixed: Emergency departments, surgery departments, specialised addiction centres, France	N=151 74% men Median age:36years Range:20-54 years	Mixed OST	Prospective cohort study	April 2008-January 2010	Retention	Retention defined as the percentage of patients still under treatment at the time of follow-up Lost to follow-up patients were analysed as failure
Brands 2008(42)	Canada, Centre for Addiction and Mental Health (CAMH)	N=172 64% male 34.6 years (8.5) NR	MMT	Retrospective cohort study	January 1997-December 1999	Dropout	Retention: only those patients who discontinued methadone counted as discharged; those who were transferred to another MMT treatment programme considered in treatment
Bukten 2014 (43)	Norway National cohort	N=2431 67% men Men 37.8(±6.5) years Range: 22–60 Women 35.5(±6.3) years Range: 20-57	Mixed OST	Retrospective cohort study	September 1997 - December 2003	Dropout	Treatment dropout defined as the first day of the period of discontinuing treatment. Termination of treatment could be either voluntary or involuntary.
Burns 2009 (44)	Australia, New South Wales Multiple settings: clinic; correctional facilities;	N=42,690 **1986** 61.1% men Median age: 27.5 **1991** 65.4% men Median age: 28.3	Mixed OST	Retrospective cohort study	1985 - 2006	Dropout	An episode of continuous treatment as one with no more than a 6-day break between treatment programmes. Where a gap of 7 days or more occurred between an exit date and a start date, a new episode of treatment was defined.

	community pharmacy; public hospital; general practitioners; other	**1996** 68.8% men Median age: 26.4 **2001** 64.7% men Median age 26.5 **2006** 71.3% Median age: 28.2					Dropout from first treatment episode was measured as date of leaving first treatment episode
Cao 2014 (45)	First 8 MMT clinics in China	N=1511 77.1% men Age: ≥30 years = 60.3% NR	MMT	Prospective cohort study	March 2004 - June 2010	Dropout	Retention: Clients who were still on methadone at the end of the study period (June 2010) considered to be retained over the six-year period. Retention duration was calculated from the date of first methadone treatment to the date of the last methadone treatment or the study end date, whichever occurred first.
Cox 2013 (46)	Canada Cape Breton Methadone Maintenance Program	N=246 68% men 31 (SD NR) years NR	MMT	Retrospective cohort study	May 2004 – May 2007	Dropout	Dropout defined as loss to follow-up: includes involuntarily discharged from the program or if they voluntarily interrupted (voluntary discharge) methadone therapy for more than 7 days. Involuntarily discharge: if they were aggressive towards clinic staff, or if they continued to use opioid analgesics or other non-prescribed substances despite numerous attempts to stay within the program. Retention: those who were active in the program as of May 1, 2007, who completed the program (patients who were stabilized on and voluntarily tapered from methadone) and those who had transferred.
Cunningham 2013 (47)	USA, Bronx community health centre OBOT	N=87 73.6% men 43.5(± 9) years NR	BUP.	Prospective cohort study	November 2004 - December 2009	Retention	Treatment retention at 6 months after participants initiated buprenorphine treatment. Participants were categorized as retained in treatment if they had either a medical visit or active buprenorphine prescription. To be considered as

							retained at 6 months, participants had to be retained at both 1 and 3 months
Davstad 2007 (48)	Sweden MMT clinic	N=204 72% men Men N=147 Age range: 21-66 Women N=57 Age range: 24-50	MMT	Prospective cohort study	1995 - 2000	Dropout	Retention in treatment at 1 year and 2 years. Subjects in treatment on 31st Dec 2000 are retained
Dayal 2017 (49)	Drug treatment centre, India	N=68 NR 22.35(±2.47) years NR	BUP.	Retrospective cohort study	January 2012 – March 2015	Dropout	Discontinuation of buprenorphine maintenance treatment was defined as 7 consecutive days without buprenorphine or buprenorphine-naloxone. Duration of time from initiation to discontinuation was time, measured in days, from first prescription to last prescription (including day's supply of last prescription)
Deck 2005 (50)	USA, Oregon and Washington MMT clinics	N=5308 45% men 38.9 (SD NR) years NR	MMT	Retrospective cohort study	1994- 1999 (2000)	Retention	Retention was defined as continuous enrolment in an index treatment episode with no discharge for at least 12 months following the admission date. The retention rates were calculated as the number of individuals retained in the MMT for 12 months divided by the number of individuals admitted to the MMT during the same period. The rates were expressed as percentages.
Dumchev 2017 (51)	Ukraine 13 OAT clinics	N=2916 77.9% men 36.4 (7.9) years Range: 18–70	Mixed OST	Retrospective cohort study	2005 -2012	Dropout	12 month retention in treatment, defined as the time between treatment initiation and discontinuing treatment for 10 or more consecutive days. Time to dropout using date of admission and date of discharge
Eibl 2015 (52)	Canada, Ontario MMT clinics	N=17211 44-50% male Median age 35 – 39 NR	Mixed OST	Retrospective cohort study	2003 - 2012	Retention	Retention: defined a patient as having been retained in treatment if they completed at least one year of continuous uninterrupted treatment (i.e. no period of 30 consecutive days without a prescribed dose of methadone or buprenorphine)

Franklyn 2017 (53)	Canada, Province of Ontario 58 OAT clinics	N=3850 60% men Median age 31.4 years	Mixed OST	Retrospective cohort study	January 2011 - June 2012	Dropout	Retention: a patient was defined as retained in treatment if they completed at least for one year of continuous and uninterrupted treatment (continuous treatment on the basis of not having a period of 30 or more consecutive days without a dose of methadone or buprenorphine/naloxone) Dropout: treatment dropout (patient did not receive methadone or buprenorphine/naloxone dose for 30 consecutive days)
Friedman 2001 (54)	USA 22 MMT outpatient clinics from Drug Abuse Treatment Outcome Study (DATOS)	Partial sample (outpatient MMT) N = 1144 60.7% male 36.2 (±7.0) years NR	MMT	Retrospective cohort study	1991 - 1993	Retention	Time (days) each client spent in treatment was found by subtracting the date of admission from date of last therapeutic contact based on information in client records. The treatment retention variable was dichotomized at retention threshold 365 days or more in treatment
Gerra 2011(55)	Italy – 3 MMT Clinics with different policies for MMT (A – strictly supervised daily consumption 6 days a week; take-home methadone on Sunday; B- take home methadone in a	N=300 (100 per clinic) A 82%, B 84%, C 81% male A (28.19); B (27.9); C (28.77) NR	MMT	Prospective Cohort Study	June 2006- June 2008	Dropout	Retention in treatment (checked every few weeks); dropout after 12 months

	behavioural/incentive perspective; C-early non-contingent take-home methadone						
Gryczynski 2014 (56)	Baltimore USA African Americans attending 2 outpatient programmes	N=297 61.9% men 46.6 years (6.5) NR	BUP.	Secondary analysis of RCT data	March 2010-March 2011	Dropout	Retention: Number of days in treatment from clinic records, 1-180 days, after which observations censored.
Gu 2012 (57)	China, Guangdong 3 MMT clinics	N=158 90.5% men Age: < 35 years = 26.5% 36-40 years = 40% 40+years =33.5%	MMT	Prospective cohort study	May 2009 - October 2010	Dropout	Dropout was defined as not having visited the MMT clinic for at least 1 month prior to the study's completion date.
Haddad 2013(58)	USA, Connecticut, Community Health Centre, 2 sites	N=266 69.2% men 40.1 years (NR) 20-64	BUP.	Retrospective cohort study	July 2007-December 2008	Dropout	Retention was defined as being on BMT at the end of the pre-specified time period, it was defined as the time until initial discontinuation of BMT
Huissoud 2012 (59)	Switzerland, Canton of Vaud	N=1666 71.4% men Age: ≥30 years = 42% ≤ 30 years = 57.9%	MMT	Retrospective cohort study	January 2001 - June 2008	Dropout	Dropout defined as ending treatment and included the following reason, dropping out, methadone withdrawal, transfer, or entry to prison
Johns 2018 (60)	Vietnam, 7 provinces MMT clinics	N = 1,021 No user fee policy 99% men	MMT	Prospective cohort study	May 2015-June 2016	Dropout	Dropout: when patient has not come for MMT for 30 consecutive days and no reason for lack of attendance given to or ascertained by facility staff. Did not include those who

		Mean age 37.7 years User fee policy 96% men Mean age 34.7years NR					stopped MMT with staff permission, and unclear if excluded those who failed a urine test
Kayman 2006 (61)	USA, New York Hospital-affiliated MMT clinic	N=338 75% men 39(±8.33) years NR	MMT	Prospective cohort study	July 1997 - May 1999	Dropout	Treatment provider provided weekly updates on list of patients who had left treatment. This detail used to identify those who had dropped out within a year after enrolment
Kelly 2011 (62)	USA, Baltimore, 6 MMT clinics	N=351 53.3% men 41.2(±8.2) years NR	MMT	Prospective cohort study	November 2004 – November 2007	Dropout	Retention: number of days enrolled in the index treatment program through 12 months (maximum number of days = 365).
Lambdin 2014 (63)	National Hospital Tanzania	N=629 93% men 32(±6) years NR	MMT	Retrospective cohort study	February 2011 - January 2013	Dropout	Dropout: Attrition, dropping out of MMT defined as 21 consecutive missed doses, and a client's last pharmacy refill was assigned as the date of dropout.
Ledgerwood 2019 (64)	USA, Detroit University affiliated urban MMT clinic	N = 290 Non Injector (n=175) 57.1% men Age : ≥55 years - 35.4% NR Injector (N= 115) 63.5% men Age : ≥55 years – 30.4% NR	MMT	Retrospective cohort study	2002 - 2009	Retention	Retention: Number of days retained in MMT

Lin 2013 (65)	Taiwan, 3 Hospital based outpatient clinics	N=368 86.4% men 37.2(±7.6) years NR	MMT	Prospective cohort study	Recruited March 2007 – July 2008 with 18 month follow-up	Dropout	Dropout at 18 months. Duration of retention was defined as entry into MMT to discontinuation of the treatment
Lin 2015 (66)	Taiwan, 4 MMT outpatient clinics	N = 128 88.3% men mean age 36.65 ± 8.34 years NR	MMT	Prospective cohort study	July 2008 – April 2010	Dropout	Patients had to go daily to clinic to receive methadone dose, and were considered treatment dropouts if they failed to take their methadone for 14 consecutive days
Liu 2017 (67)	China, Guangzhou 4 MMT Clinics	N=401 87.5% men Age: < 40 years = 29.2% ≥ 40 years =70.8%	MMT	Prospective cohort study	August 2013 - August 2014	Dropout	Dropout was defined as not having visited the clinic for at least 30 consecutive days prior to the study's completion date.
Manhapra 2017 (68)	USA, National Veterans Health administration records	N = 3,151 94.1% men 42.8 years	BUP.	Retrospective cohort study	October 2011 - September 2015	Dropout	Dropout: Duration of treatment calculated from first day of BUP filled to last day BUP was filled from 2011 to 2015
Manhapra 2018 (69)	USA, Nationwide study of insured individuals of large employers and private health plans using the MarketScan Commercial	N = 16,190 65.2% men NR	BUP.	Retrospective cohort study	Federal fiscal (FY) year 2011 – federal fiscal year 2014	Dropout	Treatment discontinuation at 3 years – time to discontinuation based on date of first day of BUP or BUP/naloxone fill in FY 2011 and last date BUP or BUP/naloxone was filled (up to FY 2014)

	Claims and Encounters Database.						
Meshberg – Cohen 2018 (70)	Veterans enrolled in BUP treatment at Veteran Affairs (VA) Connecticut Healthcare System USA	N = 140 92.9% men 45.4 (± 12.7) years NR	BUP.	Retrospective cohort study	October 2015 – March 2017	Retention	Retention: defined as sustained treatment engagement through the 6-months post-admission period as evidenced by BUP clinic attendance, pharmacy pickups, prescription renewals and no note indicating treatment dropout
Monico 2015 (71)	USA, Maryland Two outpatient programs	N=300 62% men 46 (±6.45) years NR	BUP.	Secondary analysis of a randomised control trial	NR	Retention	Retention: in treatment at 6 months. Not reported how this was ascertained (combination of self-report and clinic records)
Montalvo 2019 (72)	USA, Boston Buprenorphine clinic	N = 321 62% men 38 (± 10) years NR	BUP.	Retrospective cohort study	January 2010 – February 2016	Retention	Retention: continuous treatment with buprenorphine for greater than or equal to one year. The duration of patients' continuous treatment episodes was determined from the elapsed time between patients' initial buprenorphine prescription and the last day of an active prescription before disengaging from the treatment. Longest episode is selected
Mullen 2012 (73)	Ireland National treatment register (specialist drug treatment centres; Community drug treatment centres;	N=1269 68.6% men 26 (SD NR) years NR	MMT	Retrospective cohort study	1999, 2001, 2003	Retention	Retention in treatment at 12 months, based on entry and exit dates in national register

	primary care setting)						
Nosyk 2009(74)	British Columbia PharmaNet database all persons receiving MMT	N=17,005 66% male 65% aged 20-40 years NR	MMT	Retrospective cohort study	January 1996-December 2006	Dropout	Time to discontinuation: the length of a treatment episode was calculated as the difference between the last and first days of medication dispensed, within a period continuous retention in treatment, where continuous entailed no interruptions in prescribed doses lasting longer than 30 days
Peles 2008 (75)	USA (Nevada) and Israel (Tel Aviv) 2 MMT clinics	N=704 **Tel Aviv (492)** : 72.8% men 36.7(±8.5) years Range: 18-67 **Las Vegas (302):** 62.9% men 43.4(±9.4) years Range:19-63	MMT	Prospective cohort study	Las Vegas: February 2000 – April 2005 Tel-Aviv: June 1993 – June 2004	Retention	6 months retention, 1 year retention in treatment, and the total duration in treatment (dates of admission and date of discharge if a patient left treatment or date of end of follow-up if a patient was still in treatment for computing cumulative retention).
Peles 2018 (76)	Tel Aviv, Israel University affiliated clinic	N = 890 74.8% men Age 18-39 years – 53.6% ≥ 40 years – 46.4% NR	MMT	Retrospective cohort study	June 1993 – June 2017	Retention	Retention: first MMT admission until the patient died, left, or until the end of follow-up.
Perreault 2015(77)	Canada, Montreal Low threshold programme	N=106 74.5% men 28.5 (± 8.6) years Range: 18 to 59	MMT	Prospective cohort study	2001 - 2006	Retention	Treatment retention defined as (i) being treated in the methadone program at the 1-year follow-up period or (ii) having been transferred to conventional “regular” maintenance programs or to private physicians. Participants were considered dropouts if they did not receive methadone treatment for a month within the treatment service offered.

Perreault 2005 (78)	Canada, Montreal Low threshold clinic	N=141 51% men 26.8(±6.5) years NR	MMT	Prospective cohort study	November 1999 - October 2000	Dropout	At the end of 6 month follow-up, clients categorised at treatment failure or treatment success. Failure included dropout (clients who did not go to the pharmacy for their dose of methadone for 7 consecutive days), and administrative discharges (discharged due to violent or antisocial behaviour); Treatment success included clients who were still in treatment at end of follow-up period
Proctor 2015 (79)	USA 26 MMT clinics	N=1644 63.1% men 34.7 (± 11.06) years NR	MMT	Retrospective cohort study	January 2009 - April 2011	Dropout	Dropout: premature treatment discharge at the 6-month (length of treatment ≤179 days) and 12-month (≤364) follow-up interval.
Ren 2013 (80)	China, Shanghai MMT clinics	N=2463 77.8% men 40.9(±8.5) years NR	MMT	Retrospective cohort study	January 2007 - December 2011	Dropout	Dropout: an event with more than 30 suspended days. Suspended days: a period of time that did not have methadone dosing records continuously recorded, except if there was a temporary or permanent referral to other provinces.
Ruadze 2016 (81)	Georgia MMT clinics	N=1051 97.2% men 40.4 (SD NR) years 21 -67 years	MMT	Retrospective cohort study	2014 - 2015	Retention	Retention: (1) more than 6-months retention (≥181 days stay); (2) more than 9 months retention (≥270 days stay); (3) more than 12 months retention (≥365 days stay)
Saloner 2017 (82)	USA, 11 states Community based	N=27,273 52% men NR	BUP.	Retrospective cohort study	January 2010 - July 2012	Retention	6 month retention (binary measure of treatment episodes 180 days or longer) After 90 days of no fills the episode was defined as terminated
Sarasvita 2012 (83)	Indonesia 3 MMT clinics -	N=178 90% men 27.2(±4.8) years NR	MMT	Prospective cohort study	July 2006 – January 2008	Dropout	Retention: The duration of treatment (in days). Study participants who left treatment but subsequently re-entered within 5 days were counted as a continuous episode of treatment. Participants who re-entered after 5 days had the

							subsequent episode counted as a separate treatment episode. Dropping out of treatment was defined as a participant failing to take a daily dosage of methadone for a minimum of five consecutive days
Schuman-Olivier 2013 (84)	USA, Boston OBOT	N=328 59.7% men No BZD treatment N=270 64.8% men 35.6 (±10.5) years NR BZD treatment N=58 36.2% men 37.7 (± 11.6) years NR	BUP.	Retrospective cohort study	November 2007 - June 2010	Retention	12-month treatment retention.
Shakira 2017 (85)	Malaysia, Khota Bharu Tertiary hospital MMT programme	N = 178 98.3 % men 31.5 (± 5.2) years (18-58)	MMT	Retrospective cohort study	November 2005 – November 2010	Dropout	Dropout: failure of retention that includes voluntary dropout or involuntary dropout (due to excluded, imprisoned, transferred to other MMT or death due to any cause)
Shcherbakova2018 (86)	USA, Massachusetts Insurance claims data from a regional health plan	N = 302 71.5% men 34.5 (± 12.7) years NR	Mixed OST	Retrospective cohort study	June 2010 – January 2015	Retention	Retention (treatment persistence): The number of days from the fill date of the first buprenorphine containing prescription until more than 30 consecutive days without buprenorphine.

	Employer – sponsored and Medicaid patients						
Socias 2018 (87)	Canada, Vancouver VIDUS and ACCESS cohorts	N = 820 57.8% men Median age: 38 years (no SD) NR	Mixed OST	Prospective cohort study	December 1996 –May 2016	Retention	Retention: Defined as a self-report of being on methadone or buprenorphine/naloxone based treatment in the current and immediately previous follow-up interview (approximately a 6 month retention interval)
Stein 2005 (88)	USA, Rhode Island Primary care	N=41 58.5% men 40.1 (±7.83) years NR	BUP.	Prospective cohort study	2003	Dropout	Dropout not defined
Strike 2005 (89)	Canada Population based MMT treatment register	N = NR 9555 treatment episodes 70.3% men 34.9 (SD NR) years NR	MMT	Retrospective cohort study	January 1996 - December 2001	Retention	2-year retention (730 days), an interval of greater than 7 days between a cessation and a new MMT registration constituted cessation of a treatment episode
Sullivan 2013 (90)	China 540 MMT clinics	N=107,740 85% men 35 (SD NR) years NR	MMT	Retrospective cohort study	April 2008 - March 2010	Retention	Duration of treatment: follow-up began on the date of entry, on or later than 1st April 2008, and ended when a client missed 30 days or more or at study end (31 march 2010)
Teoh 2017 (91)	Malaysia, Kuala Lumpur Tertiary hospital MMT programme	N = 164 100% men 40.7 (± 10.1) years NR	MMT	Retrospective cohort study	2005 – 2015	Dropout	Retention: time of entry to the MMT programme either until dropout or June 2015.

Wei 2013(92)	Xi China, 8 MMT Clinics	N=5849 84.1% men NR	MMT	Retrospective cohort study	January 2006-December 2011	Dropout	Retention: Number of days from admission until the patient quit treatment or until the end of follow-up. End date Dec 2011, before this date, patients who were absent from MMT for 30 days were considered to have dropped out
Weinstein 2017 (93)	USA, Boston Office based opioid treatment	N=1237 61.4% men 38 (± 11) years NR	BUP.	Retrospective cohort study	January 2002 - February 2014	Retention	Retention defined as at least one year of continuous treatment with buprenorphine (individual was in treatment for at least 365 days, as long as any gap in care was <60 days). "≥2 year retention" was also explored
Yang 2013 (94)	China, Guangdong 6 MMT clinics	N=2728 72.8% men 36.4(±12.4) years NR	MMT	Retrospective cohort study	January 2006 - September 2010	Dropout	Retention: patients remaining in MMT along the period of study (January 1st, 2006 and September 30th, 2010) or who were temporarily referred to other MMT clinics other than the selected 6 clinics. Retention duration is calculated from first MMT entry and up to the date patients dropped out of treatment or the end of the follow-up period (September 30th, 2010).
Zhang 2015 (95)	China, Guangdong Province, 14 MMT clinics	N=1512 90.0% men, 38.6 (5.99) years Range: 21–63	MMT	Ambi-directional cohort study	2006 - 2014	Dropout	An individual was considered as 'dropout' if they missed methadone intake for ≥14 consecutive days. Participants were considered as "ever dropouts" if only he/she dropout in their initial treatments or in the subsequent period of time during the study duration. Participants who did not dropout were considered 'retained'.
Zhou 2017 (96)	China, Xi'an 2 MMT clinics, one public one private	N=1212 77.1% men 39.24 (± 6.24) years Range: 19-69	MMT	Prospective cohort study	March 2012 - March 2014	Dropout	Retention defined as premature terminations, reflecting whether patients continued MMT after the 2-year follow-up; patients who were off methadone for 7 consecutive days were considered to have terminated.

Zhou 2016 (97)	China, Xi'an 14 MMT clinics	N=10398 83.9% men 38.06 (± 6.98) years Range: 17-69	MMT	Retrospective cohort study	January 2006 - December 2013	Dropout	Dropout: patients with a difference of >7 days between the date of last methadone intake and the endpoint identified as the ‘‘dropout’’ group; patients with a difference of ≤7 days between the date of last methadone intake and the endpoint were defined as the ‘‘retained’’ group.

Appendix 7. Study results of the critical appraisal of included studies (NOS scores)

	Selection			Comparability	Outcome			
Author	**Representativeness of sample**	**Ascertainment of Exposure**	**Definition of outcome**	**Comparability**	**Ascertainment of outcome**	**Duration of follow-up**	**Adequacy of follow-up**	**Study total out of 7 stars:**
Abramsohn 2009 (140)			*		*	*	*	**4**
Adelson 2013 (141)		*	*	*	*	*	*	**6**
Amiri 2018 (142)		*		*	*	*	*	**5**
Astals 2009 (143)		*	*	*	*	*	*	**6**
Banta-Green 2009 (144)	*	*	*	*	*	*	*	**7**
Bhatraju 2017 (145)		*		*	*	*	*	**5**
Bounes 2013 (146)	*	*	*	*	*	*	*	**7**
Brands 2008 (147)		*	*	*	*	*	*	**6**
Bukten 2014 (148)	*	*		*	*	*	*	**6**
Burns 2009 (149)	*	*	*	*	*	*	*	**7**
Cao 2014 (150)	*	*	*	*	*	*	*	**7**
Cox 2013 (151)		*	*	*	*	*	*	**6**

Cunningham 2013 (152)		*	*	*	*	*	*	**6**
Davstad 2007 (153)	*	*	*		*	*	*	**6**
Dayal 2017 (154)		*	*	*	*	*	*	**6**
Deck 2005 (155)	*	*	*	*	*	*	*	**7**
Dumchev 2017 (156)	*	*	*	*	*	*	*	**7**
Eibl 2015 (157)	*	*	*	*	*	*	*	**7**
Franklyn 2017 (158)	*	*	*	*	*	*	*	**7**
Friedmann 2001(159)	*	*	*	*	*	*	*	**7**
Gerra 2011(160)	*	*			*	*	*	**5**
Gryczynski 2014 (161)	*	*			*	*	*	**5**
Gu 2012 (162)	*	*	*	*	*	*	*	**7**
Haddad 2013 (163)	*	*	*	*	*	*	*	**7**
Huissoud 2012 (164)	*	*		*	*	*	*	**6**
Johns 2018 (165)	*	*	*	*	*	*	*	**7**
Kayman 2006 (166)		*	*	*	*	*	*	**6**
Kelly 2011 (167)		*			*	*	*	**4**

Lambdin 2014 (168)		*	*	*	*	*	*	**6**
Ledgerwood 2019 (169)			*	*	*	*	*	**5**
Lin 2013 (170)		*		*	*	*	*	**5**
Lin 2015 (171)	*	*	*	*	*	*	*	**7**
Liu 2017 (172)	*	*	*	*	*	*	*	**7**
Manhapra 2017 (173)		*		*	*	*	*	**5**
Manhapra 2018 (174)		*		*	*	*	*	**5**
Meshberg – Cohen 2019 (175)		*	*	*	*	*	*	**6**
Monico 2015 (176)		*	*	*		*	*	**5**
Montalvo 2019 (177)		*	*	*	*	*	*	**6**
Mullen 2012 (103)	*	*	*	*	*	*	*	**7**
Nosyk 2009 (178)	*	*	*	*	*	*	*	**7**
Peles 2008 (179)		*	*	*	*	*	*	**6**
Peles 2018 (180)		*		*	*	*	*	**5**
Perreault 2015 (181)		*	*	*	*	*	*	**6**

Perreault 2005 (182)		*	*	*	*	*	*	**6**
Proctor 2015 (183)		*	*	*	*	*	*	**6**
Ren 2013 (184)	*	*	*	*	*	*	*	**7**
Ruadze 2016 (185)	*	*		*		*	*	**5**
Saloner 2017 (186)	*	*	*	*	*	*	*	**7**
Sarasvita 2012 (187)	*		*	*	*	*	*	**6**
Schuman-Olivier 2013 (188)	*	*		*		*	*	**5**
Shakira 2017 (189)				*	*	*	*	**4**
Shcherbakova2018 (190)	*	*	*	*	*	*	*	**7**
Socias 2018 (191)		*	*	*		*	*	**5**
Stein 2005 (192)		*			*	*	*	**4**
Strike 2005 (193)	*	*	*	*	*	*	*	**7**
Sullivan 2013 (194)	*	*	*	*	*	*	*	**7**
Teoh 2018 (195)		*		*	*	*	*	**5**
Wei 2013 (196)	*	*	*	*	*	*	*	**7**

Weinstein 2017 (197)		*	*	*	*	*	*	**6**
Yang 2013 (198)	*	*		*	*	*	*	**6**
Zhang 2015 (199)	*	*	*	*	*	*	*	**7**
Zhou 2017 (200)	*	*	*	*		*	*	**6**
Zhou 2016 (201)	*	*	*	*	*	*	*	**7**

Appendix 8. Summary of results of included studies in systematic review; potential risk and protective factors explored

First author	Retention or Dropout Rates	Outcome Model and coefficients reported	Demographics Age Gender Location Race	Substance use Poly-drug use Cannabis use BZD use Cocaine use Heroin use Alcohol use Amphetamines/ecstasy Drug use patterns	Treatment Factors Medication type Dosage Previous treatments Year of treatment intake Treatment setting Treatment facilities	Health Risk Behaviour Injecting and sexual behaviour Injecting Sharing needles	Health Symptoms Non-fatal overdose Clinical diagnosis: Mental health (self-reported) Physical health (self-reported) HIV+/- TB +/-	Social functioning Marital Status Employment status Income Education Living status Social Support Legal issues	Other variables investigated in included studies
Abramsohn 2009 (140)	Retention at 1 year (85.6%)	Retention at 1 year Survival analysis with log rank of retention			-	-	-	-	High (>130) Sense of Coherence score – S 3.50 (3.20-3.90) years Low (≤130) Sense of Coherence score – S

									2.90(2.50-3.30) years
Adelson 2013 (141)	Retention at 1 year (59.5%)	Long-term treatment retention (4.5 years) Cox regression model Hazard Ratios (95% CI)	-	-	Methadone dose (high-≥80mg/day) – S 2.20 (1.30-3.70)	-	Being sera positive to hepatitis C on admission – S 1.80 (1.10–2.80)	-	-
Amiri 2018 (142)	Retention at 1 year (50%); at 3 years (30%)	Dropout (time to dropout between 2015-2017) Cox proportional hazard model (95% CI)	Age – S 0.99 (0.98 - 0.99) Gender (ref: female) – NS 1.17 (0.96 - 1 .41) Area deprivation index :		Methadone dose (mean, SD) – S 0.98 (0.98 – 0.98) Years on treatment (median, IQR) – S 1.12 (1.06 – 1.18)			Cannabis retail outlets in neighbourhood (median) – NS 1.08 (0.99-1.18) Off-premise alcohol outlets in	Distance to OTP (ref: < 5 miles): >5 miles and <10 miles – NS 0.84 (0.65 – 1.09) > 10 miles – NS 1.12 (0.82 – 1.54)

		Hazard Ratios (95% CI)	(ref: Least deprived < 100) MOST deprived > 100 – S 1.79 (1.02 – 3.15) Ethnicity (ref: non-Hispanic white) other – NS 1.00 (0.79 – 1.26)					neighbourhood (median) – NS 0.99 (0.96-1.03) On-premise alcohol outlets in neighbourhood (median) – NS 1.00 (0.99-1.00)	
Astals 2009 (143)	Retention at 18 months (68.5%)	Dropout (follow-up 18 months) Logistic regression Odds Ratios (95% CI)	Age – NS (no figures reported) Male – NS 2.59 (0.98–6.84)	Current diagnosis of cocaine and opiates other than heroin dependence – NSU-	Methadone dose NSU	-	Co-occurring psychiatric disorders NSU	Lower educational level – NS 2.65 (0.98–7.13)	-

Banta-Green 2009 (144)	Retention at 12-months Prescription type opioid only users (54%); Those who had used heroin (46%)	Retention at 12-months Logistic regression Odds Ratios (95% CI)	Age (10 year increments) – S 1.27(1.15-1.40) Female – NS 1.12(0.93-1.34) Black (ref: white) - S 0.69 (0.52-0.91) Native American – NS 0.95(0.62-1.44) Other race – NS 0.96(0.72-1.30)	Cocaine – S 0.75(0.63-0.91) Methamphetamine – S 0.62(0.44-0.89)	In treatment for prescription-type opioid primary(vs. heroin use) – NS 1.25(0.93-1.67)		Clinical diagnosis: Medical concerns – S 0.74(0.62-0.88)	Public assistance (ref: no public assistance): GAU(low income ,temporarily disabled): -S 1.58(1.19-2.09) TANF(parenting) –S 1.89(1.37-2.60) GAX or SSI (disabled) – S 1.86(1.48-2.35) Medical assistance only – NS 1.06(0.71-1.59)Other - NS 1.42(0.37-5.46)Home conducive	Agency (ref: agency 1) : agency 2 – NS 0.57(0.30-1.08) Agency 3 – NS 0.62(0.34-1.14) Agency 4 – NS 0.90(0.57-1.43) Agency 5 – NS 0.66(0.42-1.05) Agency 6 – S 0.62(0.44-0.89) Agency 7 – NS 0.82(0.56-1.20) Agency 8 –S 0.73(0.53-0.99) Agency 9 – NS

								to recovery – S 1.52(1.26-1.84) Children under 12 at home - S 1.35(1.03-1.78) Legal system involvement – S 0.71(0.57-0.89)	0.95(0.74-1.23) Agency 10 – NS 1.15(0.79-1.66) Agency 11 – NS 0.85(0.48-1.48)
Bhatraju 2017 (145)	Median retention 57 weeks	Dropout (Time to dropout between 2006 and 2013) Cox proportional hazard models Model 1: total sample; Model 2:	Model 1 (total sample): Age - NS 0.98(0.97-1.00)Gender - NS Ethnicity- NS Model 2 (induction service users)	Model 1 (total sample): Active Cocaine use - NS 1.18(0.90–1.54) Active heroin use - NS 1.25(0.96–1.64)	Model 1 (total sample): Prior buprenorphine use – NSU Year of first visit (ref: 2007): 2008 – NS 0.81 (0.54–1.20) 2009 –S 0.67 (0.49–0.91)	-	-		-

		Induction service users Hazard Ratios (95% CI)	Age - NS 0.99 (0.97-1.00) Gender - NS Ethnicity- NS	Model 2 (induction service users) Active Cocaine use - NS 1.15(0.83–1.59) Active heroin use - NS 1.27(0.93–1.75)	2010 - NS 0.75 (0.54–1.04) 2011 - NS 0.70 (0.49–1.01) 2012 - NS 0.61 (0.35–1.05) 2013 - NS 0.62 (0.29–1.34) Inducted – NS: 1.46 (1.10–1.93) Outpatient counselling active – NSU 12 step attendance active - NSU Any induction related adverse effects - NSU Methadone to				

					buprenorphine induction - NSU Model 2 (induction service users) No factor significantly associated with time to dropout				
Bounes 2013 (146)	Retention rate at 12-months (33%)	Retention at 12-months Logistic Regression Odds Ratio (95% CI)	Gender (ref Male)-NS 1.66 (0.71-3.87) Age-(ref < 30 yrs)-NS 30-40 yrs: 1.08 (0.42-2.75) >40 yrs: 1.56 (0.59-4.18)		Type of OAT (BUP ref MMT)- S 0.33 (0.15-.072)		Acute pain exposure (ref unexposed) -NS 0.48 (0.23-1.00)		

Brands 2008 (147)	Retention at 2 years (60%)	Dropout Cox Regression analysis	Age-NS (NR) Gender- NS (NR)	Opioid history-NS (NR) Benzodiazepine-NS (NR) Opioid and Cocaine use-S (β=0.95; p=0.008) HR 2.6			Psychiatric treatment history-NS (NR)		
Bukten 2014 (148)	18 month retention rate (65.8%)	Dropout at 18 months Cox proportional-hazards regression Hazard Ratios (95% CI)	Female – NS 0.95(0.82-1.11) Age – S 0.97(0.96-0.98)	-	-	-	-	Pre-treatment offences (ref: none): Medium (1-24) offences – NS 1.03(0.87-1.22) High (25+) offences - S 1.66(1.32-2.09) Drug offences in	-

								the last 30 days – S 1.80(1.36-2.38)	
Burns 2009 (149)	Retention 1985: retention at six-months (59%); at 12-months (50%) 2000 Retention at six-months (54%); at 12-months (41%)	Dropout in the first 9 months and after 9 months Cox proportional hazards model of leaving the first treatment episode, splitting the follow-up at 9 months (1985-2000) and six-months (2001-2006).	Model 1 (1985-2000) Age(ref: <20 years) 40+ yrs - S 0.45(0.42-0.49) 30-39 yrs - S 0.55(0.53-0.58) 20-29yrs - S 0.75(0.72-0.79) Male (ref: female): - S 1.16(1.13-1.19) Model 2 (2001-2006) Age(ref: <20 years) 40+ yrs - S	-	Model 1 (1985-2000)Intake (ref:1985-1989) 1995-2000 – S 1.24(1.19-1.28) 1990-1994 – NS 0.96(0.92-1.00) f**irst 9 months of treatment (ref: clinic)** Correctional facility - S 0.61(0.56-0.65) Community pharmacy -	-	-	-	-

		Hazard Ratios (95% CI)	0.55(0.49-0.61) 30-39 yrs - S 0.75(0.69-0.82) 20-29yrs - S 0.84(0.77-0.91) Male (ref: female): - S 1.14(1.08-1.21)		S 0.68(0.64-0.72) Other - S 0.83(0.76-0.90) **after 9 months in treatment (ref: clinic)** Correctional facility - S 1.18 (1.09-1.28) Community pharmacy - S 0.86(0.80-0.92) Other – NS 1.09(.99-1.20) Model 2 (2001-2006) Buprenorphine (ref Methadone) – S 1.89(1.79-1.99)				

					first six-months of treatment (ref: clinic) Correctional facility - S 0.76(0.69-0.83) Community pharmacy - S 0.44(0.38-0.50) Other - S 0.96(0.85-1.08) **After 6 months in treatment (ref: clinic)** Correctional facility - S 1.94 (1.76-2.15) Community pharmacy - S 0.45 (0.56-0.76) Other – NS 0.63 (0.49-0.82)				

Cao 2014 (150)	Retention at 6 years (35.7%)	Dropout (follow-up time 6 years) Cox proportional hazards Hazard Ratios (95% CI)	-	Illicit drug use during treatment (ref: ≤ 10%):11-20% - S 0.55(0.42-0.73) >20% - S 0.63(0.52-0.76)	Dosage (ref: ≤ 30%) 31-60mg – S 0.57(0.47-0.71) >60mg – S 0.38(0.29-0.51)	-	-	Contact with drug users (ref: none) 1-30 – NS 0.93(0.76-1.45) >30 – NS 1.14(0.90-1.45) Relatives who were MMT clients (ref: no) Yes – S 0.72(0.54-0.96)	-
Cox 2013 (151)	Retention at 12-months (72%) Retention at 3 years (63%)	Dropout (time to dropout between 2004 and 2007) Cox Proportional Hazards Regression models of (1)	Model 1: Involuntary Discharge Sex (Female) – S 0.31 (0.13-0.71) Model 2: Voluntary discharge	Model 1: Involuntary Discharge Use of sedatives- S 3.56 (1.77-7.19) Lifetime history of opioid	-	-	-	Model 1: Involuntary Discharge Number of lifetime arrests >6 - S 2.70 (1.14-5.17)	-

		Involuntary discharge; (2) voluntary discharge Hazard Ratios (95% CI)	Sex (Female) – S 2.47 (1.11-5.54)	abuse (> 5 years) - S 2.05 (1.06-3.98) Model 2: Voluntary discharge Injecting opioids – S 4.44 (1.64-11.99) Use of sedatives- S 3.69 (1.61-8.47)				Any personal debt – S 0.44(0.21-0.91 Days of serious conflict with others (>- 1 day excluding family) - S 4.40 (2.11-9.21)	
Cunningham 2013 (152)	Retention at six-months (54%)	Retention at six-months Logistic regression Odds Ratios (95% CI)	-	Prior use of illicit buprenorphine only - NS 2.92(0.95-8.91)	Prior use of prescribed buprenorphine – NS 2.53(0.81-7.88) Prior use of any buprenorphine –S	-	-	-	-

					2.65(1.05-6.70)				
Davstad 2007 (153)	Retention at 1 year (84%); retention at 2 years (65%)	Dropout between 1995 and 2000 Poisson Regression and Spearman's rank order correlations	-	-	Last mean adjusted dose was significantly lower for discharged service users than for those who remained in treatment: 70mg vs. 76mg at six-months – S p<.0001 75mg vs. 84mg at 1 year – S p<.0001 81mg vs. 87mg at 2 years - S p<.05	-	-	-	-

Dayal 2017 (154)	Retention at six-months (19.1%); at 12-months (11.7%)	Dropout at 2 years Cox Regression Hazard Ratios (95% CI)	-	Benzodiazepine use (ref: no) - NS 0.58 (0.21-1.60)	Buprenorphine maintenance dose - S 0.86 (0.78-0.95)	Past month injection use (yes)– S 0.31(0.14-0.66)	-	Use of substance in 1st degree relatives (ref: no) – S 2.40 (1.34-4.31) Parent support (ref: no) - NS 0.99(0.57-1.73)	-
Deck 2005 (155)	Retention NR	Retention at 12-months Logistic regression Odds Ratios (95% CI)	**Oregon** Age (in 10 year increments) – S 1.25(1.09-1.43) Male – S 0.79(0.67-0.95) African American (vs Caucasian) – NS	**Oregon** Cocaine as secondary drug – S 0.69(0.62-0.88) Daily opiate use in past 30 days – S 0.68(0.49-0.94) Alcohol as secondary drug – NS	**Oregon** Prior methadone (past 2 years) – S 1.44(1.17-1.79) Prior treatment (past 2 year) – NS 1.17(0.97-1.41) Self-referral – NS	**Oregon** Needle use in past 30 days – NS 0.84(0.61-1.16) **Washington** Needle use in past 30 days – NS 0.75(0.53-1.06)	**Oregon** Disabled (vs. welfare) – S 0.60(0.43-0.84) Expansion (vs welfare) – NS 0.80(0.61-1.05) Other (vs welfare) – NS	**Oregon** Married (vs other status – NS 1.10(0.88-1.37) Never married (vs other status) – NS 1.08(0.89-1.30) Not employable – NS	**Oregon** Adjacent county (vs. county with clinic) – NS 1.11(0.86-1.44) Distant country (vs county with clinic) – NS 0.71(0.41-1.24)

			0.79(0.58-1.08) Hispanic (vs. Caucasian) – NS 1.01(0.64-1.57) Native American (vs. Caucasian) – NS 0.81(0.51-1.28) **Washington** Age (in 10 year increments) – S 1.21(1.06-1.38) Male – S 0.73(0.61-.88) African American (vs Caucasian) – S	1.03(0.84-1.26) Amphetamines as secondary drug – S 0.76(0.57-0.83) Year of opiate use (log transformation – NS 1.09(0.95-1.25) **Washington** Cocaine as secondary drug - S 0.64(0.54-0.76) Daily opiate use in past 30 days – S 0.78(0.61-0.99) Alcohol as secondary drug – NS	0.86(0.67-1.12) Stable admission cohort (vs 1994) 1995 - NS 1.23(0.95-1.58) 1996 – NS 1.29(0.95-1.75) 1997 – S 1.97(1.44-2.71) 1998 – S 3.54(2.61-4.80) 1999 – S 2.85(2.06-3.93) Treatment agency referral – NS 1.05(0.78-1.39) Legal referral - NS 1.10(0.56-2.15)		0.75(0.52-1.07) Mental health needs - NSU- Stable Medicaid eligibility - S 2.45(1.98-3.04) **Washington** Disabled (vs. welfare) – NS 1.16(0.92-1.48) Expansion (vs welfare) – NSU- Other (vs welfare) – NS 1.23(0.96-1.59)	0.83(0.67-1.04) No source of income – NS 0.90(0.74-1.10) Personal home (vs other living situation) - NS 0.94(0.74-1.17) Homeless(vs other living situation) – NS 0.99(0.70-1.41) Pregnant – NS 0.72(0.44-1.20) Arrested (past 2 years) – S 0.81(0.68-0.96)	Agency provider (vs mean) A – NS 0.97(0.79-1.20) B – NS 0.95(0.79-1.14) C – NS 0.99(0.78-1.25) D – S 1.46(1.05-2.03) E – NS 0.80(0.62-1.04) F – S 0.42(0.33-0.54) G – S 4.41(2.76-7.05) **Washington** Adjacent county (vs. county with clinic) – NS

			0.49(0.38-0.64) Hispanic (vs. Caucasian) – NS 0.96(0.67-1.40) Native American (vs. Caucasian) – NS 0.70(0.45-1.09)	1.00(0.83-1.20) Amphetamines as secondary drug – NS 1.01(0.70-1.45) year of opiate use (log transformation) – NS 1.08(0.95-1.22)	**Washington** Prior methadone (past 2 years) – NS 1.23(.97-1.56) Prior treatment (past 2 year) – NS 0.99(0.82-1.19) Admission cohort (vs 1994) 1995 – NS 1.01(0.79-1.29) 1996 – NS 1.07(0.80-1.44) 1997 – S 1.40 (1.06-1.86) 1998 – NS 1.22 (0.90 - 1.67) 1999 – NS		Mental health needs - NS 1.05(0.87-1.26) Stable Medicaid eligibility - S 1.64(1.32-2.05)	**Washington** Married (vs other status) – NS 1.26(0.99-1.59) Never married (vs other status) – S 1.24(1.02-1.52) Not employable – NS 0.89(0.71-1.11) No source of income – NS 1.08 (0.80-1.45) Personal home (vs other living situation) – NS 1.06(0.81-1.40) Homeless(v	0.99 (0.68-1.29) Distant country (vs county with clinic) – NS 0.75(0.43-1.31) Agency provider (vs mean) A - NS 0.88(0.69-1.12) B – NS 0.89(0.69-1.69) C – NS 1.24(0.95-1.63) D – NS 0.78(0.54-1.15) E – S 5.94(2.71-12.99) F – S 0.31(0.16-0.59)

					1.12(0.83-1.52) Self-referral – NS 0.96(0.72-1.28) Treatment agency referral – NS 1.48(0.92-2.40) Legal referral – NS 1.24(0.75-2.02)			s other living situation) – NS 0.87(0.58-1.32) Pregnant – S 0.42(0.26-0.67) Arrested (past 2 years) – S 0.73(0.61-0.87) Enrolled in Alcoholism and Drug Addiction Treatment and Support Act system – S 0.54 (0.33-0.89)	
Dumchev 2017 (156)	Retention Retention at six-	Dropout (time to dropout between	Age – NS 1.00(1.00-1.00)	-	Medication type (buprenorphine vs	-	Last HIV test result (negative vs	-	Site (DPSPC vs DPGP5) – NS

	months (75.8%); 9 months (70.1%); 12-months (65.8%); 18 months (59.4%); 24 months (53.8%); 60 months (39.6%)	2005 and 2012) Cox proportional hazards model hazard ratio (95% CI)	Sex (male vs female) – NS 1.00(0.94-1.07)		methadone) – NS 1.00(0.94-1.06) Last prescribed dose (high vs low) – S 0.57(0.44-0.75) Last prescribed dose (medium vs low) – S 0.57(0.45-0.71) Admission year: 2010 vs 2011-2012 – NS 1.00(0.95-1.05) 2009 vs 2011-2012 - NS		positive) – NS 1.00(0.96-1.04) Last HIV test (not tested vs positive) – S 4.44(3.10-6.35) Last HCV test result (negative vs positive) - NS 1.00(0.92-1.08) Last HCV test result (not tested vs positive) – NS 1.11(0.81-1.53) Last HBV test results (negative vs positive) - NS		1.17(0.74-1.85) Site (PNDKR vs DPGP5) – NS 0.82(0.53-1.26) Site (PNDN7 vs DPGP5) – NS 0.93(0.69-1.25) Site (VOND1 vs DPGP5) – NS 1.23(0.78-1.92) Site (VOND2 vs DPGP5) – NS 1.02(0.87-1.19)

					0.99(0.92-1.07) 2008 vs 2011-2012 - NS 1.00(0.96-1.05) 2007 vs 2011-2012 - NS 1.01(0.88-1.17) 2006 vs 2011-2012 - NS 1.00(0.94-1.06) 2005 vs 2011-2012 – S 3.39(2.04-5.63)		0.88(0.59-1.30) Last HBV test (not tested vs positive) – NS 1.12(0.80-1.57) Last TB test result (negative vs positive) – NS 0.78(0.51-1.18) Last TB test result (not tested vs positive) – S 3.34(2.23-5.01)		
Eibl 2015 (157)	Retention at 1 year NR (39.3%-48.9%)	Retention at 1 year Logistic regression Odds ratios (95% CI)	Southern Rural (ref: Southern Urban) – NS 1.06(0.92-1.22) Northern Urban – S	-		-	-	-	-

			1.14(1.02-1.27) Northern Rural – S 1.31(1.09-1.58)						
Franklyn 2017 (158)	Average retention rate at one year 43.4%	Dropout at 1 year Cox proportional hazard model Hazard Ratios (95% CI	Age - S0.98 (0.98–0.98) Gender (ref: male) - S 0.77(0.70–0.84) Location: North (ref: south) – S 0.59(0.54–0.66) Rural(ref: urban) - N S 0.98(0.86–1.12)	First-month benzodiazepine use – S 1.15(1.02–1.29)	-	-	-	-	-
Friedmann 2001(159)	Retention in MMT at 1 year (49%)	Retention at 1 year Multivariate logistic regression models	Age per 10 years - S 1.34(1.31-1.37) Gender (ref: male): female – NS	Heavy alcohol use (ref: no): Yes – NS 0.98(0.67-2.86)	Number prior drug treatments – NS 1.01(0.98-1.04)	-	Psychiatric severity composite score - NS 0.70(0.27-1.85)	Any criminal status (ref: no): Yes – NS 0.99(0.74-1.33)	Provision of transportation assistance (ref: no): Yes – S 2.97(2.10-4.20)

		Odds Ratios (95% CI)	1.20(0.91-1.59) Race (ref: Caucasian): African American - S 0.69(0.49-0.97) Other – NS 0.81(0.54-1.20)	Primary drug type (other drug: ref): Heroin – NS 1.01(0.67-1.52) Cocaine – NS 0.69(0.39-1.22) Drug severity composite score – NS 1.06(0.38-2.93)			Medical severity composite score - NS 1.15(0.70-1.90) Insurance type (ref: uninsured): Private – NS 1.36(0.84-2.21) Public - NS 1.10(0.79-1.55)	Employment status (ref: no work): Legal work – NS (0.87 0.62-1.22) Illegal work – NS 0.74 (0.51-1.07)	Individual vouchers or payment (ref: no): yes - NS 0.96(0.71-1.29) Client capacity per 10 clients – NS 1.00(0.99-1.01) Treatment readiness score – NS 1.06(0.60-1.88)
Gerra 2011(160)	Dropout at 12-months Clinic A (42%); Clinic B (26%); clinic C (50%) Retention at 12-months	Dropout at 1 year Event history analysis Odds Ratios (p values)			MMT Policy (Clinic A: under supervised daily consumption: Clinic B (contingent				

	60.66%				take home)-S 0.535 (p=0.02) Clinic C (non-contingent take home) –NS 1.144 (p=0.56)				
Gryczynski 2014 (161)	Treatment dropout at six-months 42.1%	Time to dropout at six-months Cox proportional hazards model Hazard Ratio (95% CI)	Female-NS 0.91 (0.63-1.32) Age-S 0.95 (0.91-1.00[) [time varying covariates separate model: Age-S 1.0006 (1.0002-1.0012)]	Intensive outpatient counselling (ref standard counselling) -NS 0.96 (0.67-1.38) Buprenorphine dose-S 0.84 (0.78-1.89) [time varying covariates separate model:	Injection drug users-NS 1.42 (0.94-2.13) Baseline positive cocaine urine-S 1.71 (1.18-2.48)				Intended treatment duration (weeks)- NS 1.004 (0.97-1.04)

				Buprenorphine dose-S 1.002 (1.001-1.003)]					
Gu 2012 (162)	51.3% of participants had dropped out of MMT at completion	Dropout at 18 months Cox Regression Risk Ratio (95% CI)	-	-	-	-	-	-	MMT is intended primarily for detoxification (Agree) (appropriate perception = 1): misconception - NS 2.29(0.97-5.41) After using MMT for 2-3 months one could be detoxified and can quit using MMT (Agree) (appropriate

									perception = 1): misconception – S 3.10(1.84-5.25) MMT requires a long term or even life time treatment (disagree) (appropriate perception =1): misconception – S 2.22(1.12-4.38) One should reduce the dosage of methadone as it is harmful to one's health

									(agree)(appropriate response=1): misconception – S 2.07(1.05-4.07) Number of items reflecting misconception (0-1=1): 2-3 – S 3.80(1.26-11.49) 4 – S 7.13(2.38-21.37)
Haddad 2013 (163)	56.8% retained at six-months	Dropout at 6 and 12-months Cox proportional hazard Model 1 (dropout at six-months)	**Model 1** Age-S 0.96 (0.94-0.98) Female-S 0.59 (0.37-0.92)	**Model 1** Baseline cocaine screen Positive-S 2.18 (1.35-3.50) **Model 2**	**Model 1** Receipt of substance abuse counselling-S 0.54(0.36-0.79) **Model 2**		**Model 1** Prescribed psychiatric medication-NS 0.69 (0.47-1.01) HCV Positive-S		

		Model 2: Dropout at 12-months Hazard Ratio (95% CI)		Baseline cocaine screen Positive-S 3.12 (1.57-6.16)	Receipt of substance abuse counselling-S 0.34(0.19-0.59)		0.56 (0.36-0.86) **Model 2** Prescribed psychiatric medication-S 0.36 (0.20-0.62)		
Huissoud 2012 (164)	Retention in treatment at 1 year (69%); at 3 years (45%)	Dropout (time to dropout between 2001 and 2008) Multivariate Cox regression model Hazard Ratios (p values)	Younger than 30 years – S 1.29(p = .001) Gender – NS (no figure reported)	-	Methadone maintenance dosage reached at the beginning of treatment – NS (no figure reported) Participants in a first treatment – S 1.31 (p = .001)	-	State of health as estimated by the doctor – NS (no figure reported)	No fixed abode or living in an institution/ prison – S 1.82 (p=.001)	Interaction between the mode of delivery and living condition – NS (p = 0.13) Source of income – NS (no figure reported)

					Methadone delivered (4 times a week) – NS p=0.52				
Johns 2018 (165)	Retention at 12-months (85%)	Dropout at 1 year Cox regression analyses Hazard Ratios (95% CI)	**Model 1:** Age (years) (ref: 30 – 40 years) <30 years – NS 1.58 (0.68 – 3.65) >40 years – NS 0.74 (0.28 – 1.99) Gender (percentage female) (ref: male) – NS 3.05 (0.41 – 22.50)		**Model 1:** Length of time on MMT before entering study: (ref: > 12-months to 24 months) One month or less – NS 0.18 (0.03 – 1.12) Less than one month to three-months – NS 0.53 (0.17 – 1.67) Less than 3 months to 12-months – NS		**Model 1:** HIV status at baseline (self-reported): positive (ref: no) – S 0.24 (0.09 – 0.66)	**Model 1:** Marital status at baseline (ref: widowed/divorced/separated) Single – NS 0.79 (0.30 – 2.12) Married/long-term partner – S 0.29 (0.10 – 0.80) Highest education achieved at baseline (ref: secondary/ high school or more)	**Model 1:** Travel more than 30 minutes (one way) to MMT clinic (ref: no) Yes - NS 1.50 (0.51 – 4.42) Amount paid for transport to MMT clinic at baseline (VND thousands) – 1.04 (0.69 – 1.57) Household expenditures at baseline

					0.93 (0.43 – 2.02) Methadone dose at three-months of MMT (mg) (ref: 60 or more) Less than 60mg – NS 1.36 (0.56 – 3.29) Missing – NS 0.47 (0.10 – 2.12)			Less than secondary school – NS 1.26 (0.51 – 3.12) Employment at baseline (ref: full-time, part-time, or self-employment) Homemaker, retired or student – S 2.78 (1.54-4.99) Not working (seeking or not) – NS 0.49 (0.16 – 1.45) Change of employment status in year before start of study (ref: no) – NS	(annual VND thousands) – S 0.95 (0.91 – 0.99) Income below poverty line (ref: no) – NS 1.17 (0.48 – 2.84) Clinical province had user fee policy (ref: no) – NS 0.17 (0.02 – 1.29)

								0.83 (0.41 – 1.68) Size of household (baseline) – S 0.83 (0.07 – 0.97)	
Kayman 2006 (166)	Retention at 1 year (52%)	Dropout at 1 year Logistic regression Odds Ratios (95% CI)	Mean age – NSU Female – NSU Ethnicity (white and other, African American, Hispanic) – NSU	Cocaine use in past 30 days – NSU- Alcohol use in past 30 days – NSU-	Been in MMT program – NR Ever in drug detoxification (0=no, 1=yes) – S 1.9 p=.00	Injecting in the past 30 days – NSU-	-	Never married – NSU- Lacks high school diploma – NSU-	Opinions about methadone (1-5 low score = less favourable opinions) – S 0.90 p=0.01
Kelly 2011 (167)	Retention at 12-months (58.4%)	Dropout at 1 year (starting at 3 months) Cox proportional hazards regression	Age – NS 0.98(0.95-1.02) Gender – NS 1.50(0.84-2.70) Race – NS 1.21(0.56-2.60)	**Baseline variables** Smoked crack/cocaine (lifetime) – NS 1.05(0.62-1.77)	**3 month variables** Dose – S 0.99 (0.98-1.00) Counsellor – NS 1.00 (.97 – 1.04)	-	**Baseline variables** Psychiatric composite (self-reported)– NS 0.72(0.13-3.96)	**Baseline variables** Employment composite – NS 2.43(0.68-8.65) Family/social	**Baseline variables** Problem recognition – NS 0.97(0.92-1.03) Desire for help – NS

		Hazard Ratios (95% CI)		Alcohol composite – NS 0.24(0.03-1.95) Drug composite – NS 2.90(0.15-56.82)			Medical composite (self-reported) – S 0.31(0.10-0.93)	composite – NS 3.45(0.56-21.38) Legal composite – S 3.60 (1.03-12.63) On parole or probation – NS 1.12(0.63-1.97)	0.99(0.89-1.11) Treatment readiness – NS 1.08(0.99-1.18) **3 month variables** Treatment satisfaction – S 0.91(0.84-0.99) Problem recognition – NS 1.04(0.99-1.09) Desire for help – NS 0.94(0.85-1.03) Treatment readiness – N S 0.98(0.91-1.04)

Lambdin 2014 (168)	Retention at six-months (67%); 12-months (57%); and 24 months (48%)	Dropout (time to dropout between 2011 and 2013) Cox proportional hazards Hazard Ratios (95% CI)	Age (ref: ≤ 25): 26-35 - S 0.35(0.23-0.52) 36-45 – S 0.25(0.16-0.39) >45 – S 0.11(0.03-0.38) Gender (female) 0.50 (0.28-0.90)	-	Methadone dose at initiation (ref:<40mg) 40-85mg - S 0.50(0.37-0.68) >85mg – S 0.41(0.29-0.59)	Risky sexual behaviour in the last six-months – NS 1.29(0.99-1.68)	Any history of sexual abuse – S 2.84(1.24-6.51)	-	-
Ledgerwood 2019 (169)	NR	Retention (days retained between 2002 and 2009) Multiple Linear regression analyses Beta (P values)	African American – NS 0.07 (0.398) ≥ high school education – NS -0.05 (0.446)	Early opioid use onset (< 21 years) - NS -0.06 (0.334) Past year cocaine use disorder – S -0.26 (<0.001)		Injection use – NS -0.06 (0.371)	Hepatitis C positive – NS 0.01 (0.927)		

Lin 2013 (170)	Retention at six-months (61.5%); 12-months (41.6%; 18 months (32.3%)	Dropout at 18 months (from 3 months) Cox proportional hazards model Hazard Ratios (95% CI)	Model 1: Age – NS 0.99 (0.96–1.01) Male – NS 1.34 (0.87–2.16) Location - NS Race - NS	Model 1: Severity of heroin dependence on the Chinese Version of the Severity of Dependence Scale (SDS) – NS 0.96 (0.91–1.01) Harmful impact of heroin use on the Questionnaire for the Harm of Opioid Use (Q-HOU) - S 1.04 (1.00–1.07) Lifetime methamphetamine use – NS	Model 1: Being compulsory to receive MMT by the court – NS 1.34 (0.86–2.18)	-	Model 1: Clinical diagnosis: Severity of depression on the Center for Epidemiological Studies – Depression Scale (CES-D) – NS 1.01 (0.99–1.02) Positive serum HIV antibody test – NS 0.76 (0.47–1.19) TB +/- - N/A	Model 1: Unmarried or divorced – NS 0.87 (0.60–1.30) Regular employment - NS 0.98 (0.74–1.30) Education level less than or equal to 9 years - NS 0.87 (0.65–1.16) Family support on the Family APGAR index – S 0.96 (0.93–1.00 Prior criminal records – NS 0.99 (0.73–1.34)	Model 1: High monthly cost of heroin – S 1.43 (1.07–1.91) High economic burden related to heroin use – NS 1.1 (0.81–1.49) Advantages of heroin use on the Decision Balance Scale (DBS) – NS 1.00 (0.96–1.04) Disadvantages of heroin use on the DBS - NS 0.99 (0.96–1.02)

			Model 2: Age – NS 1.00(0.98-1.04) Male – NS 1.33(0.72-2.66) Location - NS Race - NS	1.01 (0.75–1.37) Age of initial heroin use – NS 1.02 (0.99–1.05) Model 2: Severity of heroin dependence on the	Model 2: Methadone dose at 3 months after starting MMT - S 0.99(0.98-1.00) Being compulsory to receive MMT by the court – NS 1.26(0.69-2.25)		Model 2: Clinical diagnosis: Severity of depression on the Center for Epidemiological Studies – Depression	Model 2: Unmarried or divorced – NS	Travel time to MMT – NS 1.00 (0.99–1.01) Acceptable weekly expense for receiving MMT – NS 1.00(1.00-1.00) Acceptable daily time spent receiving MMT – NS 1.10 (0.94–1.27) Unfavourable attitudes towards MMT on the Client Attitudes toward Methadone Programs Scale (CAMP)- NS

				Chinese Version of the Severity of Dependence Scale (SDS) – NS 0.95(0.87-1.02) Harmful impact of heroin use on the Questionnaire for the Harm of Opioid Use (Q-HOU) - S 1.05(1.00-1.11) Lifetime methamphetamine use – NS 0.98(0.65-1.50) Age of initial heroin use – NS			Scale (CES-D) – NS 1.00(0.98-1.02) Positive serum HIV antibody test – NS 0.96(0.54-1.62) TB +/- - N/A	0.72(0.43-1.27) Regular employment - NS 0.84(0.58-1.23) Education level less than or equal to 9 years - NS 0.95(0.65-1.40) Family support on the Family APGAR index – NS 0.97(0.92-1.02) Prior criminal records – NS 1.23(0.81-1.85)	0.97 (0.90–1.05) Pre-contemplation stage on the Readiness to Change Questionnaire (RCQ-12) – NS 1.02 (0.95–1.09) Contemplation stage on the RCQ-12- NS 1.02 (0.96–1.07) Action stage on the RCQ-12 – NS 1.00 (0.93–1.08) Model 2:

				1.00(0.97-1.04)					High monthly cost of heroin – NS 1.27(0.86-1.87) High economic burden related to heroin use – NS 1.10(0.74-1.66) Advantages of heroin use on the Decision Balance Scale (DBS) – NS 1.03 (0.97-1.08) Disadvantages of heroin use on the DBS - NS 1.01(0.97-1.06)

									Travel time to MMT – NS 0.99(0.98-1.00) Acceptable weekly expense for receiving MMT – NS 1.00(1.00-1.00) Acceptable daily time spent receiving MMT – NS 1.09(0.87-1.33) Unfavourable attitudes towards MMT on the Client Attitudes toward Methadone Programs Scale (CAMP)- NS

									0.99(0.89-1.10) Pre-contemplation stage on the Readiness to Change Questionnaire (RCQ-12) – NS 1.03(0.94-1.13) Contemplation stage on the RCQ-12-NS 0.98(0.91-1.06) Action stage on the RCQ-12 – NS 0.96(0.87-1.07)
Lin 2015 (171)	Retention at six-months (73.3%); 12-	Dropout at 18 months Cox multivariate regression	Age – NS 1.01 (.98-1.04)		methadone dose after 30 days (mg) S		HIV sero-status (positive) - NS 0.55 (0.25 - 1.22)	Incarcerated during study period (no) – S	House to clinic distance(km) – S

	months (61.1%); at 18 months (48.9%)	Hazard Ratios (95% CI)	Age at first heroin use – NS 0.99(0.95-1.04) Gender (male) - S 0.45(0.21-0.96)		0.99 – S (0.98 - 0.99), Program site (new Tapei city) - S 2.84 (1.06 - 7.58) Program site (Keelung city) – NS 0.59(0.23 - 1.52) program site(Yilan city) – NS 2.8(0.96-8.73)		HCV stero-status (positive) - S 3.91 (1.01-15.12)	0.44 (0.25 - 0.76) Education (at least 9 years) – NS 1.05 (0.61 - 1.79) Employed (yes) - NS 0.76(0.40 - 1.44) Marital status (single) - NS 1.28 (0.50 - 3.30) Marital status(divorce/widowed)- NS 1.79(0.89 - 3.60)	1.08 (1.04-1.13)
Liu 2017 (172)	Dropout within 12-months (21%)	Dropout at 12-months Cox regression model Hazard Ratios	-	Over-drinking alcohol (ref: no) - NS 1.17(0.72-1.92) Drinking frequency	No. of times compulsory drug detoxification on three times or more versus never –	-	-	Current marital status: divorced or other (ref: single) – S 2.10(1.13-3.89)	-

		(95% CI)		(ref: never) at least once – NS 0.84(0.54-1.29) Drinks on a typical day when drinking (ref: 1-2 drinks): > 3 drinks – NS 1.38(0.71-2.69) Frequency of having 6 drinks or more on one occasion when drinking (ref: never) at least once – NS 1.94(1.00-3.78)	S0.36(0.16–0.83)			(data not tabulated)	

				Use of methamphetamine in the last six-months (ref: no) – S 2.26(1.15-4.43) Use of MaGU (methamphetamine and caffeine) in last six-months (ref: no) – NS 1.79(0.55-5.80) Use of ketamine in the last six-months (ref: no) – NS0.91(0.12-6.78)					

				Use of ecstasy in the last six-months (ref: no) – NS 1.63(0.22-12.23) Use of any club drugs in the last six-months (ref: no) –S 1.90(1.01-3.56) Age of first drug use – NSU Use of triazolam in the last six-months (ref: no) – NS 1.51(0.21-10.97)					

Manhapra 2017 (173)	Retention > 1 year (61.6%); retention for > 3 years (31.8%)	Dropout (follow-up 3 to 4 years) Cox proportional hazard analysis Hazard Ratios (p values)	Black race – S 1.26 (p=0.003				Charlson comorbidity index – S 1.03 p=0.013) (Visits to the emergency room during FY 2012 – S 1.03 p<0.0001		
Manhapra 2018 (174)	45% retained in treatment for more than one year; 13.7% retained at > 3 years	Dropout (follow-up 3 years) Cox proportional hazards model Hazard Ratios (95% CI)	Above median age of 31 years – S 0.82 (0.80 – 0.85) **Model 2:** Above median age of 31 years – S 0.90(0.87 – 0.93)	Any substance use under disorder diagnosis – S 1.06 (1.02 – 1.10) **Model 2:** Any substance use under disorder diagnosis – S 1.05 (1.01 – 1.10)			Inpatient mental health treatment in fiscal year (FY) 2011 – S 1.20 (1.19 – 1.30) Emergency department visits in FY 2011 - S 1.10 (1.06 – 1.14) Any psychiatric		**Model 2:** Each 30 days of insurance enrolment after buprenorphine initiation – S 0.90(0.90 – 0.91)

							diagnosis – S 1.05 (1.01 – 1.09) Any psychotherapy in FY 2011 – S 0.86 (0.83 – 0.89) **Model 2:** Inpatient mental health treatment in fiscal year (FY) 2011 – S 1.30 (1.24 – 1.36) Emergency department visits in FY 2011 - S 1.07 (1.04 – 1.14)		

							Any psychiatric diagnosis – S 1.05 (1.01 – 1.10) Any psychotherapy in FY 2011 – S 0.90 (0.86 – 0.92)		
Meshberg – Cohen 2019 (175)	Retention at six-months (64%)	Retention at six-months Logistic regression model Odds Ratios (95% CI	Age – S 1.04 (1.01 - 1.08)	Heroin use – S 0.26 (0.11 – 0.64)			PTSD diagnosis + PTSD treatment – S 43.36 (8.10 – 232.06) No PTSD diagnosis – NS 2.20 (0.86 – 5.70)		Service connection status – NS 0.95 (0.39 – 2.29)
Monico 2015 (176)	Retention NR	Retention at six-months	Age (in years) – NS	Co-occurring	Prior buprenorphine	-	-	-	-

		Logistic regression Odds Ratios (95% CI)	1.00(0.97-1.04) Gender (ref: female) – NS 0.93(0.57-1.52)	cocaine use (ref: no) – S 0.48(0.29-0.80) Prior illicit buprenorphine Use (ref: no) – NS 2.09(1.23-3.56)	treatment (ref: no) – NS 1.03(0.62-1.69) Clinic site (ref: site 1) – NS 0.97(0.59-1.61)				
Montalvo 2019 (177)	Retention at one year (52.6%); at 2 years (35.5%)	Retention at 1 and 2 years Model 1: Multiple logistic regression of retention at 1 year Model 2: Multiple logistic regression of retention at 2 years Odds Ratios (95% CI)	**Model 1:** Age – NS 1.01 (0.98 – 1.04) Gender (ref: male) – NS 0.95 (0.54 – 1.67) Ethnicity (ref: white) Black/African-American – NS 1.71 (0.67 – 4.39)	**Model 1:** Stimulant use disorder – NS 1.13 (0.56 – 2.31) Alcohol use disorder – NS 1.36 (0.63 – 2.92) Nicotine use – S 2.40 (1.35 – 4.27)			**Model 1:** Depressive order – NS 2.16 (0.99 – 4.70) Other mood disorder – S 3.42 (1.95 – 5.98) PTSD – NS 1.03 (0.56 – 1.89) Co-prescription of		

			Hispanic/Latino – NS 0.51 (0.12 – 2.17) Denied/not available – NS 0.81 (0.31 – 2.09) Other – NS 2.73 (0.08 – 88.46) **Model 2:** Age – NS 1.02 (0.99 – 1.05) Gender – S 2.08 (1.16 – 3.73) Ethnicity (ref: white) Black/African-American – NS 2.28 (0.92 – 5.64)	Other substance use order – NS 1.51 (0.86 – 2.67) **Model 2:** Stimulant use disorder – NS 0.57 (0.28 – 1.18) Alcohol use disorder – NS 1.18 (0.56 – 2.49) Nicotine use – S 2.00 (1.13 – 3.52) Other substance use order – NS			medications with buprenorphine: Benzodiazepines – S 2.44 (1.30 – 4.56) Clonidine – NS 1.29 (0.64 – 2.60) Gabapentin – NS 1.42 (0.81 – 2.47) Stimulants – NS 1.31 (0.67 – 2.54) **Model 2:** Depressive order –S 4.61 (1.49 – 14.29)		

			Hispanic/Latino – NS 0.78 (0.15 – 4.17) Denied/not available – NS 1.56 (0.59 – 4.12) Other – NS 11.55 (0.24 – 551.23)	1.46 (0.79 – 2.70)			Other mood disorder – S 3.60 (1.88 – 6.88) PTSD – NS 1.28 (0.70 – 2.35) Co-prescription of medications with buprenorphine: Benzodiazepines – NS 1.74 (0.94 – 3.25) Clonidine – NS 1.18 (0.58 – 2.37) Gabapentin – NS 1.15 (0.64 – 2.06)		

							Stimulants – NS 1.34 (0.68 – 2.64)		
Mullen 2012 (103)	Retention at 12-months (60.7%)	Retention at 12-months Logistic regression Odds Ratios (95% CI)	Gender (ref: female) – S 1.40(1.00-2.00) Age -NSU	-	Facility type (ref: primary care setting): Specialist treatment centre – S 2.00(1.20-3.50) Community treatment centre – NS 1.20(0.80-1.70) Average methadone dose (ref: 60mg or more): 59mg or less – S 3.0(2.2-4.0)	Injecting drug use - NSU-	-	-	-
Nosyk 2009 (178)	Retention at six-months	Proportional hazards frailty	Gender (ref male) –NS		Mean daily dose		Clark Chronic	Education – S	Quartile of prescriber service

	(55.5%); at 12-months (42%); at 24 months (29.5%)	models to assess time to discontinuation from recurrent MMT episodes Hazard Ratio (95% CI)	0.987 (0.955-1.019) Age at treatment entry (ref <40 yrs)- S 0.872 (0.842-0.902)		methadone (ref 40-<60) <40 mg-S 1.207 (1.161-1.255) 60-<80-S 0.70 (0.674-0.729) 80-<100- S 0.539 (0.514-0.564) 100-<120-S 0.441 (0.414-0.469) >120-S 0.377 (0.351-0.405) Episode Number (ref. 1) 2- S 0.871 (0.843-0.901) 3-S		disease score (ref 1) 2- S 0.927(0.890-0.965) 3-S 0.901(0.863-0.940) 4-S 0.904 (0.865-0.944)	1.004 (1.002-1.005) Employment-NS 0.998 (0.994-1.001) Income-S 1.003 (1.001-1.005)	users load (ref 1) 2- NS 0.976(0.938-1.015) 3-S 0.935 (0.898-0.974) 4-S 1.074 (1.030-1.121) Calendar year – S 0.98 (0.97-0.99)

					0.839 (0.803-0.878) 4-S 0.801 (0.754-0.850) 5-S 0.833 (0.77-0.902) >6-S 0.791 (0.732-0.856) Adherence (ref >90%) 70-90%- S 2.289 (2.213-2.366) <70%-S 6.835 (6.534-7.150)				
Peles 2008 (179)	Retention at six-months: Tel Aviv (83.5%); Las	Retention at 1 year Logistic regression	**Tel-Aviv Clinic** Older age – S 1.80(1.10-2.90)	**Las Vegas Clinic** No amphetamines on admission –			**Las Vegas Clinic** Sera-positive HCV – S	**Las Vegas Clinic** Having Children – S 1.90(1.10-3.30)	-

	Vegas (78.5%) Retention at 1 year: Tel Aviv (74.4%); Las Vegas (61.6%)	Odds Ratios (95% CI) Dropout (follow up 1-10 y in Tel-Aviv 1-4 y in Las Vegas) Cox PH model HR ("OR")	Cox model **Tel-Aviv Clinic** Age – NS NR **Las Vegas Clinic** Age 30 years or more on admission – S 2.2 (1.4–3.6)	S2.10(1.05-4.02) **Las Vegas Clinic** Amphetamines and cannabis use on admission – NS NR	Cox model **Tel-Aviv Clinic** Methadone dosage ≥ 100 mg/day after 1 year – S 2.1 (1.6–2.9) **Las Vegas Clinic** Methadone dosage ≥ 100 mg/day after 1 year –S 1.8(1.3–2.5)	Cox model **Tel-Aviv Clinic** No urine illicit opiates after 1 year – S 2.3 (1.7–3.1) No urine illicit benzodiazepines after 1 year – S 1.4 (1.0–2.0) **Las Vegas Clinic** No urine cocaine after 1 year – S 1.4 (1.0–1.9)	2.40(1.10-5.30) TB +/- - N/A		

						No urine amphetamines after 1 year – S 1.7 (1.1–2.7)			
Peles 2018 (180)	Retention Overall length of retention in treatment – 7.9 years (95% CI 7.4 – 8.5)	Retention at 24 years Cox multivariate analyses Hazard Ratios (95% CI)	Age ≥ 30 years (vs. < 30 years) – S 1.4 (1.1 – 1.7)	No opiate abuse after 1 year (vs. opiate abuse) – S 1.8 (1.5 – 2.1) No benzodiazepine abuse after 1 year (vs. benzodiazepine abuse) – S 1.7 (1.4 – 2.1)	Methadone ≥ 100mg/day (vs. ≤ 100mg/day) – S 1.8 (1.5 – 2.2)		Axis I psychiatric diagnosis or none (vs. Axis II only) – S 1.9 (1.6 – 2.3) Not admitted from hospital (vs. admitted from hospital) – S 1.6 (1.2 – 2.0)		
Perreault 2015 (181)	Retention at six-months (72%)	Dropout at six-months Cox proportiona	Age - NSU-Gender (female) – NS	>8 days of cocaine consumption in 30 days	-	Working in the sex trade – NS 1.70(0.85-3.35)	-	No stable income – NS 2.07(0.65-6.54)	-

		l hazards model Hazard Ratios (95% CI)	1.69 (0.79-3.60)	before treatment - S 2.17(1.02-4.64)Cocaine dependence – NS 1.12(0.52-2.40) Duration of heroin consumption – NSU- Daily usage of heroin 30 days before treatment (yes/no) - NSU- Daily usage of heroin 30 days before treatment (in days) – NSU-		Use of unclean needles – NSU-		Homelessness – NSU- Legal problems – NSU-	
Perreault 2005 (182)	Retention at one year (78%)	Retention at one year	Age – NS 1.01(0.94-1.09) Male – NS	-	Methadone dose – S 1.04(1.01-1.07)	-	Clinical diagnosis: Psychological distress – NS	Number of criminal charges – S 0.97(0.96-0.99)	Stages of change: Contemplation – NS

		Logistic regression Odds Ratios (95% CI)	0.93(0.26-3.38)				1.05(0.97-1.13)		1.10(0.33-3.64) Self-esteem – S 0.85(0.74-0.97)
Proctor 2015 (183)	Retention at six-months (46.8%); at 12-months (20.3%)	Dropout (treatment discharge) at 6 and 12-months Logistic regression Model 1(six-months); Model 2 (12-months) Odds Ratios (95% CI)	**Model 1: 6 month** Ethnicity - NR **Model 2: 12-months** Age- NR Gender- NR	**Model 1: 6 month** Intake cannabinoids - NS 0.91(0.67-1.23) Intake benzodiazepine - NS 1.33(0.98-1.80) Intake cocaine - S 1.79(1.18-2.72) Intake amphetamines - NS 1.57(0.92-2.69) **Model 2: 12-months**	**Model 1: 6 month** Average daily methadone dosage - NR **Model 2: 12-months** Average daily methadone dosage - NR	-	-	**Model 1: 6 month** Employment status- NR Marital status- NR **Model 2: 12-months** Method of payment - NR	-

				Intake cannabinoids - NS 1.39(0.73-2.65) 6 month cannabinoids - NS 1.78(0.78-2.64) Intake benzodiazepine - NS 1.18(0.66-2.11) 6 month Benzodiazepines - NS 1.19(0.55-2.58) Intake cocaine - S 3.71(1.35-10.17) 6 month cocaine UDS+ - NS 1.27(0.39-4.18)					

				Intake amphetamines NS 1.61 (0.50-5.24) 6 month amphetamines - NS 2.91(0.84-10.12) six-months opioids S 2.13 (1.10-4.12)					
Ren 2013 (184)		Dropout (follow-up 3 to 5 years) Cox proportional hazards regression Hazard Ratios (95% CI)	Age (ref: greater than or equal to 50 years): <30 – S 1.41(1.16-1.71) 30-39 - S 1.37(1.15-1.63) 40-49 - NS 1.15(0.98-1.38)	Urine test (ref: opiate-negative): positive – S 1.69(1.51-1.89)	Average methadone dose at stable stage (ref: >65mg/day): ≤35mg – S 1.39(1.19-1.63) 36-50mg – S 1.36(1.18-1.56) 51-65mg - S	Needle sharing (ref: no): yes – S1.29(1.06-1.58)	-	Education (ref: senior high school and above): Elementary and below – S 1.48(1.17-1.87) Junior high school – NS 1.00(0.90-1.10)	-

					1.20(1.03-1.39) Methadone dose change over time (ref: stable): tapering – NS 1.07(0.90-1.27) Increasing – S 0.57(0.49-0.67) Unknown - S 12.77 (11.09-14.71)				
Ruadze 2016 (185)	Retention at six-months (86%); 9 months (85%); 12-months (83%)	Retention at 9 and 12-months Logistic regression of retention at 9 months (model 1); retention at	**Retention at 9 months:** Age (>40 vs. ≤ 40 years) - S 2.33(1.53-3.55) Age (cont. variable) - S	-	-	-	-	-	-

		12-months (model 2) Odds Ratios (95% CI)	1.06(1.05-1.09) Gender (male vs. female) – S 3.18(.1.26-8.00) **Retention at 12-months:** Age (>40 vs. <= 40 years) – S 2.37(1.55-3.64) Age (cont. variable) - S 1.06(1.04-1.10) Gender (male vs. female) – NS 2.48(0.95-6.48)						
Saloner 2017 (186)	Retained in treatment for at least	Retention at six-months	Age (ref: 18-34):	-	Majority payer (ref: cash)	-	-	County median income	Metropolitan status

	six-months (41%)	Logistic Regression Odds ratio (95% CI)	35-49 yrs – S 1.16(1.09-1.23) >50 yrs – NS 1.04(0.96-1.13) Female – S 0.88(0.84-0.93) State of pharmacy (ref: Arizona) (used for location of service users) California – NS 1.47(0.93-2.32) Florida – NS 1.31(0.82-2.08) Georgia – S 1.77(1.12-2.79)		Medicaid fee-for-service – S 0.35 (0.31-0.39) Medicare part D – S 0.33(0.30–0.37) Third-party commercial – S 0.41(0.39-0.44) Majority prescriber (ref: Primary care physician): Psychiatrist – NS 1.00(0.92-1.10) Other provider - S 0.73(0.68-0.79)			(standardised) – NS 1.02(0.98-1.07)	(ref: non-metro) Large (>1 million people) – NS 0.90(0.79-1.03) Medium (>250k-1 million) – NS 0.95(0.83-1.09) Small (100-250k) - NS 1.1(0.95-1.27) County opioid overdose death rate (ref: >18.1 per 100K): <10 deaths per 100k – NS 0.93(0.83-1.03)

			Louisiana – S 1.94(1.23-3.08) Maryland – S 2.48(1.57-3.9) New jersey – S 2.37(1.44-3.91) New York – S 2.79(1.8-4.33) Pennsylvania – S 2.2(1.41-3.43) Texas – S 1.81(1.15-2.84) Washington – S 2.17(1.38-3.39) Other states – S 1.86(1.19-2.9)						10.1-14 deaths per 100k – NS 0.93(0.83-1.04) 14.1-17.9 deaths per 100k – NS 1.01(0.91-1.12) Crossed county lines for treatment – S0.92(0.87-0.97) Primary care physician to population ratio (standardized) – NS 1.03(0.98-1.08) DEA waivered ratio

			Non-minority population (standardised) - NS1.10(1.04-1.16)						(standardized) – NS 1.00(0.96-1.04)
Sarasvita 2012 (187)	Retention at six-months (61.3%)	Dropout (follow-up six-months) Cox proportional hazards model Hazard Ratios (95% CI)	Age – S 0.91(0.85-0.97)	Lifetime heroin use – NSU-	Dose – S 0.49(0.28-0.84) Take Home Dose (THD) – S 0.91(0.85-0.97)Previous Clinical experience – NS 0.60(.32-1.13) Interaction between clinic and experience and THD – S 1.07(1.00-1.15) Perceived accessibility - S	-	-	Perceived peer support – S 1.10(1.02-1.19) Family support - NSU- Imprisonment – NSU-	Belief to the program – S 0.93(0.87-0.98)

					0.95(0.92-0.98) Expense of methadone treatment – NSU- Treatment need - NSU- Pressure for treatment – NSU- Self-efficacy - NSU- Treatment participation – NSU-				
Schuman-Olivier 2013 (188)	Retention at 12-months (40%)	Retention at 12-months Logistic regression Odds ratios (95% CI)	age - NR	No difference in 12-month retention based on past-year BZD misuse; BZD prescription; or combinatio	-	-	-	-	-

				n (OR not reported)					
Shakira 2017 (189)	60.1% retention at 1 year	Dropout at 1 year Cox proportional regression Hazard Ratios (95% CI)	Sex -NSU	Lifetime on illicit drugs – NSU Relapse on illicit drugs during MMT - NSU	Level of maintenance dose (ref: low dose <30 mg) Intermediate dose 30-59mg – NS 0.55 (0.25 – 1.21) High dose > 60 mg – S 0.24 (0.09 – 0.63) Take away dose (ref: no) – S 0.18 (0.11 – 0.30)			Employment status (ref: none) Part time – NS 0.68 (0.39 – 1.20) Full time – S 0.50 (0.27 – 0.94)	

Shcherbakova2018 (190)	Retention at six-months (53.6%); at one year (40.4%)	Retention at 1 year Logistic regression analysis Odds Ratios (95% CI)	Age – S 1.04 (1.01 – 1.06) Male – NS 0.83 (0.44 – 1.58)	Non – opioid substance use disorder – NS 0.85 (0.44 – 1.63) Addiction treatment specialist (ref: yes) – S 0.40 (0.21 – 0.76) Pre-index exposure to prescription opioids – NS 1.44 (0.78 – 2.63)	Year of therapy initiation (ref: 2013): 2010 – NS 1.89 (0.69 – 5.14) 2011 – NS 1.39 (0.57 – 3.39) 2012 – NS 0.98 (0.49 – 1.98) 2014 – NS 1.09 (0.46 – 2.60)		Charlson Comorbidity Index ≥ 1 – NS 0.73 (0.35 – 1.54) Mental health disorder – NS 1.36 (0.66 – 2.80) Concomitant antidepressants – NS 1.04 (.056 – 1.94) Concomitant benzodiazepines – NS 1.17 (0.57 – 2.41) Concomitant clonidine – NS 0.78 (0.36 – 1.69) Concomitant		Insurance (ref: Medicaid) – S 0.33 (0.13 – 0.84)

							prescription opioids – S 0.25 (0.12 – 0.51) Concomitant anticonvulsants – NS 0.81 (0.35 – 1.89) Concomitant antipsychotics – NS 1.05 (0.36 – 3.10) Concomitant stimulants – NS 0.33 (0.11 – 1.01) Concomitant hypnotics – NS 1.97 (0.42 – 9.28) All-cause ER admissions – NS 0.59 (0.31 – 1.12)		

							All-cause inpatient hospitalisation – S 0.34 (0.12 – 0.76)		
Socias 2018 (191)	Retention at six-months (52.6%); 12-months (38.5%); and 18 months (31.5%)	Retention at six-months General linear mixed effects analyses of association between ≥daily cannabis use and retention Odds Ratios (95% CI)	Age (per year older) – S 1.05 (1.04 – 1.06) Gender (male) – NSU Ethnicity (Caucasian) – NSU	≥ Cannabis use – S 1.21 (1.04 – 1.41) ≥ daily heroin injection – S 0.25 (0.22 – 0.29) ≥ Daily prescription opioid use – S 0.37 (0.29 – 0.47) ≥ Daily cocaine injection – NSU	Calendar year of OAT initiation – NSU		HIV positive - NSU	≥ High school education – NSU Homeless – NSU Incarceration – NSU	

				≥ Daily crack use – NSU Heavy alcohol use – S 1.13 (1.00 – 1.26)					
Stein 2005 (192)	Retention at six-months (58%)	Dropout at six-months Log-rank test	Race (Caucasian) – NS P=.095 Age –NS Gender – NS	Cannabis use in last 30 days – NS p=.151 Benzodiazepine use – NS p=1.00 Cocaine use in last 30 days - NS p=.714 Primary drug heroin– NS p=.195 Alcohol use in last 30 days - NS p=.476	Current methadone – NS p=1.00Methadone dose – Ns p=.696 Mean counselling session/week – S p=.001 Attended any counselling – S p=.005	-	HIV+ - NS p=.290 Week 1 positive opiate test (positive) – S p=.002 Mean percentage opiate test – S p=.002	Marital Status – N/A Employed (part or full time) less likely to dropout 30% vs 72.7% – S p=.029 Lives with active user – NS p= 1.00 Lives with children – NS p=.125	-

								Insurance type – private – NS P= .378	
Strike 2005 (193)	Retention at 2 years (49.8%)	Retention at 2 years Logistic regression Odds Ratios (95% CI)	Age - S 1.09(1.05-1.13) Age squared - S 0.999(0.98-0.99) Age x group practice – S 0.98(0.98-0.99)	-	Group practice – S 4.19(2.76-6.35) Group practice and correctional - S 5.57(4.25-7.30) Group practice and individual practitioner - S 6.16(4.89-7.74) Individual practitioner and correctional - S 3.09(2.41-3.95)	-	-	-	Central East – S 0.80(0.71-0.91) Central South – S 0.79(0.67-0.93 Central West - S 1.27(1.09-1.47) East - S 0.53(0.42-0.65) North - S 1.76(1.31-2.36) Episode - S 0.79(0.74-0.86)

					Group practice, individual practitioner and correctional - S 7.51(5.49-10.28) Clinic x South region - S 2.43(1.07-5.55) Clinic x East region - S 3.41(2.32-5.22) Clinic x North region - S 0.39(0.17-0.89)				Sex x group practice/independent – S 2.38(1.09-5.21) Sex x group practice/correctional/independent – S 1.54(1.05-2.27)

Sullivan 2013 (194)	Dropout at six-months (53%); at 12-months (66%) and 24 months (77%)	Retention (time on treatment – follow-up 2 years) Accelerated failure time frailty models Times Ratios (95% CI)	Gender (ref: female) – S 0.80(0.77-0.83) Gender x dose (greater than or equal to 60mg) – S 0.92(0.86-0.98) Ethnicity (ref: Han): non-Han – NS 1.03(0.99-1.08)	No of years using drugs – NS 1(1.0-1.0) Drugs used (ref: heroin only) Other/mixed – S 1.35(1.24-1.46)	Median dose in final week (ref: <60 mg): >= 60mg/day – S 2.12(1.96-2.30) Age started MMT - S 1.02(1.01-1.02) Mean attendance (ref: 2 days or less per week (p/w)) 3 or 4 days p/w – S 0.67(0.58-0.76) 5 or more days p/w – S 0.26(0.24-0.29)	Injection drug use in six-months prior to MMT (ref: no) – NS 0.98 (0.96-1.01)	HIV status (ref: negative) – NS 0.95(0.90-1.01) Positive on ART- NS 1.15(0.98-1.36) HCV status (ref: negative) – NS 0.99(0.97-1.02)	Marital status (ref: single) Married/cohabit – S 1.06(1.03-1.09) Divorced – NS 0.99(0.95-1.03) Widowed – NS 0.91(0.75-1.09) Other - NS 1.06(.80-1.41) Employment status (ref: unemployed) – NS 1.02(0.99-1.05) Education (ref: illiterate) Primary – NS 1.03(0.95-1.12)	Commute (less than or equal to 10 mins=0) 10-30 – NS 0.97(0.92-1.03) 31-60 – S 0.89(0.83-0.96) >60 – S 0.83(0.75-0.91) Commute x Attendance: Less than or equal to 10 mins x 3-4 days p/w – S 1.48(1.25-1.75) 10-30 mins x 3-4 d/w or less than 10 mins x 5 d/w – S 1.43(1.27-1.63)

					Dose x attendance Dose >= 60mg/day x 3 or 4 days/week – NS 1.05(0.99-1.13) Dose >= x >= 5 days/week – S 1.36(1.27-1.45) Opiate test result prior to dropout or censoring (ref: positive) – S 2.15(2.03-2.27) Dose x opiate test result – S 0.93(0.88-0.98)			Junior high - S 1.15(1.06-1.25) Middle or high school – S 1.28(1.17-1.39) Junior college or higher – S 1.40(1.25-1.56) Dwelling (ref: family) Friends – S 0.92(0.87-0.97) Alone – S 0.91(0.88-0.94) Other – NS 0.76(0.53-1.08) Engagement in drug-related crimes (ref: none reported)	31-60min x 3-4 d/w – S 1.36(1.18-1.58) Greater than 60 min x 3-4 d/w S 1.27(1.16-1.40) 31-60 x 5 d/w – S 1.23(1.10-1.37)

					Opiate test result x attendance (3 or 4 days p/w) – S 1.51(1.42-1.62) Opiate test result x attendance (more than or equal to 5 days p/w) – S 4.45(4.15-4.76) Counsellor on staff – NS 1.05(0.99-1.10)			Any – S 0.94(0.90-0.98)	
Teoh 2018 (195)	Retention at 1 year (94%) and 3 years (82%)	Dropout (follow-up 10 years) Cox proportional hazards regression	Age – NSU Ethnicity – NSU	Other substance use in the month prior to MMT (ref: no): - NS 1.90 (0.97 – 3.73)	Methadone dose (ref: < 40mg/day): 40 – 79mg/day – NS 0.79(0.33 – 1.89)	Sexual partner – NSU HIV risk-taking behaviour (OTI score) – S	HIV positive – NSU Hepatitis C – NSU Hepatitis B – NSU Other medical	Social functioning (OTI score)- NSU Education level – NSU Employment – NSU	

		Hazard Ratio (95% CI)		Quantity/frequency of heroin use in the month prior to MMT (OTI score) – NSU	≥ 80mg/day – S 0.23 (0.09 - 0.55) Frequency of urine positivity within a year after initiation of MMT - NSU	1.06 (1.01 – 1.12)	illness – NSU Health (OTI score) – NSU Physical health (WHOQOL – BREF score) – NS Psychological (WHOQOL – BREF score) – NS 0.97 (0.86 – 1.08) Overall quality of life and general health (WHOQOL – BREF score) - NSU	Crime (OTI score) – NSU Social relationships (WHOQOL – BREF score) – NSU Environment (WHOQOL – BREF score) - NS 0.97 (0.88 – 1.08)	

Wei 2013 (196)	Cumulative retention rates at 1 year (87%); at 2 years (76%); at 3 years (66%); at 4 years (59%); at 5 years (49%); at 6 years (43%)	Dropout Cox proportional hazard regression (adjusted for difference across clinics) Odds Ratio (95% CI)	Female-S 0.75 (0.67-0.84) Age – S 0.86 (0.80-0.91)	Drug use history of > 6 years- S 0.92 (0.88-0.97) Needle sharing-S 0.86 (0.76-0.99) Positive urine tests (morphine)-S 0.34 (0.31-0.37)	Year of entry into treatment (ref 2006) 2007-S 1.58 (1.37-1.82) 2008-S 2.57 (2.22-2.99) 2009-S 3.36 (2.84-3.99) 2010-S 4.74 (3.84-5.84) 2011-S 5.46 (3.99-7.48) Therapeutic dose (ref dose <30) Dose >30- S 0.81 (0.76-0.87)			Living status (ref with family) With friends-S 1.45 (1.14-1.84) Living alone-S 1.12 (1.00-1.26) Being employed-S 0.93 (0.87-0.98)	

Weinstein 2017 (197)	Retention for ≥ 1 year (45.7%)	Retained in treatment for ≥ 1 year Generalized estimating equations (GEE) Logistic regression model Odds ratio (95% CI)	Age at enrolment – S 1.19(1.05-1.34) per 10 year increase Gender (ref: male) – S 1.55 (1.20-2.00) Ethnicity (ref: white) – S Black - S 0.53 (0.36-0.78) Hispanic - S 0.66 (0.48-0.92) Other – NS 2.03(0.57-7.17)	Benzodiazepine (illicit) use at enrolment – NSU Cocaine use at enrolment – NS 0.86(0.61-1.22) History of ever heroin use – NS 0.90(0.61-1.32) Alcohol use at enrolment – NS 0.88(0.63-1.23)	Past buprenorphine treatment – NS 1.14(0.88-1.48) Calendar year of treatment (ref:2003-2007): 2008-2010 – NS 0.91(0.70-1.18) 2011-2014 – S0.62(0.42-0.90) Number OBOT period (ref: 1): 2nd – S 0.39(0.28-0.53) 3rd – S	-	Any Psychiatric diagnosis – S 1.75 (1.35-2.27) HCV antibody positive – S 0.59 (0.45-0.76)	Unemployment - S 0.72(0.56-0.92)	-

					0.34(0.18-0.64) >4th – NS 0.45(0.16-1.32)				
Yang 2013 (198)	Cumulative retention rate at 1 year (53%); 2 years (35%); 3 years (20%)	Dropout (Follow-up 5 years) Cox proportional hazard models Hazard Ratios (95% CI)	Age group (ref: ≤ 30) >30 – S 0.78(.69-.88) Residence (ref: urban): rural – S 1.12(1.01-1.25)	Daily expense for drugs prior to MMT (ref:>300): ≤ 300 – S 0.80(0.71-0.90) Drug use years prior to admission - NSU	Daily treatment dose (ref: >50): ≤ 30 - S 1.44(1.29-1.61) 31-50 – S 1.33(1.21-1.48) Re-enrolled (no=0): yes – S 1.41(1.34-1.49)	Sharing needles (ref: no): yes – S 1.23(1.08-1.40)	-	Income (ref: other): Family and friends – S 0.40(0.31-0.52) Fixed income – S 0.40(0.30-0.54) Temporary income – S 0.43(0.33-0.55) Social welfare – S0.41(0.23-0.72) Relationship with family (ref: bad): Good – S 0.68(0.58-0.80)	Considering treatment cOAT suitable (ref: no): yes – S 0.71(0.60-0.84) Considering treatment operation time suitable (ref: no): yes - S 0.73(0.62-0.87)

								Communication with former drug taking peers last month(ref: yes): No – S 0.90(0.84-0.98) History of being arrested (ref: no): Yes – S 1.35(1.08-1.69) Living with family - NSU	
Zhang 2015 (199)	Dropout at 1 year (46.3%); 2 years (58.8%); 7 years (87.6%)	Dropout at 7 years Cox Regression Hazard Ratios (95% CI)	Age (10 years) – S 0.79 (0.72-0.87) Gender – NSU	-	Low methadone dosage during the first treatment episode (<50 ml versus >50 ml – S 1.84 (1.64–2.06)	-	-	Married – NSU Low education level (junior high or below versus otherwise) - S 1.21(1.05–1.40)	-

					Higher proportion of positive urine test in first treatment episode (>50% versus<50%) – S 3.72 (3.30–4.20) Last methadone dose - NSU				
Zhou 2017 (200)	Dropout At 2 years (43.5%	Dropout at 2 years Cox regression analysis to Hazard ratios (95% CI)	Age – NR Gender – NR	Drug using methods for past six-months (ref Oral) - NR Age at initial drug use (ref <= 20y) –NR Initial morphine urine test	Detoxification prior to MMT – NR Age at initial treatment (ref <=30y)	Sharing needles – NR	Clinical diagnosis: SF-36v2MCS (HRQoL, mental health component – self-reported, ref: ≤ 42) > 42 – NS 0.84(0.71-1.00)	Marital Status – NR Employment status – NR Education – NR	QOL-DAv2.0 (QoL component – self-reported) (ref: ≤66): > 66 – NS 0.86(0.72-1.03)

				result (ref Pos) Repeated termination s (ref Yes) Past treatment time (ref <1 year)			SF-36v2PCS (HRQoL, physical health component – self-reported, ref: ≤49) > 49 – S0.83(0.69-0.98)		
Zhou 2016 (201)		Dropout (Follow-up to 7 years) Cox PH regression Hazard Ratios (95% CI)	Age (ref ≤ 30 years)- S 0.85(0.78-0.92) 41-50 yrs 0.80(0.73-0.88) >50 yrs 0.74(0.60-0.91) Gender (ref: male) – S 0.89(0.82-0.96)	Drug use type (ref: heroin) – S other 1.55(1.06-2.29) Unauthorized drug use during MMT (ref: occasionally): Intermittently – S 1.73(1.59-1.87) Usually – S	Average daily methadone dose (ref: >20 mg): 21-60mg – S 0.52(0.45-0.60) >60 0.36(0.31-0.43) Readmission (ref: yes) – S 1.18(1.12 - 1.25)	Needle sharing experience (ref: yes) – S 0.89(0.81-0.99)	Initial morphine urine test (ref: positive) – S0.58(0.55-0.62)	Marital Status (ref: Married): Other – S 1.08(1.02-1.14) Employment status (ref: unemployed)– S 1.14(1.07-1.21) Stable Income (ref: yes) – S 1.11(1.04-1.20)	Time-taken to go to MMT clinic (ref: <30 min): 31-60 mins – S 1.16(1.07-1.25) >60 mins – S 1.44(1.14-1.80) Convenient MMT service time (ref: yes) – S 1.88(1.75-2.01)

				3.89(3.60-4.20)				Living with family (ref: yes) – S 1.11(1.04-1.19) Contact with peer drug users over the past month (ref: yes) – S 0.72(0.67-0.77)	Satisfaction with MMT service (ref: yes) – S 3.49(3.24-3.76)

Abbreviations:
NSU = Not significant in unadjusted analysis and hence not included in adjusted analysis
NS = Non statistically significant
S = Statistically significant
NR = Adjusted for in the model but results not reported in paper
Coefficients reported
CI = Confidence interval

Substance use
MMT = Methadone maintenance treatment
UDS+ = Urine drug screen positive
UDS- = Urine drug screen negative
Treatment Factors
Mg = Milligrams
OBOT = Office based opioid treatment
THD = Take home dose

Health Risk Behaviour
ASI = Addiction Severity Index
IDU = Injecting drug use

Health Symptoms
SF-36vMCS = Short form health survey: mental component summary
HRQoL = Health related quality of life
SF36vPCS = Short form health survey: physical component summary
HCV = Hepatitis C virus
HIV = Human immunodeficiency virus

TB = Tuberculosis
ART = Antiretroviral therapy
SMI = Serious mental illness
CORT = cortisol

Social Functioning
APGAR = Adaptation, Partnership, Growth, Affection, Resolve
TANF = Temporary aid to needy families
GAX = General assistance presumptive disability
SSI = Supplemental security income
GAU = Financial assistance for low-income people without children
GED = Graduate entry diploma

Other variables investigated in included studies
QOL – Dav2.0 = Quality of Life Scale for Drug Addicts
Mins = Minutes
D/W = days per week
RCQ-12 = Readiness to change questionnaire
Rs 100 units = Indian Rupees
Sur = Surinamese
Ant = Antillean
Mor = Moroccan
Tur = Turkish

Appendix 9. Median retention rates of included studies in sensitivity analysis of systematic review (specialist treatment settings only).

	Retention six-months % (range)	**Retention 12-months % (range)**	**Retention 2 years % (range)**	**Retention 3 years % (range)**
MMT	61.5% (46.8 – 86%) N= 7 (170, 171, 179, 183, 185, 187, 194)	60.3% (20.3 – 87%) N=16 (141, 142, 151, 153, 160, 165, 167, 170, 171, 179, 181, 183, 185, 194, 196, 198)	60% (23 – 76%) N=5 (147, 153, 194, 196, 198)	46.5% (20 – 66%) N =4 (142, 151, 196, 198)
BUP	19.1% N=1	11.7% N=1	-	-

	(154)	(154)		
Mixed OST	56.6% (54 – 75.8%) N=3 (149, 152, 156)	65.8 (43.4 – 84%) N=3 (153, 156, 158)	-	-
Overall	61.3% (19.1 - 86.0%) N=11 (149, 152, 154, 156, 170, 171, 179, 183, 185, 187, 194)	60.3% (11.7 - 87%) N=20 (141, 142, 151, 153, 154, 156, 158, 160, 165, 167, 170, 171, 179, 181, 183, 185, 194, 196, 198)	60% (23 – 76%) N=5 (147, 153, 194, 196, 198)	46.5% (20 – 66%) N=4 (142, 151, 196, 198)

Appendix 10. Synthesis of studies in specialist treatment settings

Sensitivity analysis of specialist treatment settings - synthesis of results by risk factor; reporting total number of studies and number of studies reporting significant effects (direction of effects included)

	MMT			**Bup**			**Mixed OAT**		
Risk Factor	No. of studies	Ret+/ drop-	Ret-/ drop+	No. of studies	Ret+/ drop-	Ret-/ drop+	No. of studies	Ret+/drop -	Ret- /drop+
Demographics									

Age (older)	14 (142-144, 147, 155, 170, 171, 182, 184, 185, 187, 196, 198, 201)	10 (142, 144, 155, 184, 185, 187, 196, 198, 199, 201)	0	0	0	0	1 (158)	1 (158)	0
Gender (male)	12 (142-144, 147, 155, 181, 182, 185, 194, 196, 199, 201)	1 (171)	5 (144, 155, 194, 196, 201)	0	0	0	1 (158)	0	1(158)
Race (Black/African American)	4 (144, 155, 167, 169)	0	2 (144, 155)	0	0	0	0	0	0
Race (Hispanic)	1 (155)	0	0	0	0	0	0	0	0
Area deprivation (most deprived)	1 (142)	0	1 (142)	0	0	0	0	0	0
Substance Use									
Cannabis	1 (183)	0	0	0	0	0	0	0	0
Benzodiazepine	5 (147, 172, 179, 180, 183)	0	3 (142, 179, 180)	0	0	0	1 (158)	0	1 (158)

Cocaine	8 (143, 144, 147, 155, 167, 169, 182, 183)	0	6 (144, 147, 155, 169, 183) (182)	0	0	0	0	0	0
Heroin/Opiates	5 (179, 180, 183, 184, 187)	0	4 (179, 180, 183, 184)	0	0	0	0	0	0
Alcohol	3 (155, 167, 172)	0	0	0	0	0	0	0	0
Amphetamine	5 (144, 155, 172, 179, 183)	0	4 (144, 155, 172, 179)	0	0	0	0	0	0
Treatment Factors									
OAT Dosage (higher)	14 (141, 143, 150, 153, 165, 167, 171, 181, 184, 187, 194, 196, 198, 201)	14 (141, 143, 150, 153, 165, 167, 171, 181, 184, 187, 194, 196, 198, 201)	0	0	0	0	1 (156)	1 (156)	0

Treatment setting (specialist addiction clinic/prescriber)	0	0	0	0	0	0	0	0	0
Counselling	1 (167)	0	0	0	0	0	0	0	0
Take-home OAT doses	1 (187)	1 (187)	0	0	0	0	0	0	0
Previous OAT treatments	3 (155, 187, 198)	1 (201)	1 (198)	1 (152)	1 (152)	0	0	0	0
Health Risk Behaviour									
Injection drug use	5 (151, 155, 169, 194)	0	1 (151)	0	0	0	0	0	0
Sharing needles	6 (182, 184, 196, 198, 200, 201)	2 (196, 201)	2 (184, 198)	0	0	0	0	0	0
Risky sexual behaviour	1 (182)	0	0	0	0	0	0	0	0
Health Symptoms									

Mental health	8 (143, 147, 152, 155, 167, 180, 181, 200)	0	1 (180)	0	0	0	0	0	0
Poor physical health/ increasing comorbidities	3 (144, 167, 200)	1 (167)	2 (144, 200)	0	0	0	0	0	0
HIV +	3 (165, 171, 194)	1 (165)	0	0	0	0	1 (156)	0	0
HCV+	5 (141, 169, 171, 179, 194)	2 (141, 179)	1 (171)	0	0	0	1 (156)	0	0
Tuberculosis +	0	0	0	0	0	0	1 (156)	0	0
Social Functioning									
Marital status (married/long term partner)	7 (155, 165, 171, 172, 194, 199, 201)	4 (165, 172, 194, 201)	0	0	0	0	0	0	0
Employment status (employed/source of income)	7 (155, 165, 167, 171, 182, 196, 201)	1 (196)	1 (201)	0	0	0	0	0	0

Education (higher)	7 (143, 165, 169, 171, 184, 194, 199)	3 (184, 194, 199)	0	0	0	0	0	0	0
Homeless	0	0	0	0	0	0	0	0	0
Criminal activity/arrests	9 (144, 151, 155, 167, 171, 181, 182, 187, 194, 198)	0	8 (144, 151, 155, 167, 171, 181, 194, 198)	0	0	0	0	0	0
Family support (high)	3 (144, 187, 198)	2 (144, 198)	0	1 (154)	0	0	0	0	0
Contact with other drug users	3 (150, 198, 201)	0	2 (198, 201)	1 (154)	0	0	0	0	0
Other									
Greater distance/time taken to reach OAT clinic	6 (142, 155, 165, 171, 194, 201)	0	3 (171, 194, 201)	0	0	0	0	0	0
Attitudes to OAT (positive)	4 (167, 187, 198, 201)	4 (167, 187, 198, 201)	0	0	0	0	0	0	0

Appendix 11. RCSI Research Ethics Committee approval

Royal College of Surgeons in Ireland
The Research Ethics Committee
111 St. Stephens Green, Dublin 2, Ireland.
Tel: +353 1 4022205 Email: recadmin@rcsi.ie

RCSI
ROYAL COLLEGE OF SURGEONS IN IRELAND
COLAISTE RIOGA NA MAINLEA IN EIRINN

Dr David Smith, Acting Chair
Dr Niamh Clarke, Convenor

21st May2019

Ms Aisling O' Connor
RCSI School of Pharmacy,
Ardiluan House,
111 St. Stephen's Green
Dublin 2

Ethics Reference No:	REC1596bb
Project Title:	A prospective cohort study investigating factors associated with treatment retention in MMT
Researchers Name (lead applicant):	Ms Aisling O'Connor (RCSI School of Pharmacy)
Principal investigator on the project	Dr Gráinne Cousins (academic supervisor, RCSI School of Pharmacy)
Other Individuals Involved:	Dr Mike Scully (HSE addiction Services, Cherry Orchard Hospital); Dr Fiona Boland (RCSI Data Science Centre) and Prof Joe Barry (Dept of Public Health and Primary Care, Tallaght hospital)

Dear Ms O'Connor,
Thank you for your amendment to Research Ethics Committee (REC) application REC1596b. We are pleased to advise that ethical approval has been granted by the committee for this amendment.

Content of Amendment: To use an external transcription services for the qualitative element of the study

This letter provides approval for data collection for the time requested in your original application and for an additional 6 months to allow for any unexpected delays in proceeding with data collection. Therefore this research ethics approval will expire on **1st August 2020**. Where data collection is necessary beyond this point, approval for an extension must be sought from the Research Ethics Committee.

This ethical approval is given on the understanding that:

- All personnel listed in the approved application have read, understand and are thoroughly familiar with all aspects of the study.
- Any significant change which occurs in connection with this study and/or which may alter its ethical consideration, must be reported to the REC, and an ethical amendment submitted where appropriate.
- **A final report will be submitted to the REC upon completion of the project.**

Please note: This submission has been reviewed from an ethical perspective only. It is the responsibility of the PI/sponsor/data controller and relevant Data Protection Officer to ensure and monitor compliance with any relevant legislation in the country where the study is due to take place or any local policy in the site where the study is due to take place.'

We wish you all the best with your research.

Yours sincerely,

Niamh Clarke
PP Dr Niamh Clarke (Convenor)
Dr David Smith (Acting Chair)

Appendix 12. Health Services Executive Primary Care Research Committee approval

From:	Noleen Kelly Rogers(Administrative Officer) on behalf of Teresa O"Donovan (Head of PrimaryCare)
To:	Aisling O"Connor
Cc:	"virginia.pye@hse.ie"; "david.hanlon1@hse.ie"; Teresa O"Donovan (Head of PrimaryCare)
Subject:	Application to the Primary Care ResearchCommittee
Date:	Friday, January 11, 2019 3:59:15 PM
Attachments:	image001.png image002.png

Research Application – Factors associated with Treatment retention in methadone maintenance treatment at six-months: A Prospective cohort study in the National Drug Treatment Centre

Dear Aisling

I wish to confirm that the Primary Care Research Committee considered your research application at our meeting on 13/12/2018, the following reflects the discussion and decision:

Decision: Approved

The PCRC protocol requires that the Head of Primary Care in your area will have sight of the final draft report prior to publication and that their opinion will be considered in relation to the publication, in particular items that may have a bearing on the HSE's reputation.

Kind regards,

Teresa O'Donovan
On behalf of the Primary Care Research Committee

Office of Teresa O'Donovan | Head of Primary Care | Cork Kerry Community Healthcare | Health Service Executive | Rathass | Tralee | Co Kerry| Eircode: V92 YA25

T: 353 (0)66 7184516 I Email: teresa.odonovan2@hse.ie

Appendix 13. Service user information sheet – prospective cohort study

Why people stay in opioid agonist treatment – a study

Would you like to take part in a study to help us find out why people stay or leave treatment? If you would, please read on…

It will just take you 15 minutes, and it will help others.

We will write down your answers to the survey questions, but no one will be able to identify you from the answers that you give.

About this study

Full name of this study

'Investigating the factors that motivate people to stay in opioid agonist treatment at the National Drug Treatment Centre'

This study will help treat methadone users in the future. It will help you to stay in treatment, if that's what you want to do. Research has shown that methadone users in treatment are less likely to die compared to people who leave treatment.

This study is designed to find out:

¶ What makes it hard for you to stay in treatment

¶ What helps you stay in treatment

Six-months after you complete the survey, we want to find out if the survey answers you gave affected whether or not you stayed in treatment.

This School of Pharmacy at the Royal College of Surgeons in Ireland (RCSI) is running the study.

Are you interested in taking part?

Before you decide if you wish to take part, please read the information in this leaflet carefully.

Please feel free to also talk about it with your family, friends or doctor.

What happens if you decide to take part?

If you take part in the study, we will ask you questions about:

your health,

your social life,

your drug use,

if you've ever committed a crime,

any harm you've experienced in your life, like needle sharing and risky sexual practices.

Aisling (the main researcher) will write down your answers, but the form she fills them in will not use your name. You will have plenty of time to answer the questions so you won't feel under pressure to make a quick decision.

This is the type of information we would like to get from you	
At the baseline data collection (first survey)	**Six-months after the study**
Your current dose of opioid agonist treatment	Your current dose of opioid agonist treatment
Access to your medication records.	Access to your medication records.
What non-prescribed medication (specifically Pregabalin and Gavapentinoids) you are using.	What non-prescribed medication (specifically Pregabalin and Gavapentinoids) you are using.
If you have had a clinical diagnosis of psychiatric illness or ill mental health.	If you have had a clinical diagnosis of psychiatric illness or ill mental health.

Your medication records 12-months before the first survey.	If you are currently in treatment
Your age when you were first treated.	The date you left treatment (if you have left it).
Your age at first IV drug use (if it applies).	If you have left treatment, the reason why.
	Where you are being treated if you have transferred somewhere else.

You need to give 'informed consent'

You should clearly understand the risks and benefits of taking part in this study so that you can make a decision that is right for you. This process is known as 'Informed consent'. You don't have to take part in this study and if you decide not to take part it won't affect your future medical care.

You can change your mind about taking part in the study any time you like. Even if the study has started, you can still opt out. You don't have to give us a reason. If you do opt out, rest assured it won't affect the quality of treatment you get in the future.

Why is this study being done?

Research shows that people on opioid agonist treatment are more likely to live than those who leave treatment. We are doing this study to see:

- why some service users stay in treatment, and
- why some people leave treatment.

We also want to find out if certain areas in life influence a person staying in treatment a year after they have completed this survey

This study will help treat methadone users in the future and help them to stay in methadone treatment.

Who is organising and funding this study?

This study is being carried out by Aisling O'Connor in the Royal College of Surgeons in Ireland (RCSI) as part of her studies towards a PhD. RCSI is funding Aisling to do this important study.

Why are you asking me to take part?

We are asking you to take part as you are receiving methadone from the National Drug Treatment centre. We are interested in your views on your treatment and what helps you to stay in treatment or what has made you leave treatment in the past (if you have done so).

We need 140 methadone users in Dublin to take part in the survey. If you decide to take part, it will take just 15 minutes of your time.

How will you carry out the study?

This study will take place in your clinic, from June 2019 until May 2020. If you agree to do the survey, Aisling will ask you to answer questions from the survey.

What will happen to me if I agree to take part?

If you agree to take part in this study, Aisling O' Connor will come to your clinic at a time and day that suits you best. A quiet place will be found for you and Aisling to sit down and answer the survey together. No video or audio recordings will be made of the survey. Aisling will be using paper to record your answers.

Aisling will also ask if she can look up your details in your clinical file, on the treatment register and information about your medicine prescriptions six-months after the survey to see how you get on in your treatment. You do not need to agree to this. If you do agree to this, only the investigators in charge of this study will see your details.

What are the benefits for me of taking part in this study?

There will not be any direct benefit to you for taking part in this study. Taking part in this study will help researchers in finding out why people stay in methadone treatment, and this may help other methadone users in the future. If you decide to complete the survey, you will be given a €10 gift voucher for Centra for your time.

What if something goes wrong when I am taking part in this study?

There are no physical risks to you or your health if you decide to take part in this study. You may get upset by some of the questions. We will do everything we can to make sure that nothing goes wrong when you take part in this study.

If you get upset

If you get upset you may leave the room for a break. You can also leave the study and not return. You can leave this study at any time, for any reason. We do not need to know the reason.

If you are thinking about hurting yourself

If you let Aisling know that you are thinking about hurting yourself, or another person she will have to notify the people in charge of your care and the Gardaí.

Information about child abuse

If you let Aisling know about a child that is currently being abused in any way, she will also have to notify the Gardaí.

Unhappy about your treatment

If you are not happy with how you are treated during the study you can make a complaint by contacting the people in charge of this study or the data protection commissioner (info@dataprotection.ie)

Is the study confidential?

Yes, this study will keep your data confidential at all times unless you let Aisling know that you are thinking about hurting yourself, others or a child. This is the only time that confidentiality will be broken. Aisling will have to notify the Gardaí.

We will not contact your doctors or healthcare providers

We will not contact any of your doctors or healthcare providers without your consent, unless you have mentioned that you are thinking about harming yourself or others.

Access to your information

The only people who will have access to look at the information you provide are the five people listed in number 3 on the next page.

Private and confidential

We will keep your information private and confidential. We will keep your details in a safe computer that is password protected in RCSI. We will not send your information anywhere else.

We may only keep your identity on our records with your consent

We will only keep information that can identify you if you allow us to contact you in the future to become involved in more studies. If you do not consent to this, we will not keep details to identify you (for example your name, address).

Information is kept for five years

We will keep this information about you for five years, and then destroy it.

Results

If you let the researchers know you would like a copy of the results, they will send you one when the study is finished.

We hope that the results from the study will be published in a medical journal and presented at conferences in the near future. We also hope to come back to the clinic to let you know what we found out when the research is finished. It will not be possible for anyone to identify you in these publications or conferences.

Data protection – keeping your information safe and private

Why we need information from you

We will be using your personal information in our research to help us study why people stay or leave treatment.

Law protects your information

We are legally allowed to do this research. (We do the research as detailed in the General Data Protection Regulation 2016 Act, under Article 9(2)(j) 'Scientific Research purposes',)

People who can look at your information

The people who will have permission to look at your information are called data controllers. They are:

Dr Gráinne Cousins

Dr Fiona Boland

Professor Joe Barry

Aisling O'Connor

Dr. Mike Scully

Their contact details are at the end of this leaflet.

How long we can keep your information

We will keep your information securely for a maximum of five years or for one year after the final report has been published or submitted (estimated).

Your rights

You have the right to stop taking part in this research at any time.

Where to complain

You have the right to complain to the Data Protection Commissioner if you are not happy about how your details are being used.

How you can access your information

You have a right to ask for access to your information and a copy of it, unless this makes it impossible or very difficult for us to conduct the research.

How we can use your information

You have a right to restrict or object to us using your information, unless your request would make it impossible or make it very difficult for us to conduct the research.

Information can be corrected

You have a right to have any inaccurate information about you corrected or deleted, unless this request would make it impossible or very difficult for us to conduct the research.

When you can delete your information

You have the right to have your personal information deleted, unless this request would make it impossible or very difficult to conduct the research.

Moving your information

You have the right to move your information if you move from this treatment centre to a different one. This information should be clear and easy for all to understand.

Right to object to us profiling you

You have a right to say you don't want Aisling to use the personal information she gets from you to evaluate (analyse) the factors that help you stay in treatment **and** to predict how likely you are to stay in treatment. This sort of use (processing) of your personal information is usually done automatically and is called 'automated processing' of your profile.

New research using your information

You have the right to be told about any new research that is carried out on your information. We will only do this with your written consent and approval from RCSI.

Where can I get more information?

If you have any more questions about the study or if you want to opt out of it, you can rest assured it won't affect the quality of treatment you get in the future.

For more information	
If you need any further information now or at any time, please contact:	
Name	Aisling O'Connor
Address	Royal College of Surgeons in Ireland Second Floor Ardiluan House 111 St Stephenôs Green, Dub
Phone number	01- 402 5003
Principal invest	Aisling Oô Connor
Principal invest	PhD candidate

Project supervisors	
Project supervi	**Project supervisorôs title**
Dr Gráinne Cousins	Senior lecturer, School of Pharmacy (RCSI)
Dr Fiona Boland	Lecturer in Biostatistics and Research Methods (RCSI)
Professor Joe Barry	Head of the Department of Public Health and Primary Care (TCD)

Data controllers		
Name	**Address**	**Contact details**
Dr Gráinne Cousins	Royal College of Surgeons in Ireland	gcousins@rcsi.ie
Dr Fiona Boland	Royal College of Surgeons in Ireland	fionaboland@rcsi.ie
Professor Joe Barry	Trinity College Dublin	joebarry@tcd.ie
Aisling Oô C	Royal College of Surgeons in Ireland	aislingoconnor@rcsi.com
Dr. Mike Scully	The National Drug Treatment Centre	Mike.scully1@hse.ie

Data Protection Officer	
Name	**email**
Dónal King ï Legal Counsel	dataprotection@rcsi.ie

Appendix 14. Service user consent – prospective cohort study

Service User consent form

Study title: The study will investigate the factors that motivate people to stay in opioid agonist treatment at the National Drug Treatment C

I understand this information leaflet

I have read and understood the Information Leaflet about this research project. The information has been fully explained to me and I have been able to ask questions all of which have been answered to my satisfaction.

Yes ☐ No ☐

I know I can opt out

I understand that I donôt have to take pa understand that I donôt have to give a reason f wonôt affect my future medical care.

Yes ☐ No ☐

Permission

I give permission for researchers to look at my records on the central treatment list to get information. I have been assured that information about me will be kept private and confidential.

Yes ☐ No ☐

I have been given copies

I have been given a copy of the Information Leaflet and this completed consent form for my records.

Yes ☐ No ☐

Risks and benefits

I am aware of the potential risks and benefits of this research study and I consent to take part in this research study having been fully informed of the risks and benefits.

Yes ☐ No ☐

Service User consent form

Consent

I give informed consent to have my information used as part of this research study.

Yes No ☐

How we will store and use your information

Other research that is related to this research

I give permission for related future research with two conditions

You may store my personal information for possible further research related to the current study, but only if:

I give you my permission at the time the future research is being done; and

the research is approved by a Research Ethics Committee.

Yes ☐ No ☐

I give permission for related future research with one condition

I give permission for my data to be stored for possible future research related to the current study:

without further consent being required, **but only**

if the research is approved by a Research Ethics Committee.

Yes ☐ No ☐

Other research that is not related to this research

I give permission for unrelated future research with two conditions

I give permission for you to store material or information about me for possible future research unrelated to the current study:

only if you get my permission at the time of the future research; **and**

the research is approved by a Research Ethics Committee.

Yes ☐ No ☐

I give permission for unrelated research with these conditions

I give you permission to use material or information stored about me for possible future research:

Service User consent form

unrelated to the current study,

without getting further permission from me, **but only**

if the research is approved by a Research Ethics Committee.

Yes ☐ No ☐

I am not entitled to any profits

I understand that I will not be entitled to a share of any profits that may arise from the future use of my material or information or products derived from it.

Yes ☐ No ☐

My name and signature

My name

My signature

T o d a y ô s d a t e

Appendix 15. Sensitivity analysis - prospective cohort study

Characteristics	Retained (n=96)	Dropped out (n=16)	P Value
Gender (male)	75 (78%)	8 (50%)	**0.017**
Median age at baseline (years)	37.9 [IQR32 – 43]	34.2 [IQR30-40]	0.085
Substance Use[8] N (%)			
Heroin	82 (85.4%)	13 (81.3%)	0.667
Cocaine (HCL/crack)	68 (70.8%)	15 (93.8%)	0.053
Illicit Benzodiazepines[9]	77 (80.2%)	12 (75%)	0.881
Alcohol	19 (19.8%)	0	0.051
Treatment episode characteristics N (%)			
Median MMT dose for treatment episode			
≤ 60 mg	39 (43.4%)	9 (60%)	
61 to 120 mg	51 (56.6%)	6 (40%)	0.230
Median Bup dose for episode	8 [IQR 2-8]	8[IQR 2-16]	
≤ 8mg	≤5	≤5	
>8mg	≤5	≤5	0.659
Median Take Home Dose (MMT)			
<1	66 (73.3%)	10 (66.7%)	
1>2	6 (6.3%)	≤5	
≥2	18 (18.7%)	≤5	0.218
Median Take Home Dose (BUP)			
0	≤5	≤5	
1	≤5	≤5	0.350
Treatment episode during COVID – 19	50 (52%)	9 (56.2%)	0.757
Injecting and risk-taking behaviour N (%)			
IV drug use (self-reported)	16 (16.6%)	≤5	0.420
Health (N (%)			
Diagnosis of physical illness/condition	24 (25%)	≤5	0.588
Diagnosis of mental illness/condition	22 (23%)	7 (43.8%)	0.202
Social functioning N (%)			
Experienced homelessness	45 (46.8%)	9 (56.25%)	0.487
In employment	7 (7.3%)	≤5	0.881
Crime(s) committed	24 (25%)	7 (43.8%)	0.121

[8] Any positive urine result during participants' treatment episode(s) throughout study period

[9] 26 retained participants were in receipt of a BZD prescription, 1 participant who dropped out was in receipt of a BZD prescription

Appendix 16. Service user information sheet – qualitative study

Information Sheet

Why people stay in opioid agonist treatment ï a study

Would you like to take part in a study to help us find out why people stay in treatment? If you would, please read on…

It will just take you 1 hour, and it will help others.

We will record your answers to questions, but no one will be able to identify you from the answers that you give.

About this study

Full name of this study

'Investigating the factors that motivate people to stay in opioid agonist treatment at the National Drug Treatment Centre'

This study will help treat methadone users in the future, if that's what they want to do. Research has shown that opioids agonist treatment users are less likely to die compared to people who leave treatment.

This study is designed to find out:

¶ What helps you stay in treatment

¶ How long you stay in treatment

This School of Pharmacy at the Royal College of Surgeons in Ireland (RCSI) is running the study.

Are you interested in taking part?

Before you decide if you wish to take part, please read the information in this leaflet carefully. Please feel free to also talk about it with your family, friends or doctor.

What happens if you decide to take part?

If you take part in the study, we will ask you questions about:

your health,

your social life,

your drug use,

if you've ever committed a crime,

any harm you've experienced in your life, like needle sharing and risky sexual practices.

Aisling (the main researcher) will ask you questions and record the conversation, but will make sure that no one will know who you are. You will have plenty of time to answer the questions so you won't feel under pressure to make a quick decision.

You need to give 'informed consent'

You should clearly understand the risks and benefits of taking part in this study so that you can make a decision that is right for you. This process is known as 'Informed consent'. You don't have to take part in this study and if you decide not to take part it won't affect your future medical care.

You can change your mind about taking part in the study any time you like. Even if the study has started, you can still opt out. You don't have to give us a reason. If you do opt out, rest assured it won't affect the quality of treatment you get in the future.

Why is this study being done?

Research shows that people on methadone are more likely to live than those who leave treatment. We are doing this study to see:

why some people stay in treatment, and

what helps a person stay in treatment.

We also want to find out if certain areas in life influence you staying or leaving methadone treatment.

Who is organising and funding this study?

This study is being carried out by Aisling O'Connor in the Royal College of Surgeons in Ireland (RCSI) as part of her studies towards a PhD. RCSI is funding Aisling to do this important study.

Why are you asking me to take part?

We are asking you to take part as you are receiving methadone from the National Drug Treatment centre. We are interested in your views on your methadone treatment and what helps you to stay in treatment.

We need 15 - 20 opioid agonist treatment users in Dublin to take part in this interview. If you decide to take part, it will take just up to 1 hour of your time.

How will you carry out the study?

This study will take place in your clinic, from October 2019 until May 2020. If you agree to do the interview, Aisling will ask you to answer questions and have a conversation with her about your treatment.

What will happen to me if I agree to take part?

If you agree to take part in this study, Aisling O' Connor will come to your clinic at a time and day that suits you best. A quiet place will be found for you and Aisling to carry out the interview. An audio recording will be made of the interview. It will then be transcribed by a professional who will listen to the interview and type the conversation out. They will then send the typed out conversation back to Aisling. This will be in the strictest confidence. You do not have to consent to this.

What are the benefits for me of taking part in this study?

There will not be any direct benefit to you for taking part in this study. Taking part in this study will help researchers in finding out why people stay in methadone treatment, and this may help other methadone users in the future. If you decide to complete the survey, you will be given a €10 gift voucher for your time.

What if something goes wrong when I am taking part in this study?

There are no physical risks to you or your health if you decide to take part in this study. You may get upset by some of the questions. We will take steps to make sure that you do not get upset or feel uncomfortable

when you take part in this study. We will do this by explaining the study again to you before we start and making sure we have answered all your questions.

If you get upset

If you get upset you may leave the room for a break. You can also leave the study and not return. You can leave this study at any time, for any reason. We do not need to know the reason.

If you are thinking about hurting yourself

If you let Aisling know that you are thinking about hurting yourself, or another person she will have to notify the people in charge of your care and the Gardaí.

Information about child abuse

If you let Aisling know about a child that is currently being abused in any way, she will also have to notify the Gardaí.

Unhappy about your treatment

If you are not happy with how you are treated during the study you can make a complaint by contacting the people in charge of this study or the data protection commissioner (info@dataprotection.ie)

Is the study confidential?

Yes, this study will keep your data confidential at all times unless you let Aisling know that you are thinking about hurting yourself, others or a child. This is the only time that confidentiality will be broken. Aisling will have to notify the Gardaí.

We will not contact your doctors or healthcare providers

We will not contact any of your doctors or healthcare providers without your consent, unless you have mentioned that you are thinking about harming yourself or others.

Access to your information

The only people who will have access to look at the information you provide are the five people listed in number 3 on the next page.

Private and confidential

We will keep your information private and confidential. We will keep your details in a safe computer that is password protected in RCSI. We will not send your information anywhere else.

We may only keep your identity on our records with your consent

We will only keep information that can identify you if you allow us to contact you in the future to become involved in more studies. If you do not consent to this, we will not keep details to identify you (for example your name, address). is kept for five years

We will keep this information about you for five years, and then destroy it.

If you let the researchers know you would like a copy of the results, they will send you one when the study is finished.

We hope that the results from the study will be published in a medical journal and presented at conferences in the near future. We also hope to come back to the clinic to let you know what we found out when the research is finished. It will not be possible for anyone to identify you in these publications or conferences.

Data protection – keeping your information safe and private

Why we need information from you

We will be using your personal information in our research to help us study why people stay in methadone treatment.

Law protects your information

We are legally allowed to do this research. (We do the research as detailed in the General Data Protection Regulation 2016 Act, under Article 9(2)(j) 'Scientific Research purposes',)

People who can look at your information

The people who will have permission to look at your information are called data controllers. They are:

Dr Gráinne Cousins

Dr Fiona Boland

Professor Joe Barry

Aisling O'Connor

Dr. Mike Scully

Their contact details are at the end of this leaflet.

How long we can keep your information

We will keep your information securely for a maximum of five years or for one year after the final report has been published or submitted (estimated 2021).

Your rights

You have the right to stop taking part in this research at any time.

Where to complain

You have the right to complain to the Data Protection Commissioner if you are not happy about how your details are being used.

How you can access your information

You have a right to ask for access to your information and a copy of it, unless this makes it impossible or very difficult for us to conduct the research.

How we can use your information

You have a right to restrict or object to us using your information, unless your request would make it impossible or make it very difficult for us to conduct the research.

Information can be corrected

You have a right to have any inaccurate information about you corrected or deleted, unless this request would make it impossible or very difficult for us to conduct the research.

When you can delete your information

You have the right to have your personal information deleted, unless this request would make it impossible or very difficult to conduct the research.

Moving your information

You have the right to move your information if you move from this treatment centre to a different one. This information should be clear and easy for all to understand.

Right to object to us profiling you

You have a right to say you don't want Aisling to use the personal information she gets from you to evaluate (analyse) the factors that help you stay in treatment **and** to predict how likely you are to stay in treatment. This sort of use (processing) of your personal information is usually done automatically and is called 'automated processing' of your profile.

New research using your information

You have the right to be told about any new research that is carried out on your information. We will only do this with your written consent and approval from RCSI.

Using your information in the future for other studies

What this means?

If you have agreed to take part in this study, we cannot use your information for any other reasons. It is possible that in the future, we may want to use the information you have given us to carry out another study related to this one. This will only be done when you have been told about the study and with your consent. If another study is carried out with your consent, it will be done by the persons named below in charge of this study.

What will the other studies be about?

Future studies using your information will be related to studying methadone services in Ireland and the people who provide and use these services. They may focus on the demographics of current methadone users in Ireland. We will only use the information about you that you have given us.

Do I have to agree?

You do not have to agree to let us use your information for more studies. If you do agree, the study will only go ahead with ethical approval from the RCSI. Your information will stay confidential at all times and you can always change your mind and withdraw from the study. None of your information will be shared with anyone other than the people named in this leaflet.

Where can I get more information?

If you have any more questions about the study or if you want to opt out of it, you can rest assured it will not affect the quality of treatment you get in the future.

For more information	
If you need any further information now or at any time, please contact:	
Name	Aisling O'Connor
Address	Royal College of Surgeons in Ireland Second Floor Ardiluan House 111 St Stephenôs Green, Dub
Phone number	01- 402 5003
Principal invest	Aisling Oô Connor
Principal invest	PhD candidate

Project supervisors	
Project supervis	**Project supervisorôs title**
Dr Gráinne Cousins	Senior lecturer, School of Pharmacy (RCSI)
Dr Fiona Boland	Lecturer in Biostatistics and Research Methods (RCSI)
Professor Joe Barry	Head of the Department of Public Health and Primary Care (TCD)

Data controllers		
Name	**Address**	**Contact details**
Dr Gráinne Cousins	Royal College of Surgeons in Ireland	gcousins@rcsi.ie

Dr Fiona Boland	Royal College of Surgeons in Ireland	fionaboland@rcsi.ie
Professor Joe Barry	Trinity College Dublin	joebarry@tcd.ie
A i s l i n g O ô C	Royal College of Surgeons in Ireland	aislingoconnor@rcsi.com
Dr. Mike Scully	The National Drug Treatment Centre	Mike.scully1@hse.ie

Data Protection Officer	
Name	**email**
Dónal King ï Legal Counsel	dataprotection@rcsi.ie

Appendix 17. Service user consent form – qualitative study

Service User Consent Form

Study title: To explore opioid agonist treatment s what inhibits and enables the ability to remain in treatment.

I understand this information leaflet

I have read and understood the Information Leaflet about this research project. The information has been fully explained to me and I have been able to ask questions all of which have been answered to my satisfaction.

Yes ☐ No ☐

I know I can opt out

I understand that I donôt have to take pa understand that I donôt have understand that opting out wonôt affect my future medical care.

Yes ☐ No ☐

I have been given copies

I have been given a copy of the Information Leaflet and this completed consent form for my records.

Yes ☐ No ☐

Risks and benefits

I am aware of the potential risks and benefits of this research study and I consent to take part in this research study having been fully informed of the risks and benefits.

Yes ☐ No ☐

Consent

I give informed consent to have my information used as part of this research study.

Yes No ☐

How we will store and use your information

Service User Consent Form

Other research that is related to this research

I give permission for related future research with two conditions

You may store my personal information for possible further research related to the current study, but only if:

¶ I give you my permission at the time the future research is being done; and

¶ the research is approved by a Research Ethics Committee.

Yes ☐ No ☐

I give permission for related future research with one condition

I give permission for my data to be stored for possible future research related to the current study:

¶ without further consent being required, **but only**

¶ if the research is approved by a Research Ethics Committee.

Yes ☐ No ☐

Other research that is not related to this research

I give permission for unrelated future research with two conditions

I give permission for you to store material or information about me for possible future research unrelated to the current study:

¶ only if you get my permission at the time of the future research; **and**

¶ the research is approved by a Research Ethics Committee.

Yes ☐ No ☐

I give permission for unrelated research with these conditions

I give you permission to use material or information stored about me for possible future research:

¶ unrelated to the current study,

¶ without getting further permission from me, **but only**

¶ if the research is approved by a Research Ethics Committee.

Yes ☐ No ☐

Service User Consent Form

I am not entitled to any profits

I understand that I will not be entitled to a share of any profits that may arise from the future use of my material or information or products derived from it.

Yes ☐ No ☐

My name and signature

My name

My signature

T o d a y ô s d a t e

Appendix 18. Service provider information sheet – qualitative study

Study title: Factors associated with treatment retention in OAT at six-months: A mixed methods study in the National Drug Treatment Centre (NDTC).

Principal investigator's name:	Aisling O'Connor
Principal investigator's title:	PhD Candidate
Telephone number of principal investigator:	01-4025003

Why is this study being done?

The study proposed is part of a PhD thesis aiming to generate evidence based standards to improve retention in opioid agonist treatment. This will be achieved through an in-depth analysis of factors associated with retention in OAT across three studies; it aims to identify both risk factors for treatment cessation and protective factors for retention using a mixed methods study design. The primary aim of this interview is OAT service users' and service providers' views on what inhibits and enables service users' ability to remain in OAT.

Who is organising and funding this study?

This study is being carried out by Aisling O'Connor in the Royal College of Surgeons in Ireland (RCSI) as part of her studies towards a PhD. Aisling is a third year PhD student in the School of Pharmacy. Aisling's PhD is funded by the RCSI through the StAR Scholarship.

Why am I being asked to take part?

As a staff member in the National Drug Treatment Centre, you are being asked to participate in order to gain insight into what service providers think affects retention in treatment for service users. This qualitative research piece will involve conducting five to ten one on one semi structured interviews with service providers who consent to participate in this study.

What will happen to me if I agree to take part?

You will be asked to take part in a semi structured interview that will last up to one hour. This will be audio recorded and then transcribed. You will be asked questions about what you think affects retention in treatment.

The questions will be asked are categorised as follows: a brief synopsis of professional experience and career, substance use, treatment centre dynamics, health risk behaviours, health symptoms and social functioning and its impact on treatment retention.

The interview will be audio recorded and then transcribed by a professional who will listen to the interview and type the conversation out. They will then send the typed out conversation back to Aisling. This will be in the strictest confidence. You do not have to consent to this. You have the right, should you wish, to review and edit any transcripts to which you have contributed.

What are the benefits?

There will not be any direct benefit to you for taking part in this study. Taking part in this study will benefit current research in opioid agonist treatment. Participation will also benefit Aisling's progression through her PhD. If you decide to complete the survey, you will be given a €10 gift voucher for Centra for your time.

What are the risks?

There are no physical risks to you if you decide to participate in this study. Aisling is asking for a maximum of one hour of your time to complete the study. It is understandable if you need to leave the study to return to work for any unexpected reason.

Is the study confidential?

Access to your information: The only people who will have access to look at the information you provide are the five people listed at the end of this leaflet.

Private and confidential: We will keep your details in a safe computer that is encrypted and password protected in RCSI. We will not send your information anywhere else.

Information is kept for five years: We will keep this information about you for five years, and then destroy it. Audio recordings will be destroyed following transcription. These copies of the conversation will be kept for five years and then destroyed.

Results: You are entitled to a copy of the results upon request once the study has been completed. We hope that the results from the study will be disseminated in a peer reviewed journal and presented at conferences in the near future. It will not be possible for you to be identified in these publications or conferences as your name and all identifying information will be omitted from results and publication.

Data Protection

- **Why we need information from you:** We will be using your personal information in our research to help us study why people stay in methadone treatment.

¶ **Law protects your information**: We are legally allowed to do this research. (We do the research as detailed in the General Data Protection Regulation 2016 Act, under Article 9(2)(j) 'Scientific Research purposes')

¶ **People who can look at your information:** The people who will have permission to look at your information (data controllers) are: Dr Gráinne Cousins, Dr Fiona Boland, Professor Joe Barry, Aisling O'Connor and Dr Mike Scully. Their contact details are at the end of this leaflet.

¶ **How long we can keep your information:** We will keep your information securely for a maximum of five years or for one year after the final report has been published or submitted (estimated 2021).

¶ **Data Breaches**: There is a low risk of your information being lost in the event of a data breach. All data will be pseudo anonymised when transcribed, and as such it will be difficult to identify you in the unlikely event of data becoming lost.

¶ **Your rights:** You have the right to stop taking part in this research at any time.

¶ **Where to complain:** You have the right to complain to the Data Protection Commissioner if you are not happy about how your details are being used.

¶ **How you can access your information:** You have a right to ask for access to your information and a copy of it, unless this makes it impossible or very difficult for us to conduct the research.

¶ **How we can use your information:** You have a right to restrict or object to us using your information, unless your request would make it impossible or make it very difficult for us to conduct the research.

¶ **Information can be corrected:** You have a right to have any inaccurate information about you corrected or deleted, unless this request would make it impossible or very difficult for us to conduct the research.

¶ **When you can delete your information:** You have the right to have your personal information deleted, unless this request would make it impossible or very difficult to conduct the research.

¶ **Moving your information:** You have the right to move your information if you move from this treatment centre to a different one. This information should be clear and easy for all to understand.

¶ **Right to object to us profiling you:** You have a right to say you don't want Aisling to use the personal information she gets from you to conduct profiling analysis. As this study is qualitative in nature, it is very unlikely that this will happen.

¶ **Transferring data abroad:** Will we inform you if we wish to transfer your data to a country outside of the EU or an international organisation. This is very unlikely to happen.

For more information	
If you need any further information now or at any time, please contact:	
Principal Investi	Aisling O'Connor, PhD candidate
Address	Royal College of Surgeons in Ireland Ardilaun House 111 St Stephenôs Green, Dublir
Phone number	01- 402 5003

Project supervisors	
Project supervi	**Project supervisorôs title**
Dr Gráinne Cousins	Senior lecturer, School of Pharmacy (RCSI)
Dr Fiona Boland	Lecturer in Biostatistics and Research Methods (RCSI)
Professor Joe Barry	Head of the Department of Public Health and Primary Care (TCD)

Data controllers		
Name	**Address**	**Contact details**
Dr Gráinne Cousins	Royal College of Surgeons in Ireland	gcousins@rcsi.ie
Dr Fiona Boland	Royal College of Surgeons in Ireland	fionaboland@rcsi.ie
Aisling Oô Cor	Royal College of Surgeons in Ireland	aislingoconnor@rcsi.com
Professor Joe Barry	Trinity College Dublin	joebarry@tcd.ie

Data Protection Officer	
Name: Dónall King ï Legal Counsel	**Email:** dataprotection@rcsi.ie

Appendix 19. Service provider consent form – qualitative study

SERVICE PROVIDER CONSENT FORM

Factors associated with treatment retention in OAT at six-months: a mixed methods study at the National Drug Treatment Centre

I have read and understood the **Information Leaflet** about this research project. The information has been fully explained to me and I have been able to ask questions, all of which have been answered to my satisfaction.	**Yes**	**No**
I understand that I don't have to take part in this study and that I can opt out at any time. I understand that I don't have to give a reason for opting out.	**Yes**	**No**
I consent to this interview being transcribed by an external professional transcription service.	**Yes**	**No**
I am aware of the potential risks, benefits and alternatives of this research study.	**Yes**	**No**
I have been given a copy of the Information Leaflet and this completed consent form for my records.	**Yes**	**No**
I consent to take part in this research study having been fully informed of the risks, benefits and alternatives.	**Yes**	**No**
I give informed explicit consent to have my data processed as part of this research study.	**Yes**	**No**
I consent to be contacted by researchers as part of this research study.	**Yes**	**No**

Participant Name (Block Capitals) | Participant Signature | Date

_____ _____ _____

To be completed by the Principal Investigator or nominee.

I, the undersigned, have taken the time to fully explain to the above service user the nature and purpose of this study in a way that they could understand. I have explained the risks involved as well as the possible benefits. I have invited them to ask questions on any aspect of the study that concerned

_____|_____|_____|_____

Name | Qualifications | Signature | Date

Appendix 20. Service user interview schedule – qualitative study

INTERVIEW SCHEDULE

***To be used as a guide and to help in prompting discussion. Questions are not mandatory or exhaustive.**

PART 1: A little about yourself

PART 2: Your history and current relationship with OAT

PART 3: Substance use and its impact on your treatment

PART 4: Treatment centre characteristics and its impact on your treatment

PART 5: Health Risk behaviours

PART 6: Health Symptoms (mental and physical)

PART 7: Social functioning - residence, work and training, relationships, illegal behaviours

PART 8: Any else for discussion

1. Demographics

- Age
- Level of education and qualifications
- Working life
- Family life and relationships
- Hobbies

2. Your history and current relationship with OAT

a) Can you tell me when you first started using drugs and why?

b) When did you first hear about OAT/decide to start treatment?

c) What is your current opinion with OAT? Has your opinion changed over time?

d) How are you currently feeling about this treatment episode that you've started?

e) What are your thoughts on retention in OAT (staying on OAT long term)?

3. Substance use and its impact on your treatment

a) Are you currently taking any non-prescribed drugs?

b) If so, can you tell me what you are and why?

c) If you are not taking non-prescribed drugs, what caused you to stop?

d) Do you think your current substance use affects your OAT treatment? In what ways?

e) Have there been times in the past when your drug use stopped you taking OAT? Why do you think this happened?

4. Treatment centre and its impact on your treatment

a) How do you find coming here? What do you like and dislike?

b) What were your previous treatments episodes like and how long did they last?

c) What about the treatment centre helps you to stay in treatment?

d) What about treatment centres has made you leave in the past?

5. Health risk behaviours and its impact on your treatment

(IV and IDU behaviours, sexual risk-taking behaviours)

a) Do you carry out any behaviours/actions that you think are “risky” to your health?

b) Do you think these influence your OAT treatment? How?

c) Have these actions caused you to stop or stay in treatment in the past?

d) Do you feel a need to stop these behaviours? Have you tried before?

6. Health and its impact on your treatment

a) How would you describe your physical and mental health?

b) Are you linked in with any other services for your health (counsellors, GPs, hospitals?) Do you think this helps or hinders you coming here?

c) Do you think your health impacts your treatment (positively or negatively)? In what way?

7. Social functioning and its impact on your treatment

a) Can you tell me a bit about your day to day life (relationships, family, income, housing status, legal issues (if any)?)

b) What are the biggest strengths and biggest issues in your life at present?

c) What do you think most helps and hinders you in coming here for treatment?

d) What in the past has helped and hindered your treatment?

8. Anything else to discuss

a) Can you think of anything else you would like to discuss?

b) Is there anything else that you think helps people stay on OAT?

END OF INTERVIEW

Appendix 21. Service provider interview schedule – qualitative study

INTERVIEW SCHEDULE

*To be used as a guide and to help in prompting discussion. Questions are not mandatory or exhaustive.

PART 1: Brief Synopsis of professional experience and career.

PART 2: Treatment outcomes and retention in treatment

PART 3: Current work in the context of COVID-19

PART 4: Substance use and its impact on treatment retention

PART 5: Treatment centre dynamics and its impact on treatment retention

PART 6: Health Risk behaviours and its impact on treatment retention

PART 7: Health and its impact on treatment retention

PART 8: Social functioning and its impact on treatment retention

PART 9: Anything else for discussion

1. Professional Career and Experience

a) role, length of time in role, what services do you provide/who do you interact with

b) Education and qualifications

c) Previous experience

2. Retention in treatment

a) What is your understanding of retention as a treatment outcome?

b) What is your opinion of retention as a treatment outcome?

c) Time frame of retention on OAT (12-months) treatment protocols say that 12-months on treatment should be the minimum standard

d) Is there a disparity in realistic treatment outcomes with clients?

e) Do you think clients perceive retention as a positive treatment outcome?

f) What are the main difficulties you experience when encouraging retention to treatment?

3. Continuity of treatment during COVID-19

a) Can you describe how the service is currently running on a daily basis?

b) How is social distancing being made possible (in waiting rooms and outside the clinic – supervised consumption)?

c) What new strategies and policy measures have been put in place?

d) Have any contingency plans been made in the event of shortages of staff/PPE etc?

e) How were these new strategies conceived and agreed upon across various services?

f) What are the biggest challenges in continuing treatment?

g) How are the clients reacting to the new strategies and procedures? Have they been receptive?

h) Can you describe any additional supports that have been put in place for clients accessing homeless services?

i) What strategies are being put in place for vulnerable adults who have been cocooning/self-isolating? (due to age or compromised immune systems)

j) How are clients who are cocooning/self-isolating being provided their medication?

k) Have any strategies been put in place to mitigate risks for clients vulnerable to contracting COVID (i.e. poly-drug users, IDU, those experiencing physical or mental illness) prescriptions

l) What strategies have been put in place for clients who travel long distances for their OAT?

m) Are clients reporting any difficulties in accessing the clinic (reduced public transport and 2km/5km restrictions)?

n) How have services been working together?

o) How do you think COVID will impact on retention in OAT during these current months?

p) Has there been any changes implemented during this crisis which should continue after the pandemic?

q) What positives would you like to carry forward for retention?

r) Can you recommend anyone else I can talk to about running services during COVID?

4. Substance use and its impact on treatment retention

a) What kind of impact does continued drug use by service users have on their treatment and retention in treatment?

b) Does the management of prescriptions here affect retention positively or negatively?

5. Treatment centre and its impact on treatment retention

a) How do you think service users perceive coming here? Is there a stigma to this particular clinic?

b) What is the staff/service user dynamic like (this has been cited before in other research about OAT)?

c) What impact has the dynamics have on treatment outcomes and retention?

d) What is it about the service that you think helps service users to return after a relapse?

e) Do you think improvements could be made to methadone maintenance on a national scale? What are these?

6. Health risk behaviours and its impact on treatment retention

a) In your opinion, what constitutes "risky behaviours" in terms of health and clients of this clinic? (The MAP considers unsafe sex and injection use and needle sharing)

b) How often do you experience service users' engaging in health "risky behaviours"?

c) Do you feel these behaviours impacts on their retention in treatment? In what way?

d) Do you think service users would agree that these behaviours are having such an impact?

7. Health and its impact on treatment retention

a) What are the biggest physical health issues affecting service users' treatment and retention?

b) What are the biggest mental health issues affecting service users' treatment and retention? Dual diagnosis impact?

c) How aware are service users about the impact of their health needs on their treatment?

d) How much do service users engage in psychosocial treatments? How does this impact on their treatment?

8. Social functioning and its impact on treatment retention

a) How would you describe the social functioning of service users attending this clinic? b) Do you think they would agree with your assessment?

b) What are the biggest obstacles you see in terms of social functioning for service users staying in treatment? (Housing, peer interactions, Maslow's hierarchy of needs)

c) What social functioning supports provided by the centre facilitates the service users returning?

9) Anything to add

a) What have you experienced in the past as red flags for clients who dropped out of treatment?

b) How do we improve retention?

c) What do you think could improve the services to improve retention? On a national or local scale?

d) Can you think of anything else you would like to discuss?

e) Is there anything else that you think facilitates service users' retention?

END OF INTERVIEW