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NEUROPSYCHOSOCIAL PREDICTORS OF OUTCOMES IN OPIOID DEPENDENT PATIENTS POST-DETOXIFICATION

A dissertation submitted to the University College Dublin (Trinity College Dublin) for the Degree of Doctor of Philosophy

Jo-Hanna Ivers

Trinity College Dublin, August 2015

Department of Public Health and Primary Care

Trinity College Dublin

DECLARATION

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SUMMARY

The current treatment of choice for most opiate dependent persons is long term substitute prescribing. Detoxification is not an effective stand-alone treatment. Given the weak evidence base for detoxification coupled with the increased risk of overdose following a period of abstinence, many clinicians opt to continue substitute prescribing or indeed may dissuade opiate dependent persons from detoxifying.

Aim: The overall aim of the proposed study is to investigate comprehensively rehabilitation pathways for patients post opiate detoxification in order to identify predictors of abstinence at 3, 6 and 9 month follow up.

Methods: The current study employs a multimodality approach. The first modality employs quantitative outcome measures to all 143 patients, to examine abstinence and psychosocial measures at 3, 6 and 9 months. The second modality employs qualitative interviews with a subsample of ten patients, to examine the factors that influence patients' rehabilitation pathways post detoxification. The third modality employs neuroimaging to a subsample of 60 patients, to examine whether individual differences in white matter predict outcome at 3, 6 and 9 month follow up.

All patients aged between 18 and 65 years, admitted to the three Drug Dependency Units within the stated timeframe, who detoxified from opiates between September 2012 and November 2013 were included in the study. The scanning arm of the study began in April 2013, and finished in November 2013. This was an opportunistic sample, with the first 60 volunteers that met the inclusion criteria inducted into the scanning study.

Data analysis: The analysis of the longitudinal cohort data was done within the multilevel modelling framework. A thematic analysis was utilised for qualitative data. General linear modelling was used to localize microstructure differences between three groups within the neuroimaging study.

Outcomes: In the larger cohort study the effects of the treatment path were explored in a longitudinal analysis adjusted for age and gender. Statistically significant risk for first lapse/relapse was found for both the outpatient (OR 1.17) and no formal aftercare (OR 1.75) groups (p=0.0001) when compared to those who attended inpatient aftercare. In the qualitative study five key themes emerged from the data: Addiction, Treatment, Relapse, Support and Recovery. The findings of the neuroimaging study suggest that the degree and severity of white matter impairment in opioid dependent patients were associated with duration of use.

Conclusion: While several outcomes were examined the most significant predictor of abstinence for this cohort of patients was attending inpatient aftercare.

Recommendations: Three main recommendations come from this thesis; the need to prepare patients for detoxification, the need to support the recovery model in addiction as well as the advancement of the role of neuropsychobiology in addiction. Each of the three recommendations are discussed in terms of required changes to practice and policy as well as suggested areas for research. Policy, practice and research relating to addiction in Ireland must focus on examining and applying best practices when preparing patients for

detoxification. A reorientation of current post-detoxification aftercare should be prioritised moving away from a model that focuses solely on abstinence, to begin engaging patients in the process of recovery. Neuropsychological research and technologies have the potential to provide a number of novel and promising interventions. These findings also point towards the possibility of a more rational approach to developing addiction treatments that are based on more comprehensive Neuropsychosocial theories underlying addiction.

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List of Abbreviations

AD	Axial diffusivity
BZD	Benzodiazepine
DDU	Drug Dependency Unit
DTI	Diffusion Tensor Imaging
DSM	Diagnostic Statistical Manual
EMCDDA	The European Monitoring Centre for Drugs and Drug Addiction
FA	Fractional anisotropy
FMRIB	Functional Magnetic Resonance Imaging of the Brain
FSL	FMRIB Statistical Library
GLM	General logistical model
ICD-10	The International Classification of Diseases (ICD) Version 10
LM	Logistical model
MD	Mean diffusivity
MLM	Multilevel modelling
MNI	Montréal Neurological Institute
NDTC	National Drug Treatment Centre
OD	Opioid dependent
ODP	Opioid dependent patients
QOL	Quality of life
RD	Radial diffusivity
RG	Regression model
RP	Relapse prevention
TBSS	Tract-based spatial statistic

WM	White matter
WMD	White matter disruption
WMI	White matter impairment

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1 CHAPTER 1:INTRODUCTION AND BACKGROUND TO THE STUDY

1.1 BACKGROUND TO THE STUDY

Substance misuse is a serious public health and clinical concern both nationally (1) and internationally (2). Reduction of substance misuse is beneficial at individual, family and community levels. The high rate of substance misuse and the negative impact this poses for this illness have been well established (3). The specific factors predicting motivation to change substance use and the implications these have for treatment remain largely unidentified. There is a pressing need to improve treatment outcome, in order to reduce relapse (i.e. return to drug use after a period of abstinence) and premature termination of treatment, by developing appropriate models of management. Rehabilitation pathways in addiction vary extensively. Understanding motivation to change substance use and identifying an individual's rationale for choosing a particular intervention over another is essential in order to improve treatment outcome for this population.

1.2 PROBLEM STATEMENT

At present the treatment of choice for most opiate dependent persons is long term substitute prescribing (4), a model that has received much condemnation (5-7). However, there is little evidence to justify referring patients for alternative treatment such as detoxification. Given the poor evidence base and also the increased risk of overdose many clinicians opt to dissuade opiate dependent persons from detoxifying. Thus opiate dependent persons may remain on opiate substitute prescribing indefinitely.

Opiate detoxification is not an effective stand-alone treatment for heroin dependence but is nevertheless an essential step on the path to recovery (8). The effectiveness of

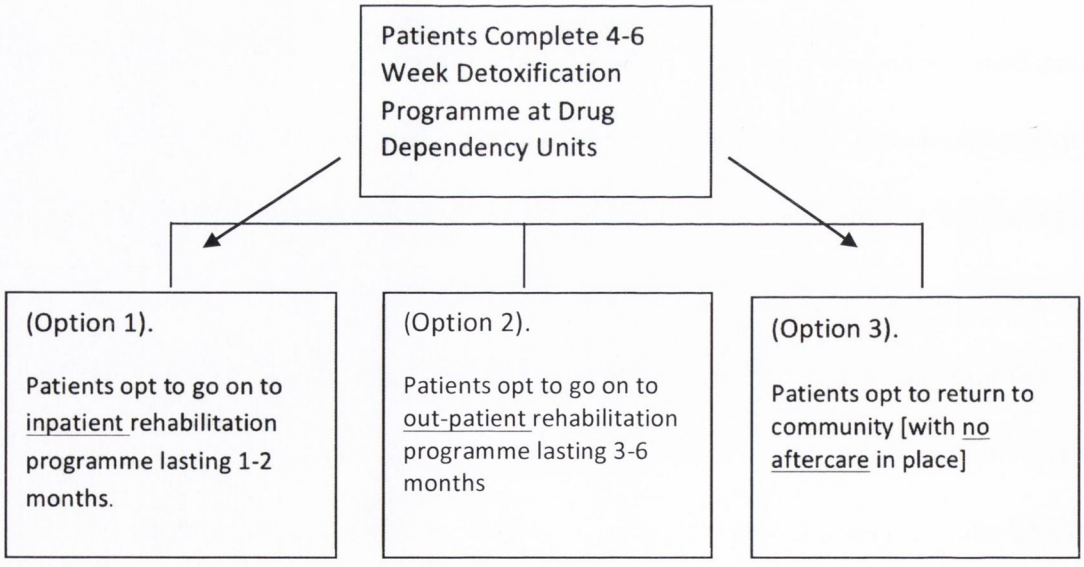
rehabilitation in the first 6 months post detoxification is marked by abstinence from drug use (9), increase in quality of life, increase in wellbeing and increase in hope for the future. There was a trend in the 1990s and early 2000s in examining outcomes for opiate dependent patients. More recently the focus has been shifted to efficacy of opiate substitution treatment, mostly methadone. However, there is no recent long-term outcome data examining these issues for this population of patients. Residential rehabilitation based on a 'therapeutic community' for drug users is a treatment option which is attractive to clinicians referring drug users for treatment. Whilst there is evidence that maintenance-based programmes for drug users are effective, there have been fewer attempts to evaluate the effectiveness of abstinence-based programmes (10).

A follow up study in 1996 of 144 patients three years after they completed the programme at Cuan Dara, the largest inpatient detoxification unit in Ireland reported a 90% relapse rate at one year (11). In 2002 a follow up two month Residential Programme (Keltoi) was added to the Cuan Dara continuum treatment package. A more recent cohort study found patients who completed the Keltoi Residential programme (focused on evidence based interventions and incorporating tight after-care planning) post Cuan Dara detoxification had significantly better outcomes with 60% opiate and alcohol free at follow up (12). At present, there are very few evaluations of such aftercare options available in the international literature, and this dissertation, examining inpatient detoxification units, provides an opportunity to explore abstinence and rehabilitation pathways for patients who have undergone detoxification in the unit and who either opt for further inpatient rehabilitation programmes, outpatient rehabilitation programmes or simply return to the community without such formal aftercare in place.

1.3 TREATMENT CONTEXT

The current study examines three major pathways culminating in either rehabilitation or relapse of opiate dependent patients post-detoxification (these pathways are illustrated in the model below). Each pathway is associated with specific vulnerability factors, demographic features and aetiological processes that may help or hinder the rehabilitation process for patients. The majority of patients that relapse do so in the first six months (1, 3, 13). Tracking patients at three, six and nine months afford an opportunity to identify factors that are associated with abstinence and relapse. Moreover, not all patients relapse (as previously noted return to daily use), rather some patients lapse (have one episode) and recover from this. Identifying factors and understanding the nuances that cause one patient to lapse and another to relapse is imperative. Having an adequate aftercare package greatly enhances patients' chances of abstaining post-detoxification (1, 3, 12).

FIGURE 1 PATHWAYS AFTERCARE MODEL



The pathways outlined above contain certain processes and symptomatic features in common but are distinguishable by their distinct clinical and community settings. Chosen pathways are assumed to be based on both internal (i.e. biological and psychological factors for e.g. gender, psychiatric co-morbidity or severity of drug use) and external (i.e.

environmental, for e.g. parenthood or being in receipt of stable accommodation) determinants. Internal factors relate to the patient's individual determinants, while the external factors relate to the individual's external determinants i.e. those factors that are conducive to recovery that create and foster an environment in which rehabilitation is socially accepted, encouraged and promoted.

A number of international outcome studies, (Treatment Outcome Prospective Study [TOPS], Drug Abuse Treatment Outcome Study [DATOS] and the National Treatment Outcome Research Study [NTORS]) have supported the general effectiveness of traditional treatment options available for opiate patients (14-17). The Research Outcome Study in Ireland Evaluating Drug Treatment (ROSIE) was the first national, prospective, longitudinal drug treatment outcome study in Ireland (18). The Study included a cohort of 404 opiate users entering treatment for the first time. Participants were interviewed at treatment intake, 1 year and 3 years after the baseline interview. The principal aim of the ROSIE study was to assess the efficacy of treatment for opiate use in Ireland. Results on treatment outcomes for opiate users were positive and encouraging from the perspective of the individual, service providers and the community. The ROSIE study offered insight into the effectiveness of treatment intervention and strategies for opiate users across all treatment modalities in Ireland. A key strength of ROSIE was that it captured a broad picture of treatment outcomes across the range of available modalities. In terms of detoxification only 20% of the ROSIE cohort had engaged in structured detoxification and a mere 8% of this cohort were involved in 'inpatient (hospitalized) detoxification'. There is, however, a need to go beyond the effectiveness of treatment interventions and further understand factors that influence outcomes and result in a positive detoxification for this population. The majority

of previous outcome studies have relied solely on self-reported behavioural measures. While such measures have shown good test-retest reliability they have been criticised for poor outcome predictability in certain clinical groups (19).

The overall aim of the proposed study is to investigate comprehensively rehabilitation pathways for patients post opiate detoxification in order to identify predictors of abstinence at 3, 6 and 9 month follow up.

This dissertation employs a multimodality approach. The first modality employs quantitative outcome measures to all patients, to examine abstinence and psychosocial indicators at 3, 6 and 9 months. The second modality employs qualitative interviews with a subsample of patients, to examine the factors that influence patients' rehabilitation pathways post detoxification. The third modality employs neuroimaging in approximately half of the patients, to examine whether individual differences in white matter predict outcome at 3, 6 and 9 month follow up. Since the detoxification was be followed by three different rehabilitation pathways (inpatient, outpatient and no formal aftercare) differential outcomes data across the three pathways is modelled to develop predictors of opiate abstinence.

1.4 SIGNIFICANCE OF THE STUDY

This current study, which is one of the first of its kind, has the ability to influence positively the lives and health status of opioid dependent individuals. The addiction services in Ireland are under political pressure to move patients away from methadone maintenance treatment. Much effort is being applied to identify more efficient and effective ways of delivering treatment services and also to identify appropriate settings. This study addresses these issues.

Moreover, it is recognised that without significant service uptake, it is impossible to reduce morbidity and mortality levels to the extent anticipated by visionary documents such as the National Drug Strategy (2009-2016) (20). Exploring patients' experiences and outcomes as well as identifying treatment factors that contribute to successful recovery represents a worthwhile focus as it seeks to understand individual as well as collective aspects of patients' treatment pathways. This perspective ultimately has the potential to contribute to effective treatment service uptake and promote recovery.

The majority of previous studies on outcomes of opioid dependent patients in Ireland (ROSIE) (21) and internationally TOPS (17), DATOS (22) and NTORS (23) have been either qualitative or quantitative and mostly limited to cross-sectional designs. While these have provided invaluable information on populations of drug users, most have had the limitation of capturing responses to single episodes that were often limited to drug use and none have observed the neurobiological as well as dynamic process of decision-making. As this dissertation employs mixed methods as well as longitudinal designs it was possible to document neurological, physiological, psychological outcomes, cultural and social processes and individual experiences across multiple episodes of treatment and rehabilitation. Precisely its distinct advantages pertain to its potential in observing sequential changes but also achieving more reliable findings resulting from capturing multiple process and outcome driven observations.

1.5 SCOPE OF THE STUDY

This PhD research study included: (i) a cohort sample of 143 patients at baseline who were followed for a period of 9 months with follow up data collected three times at three month intervals, (ii) a sub-sample of 10 patients were followed for a period of 9 months at three

monthly intervals for a longitudinal qualitative inquiry; and (iii) a sub-sample of 60 patients underwent a MRI scan. More details on each of the studies are presented in chapters 6 and subsequently in chapters 7, 8 and 9, which present individual analysis of each study.

1.6 RESEARCH CONTRIBUTION TO KNOWLEDGE

The contribution of this PhD research to current knowledge is threefold. First, it provides an in-depth understanding of the treatment pathways for opioid dependent patients post detoxification (including determinants of access to treatment services).

Secondly, it contributes to a deeper understanding of the perceptions, attitudes and personal experiences of opioid dependent patients as they navigate their way through their chosen treatment pathway.

Thirdly, it makes an original contribution to the current body of research. The cohort study is the largest outcome study of detoxification patients in Ireland and the first of its kind to apply a longitudinal approach. To the best of the candidate's knowledge the naturalistic qualitative study is also the first of its kind to apply a longitudinal qualitative approach to this patient group. The neuroimaging study is the first to identify with some precision the development of white matter impairment in opioid dependent patient groups spanning three decades. Also the neuroimaging study is the first to use Diffusor Tensor Imaging (DTI) measures to examine outcomes in opioid dependent patients post-detoxification.

1.7 ETHICAL APPROVAL

Ethics approval was obtained from the National Drug Treatment Centre Board Research Ethics Committee. The ethical approval notification letter is attached as (Appendix 2). Due to the low level of literacy in this population all potential participants were provided with a

Participant Information leaflet about the study (Appendix 3) to read, the content was also read out and explained to them during an introductory session. If they agreed to participate, participants provided written consent by signing the consent form (Appendix 4).

1.8 ORGANISATION OF THE PHD THESIS

This PhD thesis is presented in the order of chapters as outlined below:

Chapter 1 is the current chapter. It introduces the PhD research, specifically outlining the problem statement that necessitated the PhD research; background information on the patient group and current clinical context, significance of the PhD research, scope of the PhD research, contribution of the PhD research to current knowledge, ethical considerations, and outline of the structure of the PhD thesis.

Chapter 2 introduces, defines and presents national, European and international prevalence rates of opioid dependence, discusses the aetiology of opioid dependence and gives a clinical, psychological and physiological overview of opioid dependence. The neurological processes underlying dependence and a discussion of neuronal consequences of short and long-term opioid dependence are then presented.

Chapter, 3 documents a review of literature of treatment of opioid dependence. A review of treatment interventions for opioid dependence is given next. The chapter continues with a discussion of treatment outcomes post-detoxification. The neurological processes underlying dependence and a discussion of neuronal consequences of short and long-term opioid dependence are then presented. The chapter concludes with a review of literature attempting to link neuroanatomical changes to outcome across several substance dependent populations.

Chapter 4 gives a breakdown of each of the aims and objectives of the three studies that make up the PhD.

Chapter 5 presents the overall methodological approach.

Chapter 6 presents the longitudinal study of the PhD research. The baseline demographics; findings pertaining to: primary outcome of abstinence at 3, 6 & 9 months, as well as findings pertaining to secondary outcomes, wellbeing, physical & psychological health, hope for the future and quality of life. This is followed by a summary of findings: strengths and limitations and conclusion of the longitudinal study.

Chapter 7 presents the findings of the naturalistic qualitative study. The findings presented are based on thematic analysis. The first section simply presents the thematic analysis. The second section presents a brief summary of these findings. This is followed by a summary of findings: strengths and limitations and conclusion of the qualitative inquiry.

Chapter 8 presents the findings of the Diffusor Tensor Imaging (DTI) study. The findings presented are based on the association between white matter impairment and duration of dependence. These findings explore the occurrence and development of this impairment in three distinct groups spanning three decades of opioid use. An examination of this impairment in relation to patient outcomes is presented. This is followed by a summary of findings: strengths and limitations and conclusions of the DTI study.

Chapter 9 provides an integrated discussion of findings from all three studies.

Chapter 10 is the final chapter, which provides the overarching conclusions of the PhD thesis and outlines recommendations for recovery policy, practice and research.

2 CHAPTER 2:OPIOID DEPENDENCE

2.1 INTRODUCTION

Opioid use is a serious public health concern both nationally (24) and internationally (25). The rates of opioid use and the adverse impact this poses for patients are well established (26-28). Reduction of opioid use is beneficial at an individual, family and community level. Ireland has developed a comprehensive response to opioid use over the past 20 years. However, this response has focused almost exclusively on the harm reduction model whereby opioid-dependent patients receive substitution treatment on demand. While this has been hugely beneficial in public health terms (i.e. reducing drug-related mortality, transmission of blood borne viruses, in particular, HIV, as well as a reduction in drug-related crime) it has limited effect on individuals who wish to become drug free (29). There is a pressing need to improve treatment outcome, by developing appropriate models of management in order to reduce relapse and premature termination of treatment. Rehabilitation pathways in addiction vary extensively. Therefore, understanding factors that influence a patient's motivation and rationale for choosing one particular intervention over another is essential when attempting to improve treatment outcome for this population.

2.2 PROBLEM OPIOID USE

The European Monitoring Centre for Drugs and Drug Addiction defines problem drug use as 'injecting drug use or long duration/regular use of opioids, cocaine and/or amphetamine'(30). Injecting drug use and the use of opiates form the greater part of problem drug use in Europe. However, problem drug users are mostly poly drug users and more often than not live in urban areas and among socially excluded groups (30). According

to the EMCDDA, most European countries provide prevalence estimates of problem opioid use. Recent national estimates vary between one and eight cases per 1000 population aged 15-64 years old. According to the EMCDDA, Ireland is in the top three countries reporting the highest well-documented estimates of problem opioid use in the last 12 months (31). See table 1 below. TABLE 1 taken from the 2015 EMCDDA National Opioid Data Report .

Table 1: National Opioid Figures

	Problem opioid-use estimate	Treatment demand indicator, primary drug (opioid)				Clients in substitution treatment
		Opioid clients as % of treatment entrants		% Opioid clients injecting (main route of administration)		
	Cases per 1 000	All entrants	First-time entrants	All entrants	First-time entrants	
		%(Count)	%(Count)	%(Count)	%(Count)	
Belgium	-	30.8 (2 816)	13 (416)	39 (2 024)	20.1 (547)	17 482
Bulgaria	-	88.8 (1 744)	79.3 (211)	95.2 (954)	73.8 (876)	3 563
Czech Republic	1.5-1.5	17.2 (1 681)	7.8 (362)	25.6 (1 319)	89.4 (1 493)	3 500
Denmark	-	17.5 (663)	7.1 (102)	26.3 (502)	23 (20)	7 600
Germany	2.8-3.4	37.1 (29 891)	13.7 (3 217)	-	-	77 300
Estonia	-	92.9 (403)	81 (102)	98.6 (284)	84.8 (339)	1 166
Ireland		51.3 (4 451)	29.7 (1 032)	66.8 (3 291)	41.3 (1 762)	9 640
Greece	2.0-2.6	69.3 (3 367)	54.9 (1 145)	80 (2 194)	36.8 (1 227)	9 973
Spain	1.7-2.6	26.8 (13 333)	11.4 (2 866)	43.7 (10 050)	17.8 (2 195)	69 111
France	-	43.1 (15 641)	27.1 (2 690)	53.5 (11 275)	14.2 (1 836)	163 000
Croatia	3.2-4.0	80.4 (6 315)	24 (270)	90 (5 992)	73.7 (4 581)	6 357
Italy	3.8-4.9	54.7 (18 072)	37.2 (4 782)	65.7 (13 290)	57 (9 678)	94 376
Cyprus	1.2-2.1	26.5 (270)	7.7 (37)	43.8 (232)	48.1 (126)	180
Latvia	4.1-9.7	52.1 (783)	19.7 (104)	69.6 (679)	63.7 (495)	328
Lithuania	2.3-2.4	86.8 (1 918)	62.8 (214)	91.9 (1 671)	-	592
Luxembourg	5.0-7.6	50.2 (145)	42.1 (8)	49.8 (116)	48.2 (68)	1 254
Hungary	0.4-0.5	5.9 (236)	2.1 (54)	13.6 (160)	70.1 (157)	786
Malta	6.5-7.7	74.8 (1 352)	33.7 (67)	79.9 (1 285)	61.8 (816)	1 078
Netherlands	1.1-1.5	10.2 (1 195)	5.1 (343)	17 (852)	4.6 (51)	8 185
Austria	4.9-5.1	52 (1 537)	29.5 (361)	67.9 (1 176)	43.4 (536)	24 027
Poland	0.4-0.7	26.4 (724)	8.2 (91)	39.3 (621)	58 (391)	1 725
Portugal	-	54.3 (1 634)	27.3 (380)	77.6 (1 254)	15.9 (238)	16 858
Romania	-	48.8 (802)	33.6 (240)	63.3 (543)	84.5 (622)	387
Slovenia	4.3-5.8	81.5 (234)	60.6 (57)	91.7 (176)	48.7 (113)	4 065
Slovakia	1.0-2.5	24.7 (558)	16 (185)	34.1 (363)	66.8 (367)	408
Finland	3.8-4.5	64.2 (706)	40.4 (65)	69.2 (619)	81.6 (567)	2 439
Sweden	-	27.3 (7 760)	17.2 (2 211)	35.7 (5 549)	59.6 (140)	3 425

United Kingdom	7.9–8.4	50.3 (49 871)	19.7 (6 813)	66.6 (42 636)	34.5 (16 871)	172 513
Turkey	0.2–0.5	76.3 (5 542)	68 (2 540)	85.1 (3 002)	39.7 (2 201)	28 656
Norway	1.9–3.1	26.9 (2 266)	–	–	–	7 055
European Union	–	41 (168 102)	18.7 (28 425)	57.1 (109 107)	38.2 (46 285)	701 449
EU, Turkey and Norway	–	41.3 (175 910)	19.9 (30 965)	57.6 (112 109)	30.4 (48 486)	737 160

Year and method of estimate for problem opioid use vary between countries.
The treatment demand indicator monitors entrants into treatment within a given year.

2.3 DEFINITION OF OPIOID DEPENDENCE

Substance dependence (termed by the American Psychiatric Association) is defined as a maladaptive pattern of substance use leading to clinically significant impairment or distress. Opioid dependence is a medical diagnosis characterised by an individual's inability to stop using opioids (morphine, heroin, codeine, oxycodone, hydrocodone, etc.) even when objectively it is in their best interest to do so. In 1964 the WHO Expert Committee on Opioid Dependence introduced "dependence" as "*A cluster of physiological, behavioural and cognitive phenomena of variable intensity, in which the use of a psychoactive drug (or drugs) takes on a high priority. The necessary descriptive characteristics are preoccupation with a desire to obtain and take the opioid and persistent drug-seeking behavior. Determinants and problematic consequences of opioid dependence may be biological, psychological or social, and usually interact*". The core concept of the WHO definition of "opioid dependence" requires the presence of a strong desire or a sense of compulsion to take the drug (32).

Diagnostic Statistical Manual(33) (DSM-5) clinical guidelines for a definite diagnosis of "dependence" require that three or more of the following seven characteristic features be experienced or exhibited. Opioid dependence may be classified according to severity as mild, moderate, or severe.

2.4 CLINICAL OVERVIEW OF OPIOID DEPENDENCE

Some individuals who use opioids have become physically dependent on the drug with only minimal use, whereas others may use opioid-based drugs recreationally without ever developing a physical or psychological dependency (34). There are multiple factors that are involved in the development of opioid dependence.

2.4.1 TOLERANCE

Tolerance is the necessity to increase the dosage of a substance to achieve the initial effect. Tolerance to the analgesic and euphoriant effects and unwanted adverse effects, e.g. respiratory depression, sedation, and nausea, may develop. Opioid tolerance usually does not develop in patients being treated for a serious illness such as cancer and who are receiving opioids for pain management, as the necessity to increase a dose in seriously ill patients is normally due to an increasing level of pain. No consistent relationship between intrinsic efficacy and tolerance exists (35).

2.4.2 WITHDRAWAL

Continuous use of opioids leads to physical dependence and the emergence of withdrawal symptoms during abstinence. The symptoms associated with physical dependence usually ensue 2-10 days following abrupt cessation after continuous use. The onset and duration of withdrawal varies by substance i.e. meperidine withdrawal symptoms peak between 8 and 12 hours and last for 4 to 5 days, whereas heroin withdrawal symptoms usually peak between 36 and 72 hours and may last for 7 to 14 days. Symptoms of opioid withdrawal include the following:

Autonomic symptoms - diarrhoea, rhinorrhoea ("runny nose), diaphoresis (profuse sweating), lacrimation (tears [often excessive]), shivering, nausea, emesis ("vomiting"), piloerection ("*involuntary erection or bristling of hairs*").

Insomnia-sleeplessness, restlessness, tremors

Pain-abdominal cramping, bone pains, joint pains and diffuse muscle aching

Craving-substances.

Tolerance and withdrawal criteria are not considered to be met for patients taking opioids exclusively under appropriate medical supervision.

Intoxication

Mild to moderate intoxication includes psychological effects such as: euphoria, sedation, decreased anxiety, a sense of tranquility, and apathy to pain. Severe intoxication may extend to delirium and coma.

Physiological effects of intoxication include the following:

- Respiratory depression (may occur while the patient maintains consciousness)
- Alterations in temperature regulation.
- Hypovolemia (decrease in volume of blood plasma), leading to hypotension.
- Miosis (constriction of the pupil).
- Needle marks or soft tissue infection.
- Increase in sphincter tone (can lead to urinary retention).

2.5 OPIOID INDUCED PHYSIOLOGICAL EFFECTS

2.5.1 IMMUNOLOGICAL EFFECTS

According to Buenaventura and colleagues the immunomodulatory effects of opioids can be traced as far back as the 1890s when Cantacuzene showed cellular immune suppression and decreased resistance to bacterial infection in guinea pigs treated with morphine (36). More recently opioids have been implicated in the increased prevalence of infections in opioid dependent patients and as a *cofactor in the pathogenesis of human immunodeficiency* virus (36).

2.6 HYPERALGESIA (ALSO REFERRED TO AS HYPERALGIA)

Hyperalgesia is a quite newly recognised adverse effect, and is defined as *an increased pain sensitivity*. This sensitization presents as increasing pain despite increasing doses of opioids. Recent studies in opioid dependent patients *have validated the clinical impression that chronic opioid use results in an abnormal pain perception*, consistent with hyperalgesia (37, 38). Moreover, Pud et al. suggest that detoxification from opioids does not reset pain perception for at least 30 days (37).

2.6.1 HORMONAL CHANGES

Several studies have demonstrated opioid effects on a variety of hormones including but not limited to testosterone (39), estrogen (estradiol, etc.) (40), luteinizing hormone (LH) (29), gonadotrophin releasing hormone (GnRH)(41), dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfates (DHEAS) (42) adrenocorticotropin (ACTH), corticotrophin releasing hormone(CRH) and cortisol (43). The majority of studies have focused on the androgenic hormones due to their association with many symptomatic side effects of opioid use (36). Many men who are taking prescribed or illicit opioids suffer from several side

effects including sexual dysfunction i.e., erectile dysfunction, decreased libido (36). Testosterone levels diminish within 4 hours following acute administration of opioids (39) and return to normal levels within 24 hours of cessation (44). Chronic administration of opioids for nonmalignant pain results in tonic decreases in both total (TT) and free (FT) testosterone (36)

2.7 AETIOLOGY OF OPIOID DEPENDENCE

Dependence on opioids is a multifactorial condition involving pharmacological, social, genetic, and psychodynamic factors interacting to influence behaviours associated with opioid dependence.

2.7.1 PHARMACOLOGICAL FACTORS

Opioids have strong reinforcing euphoric effects as well as an ability to reduce anxiety, increase self-esteem, and help coping with daily problems. Most opioids associated with abuse and dependence are mu-agonists, such as heroin, morphine, hydrocodone, oxycodone, and meperidine. Some partial mu-agonists, such as buprenorphine, or some that have no mu-agonism, such as pentazocine, also can possess reinforcing properties. The rapid development of physical dependence is unique to opioid use, making abstinence difficult.

Martin and colleagues (45) reported chronic opioid therapy discontinuation rates after five years to identify factors associated with discontinuation. The authors found more than fifty percent of participants taking 90 days of opioid therapy over a 6-month period remain on opioids several years later. Opioid continuation was strongly associated with prior opioid exposure, daily opioid doses of 120 mg or more of morphine equivalent per day, and

possible misuse; however, the data from which these associations were made did not include clinical measures of pain or disease severity (45).

2.7.2 PHYSIOLOGICAL FACTORS

Substances, particularly opioids, produce pleasurable feelings. *Neural pleasure* – the pleasure and reward centre located in our brain produces specific chemicals responsible for neural communication that are strongly related to our ability to experience pleasure, happiness, joy, and excitement. The use of opioids results in a sudden rush of pleasure that is significantly stronger than our natural ability to experience pleasure. This instant surge of euphoria can lead quickly to dependence.

2.7.3 SOCIAL FACTORS

Ease of access and acceptable social attitudes make experimentation with substance use easy. A high rate of drug use is seen in inner-city areas with lower socioeconomic status, high rates of unemployment, and high rates of crime (46). Apart from the association between higher exposure to substance use and high rates of addiction, the exact role of social factors in producing dependent and addictive behaviours remains unclear. Between 1970 and 1972, 42% of US personnel based in Vietnam reported heroin use; one half of those became physically dependent, but very few continued to use heroin once they returned home (47).

2.7.4 PSYCHOLOGICAL FACTORS

Psychological shortcomings in certain patients are proposed to form the basis of drug use. Opioids are theorized to help individuals in managing painful effects such as anxiety, guilt, anger and early trauma (48). Adolescents with pre-existing mental health diagnoses appear

to be at higher risk for long-term use of opioids (49). Substance use and opioids in particular produce pleasant feelings that can counteract their negative mood. This instantaneous ability to cope can lead to dependence.

2.7.5 GENETIC FACTORS

Genetic factors contribute to the vulnerability to developing drug addictions and to inter-individual variability in their treatment efficacy for drug addiction. Genetic epidemiologic studies suggest a high degree of heritable vulnerability for opioid dependence. The G protein-coupled mu opioid receptor (encoded by OPRM1) is the main target of morphine, heroin, and methadone, and it plays an important role in opioid tolerance and dependence. Individual differences in response to opioid drugs may be attributed in part to genetic variations in the OPRM1 gene (50). Moreover, gene polymorphisms for dopamine receptors/transporters, opioid receptors, serotonin receptors/transporters, proenkephalin, and catechol-O-methyltransferase (COMT) all appear to be associated with vulnerability to opioid dependence (51).

2.8 NEUROBIOLOGY OF OPIOID DEPENDENCE

The notion of addiction as a brain disease is controversial and has both supporters and opposers. In their recent book "Brainwashed: the seductive appeal of mindless neuroscience," Satal and Lilienfeld (52) warn against the allure of branding addiction a brain disease. The authors suggest that while well intentioned, this doctrine is perhaps best reserved for other disorders such as schizophrenia and multiple sclerosis, as these disorders best fit the disease model "afflictions of the brain that are neither brought on by the sufferer nor modifiable by the desire to get well..... It offers false hope that an addict's condition is completely amenable to a medical cure [much as pneumonia is to

antibiotics].....It threatens to obscure the vast role of personal agency in perpetuating the cycle of use and relapse (p58). Nevertheless, the neurobiology of addiction is indisputable; addiction is tied to changes in brain structure and function (53). Moreover, the growth in literature is not limited to the biological consequences. In an effort to estimate the economic cost of brain disorders in Europe Olesen at al.(54) included opioid dependence. The authors estimate the prevalence of opioid dependence in Europe as 1 million patients. With the annual cost of opioid dependence as a brain disorder at €3,323,000,000 or €3,323 per patient. The neurobiological perspective allows another perspective and set of tools through which to investigate treatment outcomes of opioid-dependent patients.

2.9 NEUROBIOLOGICAL PROCESSES UNDERLYING TOLERANCE, DEPENDENCE AND WITHDRAWAL

Opioid tolerance, dependence and withdrawal are all manifestations of brain modifications resulting from enduring opioid use. Clinically, opioid withdrawal is one of the most powerful factors driving opioid dependence and addictive behaviours. Treatment of the patient's withdrawal symptoms is based on understanding how withdrawal is related to the brain's adjustment to opioids (55). The opioid user's battle to recover is in great part a struggle to overcome the effects of these changes. Several individual and environmental aspects affect whether any one individual who experiments with opioids will continue taking them long enough to become dependent (55). Particularly in the early stages of use, the opioid's stimulation of the brain's reward system is a primary reason that some individuals repeatedly use drugs. However, the urge to use opioids develops over time to extend beyond a simple drive for pleasure. This increased compulsion is related to tolerance and dependence. Frequent exposure to increasing amounts of opioids modifies the brain so that it functions normally when the drugs are present and abnormally when they are not

(55). Two clinically significant consequences of this modification are opioid tolerance and drug dependence.

2.10 NEUROBIOLOGICAL PROCESSES UNDERLYING DEPENDENCE

The initiation of drug-taking behaviour and vulnerability to relapse clearly involves the positive reinforcing properties of drugs, and it is widely accepted that the positive reinforcing effects of drugs are a key element of drug dependence. Moreover, major sources of reinforcement in drug dependence (i.e. positive reinforcement [the euphoric feelings induced by opioids], negative reinforcement [physical pain from withdrawal from substance], conditioned positive reinforcement [i.e. being in a place where previously used opioids, elicits eutrophic feeling without having to use a substance], and conditioned negative reinforcement [i.e. being in a place where previously used opioids, elicits feeling of pain without having to use a substance]) encompass motivation for the development, maintenance and persistence of drug dependence. Thus, drug dependence can only be explained within, but not limited by, a neurobiological context that takes account of thoughts, feelings and behaviours that lead to drug use or abstinence. An important challenge for neurobiological research is to understand the neuroadaptive differences between controlled drug use and loss of control i.e. the move from intentional controlled experimentation to uncontrolled, compulsive patterns of use (56).

Extraordinary scientific developments have emerged in the neuroscience of drug dependence that offer new insights into how chronic drug use affects the inner workings of the brain and how this leads to the abnormal behavioural manifestations of dependence (57). With the advancement in neuroimaging researchers and clinicians are afforded the opportunity to investigate the human brain in situ safely and noninvasively.

Humans, as well as other organisms, engage in behaviours that are rewarding; the pleasurable feelings provide positive reinforcement so that the behaviour is repeated (58). It is widely accepted that humans possess a 'reward pathway' (58). Indicated in the reward pathway are the ventral tegmental area (VTA), the nucleus accumbens (NA), and the prefrontal cortex (PFC). The VTA is connected to both the NA and the PFC via this pathway, and it sends information to these structures via neurons. The neurons of the VTA contain the neurotransmitter dopamine, which is released in the NA and in the PFC.

Substance dependence is marked by mild, yet pervasive, neurocognitive disruptions that accelerate its course and threaten sustained abstinence (59). Opioids can disrupt volitional mechanisms by hijacking the brain mechanisms involved in seeking natural reinforcement and weakening brain mechanisms that inhibit these processes (57). Tarter and colleagues found that neurobehavioral disinhibition in childhood predicts early adulthood onset of substance use (60). Moreover, individuals with poorer cognitive functioning have higher rates of attrition in treatment for substance use (46, 47).

2.11 LINK BETWEEN FUNCTIONAL AND STRUCTURAL CONNECTIVITY

It has been suggested that well-defined major white matter tracts underpin functional neural networks and cognitive processes. For example, language processing is supported by the arcuate fasciculus, which connects the traditional language centers of Broca's area and Wernicke's area (61). The limbic network is involved in emotional processing and appears to be linked by a number of major white matter tracts including the cingulum, inferior longitudinal fasciculus and the arcuate fasciculus (62, 63). The branches of the superior longitudinal fasciculus are thought to structurally connect brain regions within the dorsal and ventral attention networks (64) while the inferior fronto-occipital and arcuate fasciculi

appear to connect neural regions involved in visuospatial processing (63). The theory of abnormal cortical connectivity suggests that both structural and functional connectivity abnormalities contribute to the clinical deficits characteristic of many psychopathological disorders Autism (65), ADHD (66), schizophrenia (67), depression (68). Disrupted functional connectivity during language comprehension (69), emotion recognition (70), attention orienting (71) and visuospatial processing (72) have been illustrated in a number of these pathologies. The candidate could only find one paper that examined the association between disrupted structural connectivity and abnormal functional connectivity in opioid dependence (73). This study by Upadhyay and colleagues suggests that prescription opioid dependence is associated with structural changes in the brain. Patients had significant changes in axonal pathways particular to the amygdala (i.e. stria terminalis, ventral amygdalofugal pathway and uncinate fasciculus) as well as the internal and external capsules. Moreover, the study further suggests patients' duration of use was associated with greater changes in functional connectivity. The findings are clinically relevant to further understand the long-term effects of prescribed opioids on both the structure and function of the brain. However, it is of note that the population in this study was specifically dependent on prescription opioids.

3 CHAPTER 3: LITERATURE REVIEW

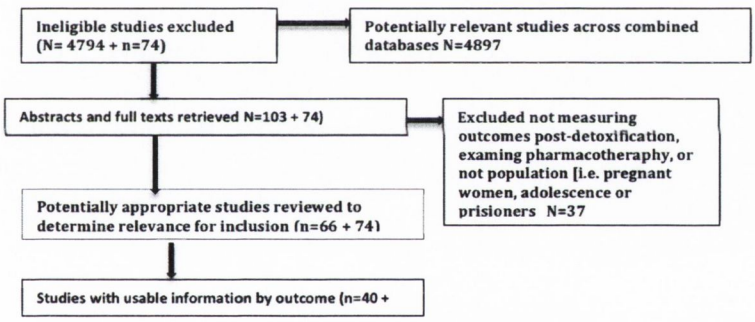
3.1 INTRODUCTION

The candidate employed four key strategies to systematically search and review the literature. (1) Online database searches, (2) hand searching, (3) 'grey literature' searches and (4) Snowballing. Literature searches for the following search string/MESH terms: *illicit and opioid and dependence and inpatient detoxification and outcome,* were used to search MEDLINE, EMBASE, Psych info (+Psych Articles by default), PubMed and the Cochrane Library. The following Boolean terms were added (for dependence OR [dependent OR dependency] and for opioids [opiates]) to increase efficacy and reduce duplication. The original search had included search string/MESH terms: *illicit and opioid and dependence and inpatient detoxification and outcome [and magnetic resonance imaging]. H*owever, no papers were returned, thus magnetic resonance imaging was removed. As previously discussed in the dissertation the area of opioid dependence and neurobiology is quite new and therefore relatively limited. All literature discussing opioid dependence and neurobiology was retrieved through hand searches and snowballing. Figure 1 below outlines the number of papers found, reviewed, included or excluded in the end review. Appendix 1 includes an example of a combined search for EMBASE and the Cochrane Library consisting of (94) papers. A short rationale is offered for the exclusion of each paper. Hand searching included reports and books both online and hardcopy. The 'grey literature' included conference listings (abstracts and posters) and online open search engines such as Google and Google Scholar for key terms. The ROSIE study was previously identified by the candidate and was instrumental in the developing of the thesis design, snow balling was employed and several outcome studies were identified from the ROSIE study (Treatment

Outcome Prospective Study [TOPS], Drug Abuse Treatment Outcome Study [DATOS] and the National Treatment Outcome Research Study [NTORS]). In addition, the candidate's supervisor had co-authored the only other Irish detoxification paper. Searches for co-authors also resulted in relevant papers. Also Both Google and Google-scholar were used to find conference abstracts and posters. The candidate found a conference poster that appeared highly relevant. However, upon contacting the PI the study was never published.

Figure 1 flow chart: literature review

Numbers in brackets in the flow chart refer to citations identified through electronic database searches + citations by other searches (hand searching, snow balling).



3.2 TREATMENT OF OPIOID USE

It is estimated that approximately one in six problem drug users globally receives treatment for drug use disorders or dependence each year (74). However, there is a greater than six-fold variation between the regions. Africa, in particular, stands out, with only one in 18 problem drug users accessing treatment services, predominantly for treatment related to cannabis use disorders. In Latin America and the Caribbean and Eastern and South-Eastern Europe, approximately one in 11 problem drug users accesses treatment services, well

below the global average. Conversely, in North America, each year an estimated one in three problem drug users receives treatment interventions. To a certain extent, these regional differences reflect varying reporting systems for treatment demand, but they also certainly demonstrate the wide disparity in the availability and accessibility of drug dependence treatment services in different regions.

3.3 PREVALENCE OF OPIOID USE

In 2013, the United Nations Office of Drugs and Crime (74) estimated global prevalence of opioid use to be between 0.3 and 0.5 %, corresponding to between 12.8 and 21.9 million people worldwide using opiates in the 12 months preceding 2011 (United Nations Office on Drugs and Crime 2013). In West and Central Europe, the prevalence of opioid use is an estimated 0.5% of the general population with the corresponding number of opioid users between 1 and 1.5 million, a slight decrease from 2009 when the number of opioid users was estimated between 1.2 and 1.5 million (United Nations Office on Drugs and Crime 2013).

In Ireland, the national prevalence estimate of opioid dependent users in 2006 was between 18,136 and 23,576 (75). According to Long & Lyons this estimate is likely to be inflated (75). The majority of cases (72%: n=14,904) lived in Dublin. Similar to many other EU countries, Ireland reported an increase in new opioid cases entering treatment since 2005. Following a decline between 2001 and 2004, the number of new opioid cases entering treatment increased between 2005 and 2007 (75).

3.4 PHARMACOLOGICAL INTERVENTION FOR OPIOID USE

At present the treatment of choice for most opioid dependent patients in Ireland and Europe is long-term prescribing of methadone maintenance treatment (MMT) (24) or with opioid agonists such as methadone or buprenorphine (76). Currently in Ireland there are 66 treatment locations providing MMT nationally. Some opioid dependent patients attend the larger addiction centres where methadone is dispensed on site while others receive MMT at satellite clinics in their local community where methadone is prescribed by medical doctors but dispensed at a community pharmacy. Patients who attend satellite clinics are more often less chaotic than those attending the larger addiction centres. All patients attending the larger addiction centres and the satellite clinics are registered on the Central Treatment List (CTL). The (CTL) was established by the Department of Health and Children under Statutory Instrument No. 225 (1998) on foot of the Report of the Methadone Treatment Services Review Group (1998). This list is administered by the National Drug Treatment Centre on behalf of the Health Service Executive and is a register of all patients receiving methadone (as treatment for problem opioid use) in Ireland. Once a patient is deemed suitable for methadone detoxification or maintenance, the prescribing doctor applies to the CTL for a place on the list, and a unique number is allocated to the patient. Thus, patients receive their methadone from one source only. Patients' demographics (i.e. name, address, date of birth, gender, date commenced on methadone, type of methadone treatment, prescribing doctor and dispensing pharmacist) are recorded. The CTL is considered accurate with respect to the number of patients who start or recommence methadone treatment since prescribing doctors have a statutory obligation to report the commencement of treatment. Once on the List, the current treatment status of the majority of patients can be traced via transfer and exit records (75).

Evidence shows that MMT lowers risk of death, reduces illicit drug use, and decreases criminal behaviours (4). Bell and colleagues explored some ethical concerns of MMT: (i) rather than being treatment of a disease, MMT is management of a social problem (ii) rather than championing abstinence and rehabilitation, MMT actually hinders rehabilitation and (iii) the notion of providing opiates to treat opioid dependence may be seen to increase vulnerability, at a profit to doctors and others involved in the treatment of opioid dependent patients (77). The authors re-examined these ethical concerns in light of recent neurobiological findings, which suggest that addiction is a chronic, relapsing disease (78-80). Bell et al. concluded, that while numerous patients recover from addiction the fact remains that not all or even most patients recover in the short or medium term. Moreover, due to the stigma and marginalization that often accompanies addicted individuals, MMT, in particular needs to be shielded from 'exploitation and poor quality of care' (79). Nonetheless, while some patients may require lifetime maintenance, the issue of rehabilitation is vital to many patients and should be discussed at regular intervals throughout the course of treatment and where appropriate supported by a menu of clinical options (81).

3.5 NEUROBIOLOGICAL TREATMENTS FOR DRUG DEPENDENCE

Several new developments have been made in Neuroscience research on new therapeutic interventions that may be beneficial in reducing the harmful effects of opioid dependence. Conversely, a number of these treatments are considered invasive and present some safety issues that are still in their infancy and as such have not been fully evaluated (82).

Nevertheless in order to provide a review of available treatments these are included. These include:

- Vaccinations - immunological technologies that bind to a particular drug of addiction and avert if from acting on the brain.

- Implants – slow release formulations of drugs such as long-acting drug implants, which last for months and have the potential to reduce the problem of poor treatment compliance.

- Neurosurgery – In China neurosurgeons have destroyed parts of the nucleus accumbens a region of the brain implicated in reward in opioid dependent patients in order to reduce rewards associated with drug use. Similarly in Russia parts of the cingulate gyrus, thought to be implicated in obsessive disorders were lesioned in an attempt to reduce relapse (83). This is an extremely aggressive, permanent and controversial form of 'intervention'.

- Deep brain stimulation (DBS) is a surgical procedure that involves the insertion of electrodes deep into the brain to control behaviour. DBS has been widely applied in the treatment of Parkinson's disease (84). More recently it has been applied to Tourette's syndrome and obsessive compulsive disorder . It has been suggested DBS may also be used to treat addiction (85). Watjas and colleagues (86) applied DBS to successfully treat gambling in patients with co-occurring Parkinson's disease. DBS also involves surgical procedure and as such carries similar, albeit reduced, risks to the neurosurgical procedures outlined above.

- Transcranial magnetic stimulation (TMS) is a non-invasive procedure that uses magnetic fields to alter brain activity. TMS is most widely applied to the treatment of depression and

has yielded significant results (87, 88). Currently clinical trials are underway to investigate whether this technology has a role in treating addiction (82). Some small success has been found with Cocaine users (89).

3.5.1 NEUROBIOLOGICAL SCREENING AND DIAGNOSTIC TECHNOLOGIES

Genetic and neuroimaging technologies may be used to: 1) screen individuals for vulnerability to developing an addiction (predictive genetic screening); 2) assist clinicians to diagnose particular deficits in addicted individuals (genetic diagnosis); and (3) identify treatments that are most likely to be effective in treating addicted individuals for example pharmacogenetics i.e. adapted to a patients genomic susceptibilities (90). However, at present considerable uncertainties exist regarding the use and validity of genetic and neuroimaging screening to pinpoint individuals who tailoring are more vulnerable to addiction. Nonetheless, the use of these genetic and neuroimaging techniques to guide treatment decisions holds more promise in screening and diagnosis and is the subject of active research (90).

3.6 PSYCHOSOCIAL INTERVENTIONS FOR OPIOID USE

The National Institute for Clinical Excellence (NICE) Guidelines suggests treatment for problematic substance misuse should always involve a psychosocial component. These guidelines recommend psychosocial interventions in the treatment of people who misuse opioids, stimulants and cannabis in the healthcare and criminal justice systems (91). Psychosocial interventions encompass a wide range of components, including "*self-management skills training, family intervention, self-help groups and other consumer-*

oriented services, supported employment and housing, and case management" Frese & Stanley 2001, P2 (92).

The type of intervention should be selected on the basis of the treatment need of the individual patient, guided by the available evidence base of effectiveness, and not by the interests of the service provider (93). Motivational interventions, contingency management and behavioural couples therapy are the key-evidence based psychosocial interventions for the management of problematic substance use. Moreover, the authors categorise these interventions as either low- or high-intensity:

- Motivational interventions (low-intensity)
- Contingency management (low-intensity)
- Behavioural couples therapy (high-intensity)

Psychosocial interventions can be delivered by a range of frontline staff (Medical Doctors, Nurses, Pharmacists, Counsellors, Psychologists, and Key-workers) with the relevant competencies. The competencies of the clinican or key-worker when delivering an intervention are imperative to service user outcomes. In a systematic review Pilling and Strang (91) emphasize some of the key competencies required as follows:

- the ability to engage a service user appropriately while demonstrating satisfactory levels of warmth, in order to build rapport and trust, which fosters an ability to adopt an 'individual approach that is consistent with and complements the service user.

- The ability to adjust the nature of the intervention according to the needs of the patient

- The ability to deal with complex emotions, as well as understanding and working with the service user's emotional context, including service user motivation.

However, Killaspy and collegues (93) emphasize that the mere publication of competencies or the implementation of appropriate training programmes are not sufficient to achieve effective service delivery. Rather they suggest that adequate supervision is required in order to consolidate training and maximise the benefit of the investment in time and resources. Moreover, in addition to training and supervision, quality assurance and clear protocols for the delivery of the interventions need to be in place if effective service delivery is to be achieved.

In a recent Cochrane review Amato and colleagues (94) compared the effectiveness of psychosocial plus pharmacological intervention with any pharmacological intervention alone for opioid detoxification. Eleven studies including 1,592 participants met the inclusion criteria for the review; these included both Randomised Controlled Trials (RCTs) and non-randomised trials. The authors concluded that 'psychosocial treatments offered in addition to pharmacological detoxification treatments [methadone or buprenorphine] are effective in terms of: 1 'completion of treatment, 2 opiate use at follow-up and 3 clinical attendance'. However, they also state that 'the evidence is limited due to the small numbers of participants in each trial and differences of assessments across trials'.

3.7 DETOXIFICATION FROM OPIOIDS

The National Treatment Agency (NTA) defines detoxification as a process supporting safe and effective discontinuation of opiates while minimising withdrawals. Detoxification may be carried out in an inpatient facility or within a community setting such as the individual's home, or day clinic (95). The process varies in duration from patient to patient, with a usual programme lasting approximately 28 days as an inpatient or up to 12 weeks as an outpatient. Detoxification in Ireland and post-detoxification treatment pathways are discussed below.

3.8 INPATIENT VERSUS OUTPATIENT OPIOID DETOXIFICATION

Day and colleagues (96) undertook a Cochrane review comparing inpatient detoxification programmes with outpatient detoxification programmes to determine which was more effective. The authors found only one study from 1975 involving 40 patients receiving methadone substitution treatment, which satisfied the inclusion criteria. The results of the study suggested that inpatient detoxification may be superior to outpatient only in the short term as all of the inpatients had relapsed within three months of detoxification. The authors' concluded one outdated study with 40 patients was not enough to offer convincing results and more research was needed.

In a later study Day and colleagues (8) undertook a Randomised Controlled Trial (RCT) on the impact of treatment setting on detoxification. In the trial, 68 opioid-dependent patients (most of whom were in receipt of methadone and all but six were also using heroin) were randomised to an inpatient or an outpatient setting. Participants in both settings received the same structured lofexidine detoxification treatment. Of the 68 patients more inpatients (51%, 18) than outpatients (36.4%, 12) completed the detoxification. This meant that less

than half of the 68 patients randomised to the different detoxification settings managed to complete the treatment. Eleven participants in all were abstinent from all opioids at one-month follow-up, and only eight at six-month follow-up, with no superior differences between the groups. The findings did not yield statistically significant results (most likely due to small numbers of participants). The authors concluded that the 'results of the trial confirm previous research findings that detoxification is an ineffective stand-alone treatment for opioid dependence.'

The fact that inpatient detoxification has many benefits remains Incontrovertible (8, 96). Most inpatient detoxification programmes are conducted in a hospital setting. In Ireland this is mostly the case, where this is not the case (e.g. inpatient settings in normal residence used, but not purposely built for treatment[1]) are overseen by a multi-disciplinary medical team, which allows for a high-level of medical supervision and safety. This is crucial as patients undergoing detoxification may require intensive physical and/or psychiatric monitoring. In addition, withdrawal is more often completed more rapidly in an inpatient setting. For certain patients, the security that an inpatient environment offers, and a period of respite from 'people and places associated with drug use', may facilitate them in their attempt to make pivotal life decisions (8). Moreover, where an inpatient programme is comprehensive, more consideration is given to family, vocational, medical, and psychiatric issues.

Nevertheless, inpatient settings are not without shortcomings. The enclosure of an inpatient unit may also be one of its main disadvantages since a main determinant of craving is the accessibility of a substance. Inpatients are unable to work, care for their families, study, or

[1] In Ireland many inpatient detoxification units that are run by charitable organisations are based in a residential house.

conduct their regular daily activities. There may also be a stigmatization attached to some inpatient service settings, which may act as a deterrent to some patients (97, 98). However, one of the primary deterrents to detoxification in inpatient settings is the delay in coping with people and places associated with drug use, which patients will inevitably encounter upon discharge. What is more, an inpatient detoxification can cost as much as 20 times the equivalent treatment in a community setting (99). In the UK, the vast majority (90%) of opioid patients seeking abstinence are offered outpatient community detoxification as the initial treatment.

The adverse nature of opioid withdrawal is a considerable barrier to achieving abstinence, and attempts at detoxification without medical supervision are often unsuccessful (100-102). One of the most widely used methods to manage opioid withdrawal involves putting the patient on reduced doses of oral methadone, and methadone has been described as the most effective pharmacotherapeutic agent currently used in detoxification (8).

In Ireland there are currently three principal pathways for patients post-detoxification 1. patients opt to go on to an inpatient rehabilitation programme lasting 1-2 months, 2. patients opt to go on to an out-patient rehabilitation programme lasting 3-6 months, or 3. patients opt to return to the community with no aftercare in place (see figure 1, p3).

3.9 OUTCOMES POST-DETOXIFICATION

Whilst there is evidence that maintenance-based programmes for opioid users are effective, there have been fewer attempts to evaluate the effectiveness of abstinence-based programmes (12, 103, 104).

In Ireland, there is a notable lack of data on the outcomes of in-patient detoxification and various rehabilitation treatment modalities. White and colleagues have produced data based on the results of a survey of patients of a residential rehabilitation facility for former opiate-dependent individuals (12). The survey was carried out to evaluate the success of a programme based on a systematic model in assisting participants to pursue a drug-free life. Two papers by Smyth and colleagues have described the characteristics of new patients presenting for treatment in one residential detoxification unit in Dublin. Both papers are descriptive, outlining the characteristics of persons presenting for detoxification in an inpatient setting. Both studies look at medium-term outcomes (12 months) for in-patient treatment of opioid dependents. The results have been disappointing in terms of the numbers staying drug-free, with (1, 11) 19% & 23% respectively drug free at follow-up.

Previous cohort studies of problem drug users in treatment such as DATOS TOPS, NTORS, capture a longitudinal snapshot of drug abuse patterns and treatment responses in the United States. As well as NTORS, the National Treatment Outcome Research Study which was carried out by the National Addiction Centre between 1995 and 2000 - the largest UK drug treatment outcome study to date and ROSIE (The Research Outcome Study in Ireland Evaluating Drug Treatment Effectiveness) which was the first national, longitudinal drug treatment outcome study in Ireland, have reported on the percentage of patients who opted for abstinence programmes. However, there are poor data on long-term outcomes, with even less information on factors influencing outcomes for these patient groups. Tract Based Spatial Statistics Studies in OpioiD dependent patients (ODP)

While it is accepted that opioid dependence is a chronic relapsing brain disease (57, 105) affecting millions of people globally, the exact neurological disorder and neuropathology

related to opioid dependence are still not fully understood (106, 107). A growing body of research has indicated significant white matter (WM) alterations in opioid-dependent patients when compared to healthy controls (108-110). In addition, there is a growing acceptance that opioid dependence is a disorder of neural connectivity (110-112). Given that abnormal connectivity may be the result of pathological changes of the white matter connections, it is paramount that we begin to understand the fundamental underlying structure of the white matter (WM) in ODP (110) Advances in MRI, and in particular diffusion tensor imaging (DTI), have afforded the opportunity to non-invasively examine neuropathological changes in WM in vivo (110, 113, 114). DTI is a technique which is sensitive to the diffusion of water molecules and provides measures of white matter microstructure. Decay or disruption of the microstructural organisation in WM is coupled with changes in quantifiable DTI parameters (115). These parameters provide three kinds of information; (i) apparent diffusion constant, or ADC (i.e. magnitude of diffusion), (ii) anisotropy of diffusion (i.e. directionality) and (iii) the primary orientation of the WM fibre bundles (116).

As previously suggested, a number of DTI studies have compared heroin dependent patients with normal controls. Nevertheless, beyond the establishment of significant differences between ODP and healthy controls several inconsistencies exist (110). This may be at least in part due to methodological choices. For example, Wang et al. opted for a region of interest method, and found no difference between the heroin dependent patients and the control group (117). By opting for a whole brain voxel-based method Liu et al. demonstrated that heroin dependent patients displayed lower fractional anisotropy (FA) in the bilateral frontal sub-gyral regions, right precentral and left cingulate gyrus, whereas Bora et al. , who performed a voxel-wise Tract-Based Spatial Statistics (TBSS) method,

reported extensive FA reductions in numerous pathways (across the corpus callosum, thalamic radiation and parietal, frontal, temporal and cerebellar tracts) in opioid dependent patients when compared with healthy controls (108). Although methodological differences and/ or patient characteristics might account for some of the differences, the discrepancy of duration of use across these studies may be a more significant confounding factor (110).

A smaller body of evidence is emerging linking duration of drug use to severity of damage in ODP (110, 117, 118). A more recent study by Qiu and colleagues (67) employed TBSS to examine the relationship between the duration of heroin use and extent and severity of WM disruption. The authors stratified their ODP patient groups into those whose duration of dependence was (i) less than 10 years and (ii) greater than 10 years, revealing significant WM alterations in both groups, with the most profound and extensive microstructural disruptions occurring in the latter cohort. The authors found the extent and severity of WM damage was associated with length of heroin dependence. While this paper was methodically sophisticated, the authors' approach to duration of use was quite basic, in that they looked at duration as either less than 10 years or greater than 10 years.

3.10 PREDICTING TREATMENT OUTCOME

While clinical research on opioid dependence has elucidated the aetiology and development of dependence, the behaviours that characterise it, and social factors associated with addiction (e.g. prevalence and demographic characteristics), it has yielded comparatively few effective treatments to reduce it (119). Neuroscientific studies of drug dependence in animals and humans are needed to understand the exact pharmacological and anatomical

modifications in brain activity that underlie the addictive process so that more effective treatments and public health policies towards drug dependence can be developed (119).

Preclinical studies suggest that ventral striatal functioning, commonly associated with motivation for drug use (i.e. impulse to use) may present risk or protection against drug use (120). Studies indicate that the integrity of both the ventral striatal system and the prefrontal control system are related to abstinence and relapse. Furthermore, the evidence suggests that individual differences in impulsivity manifest in the integrity of both these systems (120). A key finding that emerges from this proposal is that interventions that reduce impulsivity through pharmacological or cognitive training methods should reduce drug use and should, therefore, be used to complement existing drug treatment programmes (121). By providing insight into the cognitive control neurobiological systems, neuroimaging can identify which processes best predict treatment outcome and/or are most amenable to therapeutic intervention.

4 CHAPTER 4: AIMS AND OBJECTIVES

The overall aim of the dissertation is to examine comprehensively rehabilitation pathways' effects on opioid dependency post-detoxification. The thesis comprises three studies (1 longitudinal cohort study, 2 naturalistic qualitative study and 3 diffusor tensor imaging study).

4.1 STUDY 1:LONGITUDINAL OUTCOME STUDY

4.1.1 AIM:

The aim of the longitudinal quantitative approach was to follow the treatment progress of a baseline sample post-detoxification.

4.1.2 OBJECTIVES:

a) To compare abstinence rates following detoxification at 3, 6 and 9 month follow up, across each of the three chosen rehabilitation pathways.

b) To compare changes in physical and psychological health, health risk behaviour, personal/social functioning, psychological wellbeing, hope [goal-directed energy] and planning [to meet goals] and quality of life.

4.1.3 QUESTIONS:

1) Does adding aftercare rehabilitation to a continuum care package make a difference to abstinence outcomes at 3, 6 and 9 months?

2) Does adding aftercare rehabilitation to a continuum care package make a difference to: physical and psychological health, health risk behaviour, personal/social functioning, psychological wellbeing, hope, planning and quality of life at 3, 6 and 9 months?

4.2 STUDY 2: NATURALISTIC QUALITATIVE STUDY

4.2.1 AIM:

The aim of the qualitative patient interviews was to gain an in-depth understanding of patients' experiences of the treatment journey, and identify the influence of chosen rehabilitation pathways.

4.2.2 OBJECTIVES:

a) To examine why patients choose a certain pathway.

b) To identify, describe and produce an analysis of individual demographics, perceptions, attitudes and personal experiences that may have influenced a chosen pathway.

c) To identify, describe and produce an analysis of what influence this pathway had on their recovery/relapse.

4.2.3 QUESTIONS:

The research questions focus was on the factors that influenced patients' chosen rehabilitation pathway.

1) What were the influences of: age, gender, ethnicity, social class and culture on the rehabilitation pathway?

2) What were the nature, extent and effect of perceptions, attitudes and experiences, (including a desire to achieve personal goals or meet individual needs) on the rehabilitation pathway?

3) What were the nature, extent and effect of psychosocial influences (including relationships, personal and social expectations, previous experience and social role) on the rehabilitation pathway?

4) What were the nature, extent and effect of possible therapeutic methods, length of stay and type of treatment on the rehabilitation pathway?

5) To what extent do perceptions, attitudes and experiences change as patients enter and progress through their chosen rehabilitation pathway?

4.3 STUDY 3: NEUROIMAGING STUDY

4.3.1 AIM:

The aim was to examine the neuroanatomical locations and extent of WM impairment in opioid dependent patients post-detoxification.

4.3.2 OBJECTIVES:

a) To assess the association between white matter impairment and duration of dependence.

b) To explore in some detail the occurrence and development of this impairment in three distinct groups spanning three decades of opioid use.

c) To examine this impairment in relation to patient outcomes.

4.3.3 QUESTIONS:

1) Can we determine the neuroanatomical locations of WM damage in opioid dependent patients and how these impairments develop throughout the course of opioid dependence?
2) Is white matter impairment a predictor of abstinence post-detoxification?

5 CHAPTER 5:METHODOLOGY

5.1 RESEARCH DESIGN

The thesis employs a mixed method approach, utilising three data sources: quantitative, qualitative and brain imaging. A mixed methods approach was chosen because of its potential to provide a holistic picture of the phenomenon under scrutiny. This chapter outlines the collective methodology of the thesis, within which are three studies: (1) an observational longitudinal cohort study, (2) a naturalistic qualitative study and (3) a Diffusion Tensor Imaging (MRI) study. Each method is distinctive yet complementary. This chapter presents the collective methods across the three studies. In the three chapters that follow, each study's methods, design, results discussion and limitations are presented in detail.

5.2 DATA SOURCES

Data collection comprised three key components:

1. Quantitative questionnaires.
2. Qualitative interviews.
3. Diffusion Tensor Imaging.

Three sources of data were employed in order to examine predictors of abstinence at 3, 6 and 9-month follow-up. Each of the three respective sources are discussed separately below.

5.3 SETTING

The three largest residential drug dependency units (DDU) in Ireland acted as a source of patients: Cuan Dara Detoxification Unit, Coolmine Therapeutic Community, and the Peter McVerry Trust.

Cuan Dara is a detoxification unit based in a hospital setting. It is based on a traditional medical model. It is staffed by a full complement of medical staff. Each patient is under the care of a Consultant Psychiatrist. The detoxification programme is complemented with physical activity, psycho-educational group work and one-to-one counselling.

Coolmine Therapeutic Community is a detoxification unit based in a residential setting with two gender specific units. It is based on the established Minnesota model that incorporates a medically supervised detoxification programme [overseen by a GP with a nurse(s) on the premises at all times]. The programme heavily emphasises a peer support model. The detoxification programme is combined with physical work, daily chores, physical activity, psycho-educational group work and one-to-one counselling.

The Peter McVerry Trust is a detoxification unit based in a residential setting. It is based on an established Portuguese model that incorporates a medically supervised detoxification programme [overseen by a GP with a nurse on premises at all times]. The detoxification programme is complemented with physical activity, psycho-educational group work and one-to-one counselling.

Prior to admission to each of the programmes, all patients are expected to have commenced therapeutic work with an addiction counsellor in a community based treatment service. Additionally, all patients undergo a psychiatric assessment to examine such areas as psychiatric co-morbidity and motivation to detoxify. The standard treatment programme

lasts between four and six weeks. This includes a ten-day methadone detoxification and a benzodiazepine detoxification if required. Patients receive nursing, counselling and medical support throughout the duration of treatment. During treatment, patients are involved in individual therapy and group therapy. Participants were monitored by their usual key worker/case manager throughout the course of this study. A number of representatives from each of the DDU's in addition to the candidate, her supervisor and a consultant psychiatrist formed an advisory committee for the duration of recruitment.

5.4 PARTICIPANTS

All patients admitted to Cuan Dara Detoxification Unit, Coolmine Therapeutic Community, and the Peter McVerry Trust who had detoxified fully from opiates were eligible to participate in the current study.

Inclusion criteria:

All patients aged between 18 and 65 years, admitted to the three Drug Dependency Units within the stated timeframe, who have detoxified from opiates between September 2012 and November 2013 were included in the study. Once a patient was admitted to the unit a staff member made them aware of the study. In the patient's final week of detoxification the candidate would meet with them and discuss the study. Once the patient was interested the candidate read and left an information sheet with them and made a follow-up date for. Thus the candidate met with patients at least twice before inducting them to the study. Given the level of follow up and the conditions of the MRI scan (final days of detoxification) it was important that patients were fully informed before consenting. The scanning arm of the study began in April 2013 and finished in November 2013. This was an

opportunistic sample, with the first 60 volunteers that met the inclusion criteria recruited into the scanning study.

Exclusion criteria:

Patients with terminal illness or acute untreated severe psychosis were excluded from participating in the study.

5.5 FOLLOW-UP METHODS

Once patients consented to participate in the study they were asked that they nominate a next of kin, three agencies that they expect to be in contact with and their general practitioner, all of whom could be used as a point of follow-up. In addition, patients consented for the candidate to have access to their clinical records via the central treatment list. The Central Treatment List (CTL) is a complete register of all patients receiving methadone (as treatment for problem with opiate use) in Ireland. The majority of patients were contactable personally or through their nominated agencies. Follow-up questionnaires and interviews were completed in community based addiction services. In the case of one interviewee not linked with a community service the use of space was negotiated on an individual basis. Two patient's follow-up interviews were conducted in an office on the TCD main campus.

6 CHAPTER 6: LONGITUDINAL COHORT STUDY

6.1 INTRODUCTION

This chapter presents the findings of the observational longitudinal study. The chapter is divided into three sections. The first section presents demographic data, the purpose of which is to describe the patient population. The second section presents cross sectional data in order to explore associations and relationships between patient demographics and treatment choice. The third section presents the longitudinal outcome data to compare treatment choice and change over time. The longitudinal analysis is presented as first and second level analysis. The first level analysis deals with the primary outcome of abstinence. The second level analysis deals with secondary outcome measures (physical and psychological health, health risk behaviour, personal/social functioning, psychological wellbeing, hope for the future and quality of life).

6.2 STUDY DESIGN

The current study employed an observational longitudinal cohort design which involved tracking a cohort of participants who had successfully completed detoxification, at four time points, baseline, 3, 6 and 9 months, to observe specific outcomes of interest (122).

The longitudinal study design was intended to achieve objectives 1 & 2 of the quantitative cohort study, namely:

a. To compare abstinence rates following detoxification at 3, 6 and 9 month follow up, across each of the three rehabilitation pathways.

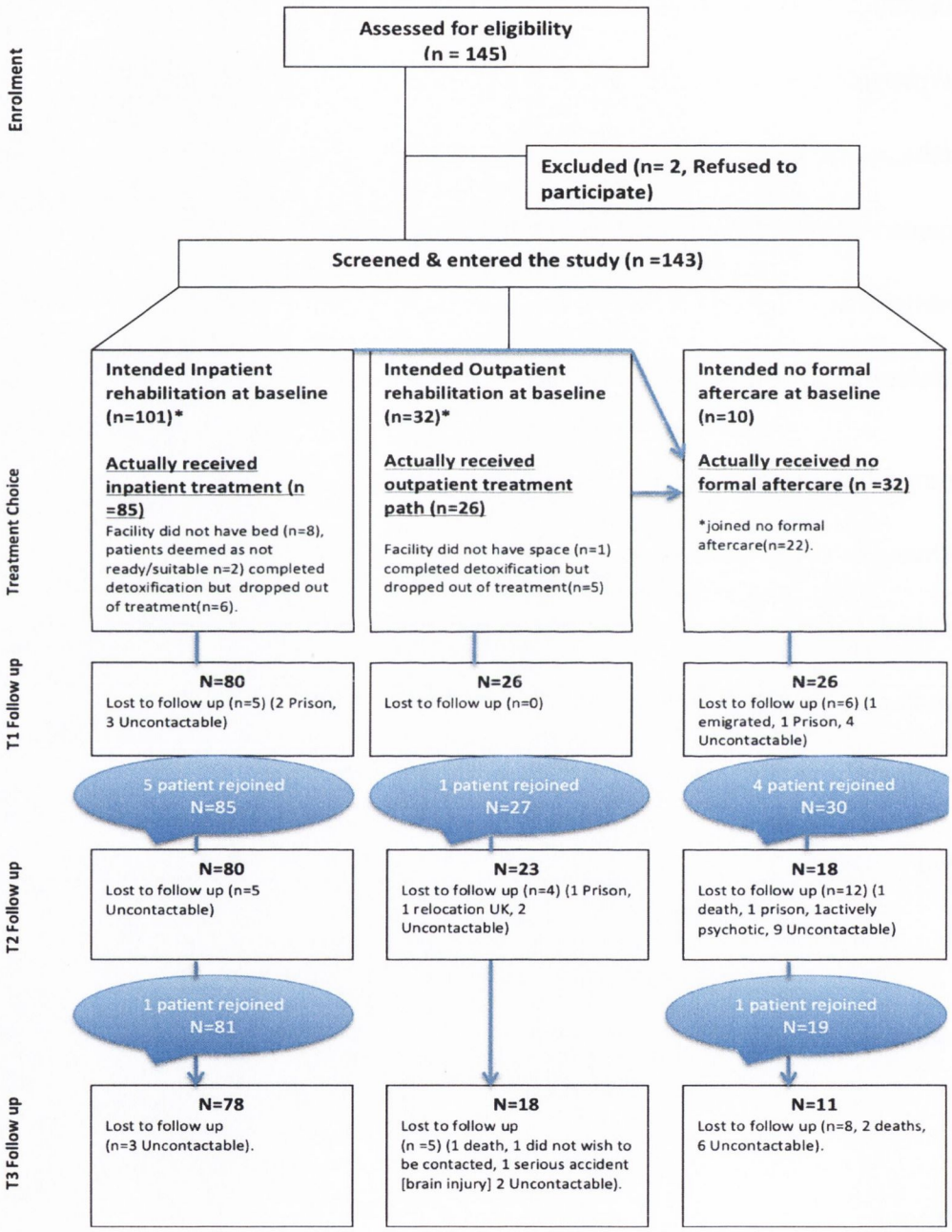
b. To compare changes in physical and psychological health, health risk behaviour, personal/social functioning, psychological wellbeing, hope for the future and quality of life.

Longitudinal studies are highly regarded due to their ability to observe time-based effect and provide opportunity for multiple observations of the outcomes of interest (123). Furthermore, an observational longitudinal cohort design affords the researcher the prospect of establishing a causal link between outcomes and explanatory variables of interest. The longitudinal design was thus chosen for this study as it provided the opportunity for time-based observation of abstinence post-detoxification.

Figure 2 below summarises the sampling frame and recruitment of intended and actual pathway over the lifetime of the study. It must be noted patients specified intended path at baseline. However, due to lack of resources at a facility or personal circumstances, it was revealed at time of follow up that they had taken a different path than intended. Thus, we examined both the intended path as well as the actual path taken.

FIGURE 2 SAMPLING FRAME, RECRUITMENT AND DATA COLLECTION

Figure 2: Sampling frame, recruitment and data collection



= Patients that could not be tracked at one time point but resurfaced and rejoined the study

6.3 METHODOLOGY

6.3.1 STUDY SAMPLE

The candidate looked at the average number of patients that successfully completed detoxification in each of the detoxification settings, over the past five years. Based on this analysis the number of available patients ranged from 120-160 annually. All patients who successfully completed detoxification in each of the three major Drug Dependency Units in the country during a fourteen month period were included in the study. All patients were measured at baseline and followed up using quantitative measures. However, it must be acknowledged that the study is not solely concerned with outcomes; rather it was also concerned with the process that occurs when patients choose, enter and progress through a particular pathway to rehabilitation. Thus the study also involves an exploration of decisions made by patients, in an attempt to understand better the process that occurred post detoxification. It is in this understanding that we can gain better insight into patients' choices.

All patients who successfully completed detoxification were screened using a battery of clinical outcome measures at baseline (n=143) and again at 3 (n=136/95%), 6 (n=124/87%) and 9 (n=115/80%) month follow up.

The tracking of this cohort post-detoxification from baseline with three follow up time points with a comprehensive battery of clinical instruments was the first of its kind in an Irish context.

6.3.2 EXPERT REVIEW OF QUANTITATIVE METHODS

Prior to the piloting of our data collection instruments a group of addiction specialists within the addiction services (two consultant psychiatrists, a senior clinical psychologist, a manager

of an inpatient rehabilitation unit and a manager of an outpatient community based rehabilitation programme) were contacted and asked to review the demographic questionnaire (appendix 5) and the proposed clinical instruments used to screen patients at baseline and follow up at 3, 6 and 9 months. The battery of clinical instruments included the Maudsley Addiction Profile (MAP, appendix 6) the World Health Organisation's Quality of Life Measure (WHO-BREF, appendix 8) and the Adult Hope for the Future Scale (AHS, appendix 7). Based on the feedback obtained from this group the demographic questionnaire was refined and the inclusion of the Core-OM (a 34 item validated clinical measure of psychological well-being appendix 9) was included in the battery of clinical questionnaires.

6.3.3 IMPLEMENTATION COMMITTEE

A number of representatives from each of the DDUs in addition to the candidate, her supervisor and a specialist addiction consultant psychiatrist formed an advisory committee for the duration of data collection.

6.3.4 QUANTITATIVE QUESTIONNAIRES:

All participants were asked to provide basic demographics (see appendix 4 for a copy of questionnaire). In addition all participants completed a battery of validated instruments administered upon successful completion of detoxification.

Instruments included:

1. The Maudsley Addiction Profile (124) (MAP) measuring problems in four domains:
    - **a)** Substance use.
    - **b)** Health risk behaviour.

c) Physical and psychological health.

d) Personal/social functioning.

2. The Clinical Outcome Routine Evaluation Outcome Measure (CORE-OM) (125) measuring psychological well-being.

3. The Adult Hope scale [AHS] (126) measuring:

- Agency [goal-directed energy]
- Pathways [planning to meet goals].

4. The World Health Organisation Quality of Life (WHOQol) Measure (127) (see appendix 6-9 for a copy of instruments).

As well as numerous studies validating the test re-test of the above measures, both the MAP and the WHO Qol have been used with opioid dependent patients in Ireland (11, 13). The MAP the WHO Qol and the CORE-OM have been used with opioid dependent patients internationally (128-130). However, the AHS has not been used with this population.

6.3.5 PILOTING OF QUANTITATIVE METHODS

Following the refinement of questionnaires they were then piloted on the first five patients at baseline and at three month follow up time points. It was decided to include the CORE-OM. Several minor additions were made to the demographic questionnaires regarding supports (being a member Narcotics Anonymous or having a clear plan post detoxification etc.) .

6.3.6 QUANTITATIVE QUESTIONNAIRES FOLLOW UP

All patients who successfully completed detoxification were followed-up at 3, 6 and 9 months post discharge. The previous battery of tests was repeated at each time point.

Change was measured by comparing a period of time with a previous point in time i.e. baseline (T1, T2 & T3).

6.4 DATA ANALYSIS

6.4.1 BASELINE DATA: DESCRIPTIVE STATISTICS

The first phase of analysis involved a description of baseline characteristics using SPSS version 21. Descriptive statistics such as frequency counts and proportions of participants were used to summarise categorical data, whereas the mean, standard deviation, median and range were used to summarise continuous data. Table 2 below illustrates data according to treatment path. As illustrated in figure 2 above 143 patients were recruited into the study across three research sites. Below is a broad profile of all participants. Table 2 illustrates clinical profile at baseline across the three treatment pathways.

TABLE 2: CLINICAL DEMOGRAPHICS

Treatment path		**Inpatient (n=85)***	**Outpatient (n=26)**	**No Formal Aftercare (n=32)**
Average age		34 yrs. (SD 1)	30 yrs. (SD 4.8)	32 yrs. (SD 1)
Gender	Male	56	23	19
	Female	29	3	13
Average age first alcohol use		13 (SD 3.3)	12 (SD 2)	12 (SD 2.2)
IV Drug users		81 (95%)	23 (88%)	31 (97%)
Average number of years using opioids		15 yrs. (SD 5.5)	13 yrs. (SD 6.7)	14 yrs. (SD 5.1)
Number of patients that had completed previous inpatient detoxifications.		57 (67%)	16 (61.5%)	16 (50%)
Number of patients that had completed previous inpatient rehabilitation.		22 (26%)	2(8%)	5 (16%)
Average longest time drug free (weeks)		40 (SD 67.6)	66 (SD 136.7)	32 (SD 18.3)
Participants receiving Methadone Maintenance prior to detoxification		76 (89%)	24 (92%)	28 (88%)
Participants engaged in preparatory work		75 (88%)	24 (92%)	26 (81%)

**Percentages are calculated by 100% of each individual treatment path.*

6.4.2 AGE, GENDER, CLASS & ETHNICITY

The mean age of the participants was 35 years, with a range from 20 years to 52 years. More than two thirds were male (n=98/68.5%). Four fifths of the 143 (n=114/80%) participants, identified as working class, while the remainder identified as middle class (n=29/20%). The vast majority of participants identified as Irish (n=133/93%), some specifically as Irish Travellers (n=6/4%).

6.4.3 HOMELESSNESS

At baseline interviews patients were asked if they had any of the following housing issue, homelessness, eviction, arrears or other. The majority of patients suggested they had a homelessness issue (n=121/85%), (n=1 had eviction) (n=7/5% arrears) and (n=3/2%had other).

6.4.4 EDUCATION & TRAINING

The majority of participants had attended at least some second level education (n=103/72%); of these 59 (41.3%) had completed the Junior Certificate and 16 (11.2%) had completed the Leaving Certificate. Four had attended college (n=3 at undergraduate level and n=1 at postgraduate level). Almost half of the 143 participants (n=68/48%) received a formal training after leaving education. This varied across a wide range of industries.

6.4.5 DRUG HISTORY

The mean age of drug initiation was 14 years, while the mean age of first alcohol use was 12 years old, with a median of 13 years. The most common trajectory of drug use began with alcohol, then progressed to cannabis, then to ecstasy and/or cocaine and then heroin. The

primary drug of choice was heroin (n=122/85%). The mean years of using drugs was 14, with a median 15 years.

6.4.6 TREATMENT HISTORY

The vast majority of the 143 participants (n=128/85.5%) were on a methadone maintenance programme prior to undergoing detoxification. The mean dose of methadone was 75 milligrams per day (SD 16.8). The majority of participants (n=94/66%) reduced by five milligrams to detoxify, with the majority (n=65/45.5%) reducing over an eight-week period. More than half of participants (n=89/62%) had previously undergone detoxification. However, less than a fifth of these (n=26/18%) had successfully completed. The mean number of prior attempts at detoxification was two. The mean longest time drug free from opiates was 10 months. However, more than one third of participants (n=52/36%) had no previous time drug free since initiation.

6.4.7 REHABILITATION HISTORY

More than two fifths of the 143 participants (n=59/41%) had attempted an abstinence based rehabilitation programme in the past twelve years. Of these almost half (n=29/49.1%) attended an inpatient facility. The average length of time spent in a rehabilitation programme was 15 weeks.

6.4.8 PSYCHIATRIC HISTORY

More than two fifths of the 143 participants (n=63/44%) had engaged with psychiatric services for an issue other than addiction. Of these, (n=55/87%) had received a diagnosis and all of these patients were prescribed medication to assist with mood or wellbeing. The most commonly co-occurring diagnosed mental illnesses were depression (n=19/35%) or

anxiety (n=11/20%). The most commonly prescribed medication was Mirtazapine (brand name) Zispin (n=33/60%) is an antidepressant. The use of prescribed medication refers to lifetime exposure rather than during the study period. The majority of the 55 diagnosed patients (n=49/89%) were treated in the community. The average amount of lifetime spent in psychiatric services was between 6 and 12 months. Of the 63 (44%) participants who had engaged with the psychiatric services two thirds of these (n=42/67%) had dropped out prior to completing treatment.

6.4.9 PREPARATORY WORK

The vast majority of participants (n=125/87%) had engaged in preparatory work prior to undertaking detoxification (i.e. linked with a therapist or support agencie[s] formulating a support plan for post-detoxification). Most of these participants (n=100/70%) engaged in structured preparatory work. The average number of hours per week engaging in preparatory work was 7, for an average of 12 weeks. The majority of this work took place with either a counsellor (n=61/43%) or a key-worker (n=39/27%).

6.4.10 CROSS SECTIONAL STATISTICS

In the current study we were interested in whether (i) patient demographics were associated with their chosen treatment pathway; (ii) whether patient treatment chosen pathway was associated with abstinence at follow up.

A chi-square test was performed on whether patient treatment choice had an effect on their abstinence rates at follow-up. The results suggest that there was a statistically significant association between treatment choice and abstinence rates at 3 month (X^2= 44.292, DF 4, p=0.01), 6 month (X^2= 44.061, DF 4, p=0.001) and 9 month (X^2= 47.211, DF 4, p=0.001) follow-up.

TABLE 3: ABSTINENCE AT T1

Table 3: Abstinence rates by treatment path at 3 month follow-up				
	Yes	No	Could not be followed (8%)	Total
Inpatient	73 (51%)	7 (L5/R2) (5%)	5(3%)	85
Outpatient	22(15%)	4 (L 1/R3) (3%)	0	26
No formal aftercare	9(6%)	17(L7/R10)(12%)	6(4%)	32
Total	104(73%)	28(19%)	11(8%)	143
L=Lapsed R=Relapsed				

At T1 follow-up almost three quarters of the entire sample was abstinent. The majority of relapses occurred within the no formal aftercare group. Patients in the inpatient group were more likely to lapse rather than relapse. Table 4 below illustrates the month that this lapse or relapse took place.

TABLE 4: LAPSE/RELAPSE T1

Table 4: The month lapse or relapse took place					
	Month use took place				Total
	None	First month	Second month	Could not be followed	
Inpatient	73(51%)	2(1%)	3(3%)	5	85
Outpatient	22(15%)	3(2%)	1(1%)	0	26
No formal aftercare	9(6%)	10(7%)	7(5%)	6	32
Total	104(73%)	15(10%)	13(9%)	11(8%)	143
L=Lapsed R=Relapsed					

Patients reported marginally higher rates of drug use in the first month post-discharge. Table 5 illustrates the abstinence rates at T2 follow-up across three treatment paths.

TABLE 5: ABSTINENCE AT T2

Table 5: Abstinence rates by treatment path at 6 month follow-up				
	Abstinent at T2 follow-up			Total
	Yes	No	Could not be followed	
Inpatient	64(45%)	16 (6L/10R) (11%)	5(3%)	85
Outpatient	14(10%)	9 (4L/5R) (6%)	3(2%)	26
No formal aftercare	5(3%)	13 (4L/9R) (9%)	14(10%)	32
Total	83(58%)	38(27%)	22(15%)	143
L=Lapsed R=Relapsed				

More than half of patients were abstinent at T2 follow up. However, all patients were more likely to relapse than lapse at T2. Table 6 illustrates the month that this lapse or relapse took place during the second follow up period.

TABLE 6: LAPSE/RELAPSE T2

Table 6: Month lapse or relapse took place

	Month use took place					Total
	N/A	Fourth month	Fifth month	Continued relapse last follow-up	Could not be followed	
Inpatient	64(45%)	12(8%)	3(2%)	1(1%)	5(3%)	85
Outpatient	14(10%)	6(4%)	3(2%)	0	3(2%)	26
No formal aftercare	5(3%)	8(6%)	3(2%)	2(1%)	14(10%)	32
Total	83(58%)	26(18%)	9(6%)	3(2%)	22(15%)	143

Consistent with earlier follow-ups patients were more likely to report having used drugs in the fourth month rather than the fifth. Table 7 illustrates the abstinence rates at T3 follow-up across three treatment paths.

Table 7: Abstinence rates by treatment path at 9 month follow up

	Abstinent at T3 follow-up			Total
	Yes	No	Could not be followed	
Inpatient	57(40%)	22 (L=13/R9) (15%)	6(4%)	85
Outpatient	13(9%)	5 (L=3/R=3)(3%)	8(6%)	26
No formal aftercare	2(1%)	8 (L=2/R=6)(6%)	22(15%)	32
Total	72(50%)	35(24%)	36(25%)	143

L=Lapse R=Relapse

Table 8 illustrates the month that this lapse or relapse took place during the third follow up.

TABLE 8: LAPSE/RELAPSE AT T3

Table 8: Month lapse or relapse						
	Month use took place					Total
	N/A	Seventh month	Eighth month	Continued relapse last follow-up	Could not be followed	
Inpatient	57(40%)	18(13%)	2(1%)	4(3%)	6(4%)	85
Outpatient	13(9%)	2(1%)	0	3(2%)	8(6%)	26
No formal aftercare	2(1%)	5(3%)	0	1(1%)	22(15%)	32
Total	72(50%)	25(17%)	2(1%)	8(6%)	36(25%)	143

TABLE 9 ILLUSTRATES THE FIRST SUBSTANCE USED AT FIRST RECORDED LAPSE OR RELAPSE

Table 9: First substance used at time of lapse/relapse							
	Substance						Total
	Heroin	Alcohol	Benzodiazepines	Cocaine	Cannabis	N/A	
Inpatient	18(13%)	8(6%)	0	1	9(6%)	49(34%)	85
Outpatient	10(7%)	0	1(1%)	0	1(1%)	14(10%)	26
No formal aftercare	15(10%)	5(3%)	0	0	3(2%)	9(6%)	32
Total	43(30%)	13(9%)	1(1%)	1(1%)	13(9%)	72(50%)	143

Cross tabulation was also used to examine whether patients' treatment demographics had an effect on whether or not they ever relapsed during the course of the study. Table 10 below illustrates significant association between patients' treatment demographics and (ever) relapsed. Table 10 illustrates the correlation between patient clinical demographics and relapse.

TABLE 10: CORRELATIONS BETWEEN CLINICAL/PERSONAL DEMOGRAPHICS AND RELAPSE

Treatment/ personal demographics	X^2	DF	P-value
Parenthood	17535	8	0.02
Psychiatric diagnosis	11.229	3	0.03
Engagement in preparatory work	8.427	2	0.01
Plan prior to entering detoxification	5.508	1	0.05
Gender	6.309	2	0.04
Education	16.683	12	0.16
Age	3.155	4	0.53

Being a female, a parent and having a psychiatric co-morbidity had a statistically significant negative association with relapse, whereas having a plan prior to entering detoxification and actively engaging in preparatory work had a statistically significant positive association with relapse. Age and education were not statistically significant for relapse.

6.5 STATISTICAL ANALYSIS FOR LONGITUDINAL DATA

The longitudinal analysis comprised two levels. The first level examined the effects of treatment path on abstinence and the second level examined effects of treatment path on secondary treatment outcomes: physical and psychological health, psychological wellbeing, hope and quality of life.

6.5.1 FIRST LEVEL ANALYSIS OF LONGITUDINAL DATA

The aim: to examine effects of actual treatment path (inpatient, outpatient, no formal aftercare) on abstinence rates at 3, 6 and 9 month follow-up.

The analysis of the longitudinal data was done within the multilevel modelling framework. This statistical technique allows for exploring correlations among longitudinal observations within and between subjects, for the presence of missing data, and for exploring the effects of multiple covariates of interest. R version 3.0.0 statistical software was used for this analysis. The response of individual subjects was first modelled, and then the estimates for each individual were combined in a group analysis. The main experimental variables were actual treatment path (inpatient, outpatient or no formal aftercare), at 3, 6 and 9-month follow-up (and time). Other covariates considered were education (no formal, primary, secondary or third level), parenthood (yes or no), number of years using opioids, previous

history of detoxing (yes or no), previous history of rehabilitation (yes or no) and engagement in preparatory work (yes or no).

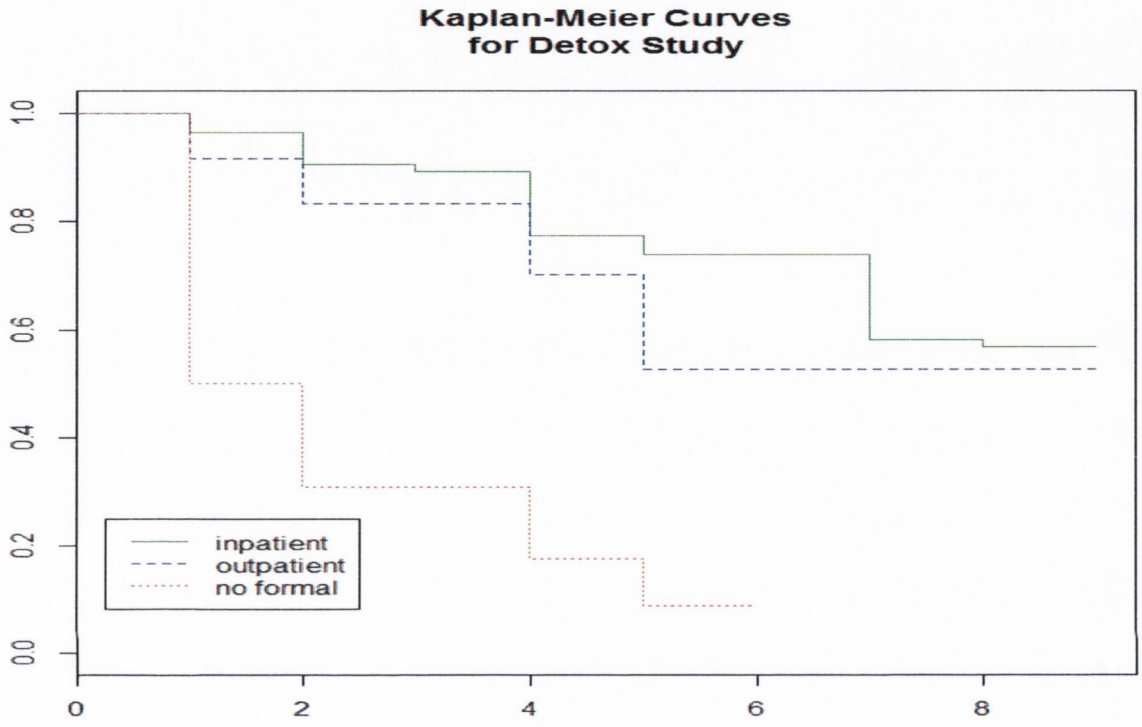
The effects of treatment path were explored in a longitudinal analysis adjusted for age and gender. Statistically significant risk for first lapse/relapse was found for both the outpatient (OR 1.17) and no formal aftercare (OR 1.75) groups (p=0.0001) when compared to those who attended inpatient care. There was a suggestive association for gender (p=0.08), however, there was no statistically significant correlation for age (p=0.87).

In addition, we also examined participants' intended treatment path versus their actual treatment path and further analysis revealed participants who intended no formal aftercare were twice as likely to relapse in comparison to participants who had the intention of attending inpatient rehabilitation (p=0.01). An analysis comparing both intention to attend inpatient, with no-intention to attend inpatient found that non-intenders yielded two times increased risk for relapse (p=0.00004).

In addition to examining effects of actual treatment path on overall abstinence, we were also interested in detecting time to first lapse/relapse post-detoxification, i.e. does time to first lapse/relapse differ between chosen treatment paths (i.e. inpatient, outpatient or no formal aftercare). In order to do this we performed an unadjusted Kaplan-Meier analysis (see below figure 3) and a Cox survival analysis on data. Survival analysis is concerned with studying the time between entry to a study and a subsequent event (lapse/relapse). We applied a Cox proportional hazards regression model as it allowed for testing differences in survival times across groups, while allowing to adjust for covariates of interest (i.e. age, gender, parenthood, preparatory work, previous attempts at detoxification, previous

attempts at rehabilitation). The purpose of this in the current study was to simultaneously investigate the effects of several variables on length of abstinence post-detoxification.

FIGURE 3 KAPLAN MEIER SURVIVAL CURVE (UNADJUSTED)



The Kaplan-Meier curve illustrates the median time for relapse for the no formal aftercare group was 1 month, whereas neither in patient or outpatient treatment group had relapsed at this rate even at nine months. At the first follow up (month 3) 70 % of the no formal aftercare group had relapsed, whereas 17 % of the outpatient and 11% of the inpatients had relapsed at 3 month. By month 5, 30% of the outpatient group had relapsed. However, the inpatient group did not reach this rate until month 7.

Employing a Cox model adjusted (age, gender and treatment path) association between actual treatment path and rate of (first) time to lapse/relapse was examined (see table 11 below). Patients who opted for outpatient treatment lapsed/relapsed at a rate of 52% more

than inpatient aftercare group, although this was not statistically significant (HR=1.52, 95% CI: 0.75 – 3.08, p=0.24). Time to lapse/relapse was dramatically greater for those who opted for no formal aftercare (668%) when compared to those who opted for inpatient aftercare (HR=7.68, 95% CI: 4.30-13.73, $p=5.75x10^{-12}$). Highlighting that any aftercare is better than no aftercare.

Table 11: Cox Model	**Estimate**	**Std.Error**	**df**	**t-value**	**P=**
Age	-0.01062	0.98943	0.02333	-0.455	0.6489
Gender	0.51200	1.66863	0.26106	1.961	0.0499 *
as.factor(Outpatient)	0.41900	1.52043	0.36010	1.164	0.2446
as.factor(No formal aftercare)	2.03893	7.68241	0.29611	6.886	5.74e-12***

Results are consistent with earlier findings: patients who enter inpatient rehabilitation appear to relapse less and are more likely to be abstinent at nine-month follow-up when compared to patients attending outpatient rehabilitation or patients with no formal aftercare in place. We found significant association for gender ($OR_{F\ Vs.\ M.}$ =1.48, p=0.05).

6.6 FIRST LEVEL ANALYSIS CLINICAL OUTCOME MEASURES

Below is analysis of change in secondary outcome measures at baseline, 3, 6 and 9 month follow-up.

A paired sample t-test comparing means on the CORE OM clinical measure of wellbeing

Table 12 illustrates significant difference between baseline, 3, 6 and 9 months follow ups.

Table 12: Clinical Outcome Routine Evaluation (CORE-OM) measure of wellbeing at baseline 3, 6 and 9 month follow up

	T-test statistic							
				95% Confidence Interval of the Difference				
	Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	df	P-value
T-test comparing baseline to 3 month follow up	.26173	.37551	.03936	.18352	.33993	6.649	90	.000
T-test comparing baseline to 6 month follow up	12.10049	17.44921	1.90387	8.31377	15.88720	6.356	83	.000
T-test comparing baseline to 9 month follow up	15.81329	17.34042	2.40468	10.98569	20.64089	6.576	51	.000

A paired sample t-test was conducted comparing means on the MAP clinical measure of physical health. Table 13 illustrates significant difference between baseline, 3, 6 and 9 months follow ups.

Table 13: Maudsley Addiction Profile (MAP) Measure of Physical Health at 3, 6 and 9 months

	T-test statistic							
				95% Confidence Interval of the Difference				
	Mean	Std. Deviation	Std. Error Mean	Lower	Upper	T	df	P-value
T-test comparing baseline to 3 month follow up	5.568	10.905	1.080	3.427	7.710	5.157	101	.000
T-test comparing baseline to 6 month follow up	5.079	10.794	1.151	2.792	7.366	4.414	87	.000
T-test comparing baseline to 9 month follow up	7.146	11.933	1.541	4.063	10.228	4.638	59	.000

A paired sample t-test was conducted comparing means on the MAP clinical measure of psychological health. Table14 illustrates significant difference between baseline, 3, 6 and 9 months follow-ups.

Table 14:Maudsley Addiction Profile (MAP) measure of psychological health at baseline, 3, 6 and 9 months

	T-test statistic							
				95% Confidence Interval of the Difference				
	Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	Df	P-value
T-test comparing baseline and 3 month follow up	3.789	7.771	.781	2.239	5.338	4.851	98	.000
T-test comparing baseline with 6 month follow up	4.449	9.198	1.004	2.453	6.445	4.433	83	.000
T-test comparing baseline with 9 month follow up	6.860	9.886	1.298	4.261	9.459	5.285	57	.000

A paired sample t-test was conducted comparing means on the AHS clinical measure of Hope. Table 15 illustrates significant difference between baseline, 3, 6 and 9 months follow ups.

Table 15: Adult Hope Scale (AHS) measure of hope measure at baseline, 3, 6 and 9 months

	T-test statistic							
				95% Confidence Interval of the Difference				
	Mean	Std. Deviation	Std. Error Mean	Lower	Upper	t	df	P-value
T-test comparing baseline with 3 month follow up	-.43902	10.65172	1.17629	-2.77946	1.90142	-.373	81	.710
T-test comparing baseline with 6 month follow up	-1.97436	8.21145	.92976	-3.82575	-.12296	-2.124	77	.037
T-test comparing baseline with 9 month follow up	-1.93155	10.18671	1.47032	-4.88946	1.02636	1.314	47	.195

A paired sample t-test was conducted comparing means on the WHO QoL clinical measure of quality of life. Table 16 illustrates significant difference between baseline, 3, 6 and 9 months follow-ups.

Table 16: World Health Organisation Quality of Life (WHO QoL) measure at baseline, 3, 6 and 9 months

	T-test statistic							
				95% Confidence Interval of the Difference				
	Mean	Std. Deviation	Std. Error Mean	Lower	Upper	T	df	P-value
T-test comparing baseline to 3 month follow up	-1.05051	1.10078	.11063	-1.27005	-.83096	6.6.1.1 _9.495	98	.000
T-test comparing baseline to 6 month follow up	-1.10588	1.12624	.12216	-1.34881	-.86296	-9.053	84	.000
T-test comparing baseline to 9 month follow up	-1.35345	1.12003	.14707	-1.64794	-1.05895	-9.203	57	.000

6.7 SECOND LEVEL ANALYSIS OF LONGITUDINAL DATA

The aim of the second level analysis was to examine effects of actual treatment path (inpatient, outpatient and no formal aftercare) on physiological health, psychological health, psychological wellbeing, hope for the future and quality of life.

In a longitudinal linear mixed model adjusted for age, gender, level of education, parenthood, preparatory work, previous attempts at detoxification, previous attempts at rehabilitation, the study examined whether inpatient aftercare significantly improved hope for the future (see 17 below). The results suggest that inpatient aftercare had a significant effect on hope for the future (p=0.001). Abstinence (p=0.001) time (p=0.01) and parenthood (p=0.05) were significantly associated with hope for the future. Patients who were abstinent for longer had more hope for the future, while patients that were parents had less hope for the future.

Table 17: longitudinal linear mixed model Hope for the Future (AHS)

	Estimate	Std. Error	df	t value	P=
Age	-0.1024	0.1018	112.7400	-1.005	0.31689
Gender	-0.7826	1.3201	118.8600	-0.593	0.55441
Abstinent	-5.7114	1.0783	292.5300	-5.297	2.32e-07***
Time	1.8410	0.5645	129.7300	3.261	0.00142 **
Children	-2.4843	1.1708	115.8000	-2.122	0.03598 *
as.factor(Outpatient)	-2.4587	1.5485	114.0900	-1.588	0.11509
as.factor(No formal aftercare)	-1.6912	1.7453	171.3600	-0.969	0.33389

In a longitudinal linear mixed model adjusted for age, gender, level of education, parenthood, preparatory work, previous attempts at detoxification, previous attempts at rehabilitation, the study examined whether inpatient aftercare significantly improved psychological health (see table 18 below). The results suggest that inpatient aftercare had a significant effect on psychological health (p=0.001). Abstinence (p=0.001) time (p=0.001) and age (p=0.05) were significantly associated with better psychological health. Patients who were abstinent for longer and younger had better psychological health.

Table 18: longitudinal linear mixed model Psychological Health (MAP)

	Estimate	Std. Error	df	t value	P=
Age	-0.09221	0.04010	122.20000	-2.300	0.023168 *
Gender	-0.08290	0.50390	130.30000	-0.165	0.869576
Abstinent	-1.99057	0.37097	329.00000	-5.366	1.52e-07 ***
Time	0.70114	0.18332	124.20000	3.825	0.000206 ***

In a longitudinal linear mixed model adjusted for age, gender, level of education, parenthood, preparatory work, previous attempts at detoxification, previous attempts at rehabilitation, the study examined whether inpatient aftercare significantly improved psychological wellbeing (see table 19 below). The results suggest that actual path had a significant effect on wellbeing (p=0.001). Abstinence (p=0.001) and time (p=0.001) were significantly associated psychological wellbeing. There was a suggestive association with

parenthood (p=0.06). Patients who were abstinent for longer and younger had better wellbeing. There was a suggestive association between parenthood and wellbeing, i.e. patients that were parents had better wellbeing.

Table 19: longitudinal linear mixed model Psychological Wellbeing – CORE –OM

	Estimate	Std.Error	df	t value	P=	
Age	0.05128	0.05362	119.30000	0.956	0.3408	
Gender	0.09647	0.67502	127.60000	0.143	0.8866	
Abstinent	2.64470	0.55918	340.10000	4.730	3.30e-06	***
Time	-1.59130	0.27225	200.30000	-5.845	2.03e-08	***
Children	1.20017	0.61384	121.60000	1.955	0.0529	.

In a longitudinal linear mixed model adjusted for age, gender, level of education, parenthood, preparatory work, previous attempts at detoxification, previous attempts at rehabilitation, the study examined whether inpatient aftercare significantly improved quality of life (see table 20 below). The results suggest that inpatient aftercare had a significant effect on quality of life (p=0.001). Abstinence (p=0.001) time (p=0.01) and parenthood (p=0.05) were significantly associated quality of life. Patients who were abstinent for longer and younger had better quality of life. Patients that were parents had lower quality of life.

Table 20: longitudinal linear mixed model Quality of Life (WHO Qol)

	Estimate	Std. Error	df	t value	P=	
Age	-0.021365	0.009767	123.700000	-2.187	0.03060	*
Gender	0.052425	0.122791	131.200000	0.427	0.67012	
Abstinent	-0.683225	0.094035	338.800000	-7.266	2.57e-12	***
Time	0.136746	0.046306	122.800000	2.953	0.00377	**
Children	-0.238031	0.111652	125.100000	-2.132	0.03497	*

6.8 SUMMARY OF FINDINGS

The longitudinal quantitative cohort study provides a large national sample that is both demographically and clinically representative of opioid dependent patients in Ireland. A total of 143 patients were included in the longitudinal study. The attrition rate was low and retention rate was high at 78%. Moreover, a comparison of characteristics between patients retained and lost to follow up in the study showed no socio-demographic or clinical differences.

At three months 92% (n=132) of the population were followed up. More than one fifth of the available patients (21%/n=28) reported using a substance between baseline and at the first follow-up. Patients who opted for no formal aftercare were most likely to have used (13%/n=17). Moreover, patients who opted for either outpatient or no formal aftercare were more likely to have relapsed than lapsed whereas patients that opted for inpatient aftercare were more likely to have lapsed. Patients reported use in first and second month, with the first month rate (10%) marginally higher than the second (9%).

At six months 85% (n=121) of the population were followed up. Almost one third of the available patients (31%/n=38) reported using a substance at the second follow-up. The incidence of reported use at the second follow-up in the inpatient group had more than doubled (n=7T1/n=16T2 lapsed/relapsed). Consistent with the first follow-up the inpatient group were more likely to have lapsed than relapsed, similarly the no formal aftercare group we more likely to have relapsed. Unlike the last follow-up the outpatient aftercare group were more likely to lapse than relapse. Patients were three times more likely to have used drugs in the fourth month (n=27) than the fifth (n=9). Moreover, the attrition in the 'no formal aftercare' group was greater than fifty percent (n=6 T1/n=14T2).

At nine months 75% of the population were followed-up. One third of the available patients 33% (n=35) reported using a substance at the third follow-up. Reported use in the inpatient aftercare group had gone up by 38% from previous follow-up (n=16 T1/22T2). Consistent with previous follow-ups the inpatient aftercare group was more likely to have lapsed than relapsed. The outpatient aftercare group was as likely to have lapsed than relapsed, while the no formal aftercare group were more likely to have relapsed than lapsed. Consistent with previous use patients were more likely to have used in earlier months, i.e. seventh rather than eighth.

The study found a statistically significant risk for relapse for both the outpatient and no formal aftercare groups when compared to those whom attended inpatient care. Participants who opted for outpatient treatment were 17% more likely to relapse while those who opted for no formal aftercare were 75% more likely to relapse. It could be argued that differences in treatment outcome might simply reflect differences in pretreatment drug use (131). However, all three groups were similar on all measures of drug use at admission.

The intention to attend inpatient aftercare had a statically significant effect on abstinence. An analysis comparing both intention to attend inpatient, with no-intention to attend inpatient found that non-intenders yielded two times increased risk for relapse.

In addition, an analysis of the clinical instruments found attending inpatient rehabilitation aftercare had a statistically significant effect on hope for the future, psychological health, wellbeing and quality of life.

6.9 DISCUSSION OF FINDINGS

In discussing the findings of the longitudinal study it is important to examine two factors; (i) how does the current study support, enhance or refute the existing literature and (ii) how should these findings be interpreted in relation to this pre-existing literature. Both these factors are discussed below.

The aim of the current study was to provide a detailed assessment of outcomes in a cohort of opioid dependent patient post-detoxification. As a result, it was possible to compare the impact of completion of detoxification treatment and subsequent aftercare on treatment outcome. Three groups of opioid dependent patients who completed detoxification were compared; those went on to an inpatient rehabilitation unit , those went on to an outpatient rehabilitation programme, and those who opted for no formal aftercare.

The current study adds to the existing literature of previous outcome studies (ROSIE, DATOS, TOPS) by examining treatment effect and change over time with abstinence being the end result. However, the current study goes beyond this basic model of tracking patients beyond treatment and examining their abstinence rates. From inception the study set out to focus on one treatment modality, detoxification and examine abstinence as an absolute starting point. To understand that abstinence is key but only the first step to recovery. To understand recovery abstinence needs to be contextualized. If a patient was not abstinent, did they lapse or relapse (132, 133), at what point in their treatment path did they lapse/relapse. The current study sought to comprehensively examine patient outcomes post-detoxification. Smyth et al. (11) had previously examined a cohort taken from one of the research sites included in the current study. However, the data was limited to the Maudsley Addiction Profile and there was huge variance between individual patient follow-

ups. Few previous studies examined secondary outcomes; of those that did they were often limited to criminal and other high-risk behaviours (i.e. sexual promiscuity and injecting practices). The current study incorporated a number of secondary outcomes (physical and psychological health, psychological well being, quality of life and hope for the future), outcomes that allow us move beyond the dichotomous abstinent or not, offering a more holistic view of treatment effect over time.

The clinical and demographic profile of the current patient group was not surprising. It was the same as the ROSIE detoxification cohort with the exceptions of level of homeless and number of females. The ROSIE detoxification cohort reported 16% homelessness at baseline; the current study found 85% of the cohort had a 'homeless issue'. While this could be a reflection of the economic change between the timing of both studies, it is perhaps better accounted for in terms of how the question was framed in the current study. Moreover, the issue of homelessness in this cohort is quite complex and the high number relates to the subjective interpretation around having a suitable stable accommodation. The current study reported a higher number of females (35.5%) than the ROSIE detoxification cohort (11%). The inflation in females between both studies may reflect the increase in females presenting for treatment, a finding that is consistent with more recent national (133) and international literature (134).

In terms of primary outcome significantly better outcomes were observed amongst those who completed detoxification and went on to spend at least 6 weeks in an inpatient or residential rehabilitation unit. It could be argued that differences in treatment outcome might simply reflect differences in pretreatment drug use. However, the three groups were similar on all measures of drug use at admission. The stabilising dose of those who

completed detoxification and went on to aftercare (inpatient or outpatient) did not differ significantly from that of the completers without aftercare. Thus, it appears doubtful that differences in treatment outcome between completers with aftercare and the other two groups can be accounted for by differences in the initial severity of dependence as defined by dose only. Between half and two thirds of patients across the three groups completed a previous inpatient detoxification. No statistical difference existed for previous attempts at inpatient detoxification across the three pathways. Table 2 p 52 illustrates previous attempts across patient pathway.

However, the superior outcome of those who received aftercare might suggest the advantage which ensues from lengthier treatment duration, a finding shown by Simpson and colleagues (135). The authors found a correlation between better treatment outcome in long-term methadone maintenance, therapeutic communities, and drug-free programmes (136). Moreover, this effect could somewhat reflect the fact that while attending an inpatient rehabilitation programme, the individual is "shielded" from the outside stresses to use drug or relapse is simply delayed (132). Nevertheless, even at 9-months follow-up, the inpatient aftercare group was significantly more likely to be abstinent from opioids than the other groups.

In the current study the inpatient group had more than 6 weeks in aftercare, which reinforces the probability of improved outcome in this group. The current study supports the finding that opioid dependent patients can have a lapse i.e. use on a single occasion without experiencing a relapse i.e. return to daily use (132, 137). The study supports the notion of a critical period of high risk following detoxification (137, 138).

6.10 STRENGTHS AND LIMITATIONS OF LONGITUDINAL QUANTITATIVE COHORT STUDY

6.10.1 STRENGTHS

The use of a longitudinal design represents one of the strengths of the cohort study as it permitted the assessment of multiple treatment modalities thereby providing more observations from the sample. Thus, multiple observations are likely to enhance the reliability of the study's findings. The longitudinal quantitative cohort study captured a large national sample of patients attending for detoxification. This immediately goes toward addressing the dearth of research on this patient population. The extremely low attrition rate across four data collection points is a key strength of the study.

6.10.2 LIMITATIONS

The current study tracked a cohort of patients for up to nine months, which in terms of recovery may be seen as a short time. While the PhD timeline would not permit, a medium (2-5 years) or long-term follow-up (5-10 year) would be more clinically relevant. Finally, as with all quantitative research the current study has a common limitation of restricted response and inability to delve deeper. This limitation should be considered in the knowledge that a mixed methods approach was used, effectively allowing for strengths of one design to compensate for limitations of another.

6.11 SUMMARY AND CONCLUSION

In summary, patients who attended inpatient aftercare were significantly more likely to be abstinent at 3, 6 and 9 months than patients who attended outpatient facilities or no formal aftercare. Being abstinent had a significant effect on quality of life and hope for the future as well as physical and psychological health for particular subgroups.

In conclusion, aftercare is usually sought late in the final stage of detoxification and current capacity means there is greater demand than available places in treatment. Increasing access to inpatient aftercare services requires addressing multiple factors at an individual, service, and broader health system level. It requires the individual patient presenting to detoxification with a clear plan and services and the health system increasing capacity to ensure a continuum of care from detoxification to inpatient rehabilitation aftercare. Several factors need to be reformed and new strategies introduced to further enhance patients' success. These reforms along with new strategies are discussed in the recommendations section 10.1.

7 CHAPTER 7: NATURALISTIC QUALITATIVE STUDY

7.1 INTRODUCTION

This chapter presents the findings of the naturalistic qualitative study. The findings presented here are based on thematic analysis. The first section presents the thematic analysis and discusses this in terms of the literature. The second section presents a summary of these findings.

7.2 STUDY DESIGN

The current study employed a naturalistic observational longitudinal design, which involved baseline screening and tracking a cohort of patients who had successfully completed detoxification, at 3, 6 and 9 months, to observe specific processes of interest (139). According to Creswell "A qualitative study is defined as an inquiry process of understanding a social or human problem, based on building a complex, holistic picture, formed with words, reporting detailed views of informants, and conducted in a natural setting" (P 14).

Prior to engaging in the interview process each patient was introduced to the researcher on the detoxification unit a few days in advance of the scheduled interview. This helped to build rapport and provide each participant with a brief overview and context of the research process. The interview process was broken down into phases. The first and second interviews were concerned with background information and allowing the patient to settle and feel comfortable with the researcher, while the third and fourth interviews focused on the lived experience of the patient. This phased interview process allowed the researcher to explore the patients' attitudes, feelings, beliefs and experiences and all the while build and maintain rapport (140).

Ten patients participated in the qualitative study, 6 males and 4 females. It was planned to interview each patient at three time points (3, 6 and 9 months). As this was a naturalistic study no attempt was made to influence a patient's pathway; thus two patients who had not gone on their original 'chosen path' and were not available for all three interviews were interviewed when available. As a consequence one female was only available at baseline and 9 month follow-up and one male participant missed his 3-month follow-up.

All qualitative data collection took place in a local community-based organisation, which provided a secure and comfortable response environment - critical in accessing and eliciting deeper, emotive responses (141, 142).

The qualitative longitudinal study design was intended to achieve objectives 3, 4 and 5 of the PhD research, namely:

a. To observe patients' individual treatment pathways.

b. To identify, describe and produce an analysis of individual demographics and personal circumstances that may have influenced a chosen pathway.

c. To identify, describe and produce an analysis of what influence this pathway had on their recovery/relapse.

7.3 METHODOLOGY

7.3.1 STUDY SAMPLE

A convenience sample of 10 patients, across each of the three pathways (inpatient, outpatient, no formal aftercare) were recruited into the qualitative study. Patients were approached in the week leading up to discharge from one of three inpatient detoxification facilities. Ten patients were invited to participate in qualitative interview at baseline and

again at 3, 6 and 9 month follow up. Creswell recommends a sample of this size for in-depth interviewing (143). Two key criteria were important (1) that each of the pathways were represented and (2) both females and males were represented equally.

This in-depth investigation of opioid dependent patients at baseline and again at three follow up time points was completely new within an Irish context. Both positive and negative experiences with the treatment services, and structural barriers that hamper its full utilisation, were identified. The qualitative data yielded crucial information on differences in relation to the treatment needs that opioid dependent patients experience and on how best to realign services within the current treatment system to adequately meet these needs. The longitudinal element really helped to build rapport as evidenced by the depth and richness of data that emerged.

7.3.2 EXPERT REVIEW AND CONSULTATION

The candidate and her supervisor enlisted the help of a qualitative expert colleague, Prof. Fiona Larkan, at the Centre for Global Health, Trinity College Dublin to develop the qualitative interview schedules. Prof. Larkan agreed to be the qualitative advisor to the candidate.

7.3.3 PILOTING OF QUALITATIVE METHODS

Following the refinement of questionnaires they were then piloted on the first five patients at baseline and at three month follow up time points. Several minor additions were made to the demographic questionnaires.

The interview schedule was then piloted on one patient and based on the pilot interview schedules were then refined. It was decided that the study would employ a

phenomenological approach allowing the lived experience of the patient's recovery unfold and the schedule to act as a guide not to be followed rigidly.

7.3.4 IN-DEPTH INTERVIEWING

Patients were interviewed at follow-up to identify interacting factors associated with the rehabilitation pathway choices and to determine whether and to what extent these factors change as patients enter and progress through their chosen pathway. A purposive sample of 10 patients was selected to participate in a qualitative interview at baseline, 3, 6 and 9 months post detoxification. A sample of this size is recommended for qualitative interviewing, due to the in-depth nature of phenomenological inquiry (144).

7.3.5 QUALITATIVE ANALYSIS

To enhance validity, a summary of the main points was given at the end of each interview and participants were asked if it was an accurate portrayal of what had been discussed. An idiographic approach to analysis was adopted, and each transcript was examined in detail. Rigorous line-by-line coding was applied, with a focus on experiential claims and concerns (145). The first step in the coding process is assigning each line of the data a descriptor and then grouping data in terms of meaning. According to Strauss & Cobin coding refers to a "process of breaking down, examining, comparing, conceptualising and categorising data" p61 (146). Sbaraini et al. best describes the coding approach applied in the current study (i) begin with raw data, (ii) Initial coding i.e. compare experinces, (iii) *focused coding* i.e. seeeking out evidence – gathering and comparing (iv) *theoretical coding* i.e. making sense of the data and constructing knowledge (147). Coding is a crucial step in the process of a qualitative analysis (147), providing the essential link between collecting and explaining the data. Both the candidate and the supervisor coded the data independently before

regrouping to finalise codes. Some data were assigned more than one code. This was resolved through dialogue, questioning and reassessing the meaning to both parties. In the majority of the cases one party had taken more of a macro approach while the second party applied a micro approach e.g. *'I can struggle with that. So it's about just naming it, really, you know?'* was originally coded as relapse. However, when you reflect further there is clear insight – thus the data was reassigned relapse prevention. All codes that were different were resolved in this way. Patterns in the data were then clustered into a thematic structure.

The texts then underwent triangulation i.e. emerging themes were reviewed by the candidate, her supervisor and her qualitative advisor, all of whom had varying levels of immersion in the project. The candidate conducted the interviews and with her supervisor developed the detailed coding theme. A third person who had not been involved in either the study design or data collection, but who is familiar with qualitative methodologies, reviewed the coding frame and original text independently. Any differences in interpretation by the researchers was resolved through discussion.

7.3.6 QUALITATIVE FINDINGS

TABLE 21: DEMOGRAPHICS QUALITATIVE SAMPLE

Name	Age	Parent	No Previous successful treatment attempts*1	Living stable accommodation	Treatment pathway*2	Highest level of education
Catherine	27	Yes	0	No	Inpatient	Primary
Colm	41	Yes	4	Yes	Inpatient	Secondary
Daniel	35	No	3	No	Outpatient	Secondary
Harry	36	No	2	No	No aftercare	Third level
Hazel	34	Yes	2	No	Outpatient	Secondary
Martin	30	No	2	No	Inpatient	Secondary
Michelle	40	Yes	2	Yes	No aftercare	Primary
Melanie	37	Yes	3	No	Outpatient	Primary
Susan	38	Yes	2	Yes	Inpatient	Secondary
Wayne	36	No	0	No	Outpatient	Secondary

*1 Refers to previous successful attempts of formal treatment programme post-detoxification (inpatient or outpatient).

*2 Refers to treatment path at time of detoxification – some patients did not go on planned path and or re-entered treatment.

The majority of patients that were interviewed in this study, identified as early school leavers and reported high level of poverty and social disadvantage (148) only two had completed formal exams and most had poor literacy and numeracy skills. Moreover, the majority many of the patients spoke of familial addiction, mostly parental alcohol abuse (148).

7.4 THEMATIC ANALYSIS

Five key themes emerged from the data: Addiction, Treatment, Relapse, Support and Recovery. A topic emerged as a theme if at least four patients cited it (149). Each key theme is listed below with relevant sub-themes, followed by a summary of these findings.

7.4.1 ADDICTION

Naturally addiction emerged as a major theme throughout the course of the interviews. The baseline interview was conducted in the final week of detoxification and so addiction was only days behind patients.

'BEING IN ADDICTION'

Addiction was spoken about as a monotonous cycle, consuming days and leaving little room for anything else, a torturous existence that patients were happy to have left behind.

> *Getting up doing the same thing over and over again – that was my life.....that was it! I had nothing else going on other than drugs.... I didn't want anything else (Michelle interview 3).*

Hell, hell on earth that's what being an addict is (Daniel interview 2).

That was just my way of life. I'd get out - me main goal in life was to be asleep....just zoned, being practically asleep..... There was nothing to look forward to. I'd no purpose in life, I'd no identity. The only identity I had was I was a junkie that was going nowhere fast. I'd no education, I - all me dreams, me hopes, all that - me future was just bleak. Everything, all me beliefs, me morals were gone down the drain. I done anything to get drugs (Catherine interview 2).

Standing still and acknowledging the cultural and social transition and personal transformations that they had made was a powerful exercise for these patients. Rhodes and Bivol (150) emphasize the importance of the narrative in capturing the transition from the 'back then' to the 'nowadays'. The ability to see the contrast in tangible terms was quite encouraging.

'DECISION TO CHANGE'

The decision to change was cited strongly throughout the course of the interviews. Decision making refers to judgment and the cognitive processes that made the patients determined to take action to seek treatment (151). In some cases the decision to change for some patients was literally a case of *life or death*.

I didn't see meself as an addict. I seen meself as somebody with a mild heroin problem, you know? [half laughs] that was it, you know? But this time in the addiction I knew that I had to do something about it. That, you know, the depression

and the anxiety and everything were hitting me full force, you know, when you're contemplating, you know, not anything to wake up again after you use, like, it's time to do something, you know? (Harry interview 1).

Di Clemente et al. emphasize the importance of shifting from contemplation to readiness. The authors highlight the role of personal motivation in addiction treatment and further suggest this changed with the advent of the Transtheoretical Model of intentional behaviour change, by shifting our thinking away from *why* and into *how* behaviour changes. Offering practitioners a better understanding of relapse, and a shift in focus from denial to readiness, (152). Moreover, Andrews et al. suggest the theory of Self-Determination as a framework to interpret the difference between how and why people enter treatment (153). The theory examines intrinsic and extrinsic motivators. According to Andrew's and colleagues intrinsic motivators possess the greatest amount of autonomy and thus tend to be the strongest motivators. Unlike Andrews patients who entered treatment at the behest of family and friends, in the current study the patients motivation for treatment was self-directed and may account for their sustained recovery and perhaps fall closer to Andrews et al. alternative theory of 'hitting rock bottom' as a motivation to enter treatment.

Change is spoken of in paradoxical terms; patients believed that '*this was it*' - if they did not do something at that time i.e. detoxification, that they would '*end up dead*' - the sheer will to carry on had reached its tipping point.

I had too...I was fed up of being fed up, I wanted to die, I didn't want to live anymore. I didn't - I wouldn't answer me hall door, I wouldn't answer me phone, I wouldn't open the curtains. I didn't want to be a part of society and I didn't even know when I was in it. ... so, not wanting that life anymore, wanting to be happy and have a bit of

peace of mind. I was a prisoner in me own mind, that was big one for me, that one was (Catherine interview 2).

Yet there was a hope, a *'chance'* at a better life, different from what they had currently.

I want to live, I want to be happy. Just to be content and to be at peace of mind with meself is - is more than I can ask for. Because if I have peace of mind I can give the right love, the right - be clear, have clarity, like, the world's your oyster once you find that. It's just a long battle (Susan interview 2).

This notion of contentment being the ultimate achievement in the recovery process supports earlier findings cited by Neale et al. (154). In their study Neale and colleagues found patients were far more likely to value self improvement and personal growth over material success.

'CHAOS'

Some patients spoke of the chaotic existence of addiction, while others spoke of how manageable it was.

I stopped going to get methadone and I got really sick. It was, like, when I was taking I just said "I'm not getting that anymore" and I got massively sick and I was in hospital. I was drinking, like, so much more than that, it must have been up to nearly a litre bottle a day and then - then I was completely off methadone and I didn't care but I kept getting all my tablets but I wasn't taking them right, I was taking massive amounts and only when I felt like it. It was just all messed up, like, it was like if I couldn't get a drink I'd take more or I would, like, wreck the - I was just - like, taking them all (Hazel interview 1).

...it's a situation like that where everybody's screaming and shouting I'd just - that would be the response, like it would bring me back to that kind of thing but I'm able to cope with that kind of stuff much better now than I would have been then, you know, my default would have been just go and use and then, you know, they can shout all they want, the heroin turns the volume down or whatever (Harry interview 2).

'MANAGING'

Others spoke about managing their addiction with precision and organisation. Echoing an earlier finding by Lawn et al. (155) who talk about substances 'bringing order to the chaos'. This was certainly true in the case of some patients.

I'd have my methadone at a regular time and I wouldn't be abusing tablets and my drinking - it would never, I'd never get - I wouldn't be having blackouts or I wouldn't be having seizures but I'd be drinking throughout the day but at a steady pace, like, I wouldn't, you know, lash it into me all night when they went to bed. I'd be taking little capfuls throughout the day and I'd be at a steady - do you know what I mean (Hazel interview 2).

Their day was centred around obtaining, consuming and maintain a substance. Best et al. talk about 'breaking the habit' of the monotonous lifestyle (46).

I'd go out, get me drugs, get me methadone and back home and get a few messages, probably the odd time and then shoplifting all the time (Catherine interview 2).

7.4.2 TREATMENT

Despite the fact that methadone has multiple benefits for heroin users and is an evidence-based major component of international treatment (156) patients in the current study were reluctant to access methadone. Methadone was seen as a means to an end (157). Patients appeared to have exhausted most avenues before accepting methadone treatment, as they believed that detoxification was more difficult while on methadone.

> *It's been up and down I suppose, a rollercoaster because I ended up going back on - on the heroin. I had to go back on the methadone to get in here because I couldn't give a clean urine, so it was either go on the methadone or else stay out there, you know what I mean, so I decided to go back onto 15mls of methadone and then come in here (Colm Interview 2).*

> *I didn't want to go on methadone again, to be honest; I was on it too long. I was on it nearly 16 years. .... And I just didn't want to go back there again but I couldn't come off the heroin, I couldn't do it in me own so I had to do something. It's knowing that I'll be a lot - I'll be a lot longer coming off me sickness than I would've been on heroin (Michelle interview 2).*

'APPROACH'

Patients had great insight into the treatment that they received and were quite articulate about the various experiences they had had, were really good at discerning how different agencies approached treatment and how this worked for them

I've been in treatment a number of times over the years - over the years and I've never got what I've got in [name of treatment centre removed]. Do you know what I mean? [name of treatment centre removed] is very different from other treatment centres, the approach - they just have this kind of gentle approach and other places have a very confrontational approach and it's nearly more about - in other places I've noticed it's nearly more about telling people what's wrong with them and what's the bad in them than actually affirming them (Wayne interview 1).

Very unique [treatment approach]that they seem to cater for individuals rather than having structured programme for everyone it's like you work with - like, they needed to work with, say, me personally around being intolerable it's like you resist but they don't buy into it with you, do you... No, they let you - and I felt for me I needed that. I didn't need - I was after giving meself enough of a whipping so I certainly didn't need anyone else - and plus, it's a form of deflection when you're getting that challenge but up there you're left literally with a lot of time to - for you to sit with you (Colm interview 1).

Patients favoured the non-judgmental peer lead treatment approach.

The judging part is a big thing as well, people not judging. Because my kids are a lot older now and I've never been clean with my kids. My eldest son is 20, he's never seen me clean. Don't get me wrong he's seen me clean for a few weeks here and there you know what I mean, the child's life and I suppose helping me around me children I think the keyworkers are great. And which is great as well with [name removed], a lot of them has went around as you went [life experience] - not the exact

same but they've - a lot of them has went... down the same route. They can relate. You know, which is great as well (Michelle interview 2).

Banazedah et al. reported that a positive therapeutic relationship plays a significant role in treatment outcome. In particular participants valued being respected and not being judged (29). Moreover, Bobrova et al. cite judgmental service providers as the main reason for premature treatment exit in opiate dependent participants (158).

'GENDER DIFFERENCES'

Interestingly, all of the female patients believed that mixed gendered treatment was not a good idea. A key component that women suggested would affect them within mixed gendered groups was the sense of safety. Although safety is a changeable term for the current patients for some it was the threat of intimacy:

I was in treatment and I got real close to a fella and he left and then I left and then I was in another one and I'm always around fellas, I actually get on better with fellas, I ended up getting two of them to - jumped over the wall to get me drugs...
I was talking to someone last night about this - and I said "I need to be around women, you know, men just distract me too - I'll never fucking get clean with...". So, yeah it was a conscious decision to go in there with all women and it was the right decision and it was the best decision I made me whole life, like. It was (Catherine interview 2).

It's bad news [mixed treatment]. Because you're looking for - especially if you're feeling a bit raw or feeling a bit lost, you're looking for a feel good factor and if someone's telling you all the things you want to hear you're going to latch on. I've

done it meself. I'm saying from experience....You latch on and then it does stop you opening you up and it does keep you kind of rigid and it does [pause] it makes you more fucked up actually in the end of it but in the initial thought you think that's helping you cope along the way. Some days it might but when you get too - too close it can really hold you back (Susan interview 2).

For others being in the all women groups enabled them to be "oneself." Shared experiences among women group members created a safe atmosphere that enabled patients to talk about sensitive issues without feeling pressure, questioning, or sexual tension. For example, women in the single-gender groups felt that they could be fully honest:

.... having males in group and stuff, I think it's a massive difference. It's like, you're not going to talk honestly and your head's going to be distracted if there's males there, it's as simple as that. Because we're two different - it's just different, like. I think it was beneficial now but I wouldn't have - I wouldn't have seen that back then and I wouldn't have opted for it but now I think, yeah, I think it's better. The stuff that you carry in - for me personally I think it benefitted being all-women because it's safer.....I think to feel safe is good even if - even if you don't voice it because if I had been in [name of treatment centre removed] like, where it was mixed I wouldn't have said "Oh this is... ", do you know what I mean? I probably wouldn't have even known how to say "This is not right because it's men" but it would have been different, like (Hazel interview 2).

Similarly to Neale and colleagues gender was an imperative influencing factor in the female patients' experiences. However, there was no evidence of a fundamental 'female recovery experience' and the females interviewed did not necessarily have fewer recovery resources than men (154). Andersen et al. illuminates the importance of the storytelling in drug treatment and in particular how some stories on gender and drug use are silenced, while others are encouraged (159).

'PARTNER IN RECOVERY'

Intriguingly the male patients who were interviewed believed that having a partner in recovery 'would be too much'. It is noteworthy that all but one of the females had a partner in recovery at the time of interview(s) a finding that is consistent with treatment literature (160-162).

> *.... like, managing and reconnecting in the home environment, like, me partner's in early recovery as well and we've never been with each other kind of clean in recovery, so, like, it's exciting but it's a challenge as well... (Susan interview 3).*

> *I wouldn't do it ....if I was with somebody that was in that situation [recovery] it would probably be too much. Everything would be recovery...(Martin interview 3).*

> *No. that wouldn't work for me.....having a partner in recovery. No (Wayne interview 3).*

'AFTERCARE'

Aftercare emerged as a subtheme throughout the interview process. Aftercare was seen as a vital step in the recovery process. None of the patients interviewed believed that detoxification was stand-alone treatment.

> *Oh it'd be very hard [having no aftercare] after five months of a programme? [breathes in] It'd be very hard because ahh when I came out of [detoxification unit name removed] I thought I had it all, like, I thought I was great but a week and a half later or two weeks later I was back using (Michelle interview 2).*

> *I couldn't have - like, in hindsight now, I felt I needed it at the time but definitely to have just detoxed and went back into the community it'd have been a lot more difficult if I'd done it at all. ...Because detoxification [name removed] is a great place, you get that, you know, the care off them and stuff like that but then yeah I needed to go on up there, it did complement it very well. It was, like, basically phase 1 and 2 and that's... exactly how it felt, it fitted (Colm interview 2).*

> *No. No. I needed to go in somewhere for five months, then I done four months in me Step Down an I'm doing once a week in me aftercare and I need structure as well, I need to be doing something every day. It wouldn't be a great idea for me to be sitting around doing nothing, I need to be getting in and interacting with people every day as well because I can get very into meself because I'm used to being in me bedroom on me own (Catherine interview 3).*

These findings are in keeping with the current body of outcome based research suggesting that detoxification is not a standalone treatment (11, 23, 103, 133).

'DOING THE WORK'

There was an eventual acceptance that recovery was not just going to happen; it required work and effort.

> *I suppose what's different for me is that I was willing to drop - to do anything I could when I came in here and me keyworker told me that when I came in here that I told her out straight that I was willing to try anything that I wanted to stop drugs but I didn't know how. Didn't know how to stay clean (Michelle interview 3).*

> *I was always - "No I'm not telling anybody anything, I don't need to, you know, I'll just go to the meetings and a magic wand is going to happen, you know, and it's just going to work without doing any work" that doesn't happen (Harry interview 2).*

'ACCESS'

Patients' experiences and perceptions of the time that it took to access treatment were very different. This was quite an emotional time for patients.

> *... to have been able to access them services, very lucky. What I would change is - is the length of time it took me to get into detoxification [unit name removed]. It was ten months (Colm interview 3).*

> *That was just horrible [waiting for detoxification], really was. And it was basically a year of going in and out to a clinic, waiting on a waiting list to get into a detoxification like, there's some - I know that they have to vet people and all of that kind of stuff and make sure people are ready to go in but if I could have got into*

[detoxification unit name removed] when I first kind of - within a couple of weeks of first presenting meself to, let's say [the clinic]... that would have been much more beneficial for me, you know? (Harry interview 2).

Not surprisingly patients reported being in a better place, at the time of the second and third interviews. In particular their perception of accessing treatment was more positive, a finding that supports the current literature (156).

Looking back on it, it was fairly quick. It was only five months maybe. I mean I thought it might have been sooner, you know, just with places coming up and I could have got in. Yeah, but realistically to get in to, you know, starting off with a clinic to getting into detoxification five months maybe isn't bad. It's not bad (Harry interview 3).

Moreover, when Neale and colleagues examined heroin users' views and experiences of treatment duration, they found that those accessing and completing detoxification quickly were prone to relapse (163). While patients indicated their frustrations at waiting to enter treatment there was awareness that rapid entry was not necessarily a positive, - rather preparation and reasonable pace would bear most fruit.

like, in hindsight now, I felt I needed it at the time but definitely to have just detoxed and went back into the community it'd have been a lot more difficult if I'd done it at all. I've done it before in and out and thought I was sorted; you're fooling no one. (Colm interview 2)

7.4.3 RELAPSE

Patients had great insight and learning from relapses both current and past. They viewed them as part of the recovery process (164) citing the traps and pitfalls with an awareness that would later guide their recovery, a finding that is consistent with the findings recent research (165).

> *And it went on and on till it led me right back and I was actually worse. I found it a lot worse this time round. Because it took an awful lot out of me, like, shoplifting charges, me son was taken away from me and he's me rock. He's everything to me, so - bills galore, loans and it just - it just - it came so fast. You don't realise it, you think that you get away with it but you don't get away from it, it's a 24 hour job, a moment at a time. (Susan interview 2)*

The patients expressed a good understanding of their personal triggers and had learned methods of coping that helped them abstain from relapse.

> *... you know, and me behaviours were off the wall and they were very - I was very erratic, you know, and I was looking for all stuff outside meself to make me feel better and it just wasn't working, you know, because I wasn't putting anything into me recovery, like, I had nothing to fall back on. I had no resources to draw from to kind of keep meself alright, you know (Wayne interview 3).*

'RISK OF RELAPSE'

Understanding and preventing relapse are among the greatest challenges facing patients and practitioners in the field of addictions (166). Harris et al. highlight the need to attend closely to reports of negative emotions such as boredom and loneliness (167). Although

these affects may not have the intensity of clinically diagnosed mood disorders, they frequently serve as triggers for relapse, a notion that is supported by the current data.

> *Overwhelming, too much too soon, like, thinking that you're okay because we're all safe and... there's no real life issues in here but when you go outside and face them they can be high risk factors if you're mentally not prepared for it, do you know what I mean, because emotive - when your emotions gets the hang of you what do is run on it and even if it's gambling, even if you don't pick up a drug, even if it's gambling, even if it's - that's happened to me before, even if it's picking up anything else, like, and I just don't want to go there again (Susan interview 1).*

> *I found that I have to keep things diverse. If everything is just, like, narrow-minded recovery, recovery, meetings, meetings, Steps, Steps, Steps it just gets old hat and boring (Harry interview 2).*

> *I had a couple of weeks back home before I went into [inpatient facility name removed] where I felt very kind of uncomfortable just - just even sitting down with my girlfriend and having dinner and stuff like that, I really didn't know what to be saying to her, you know, except quoting stuff out of, you know, books or whatever, you know, and the first week or two in [inpatient facility name removed] I found it incredibly difficult because in the three weeks that I was home I kind of slipped back into getting up late and not having a routine again, you know? (Harry interview 2).*

'ALCOHOL AS A GATEWAY'

Alcohol was something that was either off limits for a lifetime or at least for the foreseeable future. It was cited by most as a gateway to relapse. Examining the 'gateway theory' in an

adolescent population of substance users, Brown et al. found that despite alcohol not being the primary drug of choice it was substantially involved in relapse to other substances post treatment, a finding that is echoed by the patients in the current study (168).

> *And plus, it leads you back to drugs because then you don't get enough out of the drink and you move to something else. And I've already tried every drug under the sun, you know what I mean - so I know that I'm not - I'm not, I've tried everything. I may forget about it. It's not for me. Definitely not. (Michelle interview 3).*

> *...when I slipped before I took a drink first...you know, and once the drink was inside me (Colm interview 3).*

> *But drink brought me back the last time to drugs, do you know what I mean, and - and I came into recovery this time, you know, I have no reservations about alcohol now I let it go it was like everything started going downhill, I stopped paying my bills, started picking up, like, since I picked up a drink it opened that gateway thinking "I got away with this so I can have a joint. I got away with that, so I can have a smoke. Got away with that...", you know? (Susan interview 2).*

'PARTNER IN RECOVERY'

Intriguingly the male patients who were interviewed believed that having a partner in recovery 'would be too much'. It is noteworthy that all but one of the females had a partner

in recovery at the time of interview(s) a finding that is consistent with treatment literature (160-162).

> *.... like, managing and reconnecting in the home environment, like, me partner's in early recovery as well and we've never been with each other kind of clean in recovery, so, like, it's exciting but it's a challenge as well... (Susan interview 3).*

> *I wouldn't do it ....if I was with somebody that was in that situation [recovery] it would probably be too much. Everything would be recovery...(Martin interview 3).*

> *No. that wouldn't work for me.....having a partner in recovery. No (Wayne interview 3).*

REASON FOR RELAPSE

During the course of the interviews some patients had lapsed and/or relapsed. However, all had, at some point, experienced (re)lapse thus they provided detailed accounts of the types of factors that could prompt a (re)lapse, as well as some useful strategies for handling and evading the temptation to use (169). Family, having a drink and withdrawing from supports were the three most common citings for relapse.

> *Coming from a family with, say, three heroin addicts in it, you know, and a family business as well where the three of us worked for it. Like, I noticed - well I know now that work and going back into a stressful environment like that is just not possible, you know. There'd be certain triggers, say in the way that the family would*

communicate with each other as well. It's one of those families where everybody - whoever screamed loudest got heard and that kind of thing (Harry interview 3).

I stopped using me supports like NA and picking up the phone, like, doing the simplest things like painting and out in the garden, going for walks, like, I just got stuck into the house and then I was on such a high not realising that the drop is - was about to come (Susan interview 1).

'RECOVERING FROM RELAPSE'

Relapse was not always viewed as negative, - hindsight afforded an opportunity to reflect and key insights were gained.

I think in hindsight it's a great thing because what happened last week, picking up that drink and the way I felt the next day and me conscience this time is much bigger than it was before. It's saying "You can't do this" and I've listened to it and I have to say I'm grateful for them, like, it's not easy. Recovery isn't easy, especially early recovery so I'm not going to paint a picture because it's not a pretty picture sometimes but I think this time it's about keeping it in the day, the 24 hours, because I tended to before think I'd be past stuff and that'd make me more depressed and more shameful and guilty and all the rest...(Susan interview 2).

I've been showing back up to me one-to-ones every week, I've been going to NA every day since. So I've been trying to stay around with other people. Just not let meself, you know what I mean... Just trying to - I'm trying to feed me spirit now with positivity instead of negativity, you know? (Wayne interview 3).

There was a recognition that at some point a line would have to be drawn and recovery recommenced as relapse and the guilt that goes with breaking abstinence often provides an excuse to use drugs again.

> *Well I beat meself up for a while because people clean time doesn't mean anything but for me it did because I was never that clean for that length of time – but what can I do I had to put it behind me. Otherwise I'd use on the back of the guilt (Martin interview 2).*

7.4.4 SUPPORT

Support emerged as a theme throughout the interviews. Patients were quite insightful regarding support, both existing and lacking.

'FAMILY SUPPORT'

In contrast to gender sameness research in addiction (154) in the current study males were just as likely as females to cite family as a support.

> *I have a family that supports me, you know, and having had a brother in addiction - he has long-term sobriety, six or seven years now, the family are well aware of, you know, where - you know, to keep an eye on me if needs be and to see any slip or any change of, you know, behaviour or anything, so - like, recovery starts at home, I've been doing a lot of work with, you know, repairing bridges and, you know, so I've got a strong family base support and, you know, everything stems from that and once that's right and I'm right ...(Harry interview 3).*

'PEER SUPPORT'

The support that patients received from their peers in treatment was highly valued. The safety in numbers, knowing that you are not alone but have a shared experience, was a great source of comfort.

> *... it's not only in my head, you know what I mean? Plus the feedback from the life story as well you get of your peer thinking that you're the only one that went through this and went through, you're not. So that's what I got out of it....[treatment] like it's a lot (Michelle interview 3).*

Andersen et al. highlights the importance of how individuals in recovery need stories, 'narratives' that make sense of past drug use as these narratives facilitate constructions of future, non-addict identities (159).

'FRIENDS'

Friends were cited over the course of the interviews as a scarcity. Patients did not have a lot of friends and the friends that they did have tended to also have addiction issues.

> *I've only one friend. And she's still on methadone at the moment, she's on 20mls of methadone, she's trying to get into a place herself. She'd be the only one that I'd see (Catherine interview 3).*

> *I have a couple of friends in recovery that I'm linking back in with (Susan interview 1)*

'NARCOTICS ANONYMOUS' (NA)

NA was a particular theme that divided the group. NA was both a source of support .....

> *That was always going to be the plan, I knew - I was never going to be doing a day programme so I had to get something else to fill it and I always knew there was a hole inside, you know, the 12 Step thing is, you know, it's unifying (Harry interview 3).*

> *I think it's a fantastic place to stabilise, to get started, as a stepping stone in recovery but I think it can also - people can also stagnate there. And for me I - I - I, like, from what I read on the book on the Steps and stuff - I still practice parts of it because really it is just a blueprint on how to be a good person (Harry interview 2).*

..... and a potential trigger for relapse.

> *the system itself is good, I thought - I suppose for me personally it depends on who's there on the night, you know, it's...(Daniel interview 1).*

> *when I came out [of treatment] I knew that I should go to them but it's not easy. I won't go to the meetings in [name removed] because any time that I have went when I was clean before I know too many of them that are using and a lot of the time it has brought me back using (Martin interview 2).*

7.4.5 RECOVERY

Recovery emerged as a major theme and was something that was explicitly spoken about throughout the course of the interviews. It was seen as a process, (170, 171) something that

was attainable, but had to be worked at. Each patient had 'recovery capital', some higher than others. For some it was their insight, for others it is more of a social currency, support, education; factors which by their existence would contribute to an individual's success while their absence would hinder it. The process of recovery, however, was quite an individual path or perhaps more aptly stated, many roads lead to recovery (171, 172).

'INSIGHT'

As previously noted patients had great insight and learning from relapses both current and past. They viewed them as part of the recovery process citing the traps and pitfalls with an awareness that would later guide their recovery.

> *Because they say when you come in here you took drugs for a reason but I didn't believe that. I believed that I took drugs because I liked taking drugs. But I suppose continuing of taking drugs all the time over and over and over again. I still believed that I liked them till it got to the stage where I couldn't handle them. In me life story I realised why I took drugs. And that was with me mother and the way things were going on in me family home. I actually thought I had an alright life until I started writing me life story, you know, so I found it very hard. Plus, I found it very hard to talk about me mother in me life story because it would be something that I wouldn't do, you know? (Michelle interview 2).*

> *I have it nailed down, I have it down to four. The four things that I think are most important in turning around for me was addressing the childhood trauma... changing my core beliefs. Changing all the automated programming, automated responses that I have and becoming aware and changing all the destructive behaviours and*

that's what I've been... they're the four things that I've been focusing on (Harry interview 3).

Some of the most striking insights were those gained during treatment. Treatment 'lifted the veil' offering awareness into their behaviours that appeared to be quite profound.

Definitely. I thought I knew everything about drugs because I was on drugs 25 years but no, I knew nothing. I mean I only knew how to take them and buy them, you know what I mean, I knew nothing else (Michelle interview 3).

... it was great to finally know that I wasn't mentally ill or anything like that. That I was just - I was an addict and I needed to deal with my addiction, you know? (Harry interview 2).

I think it just - the realisation that you can sit in therapists' offices all day and be in treatment for the rest of me life and they'd never fix me because the fixing starts and ends with me. I think I - that came to me a couple of weeks ago (Colm interview 1).

'EDUCATION'

Most individuals interviewed had left school during early adolescence often with very few academic qualifications. Two had obtained vocational qualifications from college. Most had worked in the past, usually in unskilled, semi-skilled, casual or temporary jobs. Despite this,

several aspired to return to study and most of them had begun the initial application process by the end of the interview period.

> *.... but that's why I'm so kind of determined to get into the education part of things, so that I'm prepared for these things when they happen to me in the future if I do go back working again, you know? (Harry interview 2).*

Consistent with the argument that education is a form of recovery capital (148, 154, 173, 174) the patients interviewed consistently stated the many benefits of attending college, more specifically allowing them to re-establish structure in their lives, providing enjoyment, boosting self-esteem, and improving their future employment prospects.

> *I want to do social policy, Yeah it'd be kind of both I Addiction/Homeless services obviously yeah but wider social change as well (Wayne Interview 3).*

> *that there's a placement going in [treatment centre name removed] on the CE scheme as a peer support worker so I said I'd do that it's a chance of giving back (Colm Interview 3).*

Many individuals, particularly the males, said that they wanted to gain employment in the field of addiction rehabilitation. However, our patients ' main reasons for wanting to gain employment in this area did not appear to be financially motivated (154); rather, they stated that this would be a way of 'giving back' - a means of contributing back to society.

'BEING IN RECOVERY'

There was a sense that recovery took effort – it wouldn't 'just happen', a misconception that most patients interviewed had suffered in the past. There was awareness that it took

work and that it was a long road. Recovery meant much more than abstaining from drug use (163).

> *.... thinking, like, because I'm not using now I'm grand, do you know what I mean, like you're not - getting off the drugs is only the start of it, it's only the start of the work you have to do on yourself, do you know what I mean, so that's kind of the next bit to move forward on that I've never done before, do you know what I mean? I've got off drugs a few times – but now I'm in recovery! (Wayne interview 3).*

Patients articulated the magnitude of change between addiction and recovery with great insight. The contrast between the two was so great – relapse is always looming in the back background, but ultimately they reached a place where the drugs had lost their allure.

> *So, this time, like, the difference between, let's say, my darkest days of the last stint I had in addiction and now is just massive, it's night and day, you know? I - I hope I've dealt with it, you know, I really do and I think - I think I have.....So, like, there's no physical craving or even the odd thought because, you know, I know what it was masking up before, what I couldn't face up to in meself and I've tried to tackle that so it's not even a runner. Now it's still there in the background, you know, but I don't entertain it, you know, I don't feel the need to. I know what I would lose if I was to go back and it doesn't look attractive at all in the slightest (Harry interview 2).*

'RECOVERY AS A LIFETIME COMMITMENT'

One of the more controversial issues in recovery is the notion that recovery is a life long commitment (171). The current study further stressed this divide. Some patients believed that recovery was a lifetime task ....

> *No, there's no next, it's just living now. Just living now. Just getting on with life. I don't, you know, feel that I'm this troubled addict now that has to be careful of me Ps and Qs everywhere and, you know, I can't go here, can't go there, you know, I just have to mind meself and be aware of it. Recovery, you know, it's a part of me but, you know, it's not a label I want to wear around me neck, you know, I want to get on (Harry interview 3).*

> *Not a day at a time, it's definitely a moment at a time. For me anyway, personally (Susan interview 2).*

.... while others believed that recovery could be achieved within a definitive timeline.

> *..recovery is a lifetime commitment [hesitates] but I think they kind of say the first two years is where you have to be really strict with yourself like that and that's when it starts getting easier then. (Wayne interview 3).*

Reflecting upon this, the notion of recovery as a 'lifetime commitment' in the current population appears to be linked with patients who attended NA and abstinence based aftercare programmes. However, this belief may be not so much the result of the *'intrinsic*

nature of the recovery process' but rather a *'socially constructed narrative'* developed in conjunction with those working in the treatment services (175). Thus, this belief is linked to a rule or guideline rather than an inherent way of thinking or living.

'FEARS'

Fear emerged as a sub theme within the current study. In part patients feared the ordinary the normal everyday issues such as routine and work – a finding that is consistent with the literature. Nettleton et al. concluded that the negotiation of normality is a hazardous route for this population(176). Expressions of aspiration to be 'normal' are rife with apprehensions; there are manifestations of both resistance and resignation (176). They also naturally feared failing.

> *I never done anything. I never done them things ordinary people do. Fearful of it. Having to find something that I could be like ordinary people going to work in the morning and in the evening and not fucking it up. Fearful of fucking it up (Colm interview 2).*

They feared that if they took their eye off the ball it would all come crashing down, - a fear that was quite understandable and logical.

> *because I'm full of fear. I'm running on fear that I'll go back. I've no desire to use whatsoever, I don't, but that little thing in my head "Well if you keep doing that you're doing the same thing over and over and you're not changing it. Something's going to give..." it's not good either because I'm striving for perfection because I - I just so don't want to go back to that place (Catherine interview 3).*

Others appeared to be contradictory with an indiscriminate catalogue of fears listed off without any real thought, - the useful jumbled up with the not so useful.

> *My biggest fear would be being vulnerable towards other people, you know that kind of way, maybe trying to fit in but - or being too cocky even about it. you know, not really talking about how I feel, sometimes you won't know how you feel and you don't really want to talk to anyone so it all builds up, you know that kind of way but you have to talk and learn how to talk to people and all, you know, it's different when they see you and you go to all the meetings (Melanie interview 2).*

'HOPES & ASPIRATIONS'

Patients commonly cited hopes and aspirations for the future. At the time of interview the majority did not have a lot going on outside of recovery.

> *I can't really think of anything that's any fun - fun that's going on outside of recovery at the moment but I'm working towards that because that - life - your whole life doesn't revolve round NA, do you know what I mean, you have a life and you have NA. It's a part of your life... So I think that's the way it had to be for a while with me but I'm not as dependent - as I said.. so I'm working on it, it's a work in progress. I'm very aware, I'm very aware of it that I don't want me whole life to be around NA, you know what I mean (Catherine interview 3).*

It is notable that bar two males, none of the patients interviewed had any hobbies or interests outside of their recovery. However, when asked about their hopes and aspirations for the future the majority mentioned hobbies and interests. McIntosh et al. emphasize the

importance of constructing a non-dependent identity in order to succeed in recovery – even at the very early stages of recovery (175).

> *I'd just like to have me family around me, you know what I mean, me children especially. Like, I'd like to have a home where they could come. Have something that I enjoy doing, you know what I mean. A job (Colm interview 2).*

> *I can't go back there and just exist anymore while - I want to exist but in a different light, do you know what I mean? Have more to me (Susan interview 2).*

In relation to hopes and aspirations, there were also very few apparent differences between the male and female patients. Key ambitions for all included: to maintain their recovery, (some consuming alcohol in a controlled way as part of this); to attend college; to secure employment; to be part of a loving partnership; to secure stable accommodation; to travel; and, ultimately, to be happy and gain peace of mind.

> *I'd be still clean, I'd [pause] I'd just - I'd have a lot more peace in meself, I'd be a lot more comfortable in meself (Wayne interview 3).*

> *Starting to recover, you know, continue doing a bit of work on meself and, you know, just being happy in meself, have a bit of peace of mind, maybe be in a relationship, I'd like to do a bit of travelling and maybe have a little job for meself and me own place, nothing major (Catherine interview 3)*

Although a few individuals said that they would like to have a car or a little more money so that they did not have to worry about buying food and paying bills, nobody seemed particularly materialistic (154).

> *..... Just the simple things in life. I remember I used to say that to meself "I just want the simple things in life", you know, and still I don't want anything big, I don't want anything major, I don't want all these fancy cars or anything like that. Yeah, they'd help along the way, don't get me wrong, but it's the small things that I appreciate in life now (Catherine interview 3).*

> *.....I mean material things, that's - that'll come eventually I suppose, do you know what I mean that's not really what I'm chasing at the moment (Wayne interview 3).*

Indeed, some explicitly said that they did not want money or material possessions. Thus, the patients appeared to have somewhat modest goals, prioritising people and relationships (social capital) over wealth (physical capital) (154).

'COPING WITHOUT DRUGS'

Coping without drugs emerged as a theme in the current research. However, patients shared experiences of coping without drugs and the toll that this took.

> *.... the realisation that without a drug these things [going home between treatment episodes] affect me not only mentally but physically, it kind of - I was just drained (Daniel interview 1).*

You get agitated about... these sensations that...you're - because they keep telling you - you can feel good and go back to drugs and you can feel fucking bad when you go back to drugs so every feeling you get can send you back the wrong way (Martin interview 3).

These experiences were not always negative but were experiences that would have been previously masked with drugs.

....it was a pleasant experience [visit from daughter], you know what I mean? I shouldn't have been wary of it because afterwards when I realised, because it's only an hour and the hour just went like five minutes, it was so easy to sit with her and be comfortable around them. For her, you know what I mean, the way - she's me daughter and she has that unconditional love and I have it for her and to kind of feel it for the first time, because I was in addiction when she was born and... I knew I loved me children but never had that physical feeling, you know what I mean, because I was taking too much drugs ...that was a pleasant knock, you know what I mean, but still afraid of it when it happens (Colm interview 2).

I think something that I took for granted in the past when I was taking drugs - me children, like, I've always known I love them, you know, I've always... ... known I care for them and I done me best by them and I've always been, like, giving them hugs and I'd be that kind of a father, you know what I mean, like I'd never be a - when - when the first time I done the detoxification [centres name removed] two and a half, nearly three year ago, I was nine months, eight or nine months clean and me son's

birthday came up and I got all caught up in me bleedin' head about giving him a hug. Like, he could do it but I kind of got caught in the moment thinking the whole fucking street was looking at me and it does just disturb me, you know, it did and then it was like a fucking overload of everything started hitting me, you know what I mean? .....guilt, shame, I don't know what it was, you know, but that was the kind of things that knocked me over, you know what I mean? Just something that I took for granted for so many years and that was it, everything came hurtling in after that day, you know what I mean, because I left - it happened and for me it was probably a simple moment but it seemed a lot longer than what it was. The hug or me getting caught in me head and thinking everybody was... As I say these things came so natural when I was on drugs but me getting caught up in me head actually doing something that I'd done for years for some reason just got the better of me that day (Colm interview 2).

'CHALLENGES'

Similarly to their fears, the patients cited their challenges as 'normal' 'ordinary'. The biggest challenges were around time management, housing and housekeeping. Life skills are a big challenge for patients in recovery and are often a commonly cited reason for relapse, forming an integral part of most relapse prevention strategies (177-180).

Because it's so busy and I'll be busy as well, like, outside but it's the, like, managing and reconnecting in the home environment, like, me partner's in early recovery as well and we've never been with each other kind of clean in recovery, so, like, it's exciting but it's a challenge as well... When I'm feeling stuff, stuff could be cropping up for me and I have it in me head and I'm not pulling anyone or else I'm running

from them before they pull me in. So that's the biggest challenge, not reaching out and saying "look, I need to talk" but I'm working on that, like, I can struggle with that. So it's about just naming it, really, you know? (Susan interview 3).

There's no accommodation after here, you know what I mean like, you apply for all these things that - well in my experience now at the moment is that I'm limited now to two options and whether they have a place for me. It's touch and go. And then after that I have to go on me own options, you know what I mean? (Colm interview 2).

And when you come in here it's like, "oh you have to pay bills. Oh you have to do this...", you know, just every day stuff that I struggle with - cleaning me flat, going for messages, getting here on time every day. Even meeting yourself, kept missing you and all, it was just, like, it was a struggle. I still struggle around everyday stuff (Catherine interview 2).

7.5 DISCUSSION OF FINDINGS

Addiction is spoken of in paradoxical terms, patients believed that *'this was it'* - if they did not do something at that time i.e. detoxification that they would *'end up dead'* - the sheer will to carry on had reached its tipping point. Yet there was a hope, a *'last chance'* at a better life, different from what they had currently. Addiction was both manageable and chaotic.

Patients had great insight into the treatment that they received and were quite articulate around the different interventions they received, and were really good at distinguishing how

the various agencies involved in their care approached treatment. For the most part the males and females did not differ greatly in experience or opinion. The female patients who were interviewed did, however; feel quite strongly about gender specific treatment, while the males were quite explicit about entering into a romantic relationship with a female drug user. There is a growing body of evidence to support gender specific treatment approaches (181-183), with studies reporting better outcomes for females attending female only facilities (184). However, evidence is increasingly suggesting that treatment must also be tailored to the needs of females rather than simply providing traditional treatment in a female only facility (182, 185).

Unlike the other two studies set out in this thesis, the qualitative study sought to take a naturalistic approach to the data that unfolded and inductively elicit the individual benefits of a chosen aftercare pathway post-detoxification. As such, benefits of a particular pathway are more implicit. That said aftercare was seen as a vital step in the recovery process. None of the patients interviewed believed that detoxification was stand-alone treatment. There was a sense that recovery took effort – it wouldn't *'just happen'*; it is a process that takes effort and cannot be rushed. Experience has taught them that treatment is necessarily a lengthy, complex journey requiring intensive therapeutic engagement (163). evidence

Moreover in some cases, the idea that recovery was a life long commitment divided the group (171). Alcohol was something that was either off limits for a lifetime or at least for the foreseeable future. It was cited by most as a gateway to relapse.

Recovery capital emerged as an overarching theme in the current study, offering a useful framework for exploring several sub themes. According to recovery capital theory (148, 171, 173, 174) physical capital (defined mostly in materialistic terms) is viewed as a crucial

component of recovery capital; however, very few of the patients interviewed were materially well off, despite the fact that some came from relatively affluent backgrounds. Nonetheless, during the interview period, access to physical capital of any kind was very limited. In addition, most of the patients interviewed were accessing treatment and thus unavailable for work. As such they were heavily reliant on state benefits and family support.

Moreover, excluding the period when patients interviewed were attending inpatient facilities, they all had typical overheads, such as rent, utility bills, mobile phone costs, groceries, and personal care. Some also had financially dependent children or were expected to contribute to wider family overheads. Additionally, they often had debts, utility and housing arrears, and/or unpaid loans that needed to be repaid. This meant that most individuals in the study had very little disposable income and none had any savings.

Although property constitutes an important source of material resources, only one of the patients owned their own home. A very small number of individuals, mostly the females, lived in relatively secure social housing. More often individuals inhabited insecure private rented accommodation that was low standard, poorly maintained, and shared with other drug users. Episodes of homelessness, meanwhile, were common – particularly amongst the men who seemed less able to rely on relatives for accommodation and less likely to receive social housing because they did not have resident children. Repeatedly, our male patients described having to sleep rough, stay in emergency hostels and night shelters, and sleep on sofas without knowing for how long they would be welcome, on returning home from residential treatment. The model of recovery capital has gained much acclaim in addiction literature, reflecting on the attributes of the patients interviewed. It became a very useful framework in which to place the findings.

The current data however, illuminate a possible shortcoming. Insight was a thread that ran through most themes and sub themes in the current study. Recovery appeared to be an accumulative effect of addiction and treatment experiences. Most patients had several attempts at recovery, some quite substantial – each contributing to the current episode. Yet insight is not explicitly referred to in the current model of recovery capital. It could be argued that insight is accounted for in the current model under 'human capital' within 'skills and attributes'. However, given the role insight plays in any learning and growth experience and the emphasis that is placed upon it within the treatment journey, insight is a fundamental underpinning to any real growth and development. It would therefore seem appropriate to view insight as constituting a more explicit role in the model of recovery capital.

7.6 STRENGTH AND LIMITATIONS OF THE NATURALISTIC QUALITATIVE STUDY

7.6.1 STRENGTHS

This study was the first study in Ireland to apply a longitudinal qualitative approach to gain insight into the experiences of opioid dependent patients. The use of longitudinal methods involving as many as 3 interviews and an introductory session with each patient, from whom a rich wealth of data was obtained, is a key strength of the current study. This method allowed for intense exploration of the phenomena from various qualitative data transcripts. In addition, this study used a rigorous method of analysis, which allowed the researcher full immersion in the data, while also reducing bias, ultimately enhancing the validity of the study's findings. The involvement of a primary researcher (the candidate) at all stages of the study helped to build and maintain rapport creating a safe and stable space for the

patient to share their experiences. The number of females to males ensured that the chosen sample was representative of gender presentation across the addiction services.

7.6.2 LIMITATIONS

The study might have benefited from the inclusion of other key-informants, such as treatment providers and patients' significant others. The inclusion of key-informants from both detoxification units as well as aftercare services could have offered an insightful dimension into the external influences on a patient's treatment path. This was originally conceived. However, the opportuneness of time within the larger scale of the thesis did not permit the additional stage of analysis the generated data would require. Finally, as with all qualitative research, the current study has universal limitations of generalisability, although the current sample was drawn from a larger quantitative sample where every effort was made to capture all patients from the population of interest.

7.6.3 SUMMARY AND CONCLUSION

In summary, the qualitative study has shown that patients who accessed aftercare had positive experiences and believed that they had taken the right treatment path for them. Aftercare was seen as a vital step in the recovery process. None of the patients interviewed believed that detoxification was stand-alone treatment. Recovery was seen as a process that wasn't always linear and lapse and relapse were often par for the course. Patients had great insight into 'risk factors for relapse', information and knowledge that they had mostly gained over several years and many treatment episodes. Relapse most often occurred when patients had recently left the treatment service or became casual around their supports, lending support to the argument that treatment exit should be phased.

Interestingly one of the female only inpatient aftercare facilities that participated in the study took a 'step-down' approach, whereby patients were given overnight visits home in the last month of the programme. Moreover, if the patient did relapse she had 24 hours to return to the facility where she would undergo a segregation period for 48 hours and then return to the general population. This was a policy favoured by patients. While most of them had not availed of it they took comfort in knowing it was available.

In conclusion, this chapter has sought to provide a balanced account of patients' experiences and the ways that these experiences relate to recovery. In doing this it is the hope that the qualitative analyses have added depth and nuance to current understandings of the addiction recovery process. The data in the current study highlighted new dimensions of recovery capital. While insight may be implied in the existing model (173) in the current study it was an explicit function of patients' success, lending support to theory that recovery capital is an evolving concept (154).

8 CHAPTER 8: NEUROIMAGING STUDY

8.1 INTRODUCTION

This chapter presents the findings of the neuroimaging study. The chapter is divided into two sections. The first section presents neuroimaging results and examines these in relation to duration of use. The second section examines the neuroimaging results in relation to abstinence and a range of clinical outcome measures.

8.1.1 TYPICAL WHITE MATTER DEVELOPMENT

Diffusion MRI studies have established that the organisation of white matter microstructure, commonly referred to as structural connectivity, changes across the lifespan (186-194). These studies have consistently demonstrated that Fractional Anisotropy (FA) increases during childhood into adolescence and plateaus in adulthood. It appears that the trajectory of white matter development is tract-specific whereby white matter tracts reach peak FA values at different ages. Moreover, it is noteworthy that this crucial period of development coincides with the most vulnerable time for initiation of drug use(195). As white matter microstructural development has been shown to differ across ages, between genders (187, 192-194) and maybe affected by certain vulnerabilities (195) it is therefore important to consider gender, age and development when interpreting results from these studies.

8.1.2 LIMITATIONS OF PREVIOUS STUDIES EXAMINING WHITE MATTER DAMAGE IN ODP

As previously suggested, a number of (DTI) studies have compared heroin dependent patients with normal controls. However, apart from the establishment of significant differences between ODP and healthy controls several inconsistencies exist (110). This may

be at least in part due to methodological choices (see chapter 2, p32 for review of literature).

A small body of evidence exists linking duration of drug use with severity of damage in ODP (110, 117, 118). A single recent study by Qiu and colleagues employed Tract-based spatial statistics to examine the relationship between the duration of heroin use and extent and severity of WM disruption. The authors stratified their patient groups into those whose duration of dependence was (i) less than 10 years and (ii) greater than 10 years, revealing significant WM alterations in both groups, with the most profound and extensive microstructural disruptions occurring in the latter cohort. The authors found the extent and severity of WM damage was associated with length of heroin dependence. While this paper was quite methodically sophisticated, the authors' approach to duration of use was quite basic, in that they looked at duration as either less than 10 years or greater than 10 years. Moreover, there is a paucity of research examining white matter integrity in opioid dependent patients (73). The candidate has carried out a literature search and found no studies examining the association of treatment outcome in opioid dependent patients, using DTI.

8.2 STUDY DESIGN

The Structural MRI is a nested study examining white matter damage in opioid dependent patients post detoxification. The study employed DTI to examine white matter damage. DTI is a technique which is sensitive to the diffusion of water molecules and provides measures of white matter microstructure. Decay or disruption of the microstructural organisation in WM is coupled with changes in quantifiable DTI parameters (115). These parameters provide three kinds of information; (i) apparent diffusion constant (i.e. magnitude of

diffusion), (ii) anisotropy of diffusion (i.e. microstructural organisation) and (iii) the primary orientation (116).

The DTI study design was intended to achieve objectives 6, 7 & 8 of the PhD research, namely:

a. To assess the association between white matter impairment and duration of dependence.

b. To explore in some detail the occurrence and development of this impairment in three distinct groups spanning three decades of opioid use.

c. To examine this impairment in relation to patient outcomes.

8.3 METHODOLOGY

8.3.1 EXPERT REVIEW AND CONSULTATION

The candidate and her supervisor enlisted the help of an MRI imaging expert, Professor Thomas Frodl, at Trinity College Institute of Neuroscience, to develop the MRI aspect of the study. Prof. Frodl agreed to become the MRI advisor for the candidate.

8.3.2 PILOTING OF MRI METHODS

As a paradigm that had been previously used by Prof. Frodl's group we had a single subject test run, which was sufficient. No changes were made following this test run.

8.3.3 STUDY SAMPLE

A convenience sample of 60 patients, across each of the three pathways (inpatient, outpatient, no formal aftercare) was selected to participate in the MRI scan, in the week leading up to discharge from one of three inpatient detoxification facilities.. The scanning arm of the study began in April 2013 seven months into the data collection of the larger cohort study and finished in November 2013, allowing for piloting and finalizing of the scanning protocol.

All the 60 patients were recruited from the larger longitudinal sample of 143 patients who had successfully completed detoxification from opioids in the week preceding the scan. Daily urine analysis was taken by the DDU and all patients tested negative for all drugs immediately prior to scanning. Upon commencement of the detoxification programme patients had been screened using the Structured Clinical Interview (SCID-IV) for the Diagnostic Statistical Manual of Mental Disorders (33), Fourth Edition (DSM-5) to confirm the diagnosis of opioid dependence according to the criteria set forth in the DSM-5. In addition, each patient tested positive for methadone or opiates before commencing the detoxification programme.

Additional exclusion criteria for scanning patients: neurological illness, pregnancy, active psychosis or prior significant head trauma. Moreover, patients were also excluded when they met MRI exclusion criteria. The majority of patients (n=48) were on a methadone maintenance programme and generally stable prior to detoxification. The candidate met with each of the MRI patients at least three times prior to scan. The purpose was to ensure consent was informed as well as taking them through a brief in scanner training (this

consisted of a short slide show on what to expect). The candidate was also present for all 60 scans to greet and debrief patients as they entered and exited the scanner.

8.3.4 MAGNETIC RESONANCE IMAGES

Magnetic resonance images were obtained with a Philips Achieva MRI scanner (Philips Medical System, Netherland B.V., Veenphuis 4-6, 5684 PC Best, The Netherlands) operating at 3 Tesla.

8.3.4.1 STRUCTURAL MRI ACQUISITION

A sagittal T1 three dimensional TFE (turbo field echo) was used to scan all participants (TR/TE: 8.5/3.9 msec; total acquisition time of 7 minutes; field of view (FOV) of FH (foot to head): 256 mm, AP (anterior to posterior): 256 mm, RL (right to left): 160 mm; and a matrix of 256×256). Voxel size was 0.9x0.9x0.9 mm.

8.3.4.2 DIFFUSION TENSOR IMAGING

A series of high angular resolution diffusion tensor images were acquired on a 3 Tesla Philips Achieva scanner at the Centre for Advanced Medical Imaging (CAMI), Dublin, Ireland. DTI data were recorded in 61 noncollinear directions (field of view 200 ´ 257 ´ 126 mm, 60 slices, no gap, spatial resolution 1.8 ´,´ 2.1 mm, repetition time 12561 ms, echo time 59 ms, flip angle 90°, half k-space acquisition [half scan factor = 0.68], sensitivity encoding parallel imaging factor 2.5, b-values 0, 1200 s/mm^2, with spectral presaturation inversion recovery fat suppression and dynamic stabilization in an image acquisition time of 15 min, 42 s).

8.4 DATA ANALYSIS

8.4.1 DIFFUSION MRI DATA PRE-PROCESSING

Data were converted from a Philips PAR/REC format to NifTI and B-matrix text-file formats using ExploreDTI. Thereafter, data were transferred to an ExploreDTI file and transferred to a voxel size of 2x2x2mm. With our acquisition voxel size, there is no significant partial volume effect associated with this technique. Diffusion tensor estimation was linear.

Preprocessing of diffusion data was completed using ExploreDTI software v4.8.3 (http://www.ExploreDTI.com) (196). Firstly, raw diffusion MRI files were converted to matlab files. During this conversion, the tensor model was applied to the data using the robust estimation of tensors by the outlier rejection (RESTORE) method, which acts to improve tensor estimation by correcting for image distortions including subject motion, cardiac pulsation and fat suppression (197). Each dataset was visually inspected to ensure orientation of gradient components was maintained during the conversion. Data quality checks were then performed. Diffusion weighted images (DWI) were looped and visually inspected in addition to eye-balling of residual and outlier profiles to assess the presence of gross artifacts. Subject motion and eddy current induced geometric distortions are the most frequently detected artifacts in diffusion weighted data (198) and, more recently, the issue of echo-planar imaging (EPI) geometric and intensity distortion for DTI tractography has also been highlighted (199). Each of these distortions was corrected for in one interpolation step to minimise blurring effects. B-matrix reorientation was also performed within this single step to adjust for any rotational differences that may occur during data correction (200).

Bach et al. (2014) reported general methodological considerations for TBSS (201), which are not currently incorporated into the standard processing pipeline used in the current study. This paper indicated that the standard approach is susceptible to anatomical inaccuracies and bias during the skeleton projection step and noise-dependent FA skeleton irregularities, which may affect the reliability of TBSS results. Other research illustrated that the statistical sensitivity of the FA skeleton is not optimal (202) and may be underpowered to detect significant between-group differences with small samples and/or subtle effects (203).

Moreover, motion correction was applied to all data to adjust for movement during scanning using a cubic interpolation and restore function with the lowest speed but highest accuracy. ExploreDTI also allowed us to look at the residuals and the outlier profiles, which on inspection were acceptable. Finally the motion correction parameters were checked. Movement during scanning was less than 2 mm in any direction and less than 3° rotation in sagittal, coronal or axial planes for all participants.

8.4.2 TRACT-BASED SPATIAL STATISTICS (TBSS)

Tract-based spatial statistics (TBSS; http://www.fmrib.ox.ac.uk/fsl/tbss/) is a method that was developed to correct for previous voxel-based white matter issues with registration, smoothing and partial volume effects, which may have flawed results (204). TBSS performs automated analysis of white matter structure using non-linear registration (205) and projection of individual subject FA data onto a common FA (fractional anisotropy) skeleton (117) thus eliminating any variation within voxels at the extremities of the white matter.

In their review of Diffusion Tensor Imaging Alexander et al. give an excellent overview of cellular pathology (206). The authors suggest diffusion of water in biological tissues occurs

inside, outside, around, and through cellular structures. Water diffusion is predominantly produced by random thermal oscillations. This is further moderated by the communications *with cellular membranes, and subcellular and organelles*. Cellular membranes hamper the diffusion of water, triggering water to take more circuitous pathways, thereby lessening the mean squared displacement. The diffusion pathway and matching diffusivity may expand by either *cellular swelling* or enlarged *cellular density*. Equally, necrosis, the outcome of an interruption to cellular membranes, reduces tortuosity and increases the apparent diffusivity. Intracellular water inclines to be more limited, rather than hampered by cellular membranes. Limited diffusion also reduces the apparent diffusivity, but levels off with increasing diffusion time. Together the hampered and limited diffusion reduces the evident diffusivity of water. In fibrous tissues such as white matter, water diffusion is relatively unhampered in the direction parallel to the fiber orientation. Equally, water diffusion is extremely limited and hampered in the directions perpendicular to the fibers. Consequently, the diffusion in fibrous tissues is anisotropic. Many age-related and pathological processes effect the microstructural organization and architecture of the affected tissues.

The diffusion of water within the tissues will be altered by changes in the tissue microstructure and composition; thus, diffusion-weighted MRI methods including DTI are potentially powerful probes for characterizing the effects of such microstructural change. The uses of DTI imaging is quickly growing since the method is extremely sensitive to changes at the cellular and microstructural level (206). Different DTI measures such as anisotropy (fractional anisotropy-FA) and diffusivity (mean diffusivity- MD; radial diffusivity-RD and axial diffusivity- AD) can be obtained, all of these are sensitive to different aspects of white matter impairment, including composition (myelination) (FA, RD), axonal

density/diameter (FA), axonal damage or loss (AD) (207). However, several age-related (208), genetic (207) and gender related hormonal factors (208) may contribute to the integrity of white mater.

Four diffusion metrics are typically evaluated using TBSS: fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD).

FA is a summary measure of microstructural integrity. While FA is extremely sensitive to microstructural changes, it is not precise as to the nature of this change. Thus it is advisable that additional DTI measures are included in the analysis (209) . Axial diffusivity (AD) and radial diffusivity (RD) provide more direct measures of the microstructural dimensions. AD tends to be variable in WM changes and pathology. In axonal injury AD decreases. The AD of WM tracts have been reported to increase with brain maturation, whereas imitations in RD are understood to be primarily caused by axonal and myelin membranes making RD potentially sensitive to myelination (210). Changes in the axonal diameters or density may also influence RD (209). MD is an inverse measure of the membrane density and is very similar for both GM and WM. MD is sensitive to cellularity edema, and necrosis (209). Mean diffusivity in both grey and white matter decreases with age because increasing structure within cells impedes water diffusion (211). In addition, some brain regions may be more vulnerable to myelin damage whereas others may be more susceptible to axonal injury or dendritic arborisation, all of which must be considered when interpreting DTI findings.

Several studies have illustrated the sensitivity of this analytic approach for detecting white matter abnormalities in clinical populations (212), attention deficit/hyperactivity disorder (213) and depression (214, 215) as well as opioid dependence (110).

Fractional anisotropy data were extracted from pre-processed images in ExploreDTI and converted to NifTI format before exporting to FMRIB Statistical Library (FSL). In the first phase of TBSS, all data were projected onto a mean FA tract skeleton. Voxel-wise statistics were then applied to this image. First, all FA data were aligned to a common 1x1x1mm space using nonlinear registration. Every FA image was aligned to every other one to identify the most representative subject in the dataset. This subject was then used as the target image. This image was affine-aligned into MNI152 standard space and then every image was transformed into 2x2x2mm MNI152 space by the combination of the nonlinear transform to the target FA image with the affine transform from that target to MNI space. The standard-space version of each subject's FA image was merged into a single 4D image. The mean of all FA images was created and fed into a script that produced the mean FA tract skeleton. Each subject's FA data were subsequently projected onto this skeleton and the FA skeleton was threshold at 0.2. This image was then fed into a voxel-wise cross-subject statistical computation.

Statistical analysis was carried out using FSL's 'RANDOMISE' algorithm. This is a stringent, parametric comparison incorporating a robust cluster-based thresholding option known as Threshold-Free Cluster Enhancement (TFCE). TFCE was selected using 5000 permutations per test. Threshold-free cluster enhancement produced an output image from a raw statistical image. The voxel wise values in this output image represented the amount of cluster-like local spatial support (216). Each TFCE score of each voxel was given by the sum of the scores of all supporting sections. This enhanced cluster-like structures in an image without having to initially define an arbitrary cluster-forming threshold and without a large

amount of data smoothing (216). These steps were repeated for mean diffusivity, radial diffusivity and axial diffusivity diffusion metrics to explore further specific changes in white matter organisation.

The statistical threshold was set at $p<0.05$, fully corrected for multiple comparisons using TFCE across the whole brain to find differences between ODP patients groups. Diffusion metric values were then extracted from significant clusters for further graphic representation, and areas of significant differences were identified using the following FSL tools: the Harvard-Oxford Structural Atlas, the Johns Hopkins University Atlas, Johns Hopkins University White matter tractography Juelich Atlas atlases (www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html#wm).

To localize WM microstructure differences in the skeletonized FA maps between the three groups, voxel-wise based analysis of covariance (MANCOVA) with a standard general linear model design was used for each diffusion metric. A statistical significance level of $p<0.05$ was set (family wise error (FWE) corrected) and adjusted for age and gender.

8.5 RESULTS

Sixty patients were recruited into the study; however, following pre-processing two patients were lost due to excessive head motion greater than 2mm (see section 7.4.1). Thus, fifty-eight opioid dependent patients, 20 females and 38 males, were included in the analysis. The mean age was 35 years (with a range of 20 years to 52 years). Patients were placed, according to duration of opioid use, into one of three groups; less than 10 years' use (n=18) Group 1, 10-15 years' use (n=26) Group 2 and 16-25 years' use (n=14) Group 3. In addition to a completed scan all patients in the MRI study also completed a battery of clinical

instruments as part of the larger longitudinal study (details of these measures can be found in Chapter 5).

In the 58 patients only 49 had a history of intravenous drug use, spread across all three groups. As previously mentioned the majority of patients (n=48) were on a methadone maintenance programme prior to detoxification. There was no significant difference in average daily dose across the three groups (X^2=174.000, DF 177, p >0.42). In addition, no significant difference existed in average reported history of average daily heroin consumption (high, medium or low) between groups (X^2=232.000, DF 228 p >0.41). Table 22: Patient demographics and clinical factors across three groups

TABLE 22: DEMOGRAPHICS OF MRI SAMPLE

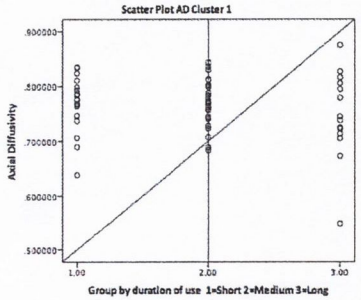
	Group 1 n=18 (less than 10 years)			Group 2 n=26 (10-15 years)			Group 3 n=14		
Treatment Pathway	IP	OP	NFA	IP	OP	NFA	IP	OP	NFA
	15	1	2	20	5	1	12	2	-
Gender	M (10)/ F (8)			M (18)/ F (8)			M (10)/ F (4)		
Mean Age	28 Yrs. (SD=3.46)			37 Yrs. (SD=3.24)			42 Yrs. (SD=3.81)		
Mean Yrs. Use	7 Yrs. (SD=4.23)			15 Yrs. (SD=5.51)			20 Yrs. (SD=5.79)		
No. of Patients Previously Receiving Methadone	13			23			12		
Benzodiazepine User	Y (12)/N (6)			Y (12)/No (14)			Y (8)/N (6)		
Mean Age First Used Alcohol	12 Yrs. (SD=1.29)			13 Yrs. (SD=1.46)			12 Yrs. (SD=1.72)		
Intravenous users (IV)	14			22			13		

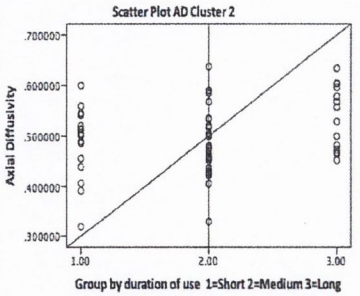
IP = Inpatient, OP = Outpatient and NFA = No formal aftercare.

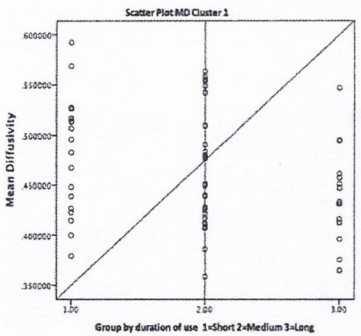
8.5.1 ANALYSIS DIFFUSION METRICS

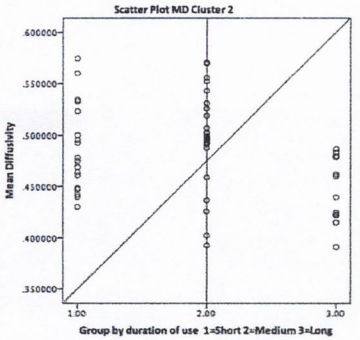
There were significant differences in the white matter diffusion metrics AD, MD and RD. Below table 23 uses scatter plots to illustrate this data across the three groups. TBSS revealed significantly greater RD, MD and AD in group 3 (long-term users) relative to group 1 (short-term users) differences (see Tables 24, 25 and 26 for relevant statistics). TBSS also revealed a reduction in FA approaching statistical significance in group 3. However, this did not survive correction for multiple comparisons. The cluster tool in FSL was used to extract the cluster mean (217), of brain regions that were significant.

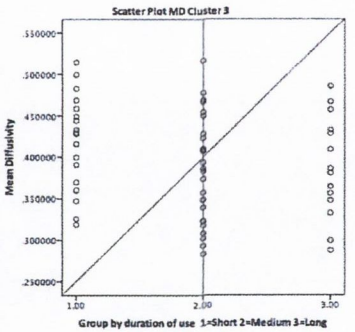
Table 23: Scatter plots of significant clusters across DTI metrics

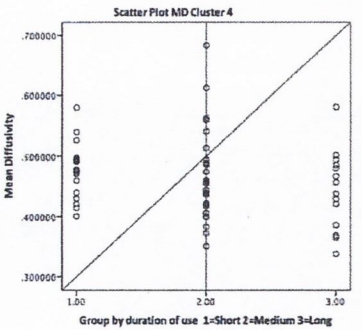


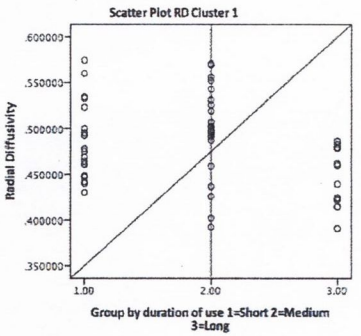


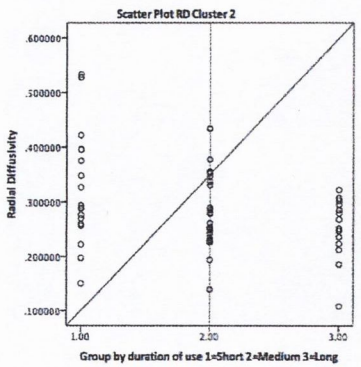


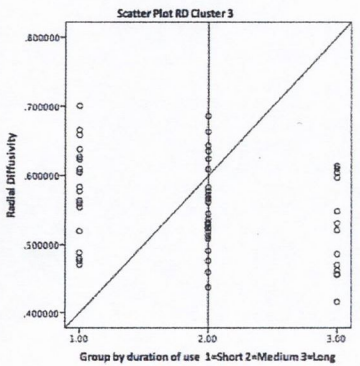


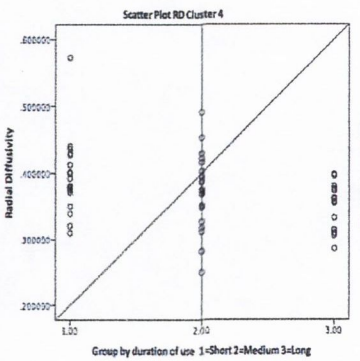












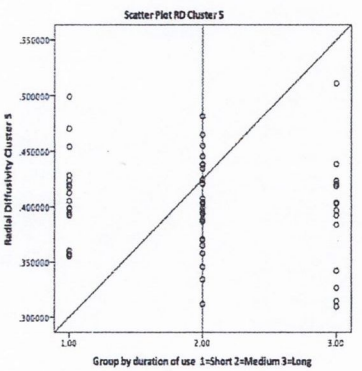


FIGURE 4 ILLUSTRATES SIGNIFICANT DIFFERENCE IN AD BETWEEN GROUPS

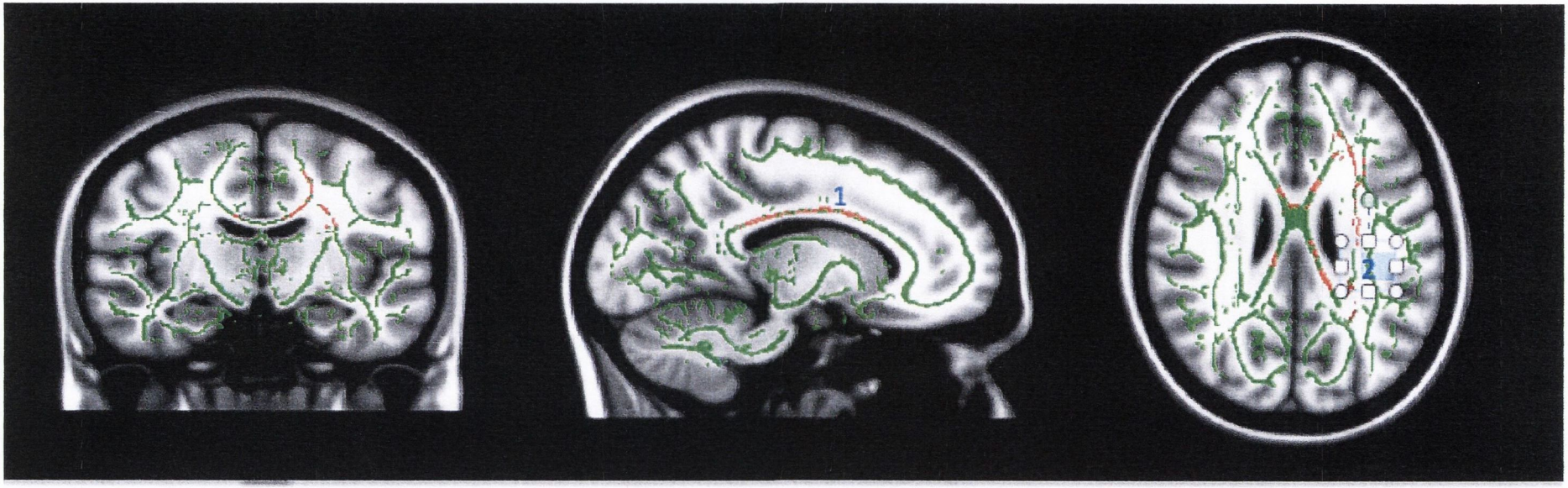


Figure 4 above illustrates the significant difference in AD when comparing short-term to long-term groups. Increased AD in the long-term group is shown in red. Images are displayed in radiological convention (left is right). All data is corrected for multiple comparisons, $p < 0.05$.

Table 24: illustrates the regions as well as major fibres of the main clusters with significant difference in AD between groups.

TABLE 24: *DTI METRIC 1 (AD) DIFFERENCES BETWEEN GROUPS*

Cluster Index	Voxels	P value	MNI Co-ordinates			Major fibre tracts		
			MAX X	MAX Y	MAX Z	JHU Atlas ICBM-DTI	JHU White matter tractography	Juelich Atlas
1	3140	0.04	79	113	102	Body of corpus callosum	3% Superior longitudinal fasciculus (temporal part) R, 3% Superior longitudinal fasciculus R	94% WM Callosal body, 18% WM Cingulum R
2	202	0.05	115	87	98	Posterior corona radiata L	16% Anterior thalamic radiation L	65% WM Callosal body

*P-value indicates cluster mean Montreal Neurological Institute (MNI), JHU= Johns Hopkins University WM=white matter
Z, Y, X = Peak

Figure 5 illustrates major fibres of the main clusters with significant difference in MD between groups

FIGURE 5 ILLUSTRATES SIGNIFICANT DIFFERENCES IN MD BETWEEN GROUPS

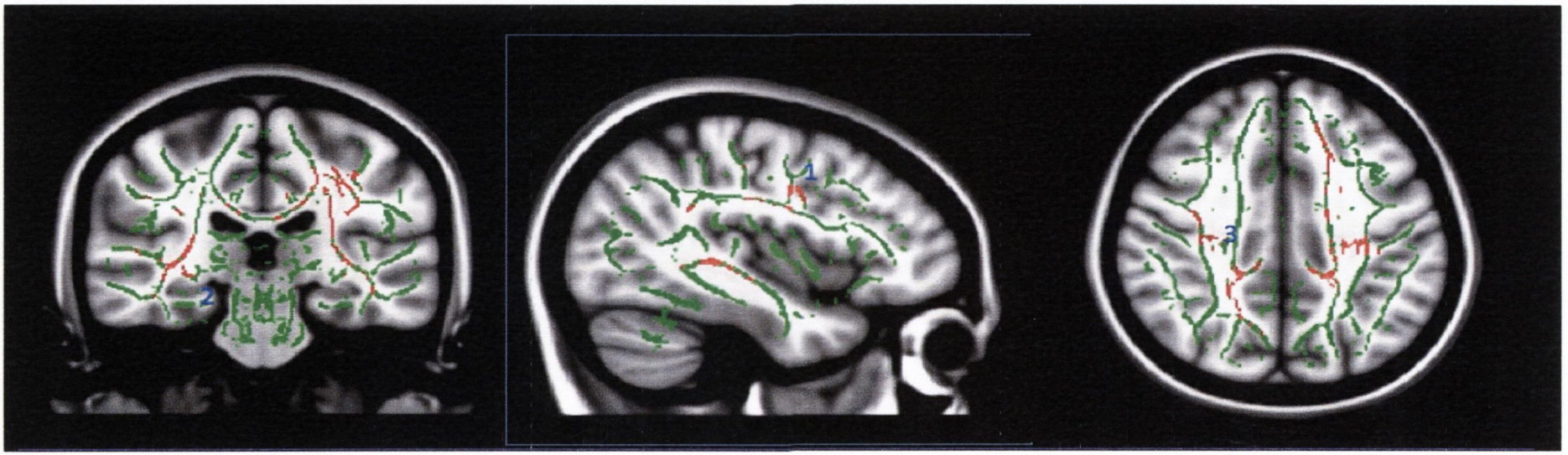


Figure 5 above illustrates the significant difference in MD when comparing short-term to long-term groups. Increased MD in the long-term group is shown above in red. Images are displayed in radiological convention (left is right). All data is corrected for multiple comparisons, $p < 0.05$. Table 25: illustrates the regions as well as major fibres of the main clusters with significant difference in MD between groups.

TABLE 25: DTI METRIC 1 (MD) DIFFERENCES BETWEEN GROUPS

Cluster Index	Voxels	P value	MNI Co-ordinates (mm)			JHU Atlas ICBM-DTI	Major fibre tracts	
			MAX X	MAX Y	MAX Z		JHU White matter tractography	Juelich Atlas
1	7427	0.04	130	125	104	Unclassified	3% Superior longitudinal fasciculus L	11% WM Corticospinal tract L
2	5081	0.04	58	99	69	Unclassified	No label	46% WM Optic radiation R,
3	360	0.04	62	106	110	Unclassified	24% Superior longitudinal fasciculus R, 5% Corticospinal tract R, 3% Superior longitudinal fasciculus (temporal part) R	80% WM Corticospinal tract R, 16% 14% WM Superior longitudinal fascicle R

*P-value indicates cluster mean Montreal Neurological Institute (MNI), JHU= Johns Hopkins University WM=white matter
Z, Y, X = Peak

FIGURE 6 ILLUSTRATES SIGNIFICANT DIFFERENCE IN RD BETWEEN GROUPS

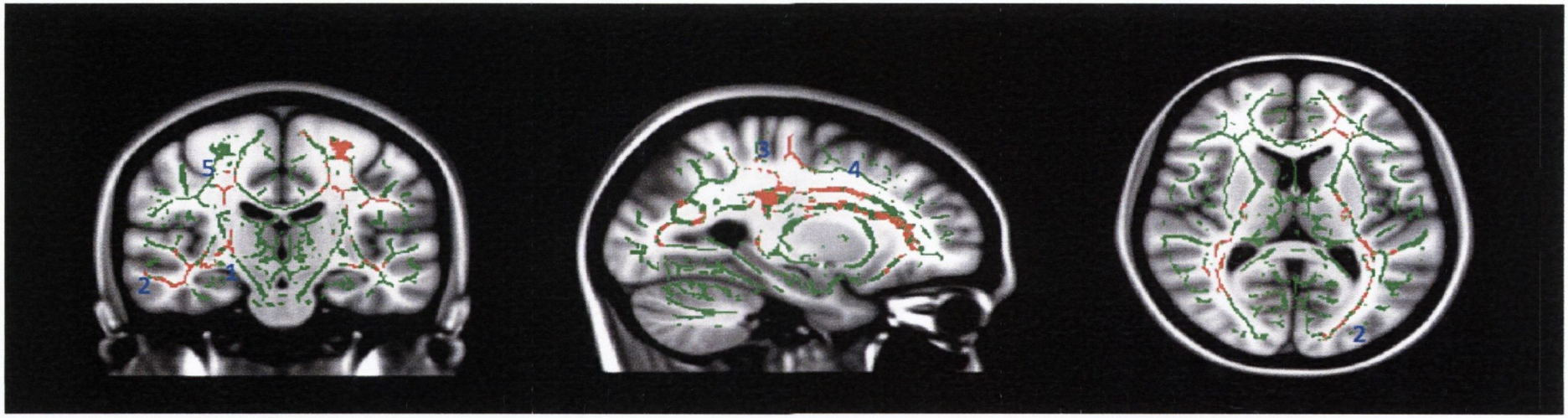


Figure 6 above illustrates the significant difference in RD when comparing short-term to long-term groups. Increased RD in the long-term group is shown in red. Images are displayed in radiological convention (left is right). All data is corrected for multiple comparisons, $p < 0.05$.

Table 26: illustrates the regions as well as major fibres of the main clusters with significant difference in RD between groups.

TABLE26: DTI METRIC 1 (RD) DIFFERENCES BETWEEN GROUPS

Cluster Index	Voxels	P value*	MNI Co-ordinates(mm) MAX X	MAX Y	MAX Z	JHU Atlas ICBM-DTI	Major fibre tracts JHU White matter tractography	Juelich Atlas
1	14486	0.04	58	99	69	Unclassified	No label given	46% WM Optic radiation R, 4% 3% WM Fornix
2	153	0.05	99	44	71	Unclassified	3% Inferior longitudinal fasciculus L	3% Inferior longitudinal fasciculus L
3	111	0.04	70	90	126	Unclassified	8% Corticospinal tract R	9% WM Corticospinal tract R
4	51	0.04	65	140	106	Unclassified	No Labe given	Unclassified
5	43	0.05	63	119	103	Unclassified	Superior corona radiata R	50% WM Corticospinal tract R

*P-value indicates cluster mean Montreal Neurological Institute (MNI), JHU= Johns Hopkins University WM=white matter

Z, Y, X MAX = the value of the maximum "intensity" within the cluster.

8.6 BRIAN REGIONS WITH SIGNIFICANT INCREASE IN DTI METRICS AND THERE IMPLICATIONS

8.6.1 CORPUS CALLOSUM (CC)

The CC is a wide bundle of neural fibers beneath the cortex in the brain at the longitudinal fissure, connecting the left and right cerebral hemispheres. The genu of the CC links frontal regions bilaterally, the body of the CC structurally connects bilateral parietal regions and the splenium of the CC provides interhemispheric connections between posterior parietal and occipital regions. The CC provides the main route of communication between the two hemispheres of the brain and facilitates inter-hemispheric communication. Abnormalities in white matter integrity, particularly in CC, may affect inter-hemispheric resting state functional connectivity (RSFC) (218), which is fundamental to integrative attention processing and cognitive control. In this study, white matter disruption was demonstrated bilaterally in the genu, body and splenium of the corpus callosum.

8.6.2 CORTICOSPINAL TRACT

The corticospinal tract conducts impulses from the brain to the spinal cord. It is made up of a lateral and anterior tract. The majority of fibres of the corticospinal tract cross over in the medulla, resulting in muscles being controlled by the opposite side of the brain. The corticospinal tract is involved in voluntary movement.

8.6.3 SUPERIOR CORONA RADIATA R

The anterior and posterior corona radiata consist of projection fibers, which radiate out from the brain stem to the cerebral cortex via the anterior and posterior limb of the internal capsule respectively. The projection fiber system differentiates into two principal systems; ascending fibers from the thalamus to the cerebral cortex and descending fibers from the

fronto-parietal cortex to the subcortical nuclei including the basal ganglia and corticospinal tract (63) and is thought to facilitate perceptual, motor and higher cognitive functions (219).

8.6.4 OPTIC RADIATION R,

The optic radiation (posterior thalamic radiation) are axons from the neurons in the lateral geniculate nucleus to the primary visual cortex. The optic radiation receives blood through deep branches of the middle cerebral artery and posterior cerebral artery. They carry visual information through two divisions (called Upper and Lower division) to the visual cortex (also called *striate cortex*) along the calcarine fissure.

8.6.5 SUPERIOR LONGITUDINAL FASCICULUS

The superior longitudinal fasciculus (SLF) is a long-range association white matter tract, which connects parietal, frontal and temporal regions (220). The SLF is thought to play an important role in language processing (221-225), spatial working memory (226, 227), attention orienting (228), and cognitive control (229, 230). In the current study, a posterior region of the SLF within the parietal lobule showed abnormal microstructural organisation characterised by increased AD, MD and RD.

8.6.6 FORCEPS

The forceps minor connects the lateral and medial frontal regions across the midline via the genu of the corpus callosum. The forceps major appears to play an important role in visual perception, processing visuospatial information, memory and topographical orientation (231).

8.6.7 LEFT INFERIOR LONGITUDINAL FASCICULUS

The inferior longitudinal fasciculus (ILF) is a major ventral fiber tract that projects from the visual association cortex through the inferior temporal lobe to the anterior temporal pole. Short fibers of the ILF connect visual areas to subcortical structures, the hippocampus and the amygdala.

8.6.8 LEFT SUPERIOR LONGITUDINAL FASCICULUS (SLF)

The SLF has been linked with expressive language areas. The latter is located in the pars opercularis (Broca's area) of the left inferior frontal gyrus. The findings of the current study are inkeeping with Qui and collegaues, who examined white matter integrity in opiate dependence patients (110).

8.6.9 THE CINGULUM

The cingulum is a long medial association fiber within the cingulate gyrus that extends along its length from the orbitofrontal cortex into the parahippocampal gyrus and is defined dorsally by the corpus callosum projecting into the temporal lobe along the ventral/medial wall of the hippocampal gyri. The cingulum is part of the limbic system that is involved in attention, memory and emotional processing.

8.7 STATISTICAL ANALYSIS OF DTI METRICS WITH PATIENT ABSTINENCE

Permutation based methods were used to investigate between group differences in AD, RD and MD. Permutation approaches are used for inference or thresholding when the null distribution is unknown and are effective in controlling against false positives (232). "Randomise" is a permutation program in FSL which thresholds statistical images using a standard general linear model (GLM) design. Independent t-tests were run using *randomise*

to examine between group differences in the diffusion metrics. Age and intracranial volume were demeaned and included in the model. Statistical thresholding was applied using threshold-free cluster enhancement (TFCE) with 10000 permutations at $p < 0.05$, which is sensitive to spatially extensive areas of significance difference (216). A GLM was used to examine between group differences for patients that had relapse compared to those who were abstinent at follow up. The model controlled for age, gender, duration of use, time drug free, rehab length and detox completed. We did not include treatment path as some pathways in scanning data (no formal aftercare) had only 3 patients. No statistical difference was found between groups ($p > 0.05$).

8.8 CORRELATION ANALYSIS OF DTI METRICS WITH CLINICAL OUTCOME MEASURES

Partial correlations (covarying for age) were performed to investigate the relationship between clinical outcome measures (physical health, psychological well being and quality of life and hope for the future) and white matter microstructural differences in ODP. For diffusion measures showing significant between group differences, correlation analyses were carried out investigating relationships between these and clinical measures.

Correlations between DTI metrics showing significance and clinical outcomes were computed.

Table 27 below illustrates correlation between clusters with significant AD and clinical measures at baseline. No statistically significant correlations were found between baseline clinical measures and clusters with significant AD.

Table 27: Correlation of Axial Diffusivity and clinical measures at baseline

Brain Regions with Significant Clusters Axial diffusivity	Test Statistic	Total baseline Physical health	Total baseline Psychological health	Total baseline QOL	Total baseline CORE	Total baseline HOPE
Body of corpus callosum[1]	R	-.013	.003	.232	.127	.109
	p-value	.929	.986	.108	.386	.454
	df	47	47	47	47	47
Posterior corona radiata L[1]	R	.056	.032	-.041	.027	.097
	p-value	.702	.830	.778	.854	.509
	df	47	47	47	47	47

1 = Regions identified from the Johns Hopkins University Atlas ICBM-DTI (please note were multiple regions identified region with highest percentage assigned for this task table 24 offers full break-down of regions identified).

Table 28 below illustrates correlation between clusters with significant AD and clinical measures at 3 month follow up. No statistically significant correlations were found between clinical measures at 3-month follow up and clusters with significant AD.

Table 28: Correlation of Axial Diffusivity and clinical measures at T1

Brain Regions with Significant Clusters Axial diffusivity	Test Statistic	Total T1 Physical health	Total T1 Psychological health	Total T1 QOL	Total T1 CORE	Total T1 HOPE
Body of corpus callosum[1]	r	.163	-.099	-.172	.060	-.096
	p-value	.239	.477	.214	.669	.490
	df	52	52	52	52	52
Posterior corona radiata L[1]	r	.166	-.116	-.013	-.004	-.072
	p-value	.232	.403	.923	.977	.607
	df	52	52	52	52	52

Table 29 below illustrates correlation between clusters with significant AD and clinical measures at 6 month follow up. No statistically significant correlations were found between clinical measures at 6-month follow up and clusters with significant AD.

Table 29: Correlation of Axial Diffusivity and clinical measures at T2

Brain Regions with Significant Clusters Axial diffusivity	Test Statistic	Total T2 Physical health	Total T2 Psychological health	Total T2 QOL	Total T2 CORE	Total T2 HOPE
Body of corpus callosum[1]	r	.077	-.119	-.200	.164	-.210
	p-value	.589	.401	.155	.245	.136
	df	50	50	50	50	50
Posterior corona radiata L[1]	r	.179	-.073	.063	.303	-.073
	p-value	.205	.607	.659	.029	.608
	df	50	50	50	50	50

Table 30 below illustrates correlation between clusters with significant AD and clinical measures at 9 month follow up. No statistically significant correlations were found between clinical measures and cluster 1. However, a significant correlation was found between clinical measures at 9 month follow up and cluster 2 with significant AD in the posterior corona radiata (L).

Table 30: Correlation of Axial Diffusivity and clinical measures at T3

Brain Regions with Significant Clusters Axial diffusivity	Test Statistic	Total T3 Physical health	Total T3 Psychological health	Total T3 QOL	Total T3 CORE	Total T3 HOPE
Body of corpus callosum[1]	R	.144	-.141	.037	-.070	.069
	p-value	.325	.335	.801	.630	.637
	df	47	47	47	47	47
Posterior corona radiata L[1]	R	-.017	.267	.027	.189	-.291
	p-value	.908	.064	.853	.194	.042
	df	47	47	47	47	47

Table 31 below illustrates correlation between clusters with significant MD and clinical measures at baseline. No statistically significant correlations were found between baseline clinical measures and clusters with significant MD.

Table 31: Correlation of Mean Diffusivity and clinical measures at baseline

Brain Regions with Significant Clusters Mean diffusivity	Test Statistic	Total baseline Physical health	Total baseline Psychological health	Total baseline QOL	Total baseline CORE	Total baseline HOPE
Superior longitudinal fasciculus L[1]	R	.052	-.253	.209	-.131	.126
	p-value	.723	.079	.149	.370	.388
	df	47	47	47	47	47
No label	R	.190	-.096	-.023	.178	-.050
	p-value	.192	.512	.877	.221	.733
	df	47	47	47	47	47
Superior longitudinal fasciculus R, (temporal part) R[1]	R	200	.181	.035	-.096	-.050
	p-value	.167	.214	.812	.510	.734
	df	47	47	47	47	47

1= Regions identified from the Johns Hopkins University Atlas ICBM-DTI (please note were multiple regions identified region with highest percentage assigned for this task table 26 offers full break-down of regions identified).

Table 32 below illustrates correlation between clusters with significant MD and clinical measures at 6 month follow up. No statistically significant correlations were found between clinical measures at

3-month follow up and clusters with significant MD.

Table 32: Correlation of Mean Diffusivity and clinical measures at 3-month follow-up

Brain Regions with Significant Clusters Mean diffusivity	Test Statistic	Total T1 Physical health	Total T1 Psychological health	Total T1 QOL	Total T1 CORE	Total T1 HOPE
Superior longitudinal fasciculus L[1]	r	.013	.058	-.044	-.120	-.240
	p-value	.925	.677	.751	.388	.081
	df	52	52	52	52	52
No label[1]	r	.070	.099	-.017	.242	-.214
	p-value	.615	.476	.902	.078	.120
	df	52	52	52	52	52
Superior longitudinal fasciculus R, (temporal part) R[1]	r	-.124	-.080	-.090	-.014	-.104
	p-value	.373	.564	.517	.921	.454
	df	52	52	52	52	52

Table 33 below illustrates correlation between clusters with significant MD and clinical measures at 6 month follow up. No statistically significant correlations were found between clinical measures at 6-month follow up and clusters with significant MD

Table 33: Correlation of Mean Diffusivity and clinical measures at 6-month follow-up

Brain Regions with Significant Clusters Mean diffusivity	Test Statistic	Total T2 Physical health	Total T2 Psychological health	Total T2 QOL	Total T2 CORE	Total T2 HOPE
Superior longitudinal fasciculus L[1]	r	-.109	-.106	-.085	.149	-.050
	p-value	.440	.456	.551	.292	.726
	df	50	50	50	50	50
No label[1]	r	.067	.075	-.139	.192	-.074
	p-value	.638	.598	.325	.172	.603
	df	50	50	50	50	50
Superior longitudinal fasciculus R, (temporal part) R[1]	r	.096	.052	-.081	-.057	-.183
	p-value	.499	.716	.567	.688	.193
	df	50	50	50	50	50

Table 34 below illustrates correlation between clusters with significant MD and clinical measures at 9 month follow up. No statistically significant correlations were found between clinical measures and cluster 1, or 2 however, significant negative correlations were found between clinical measures of Hope (p=0.05) and at 9 month follow up and clusters 3 with significant MD in the Superior longitudinal fasciculus R, and the corticospinal tract.

Table 34: Correlation of Mean Diffusivity and clinical measures at 9-month follow-up

Brain Regions with Significant Clusters Mean diffusivity	Test Statistic	Total T3 Physical health	Total T3 Psychological health	Total T3 QOL	Total T3 CORE	Total T3 HOPE
Superior longitudinal fasciculus L[1]	r	169	-.002	.104	-.206	.111
	p-value	.245	.987	.478	.155	.447
	df	47	47	47	47	47
No label[1]	r	-.045	.066	-.093	.176	-.152
	p-value	.759	.654	.524	.225	.296
	df	47	47	47	47	47
Superior longitudinal fasciculus R, (temporal part) R[1]	r	148	-.101	.092	-.168	.277
	p-value	.310	.492	.531	.249	.054
	df	47	47	47	47	47

Table 35 below illustrates correlation between clusters with significant RD and clinical measures at baseline. No statistically significant correlations were found between baseline clinical measures and clusters with significant RD.

Table 35: Correlation of Radial Diffusivity and clinical measures at baseline

Brain Regions with Significant Clusters Radial diffusivity	Test Statistic	Totalbaseline Physical health	Total baseline Psychological health	Total baseline QOL	Total baseline CORE	Total baseline HOPE
Corticospinal tract R[1]	r	-.023	-.082	.147	-.097	.058
	p-value	.874	.575	.313	.506	.694
	df	47	47	47	47	47
Unclassified[1]	r	.057	.143	-.130	-.010	-.098
	p-value	.696	.328	.374	.947	.502
	df	47	47	47	47	47
	r	.031	.138	.131	.085	-.161
Corticospinal tract R[1]	p-value	.835	.343	.368	.563	.269
	df	47	47	47	47	47

1= Regions identified from the Juelich Atlas (please note were multiple regions identified region with highest percentage assigned for this task table 27 offers full break-down of regions identified).

Table 36 below illustrates correlation between clusters with significant RD and clinical measures at 3 month follow up. No statistically significant correlations were found between clinical measures at 3-month follow up and clusters with significant RD.

Table 36: Correlation of Mean Diffusivity and clinical measures at 3-month follow-up

Brain Regions with Significant Clusters Radial diffusivity	Test Statistic	Total T1 Physical health	Total T1 Psychological health	Total T1 QOL	Total T1 CORE	Total T1 HOPE
	r	.070	.099	-.017	.242	-.214
	p-value	.615	.476	.902	.078	.120
Optic radiation R,[1]	df	52	52	52	52	52
Inferior longitudinal	r	.061	.174	.061	-.142	.027
fasciculus L	p-value	.660	.209	.662	.305	.847
	df	52	52	52	52	52
Corticospinal tract R[1]	r	-.006	-.169	.007	-.146	-.040
	p-value	.963	.222	.957	.293	.774
	df	52	52	52	52	52
Unclassified[1]	r	-.204	.034	.202	-.114	-.070
	p-value	.139	.806	.144	.413	.617
	df	52	52	52	52	52
	r	-.078	-.086	.021	-.031	-.109
	p-value	.575	.534	.882	.823	.432
Corticospinal tract R[1]	df	52	52	52	52	52

Table 37 below illustrates correlation between clusters with significant RD and clinical measures at 6 month follow up. No statistically significant correlations were found between clinical measures at 6-month follow up and clusters with significant RD

Table 37: Correlation of Radial Diffusivity and clinical measures at 6-month follow-up

Brain Regions with Significant Clusters Radial diffusivity	Test Statistic	Total T2 Physical health	Total T2 Psychological health	Total T2 QOL	Total T2 CORE	Total T2 HOPE
	r	.067	.075	-.139	.192	-.074
	p-value	.638	.598	.325	.172	.603
Optic radiation R,[1]	df	50	50	50	50	50
Inferior longitudinal	r	.163	.015	-.078	-.028	.163
fasciculus L	p-value	.248	.917	.584	.844	.248
	df	50	50	50	50	50
Corticospinal tract R[1]	r	-.010	-.062	-.013	.051	-.046
	p-value	.945	.660	.927	.718	.744
	df	50	50	50	50	50
Unclassified[1]	r	.057	.121	-.039	-.148	-.192
	p-value	.688	.392	.785	.294	.172
	df	50	50	50	50	50
	r	.031	-.103	.088	.062	-.112
	p-value	.828	.468	.536	.661	.430
Corticospinal tract R[1]	df	50	50	50	50	50

1= Regions identified from the Juelich Atlas (please note were multiple regions identified region with highest percentage assigned for this task table 27 offers full break-down of regions identified).

Table 38 below illustrates correlation between clusters with significant RD and clinical measures at baseline. No statistically significant correlations were found between baseline clinical measures and clusters with significant RD.

Table 38: Correlation of Mean Diffusivity and clinical measures at 9-month follow-up

Brain Regions with Significant Clusters Radial diffusivity	Test Statistic	Total T3 Physical health	Total T3 Psychological health	Total T3 QOL	Total T3 CORE	Total T3 HOPE
	r	-.045	.066	-.093	.176	-.152
	p-value	.759	.654	.524	.225	.296
Optic radiation R,[1]	df	47	47	47	47	47
Inferior longitudinal	r	.122	-.091	-.014	-.088	.145
fasciculus L	p-value	.404	.533	.924	.546	.319
	df	47	47	47	47	47
Corticospinal tract R[1]	r	-.050	-.009	-.059	-.026	.040
	p-value	.731	.951	.686	.861	.783
	df	47	47	47	47	47
Unclassified[1]	r	-.215	.035	.084	.080	.049
	p-value	.138	.814	.565	.586	.739
	df	47	47	47	47	47
	r	-.131	-.100	.228	-.100	.194
	p-value	.370	.496	.115	.494	.182
Corticospinal tract R[1]	df	47	47	47	47	47

1= Regions identified from the Juelich Atlas (please note were multiple regions identified region with highest percentage assigned for this task table 27 offers full break-down of regions identified).

8.9 DISCUSSION

The main aims of this study were (i) to assess the association between white matter impairment and duration of dependence, and (ii) to explore with some accuracy the occurrence of this impairment in three distinct groups spanning three decades of use. The findings suggest that the degree and severity of white matter impairment in ODP were associated with duration of use. The findings of our study support the findings of earlier studies (110, 118) suggesting that duration of opioid use is strongly associated with WM damage. However, the current study further shows that the longer the subjects were dependent on opioids, the more widespread and serious the white matter was disrupted (see table 24, 25 and 26). Age was used as a covariate in the analysis so that influences from age appear to be limited. An alternative hypothesis worth considering is that those with more severe white matter impairment show more severe drug dependency, a theory that has been supported with other substance using populations, such as alcohol (233), cocaine (234) and methamphetamine(235).

The change between connections in subcortical regions is pronounced in long-term users compared to short and medium term users (see table 24 cluster 2). The subcortical brain structures play a significant part in the regulation of a variety of cognitive and emotional processes. The basal ganglia and thalamus, along with the surrounding limbic structures, comprise MacLean's paleomammalian brain (236) a region that seeks to integrate an individual's desire to approach or avoid environmental stimuli. More recently the paleomammalian brain has been implicated in certain tasks, such as 'action selection' the task of choosing "what to do next". The consequence of changes in the subcortical region

has serious repercussions for opioid dependent patients, as the struggle for recovery is for the most part a struggle to regulate cognitive and emotional functions.

Areas of the neocortex were implicated in the current study. The neocortex is involved in higher functions such as: sensory perception, motor commands, spatial reasoning, conscious thought and language (237). While all of these functions are key to daily life, both language and conscious thought are crucial functions when attempting to rehabilitate a patient. It is these function we rely upon to ensure that the patient can adapt and apply the skills imparted on them during treatment.

The findings on longer-term use indicate that longer exposure to opioids is associated with more cortical (see table 24, 25 and 26) as well as subcortical connectivity (see table 24) alterations in white matter integrity. Patients with longer exposure to opioids showed reduced white matter in the superior longitudinal fasciculi and the Inferior fronto-occipital fasciculus, suggesting that prolonged use is associated with structural pathophysiology in white matter (110).

Moreover, the findings also support earlier findings of white matter changes in the Corpus Callosum (CC) in substance users, and that these changes, particularly in the prefrontal white matter and genu of the CC, are negatively correlated with duration of use (118, 238). Two previous studies by Lui and colleagues (118) and Bora and colleagues (108) with short-term opioid users, i.e. patients with less than 10 years (5.6 years and 8.9 years respectfully) found significant differences in opioid users when compared to healthy controls. Moreover, the development of damage in the current study appears to be relatively rapid, when

comparing patients in group 1 with group 3. Less than a decade later patients appear to show severe diminishment of white matter when compared to short-term group.

The treatment of opioid dependence is important in reducing its significant health and social consequences and in improving the well-being and social functioning of people affected (239). Unlike other substances, globally the primary treatment option for opioid dependency is an opioid substitute (240). Moreover, in Ireland patients tend to remain on long term methadone maintenance (241) with less than 5 percent attempting detoxification annually. Our findings have policy and treatment implications, which need to be followed up with longer-term studies; most notably the implication of continued treatment of opioid dependence with an opioid substitute, a substitute that may contribute to the damage in areas of the such as the subcortical brain structures, which as previously suggested plays a significant part in the regulation of higher cognitive functions that are vital for long-term recovery. However, this is a double-edged sword as detoxification, while it may seem an obvious course of treatment for patients with less exposure to opioids, may not be a suitable solution for patients who have been treated for several decades with opioids.

8.10 STRENGTHS OF THIS STUDY

This is the first study to identify with some precision development of WM impairment in opioid dependent patient groups spanning three decades. It is the first study to use diffusor tensor imaging measures to examine outcomes in opioid dependent patients post-detoxification.

8.11 LIMITATIONS OF THIS STUDY:

Limitations of the current study include the lack of post-treatment DTI measures to examine the extent to which WM integrity changes during abstinence from opioids, and moreover, the omission of how DTI measures may change during the course of a specific treatment pathway. Future studies should measure WM integrity repeatedly, and examine the relationship between DTI measures and treatment outcomes for specific treatment pathways for opioid dependence post-detoxification.

A discernible limitation of the study design of the present study is in its inability to resolve conclusively the pre-existing versus acquired nature of the observed alterations. Conclusive resolution of this issue may require prospective and/or twin studies. Such study designs afford the possibility to track a cohort over time, for example a group of patients as they enter and progress on a MMT programme to quantify and pinpoint the development and progression of this impairment across the treatment journey. The observed changes in the current study were significantly correlated with the duration of opioid dependence while there was a significant correlation between functional connectivity and structural changes. Although such correlation does not prove direct causality, it is compatible with a causal model in which the use of opioids causes cumulative anatomical changes. Moreover, the multiple comparisons of the clinical correlation data and the risk for false positives that this poses must be considered. This risk is particularly heighted in the analysis of high-dimensional data and more especially medical imaging data (242).

8.12 CONCLUSIONS

Long-term opioid dependent patients in this study showed significant WM impairment when compared to short or medium-term users. This is the first study to identify with some precision development of WM impairment in opioid dependent patient groups spanning three decades. Moreover, the potential to identify a period of use without consequential damage to the brain offers great promise for treatment and detoxification.

9 CHAPTER 9: INTEGRATED DISCUSSION OF FINDINGS FROM THREE STUDY DESIGNS

9.1.1 INTRODUCTION

This PhD research investigated predictors of outcome in opioid dependent patients post-detoxification. The overall aim of the dissertation was to examine comprehensively rehabilitation pathways' effects on opioid dependency post-detoxification.

To the PhD candidate's knowledge, it is the first time that these three robust mixed methods were applied to examine outcomes in opioid dependent patients post-detoxification.

9.1.2 OVERALL DISCUSSION OF FINDINGS

At a global level the DTI study contributed to the current paucity within the literature examining opioid dependent patients. However, within the thesis the DTI study offers a new dimension that was not possible from either the quantitative or qualitative data. The DTI study gave insight into areas of the brain that showed damage relative to duration of use across this patient population. It is paramount that we begin to understand the areas of the brain that are involved in opioid use and the effects that these may have long term, as these may have very practical implications at a clinical level. Areas of the brain that house higher functions, for e.g. functions in the mid brain responsible for motivation, learning, emotion, reinforcing pleasurable behaviour were identified as showing damage (see table 24). Clinically these functions are extremely relevant when motivating and reinforcing treatment effects. Similarly areas identified in the mid-forebrain were also implicated in the

current study (see table 25 and 26). These areas are responsible for abstract thought, planning, associations of thoughts and memories, which are key for treatment strategies such as relapse prevention. The DTI data offers a new perspective on opioid dependence that enhances the quantitative and qualitative data.

The longitudinal cohort study set out to enhance the existing literature by capturing both primary and secondary outcome data on a large number of patients across a number of time points. Previous outcome studies that included secondary outcomes tend to have focused on negative behaviours associated with addiction, such as reduction in criminal or risk behaviours. In an attempt to better understand the constructive aspects of recovery - the current study took more of a holistic approach by examining physical and psychological health, wellbeing, hope for the future and quality of life, while also allowing for challenging phases to be documented, the consequence of which is a more complete picture of recovery.

By including quantitative, qualitative and DTI data the current study gains a more rounded theoretical as well a clinical picture. The combination of both the quantitative and qualitative data offers key insights into bio-psychosocial outcomes and the process that drives them. Individually these two studies stand alone. However, when combined, the data allows for a clear picture of treatment effect and a mechanism to further interpret this effect. The majority of studies conducted on this population have focused on treatment effect in terms of abstinence, limiting the effect to yes or no, with no account given to other factors or the dynamics that progress abstinence to recovery. Documenting the patients' treatment journey progresses this dichotomous yes or no to a how and why. The patients interviewed focused on a need to 'recover' from drug use rather than simply abstain.

Recovery is a process that is not always linear as evidenced in both the quantitative and qualitative findings. For e.g. lapse and relapse were sometimes par for the course, illustrating the importance of capturing the process. A study that is limited to abstinence as an outcome fails to take account of the key leanings that can occur during the treatment journey. Each patient interviewed had individual attributes, resources, 'capital' that had helped sustain their recovery, -resources that they had accumulated through their personal journey into addiction and then into recovery and sometimes back to addiction. That could not have been captured in an outcome driven study.

9.1.3 INTERACTION BETWEEN THREE STUDIES

Significantly better outcomes were observed amongst those who completed detoxification and went on to spend at least 6 weeks in an inpatient rehabilitation unit. The patients that were interviewed echoed this; aftercare was seen as a vital step in the recovery process. None of the patients interviewed believed that detoxification was stand-alone treatment. However, the superior outcome of those who received aftercare might suggest the advantage, which ensues from lengthier treatment duration a finding shown by Simpson et al. (135). In their study the authors found a correlation between better treatment outcome in long-term methadone maintenance, therapeutic communities, and drug-free programmes (136). Moreover, this effect could somewhat reflect the fact that while attending an inpatient rehabilitation programme, the individual is "shielded" from the outside stresses to use drugs (136) or relapse is simply delayed (132). Nevertheless, the longitudinal cohort study found even at the 9-month follow-up the inpatient aftercare group was significantly more likely to be abstinent from opioids than the other groups. Moreover, the cohort study found patients were more likely to have a lapse i.e. use on a single

occasion without experiencing a relapse i.e. return to daily use. These findings render support to earlier studies (132, 137). These are findings that were both supported and refuted by the qualitative study. Patients that shared their experiences of relapse were also patients that attended inpatient aftercare and in some cases they used early in their recovery. However, in support of the larger cohort study they were more likely to lapse rather than relapse.

In the cohort study the inpatient group had more than 6 weeks in aftercare, which reinforces the probability of improved outcome in this group. It could be argued that significantly better outcomes observed in those who attended inpatient aftercare when compared to the other two groups might simply reflect differences in pre-treatment drug use. However, the three groups were similar on all measures of drug use at admission. The stabilising dose of those who completed detoxification and went on to aftercare (inpatient or outpatient) did not differ significantly from that of the completers without aftercare. Thus, it appears doubtful that differences in treatment outcome between patients with inpatient aftercare and the other two groups can be accounted for by differences in the initial severity of dependence as defined by dose or duration of use. This is also supported by the findings of the DTI study where no significant differences were found between duration of use and abstinence at follow-up.

Consistent with the existing literature some gender specific issues arose. The female patients who were interviewed felt quite strongly about gender specific treatment. In the longitudinal cohort study males were twice as likely to attend inpatient aftercare as female counterparts. The males that were interviewed were quite explicit about entering into a

romantic relationship with a female drug user. This is a finding that was strongly supported by the findings of the longitudinal cohort study where females were three times more likely to be in a relationship with another drug user.

Interestingly the majority of patients in the larger cohort study did not view alcohol as a drug. When asked what was the mean age of drug initiation patients reported 14 years old, while the mean age of first alcohol use was reported as 12 years old. In the qualitative study alcohol was something that was either off limits for a lifetime or at least for the foreseeable future. It was cited by most as a gateway to relapse. Similarly in the longitudinal cohort study alcohol was cited as the second most common substance used during lapse/relapse.

9.1.4 KEY INSIGHTS

Attending any rehabilitation aftercare significantly increases abstinence rates at 3 months. Attending inpatient aftercare significantly increases abstinence rates at 9 months. The intention to attend inpatient aftercare had a statistically significant effect on abstinence. An analysis comparing both intention to attend inpatient with no intention to attend inpatient found that non-intenders yielded two times increased risk for relapse. In addition, an analysis of the clinical instruments found attending inpatient rehabilitation aftercare had a statistically significant positive effect on hope for the future, psychological health, wellbeing and quality of life.

Recovery is an accumulative process and the resources that an individual acquires and develops are key to their success and sustainment of this recovery.

DTI measures showed significant changes in WM impairment in opioid dependent patients post-detoxification. This is the first study to identify with some precision development of WM impairment in opioid dependent patient groups spanning three decades. Moreover, the identification of a period of use without consequential damage to the brain offers great promise for treatment and detoxification.

9.1.5 DEVELOPING PREDICTORS OF OUTCOMES POST-DETOXIFICATION

The current literature pertaining to outcomes post-detoxification suggests age, gender, duration and severity of use and previous attempts at treatment are all predictors of outcome. This dissertation validated, refuted and enhanced the literature by adding to these demographic and clinical factors, while also capturing more nuanced processes such as intended pathways and lapse versus relapse. The qualitative study findings develop the theory of recovery capital as a predictor of treatment success and drive forward the recovery model. Perhaps the most significant is the validation of the relationship between WM damage and opioid dependence and the progressing of the literature towards pinpointing the development of this impairment and beginning to look at WM damage as a predictor of treatment outcomes post-detoxification.

9.1.6 IMPLICATIONS OF CURRENT PRACTICE AND POLICY

The longitudinal study found that engaging in aftercare was key to better outcomes. Moreover, even the intention to attend aftercare had significantly better outcomes. Preparation and continuity of care should be a priority so as to provide a unified service for

patients. Strategies to enhance and develop patients' preparation for detoxification are key to a seamless process.

9.1.6.1 CURRENT CLINICAL PRACTICE PREPARATION FOR DETOXIFICATION

At present Drug Dependency Units require the patient to engage in preparatory work with a counsellor for a minimum of three sessions prior to making an application for detoxification. Understandable heavy emphasis is placed on stabilization as evidenced by urine analysis. However, the level of engagement differs greatly. Some patients did not engage at all, a high proportion (30%) only engaged in the mandatory three sessions and of those who engaged for longer the level of engagement was quite varied. The number of weeks of engagement ranged from 1 to 104 (with a mean of 10 weeks) and the numbers of hours per week ranged from 1 to 48 (with a mean of 5). The type of service providers patients engaged with also varied greatly from Counsellor, General Practitioner, Psychiatrist, Fellowship Sponsor (AA, NA, CA) Keyworker. Furthermore, at time of first follow-up 15% of patients in the longitudinal cohort study had not taken their intended path to aftercare (see p41 figure 2). Two reasons were given for this change in plan - either the facility did not have a bed, or patients did not make the transfer due to a personal issue, such as lack of childcare, relapse, not ready. In addition, although patients may have had a plan to attend aftercare post-detoxification, applications for aftercare are only accepted during the detoxification period. In most cases patients have less than two weeks to secure a place on a programme. Lack of resources coupled with long waiting lists further complicate this pressured situation.

9.1.6.2 CURRENT POLICY PREPARATION FOR DETOXIFICATION

At present no national protocol exists around residential detoxification. Admission criteria,

assessment and selection process for detoxification are at present happening on an ad hoc basis and vary greatly across service providers. Patients and service providers would benefit from the development of a set of national guidelines and protocols for patients accessing residential detoxification.

9.1.6.3 CURRENT PRACTICE OF RECOVERY IN IRELAND

The findings of the naturalistic qualitative study found that patients experienced the process of recovery rather than mere abstinence. The study sustains the view that recovery is a voluntarily-maintained lifestyle, suggesting that recovery cannot be coerced, but patients should be motivated and supported in order to fully embrace recovery from dependent drug use. This means giving them a range of options and supporting them in their recovery journeys with the options that work best for them and tailored to their specific needs (such as gender or co-morbities). Detoxification does not ensure long-term abstinence from opioids, and should be regarded as a starting point for ongoing treatment, rather than as a complete treatment in its own right.

9.1.6.4 CURRENT POLICY ON RECOVERY IN IRELAND

Both nationally and internationally the recovery model has gained in popularity over the last decade. However, at frontline services in Ireland 'recovery' happens in quite a haphazard fashion. It lacks standardisation and continuity across services. Moreover, the level of support around 'recovery' implementation at a national level is small.

9.1.6.5 CURRENT PRACTICE NEUROBIOLOGY OF ADDICTION IN IRELAND

The neuroimaging study found the severity of white matter impairment in ODP was associated with duration of use. Moreover, this impairment was found between connections in subcortical regions. The subcortical brain structures play a significant part in

the regulation of a variety of cognitive and emotional processes. The regulation of such processes form an integral part of relapse prevention strategies. Although in its infancy the role of MRI has great potential to change the way we think about and respond to opioid dependence.

9.1.6.6 CURRENT CLINICAL PRACTICE

No current provision exists for the neuropsychobiology approach to addiction in Ireland.

9.1.6.7 CURRENT POLICY NEUROBIOLOGY OF ADDICTION

At present no forum exists to support and promote neuroscience and addiction in Ireland. In the UK (Home Office), Europe (WHO), the US (NIDA, NIAAA, NIH) and Australia (NCeNTA), we have seen unprecedented interest and funding for Neuroscience in general and in particular its application to better understanding of various disorders. In the US, addiction and neuroscience have had funding from two major research institutes (NIDA and NIAAA), which have been dedicated to understanding the neurobiology of addiction for over 3 decades. Moreover, both Australia and the US have developed a national strategy for neurobiology and addiction.

9.1.7 METHODOLOGICAL INSIGHTS AND LIMITATIONS OF THIS DISERTATION

The use of mixed methods research represents a significant strength of this PhD research as it allows drawing conclusions from different perspectives, thereby broadening the scope of understanding of the phenomenon of interest. Furthermore, weaknesses of one method are compensated by strengths of the other effectively contributing to reliability of the findings. One example in this research is how issues emerged in the qualitative study and were supported in the quantitative longitudinal study. In particular, utilising mixed methods in

this PhD provided a rounded view while also incorporating one of the latest advances in the field of addiction research.

In both the cohort and the imaging studies several correlations were showing significance but later failed to cross the threshold. One very plausible explanation for this is sample size. While the statistical modeling for the larger cohort study was quite sophisticated this level of modeling is often applied to large epidemiological datasets; the sample size coupled with the number of covariates of interest may have had an effect on statistical power. Similarly with the imaging study once patients were allocated to one of three respective groups the end number was quite small. In one group there were 14 patients.

A discernible limitation of the neuroimaging study design is its lack of a control study and the challenge this poses when attempting to compare the pre-existing versus acquired nature of the observed alterations. Moreover, the fact that some patients had recorded a history of psychiatric illness and the overlap between the psychiatric co-morbidities and their known associated white matter deficits must be considered when interpreting the findings of this study.

9.1.8 CONCLUSION

In conclusion in discussing the findings from all three study designs, this chapter has demonstrated many areas in which the findings agree. However, there are some areas in which different findings have been noted, thereby providing alternative perspectives on various areas of interest. While several outcomes were examined within three different methodologies the most significant predictor of abstinence for this cohort of patients was attending inpatient aftercare.

10 CHAPTER: RECOMMENDATIONS

Three main recommendations come from this thesis:

1. Preparing patients for detoxification
2. Supporting the recovery model in addiction
3. Advancement of the role of neuropsychobiology in addiction

Each of the three recommendations are discussed in terms of required changes to practice and policy as well as suggested areas for research.

10.1 RECOMMENDATION 1 PREPARING PATIENTS FOR DETOXIFICATION

10.1.1 RECOMMENDATIONS FOR PRACTICE:

The following recommendations focus on the required changes to current practice around detoxification.

Overview: specific therapeutic elements needed

I. Focus on client motivation. Contingency management strategies should be employed whereby patients who are proactively engaging in preparation work are given priority for detoxification (see figure 8 below for a proposed pathway to detoxification). Elements of preparatory work should include:
    a. Significant period of counselling (12+ sessions).
    b. Completion of preparatory module over 10- 12 sessions (see below for outline of proposed module).
    c. Engagement with pre-entry programmes.
    d. Engagement in non-addiction activities (personal development, hobbies,

community engagement).

II. In order to help clients develop awareness of repetitive patterns (thinking and behaviour that perpetuate drug use). Patients should be required to complete a preparatory module and submit a written or audio piece (in case of literacy issues) outlining work undertaken as well as a plan for post-detoxification (inclusive of previous experiences, high risk situations and triggers as well as relapse prevention strategies).

III. Ensure therapist attends to affective experiences of clients. Consider the role of conditioning in the development and maintenance of substance use disorders. This is a practice that currently occurs in a haphazard way. Including a section in the application process to identify and document these experiences would ensure common practice.

IV. Ensure current best practice is followed to carefully assess for indicators of specific conditioned responses to alcohol or drugs and develop ways to change these conditioned responses. As with above ensure these responses are documented and form an important part of the preparation process.

V. Enhance positive outcome expectancies.

VI. The referral agent should act as a case manager who supports the development and execution of a care plan for detoxification. The care plan should include:

    a. Assessment for detoxification inclusive of preparation work.

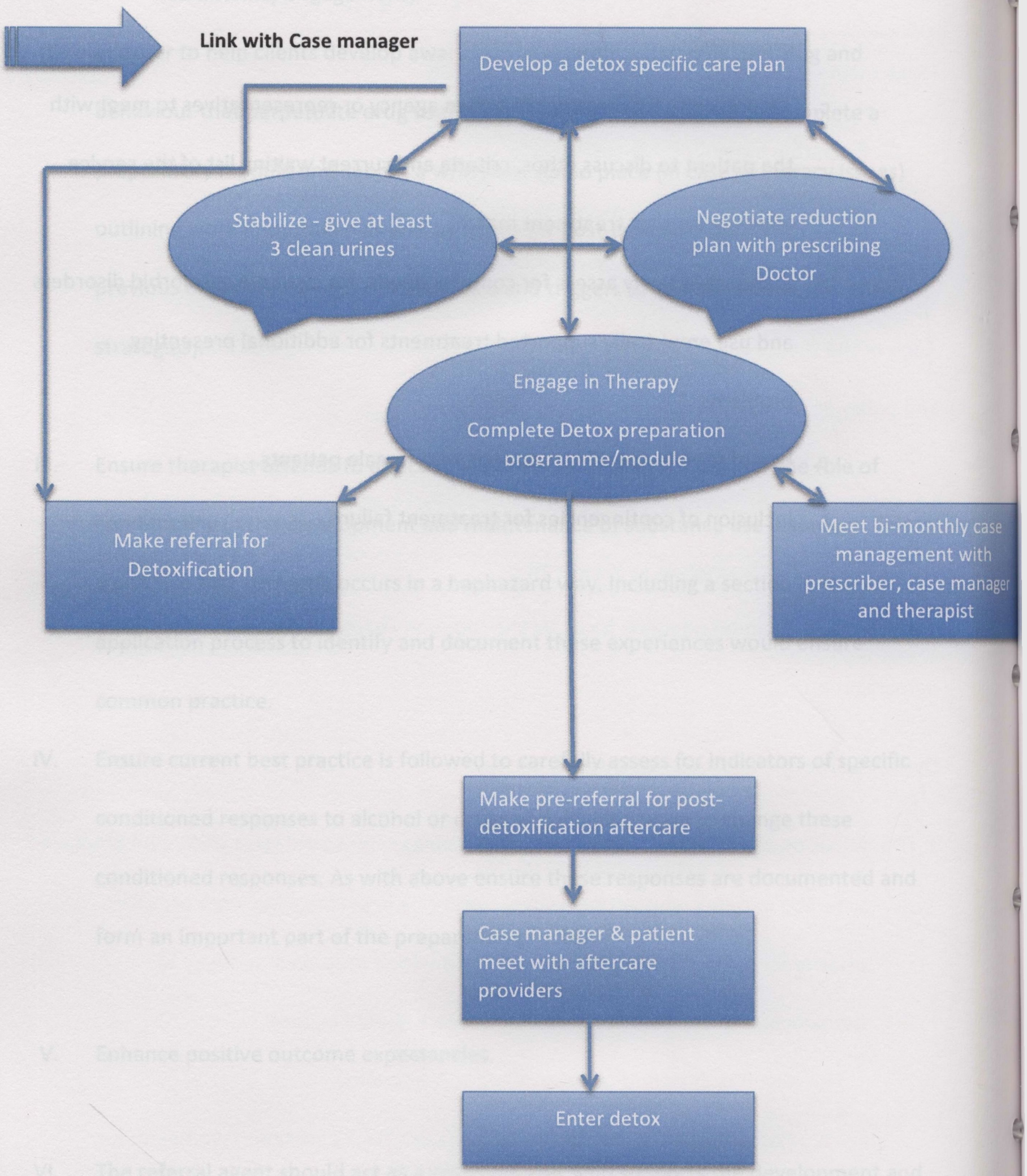
b. Pre-assessment for post-detoxification aftercare (can include several providers).

c. Opportunity for meetings between agency or representatives to meet with the patient to discuss ethos, criteria and current waiting list of the service allowing for best treatment match.

d. Comprehensively assess for complex needs, for example co-morbid disorders and use empirically supported treatments for additional presenting problems.

e. Use of female-specific treatment with female patients.

f. Inclusion of contingencies for treatment failure.


Link with Case manager
Develop a detox specific care plan
Stabilize - give at least 3 clean urines
Negotiate reduction plan with prescribing Doctor
Engage in Therapy
Complete Detox preparation programme/module
Make referral for Detoxification
Meet bi-monthly case management with prescriber, case manager and therapist
Make pre-referral for post-detoxification aftercare
Case manager & patient meet with aftercare providers
Enter detox

10.1.2 RECOMMENDATIONS FOR POLICY:

Guidelines and protocols should include:

I. Protocols to ensure patient choice to enter detoxification after a period of stabilisation.

II. A review of the current policy and practice around reducing methadone dosage following a period of stabilisation in preparation for detoxification.

III. The development of common protocols around application criteria, assessment and selection processes.

IV. The designation of a key individual who would manage a comprehensive care plan and ensure continuity of care from assessment through to two-year aftercare plan.

V. The development of a portfolio for patients presenting for assessment to showcase their preparatory work.

VI. Contingency for pre-assessment and engaging with aftercare services prior to detoxification.

VII. Opportunity and supports to enable patients to access detoxification

VIII. Protocols to ensure patient continuity from detoxification to aftercare.

IX. Protocol for contingencies for treatment failure

10.1.3 AREAS FOR FUTURE RESEARCH

Further research should include the following:

I. National evaluation of current practices and policies on admission to detoxification and post-detoxification aftercare.

II. Review of national and international research on best practice guidelines for

preparing patients for detoxification

III. Review of national and international research on best practice guidelines for detoxification

IV. A Delphi study to elicit expert opinion on the development of national guidelines and protocols for detoxification.

10.2 RECOMMENDATION 2 SUPPORTING THE RECOVERY MODEL

10.2.1 RECOMMENDATIONS FOR TREATMENT PROVIDERS:

- The recovery model requires standardised implementation at a national level.
- Client-treatment matching. Comprehensively assess patients and actively engage them in their treatment choices.
    - Assess for co morbid disorders and use empirically supported treatments for additional presenting problems.
    - Use female-specific treatment with female clients.
- Carefully assess for indicators of individual's specific skills, insights, assets, attributes and resources and assist patient to drawn upon and enhance these.
- Place education and vocational training at the centre of patient care.
- Place more emphasis on educating patients around relationships and intimacy in the recovery process.
- Instill a sense of expectation of recovery.

10.2.2 RECOMMENDATIONS FOR POLICY MAKERS:

While the recovery model has great credence at a grass roots level the natural progression is to get support from top down.

- Gain political will and the support of the Minister.
- Put post-aftercare housing back on the political agenda.
- Prioritise recovery over harm reduction.
-

Patients from the qualitative study highly valued education. Returning to education was seen as instrumental to build necessary recovery capital to assist them and support them to continue their recovery. Practice can be supported by policy, renewing the role of education in developing recovery capital among individuals in recovery.

10.2.3 AREAS FOR FUTURE RESEARCH

Further research should include the following:

A review of national and international literature examining the implementation of a recovery model.

Evaluation and mapping of current services engaging patients in the recovery process.

10.3 RECOMMENDATION 3 ADVANCEMENT OF THE ROLE OF NEUROPSYCHOBIOLOGY IN ADDICTION

10.3.1 RECOMMENDATIONS FOR TREATMENT PROVIDERS:

These findings have treatment implications, which need to be followed up with longer-term studies. However, they raise concerns about continuing to treat opioid dependent patients with Opioid Substitute Treatment (OST).

The following recommendations focus on the required changes to practice.

Overview: specific therapeutic elements

- Taper dose response relationship between length of time on OST dose and neuropsychological impairment.

- Integrate neuropsychological instruments into routine assessment and clinical review with ODP.

- Include neuropsychobiology in the education and treatment of patients.

  Clinical insight of the neurobiological basis of opioid dependence, and psycho education with patients, can provide awareness into patient behaviuors, presenting issues and offer clarification and motivation for treatment methods and goals.

10.3.2 RECOMMENDATIONS FOR POLICY MAKERS:

- Dissemination will form an important platform for progressing this research area as it develops. Key informants will include political, policy, provider, service user and community components. The advancement of this neuropsychobiology of addiction would benefit greatly from representation on intergovernmental committees such as the National Advisory Committee for Drugs and Alcohol (NACDA). A key responsibility of this committee is to advise the Minister on new developments in addiction.
- Develop policy on the appropriateness and safety of initiating OST in potentially vulnerable at risk patients.
- Develop guidelines on dose response relationship between length of time on OST and neuropsychobiological impairment.

- Develop guidelines on inclusion of neuropsychobiological instruments into routine assessment and clinical review with ODP.
- Investment in furthering research examining neuropsychobiological impairment in ODP, allowing Ireland to contribute to the international literature.
- Include neuropsychobiology of addiction in undergraduate and postgraduate health sciences education.

10.3.3 AREAS FOR FUTURE RESEARCH

Further research should include the following:

- Large scale neuroimaging and longitudinal studies on opioid dependent patients post-detoxification.

- Examining neuropsychological functioning in opiate dependent patients commencing and progressing on methadone maintenance.

- Collaborations between clinicians, researchers neuroscientists and geneticists working in the field of addiction with a specific emphasis on translational research, include biological sampling to enable genotyping this population.

10.3.4 CONCLUSIONS

Finally policy, practice and research in the field of addiction in Ireland should focus on investigating, developing and implementing best practices around preparing patients for

detoxification. A reorientation of current post-detoxification aftercare should be prioritised moving away from a model that focuses solely on abstinence, to begin engaging patients in the process of recovery. Neuropsychological discoveries have the potential to provide a number of novel and promising sites for intervention. These discoveries also point towards the possibility of a more rational approach to developing addiction treatments that are based on more comprehensive theories of the brain mechanisms underlying addiction.

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Appendix 1
EXAMPLE COMBINED EMBASE SEARCH QUERY – papers returned, review and either included or excluded.

Search string/ MESH terms: illicit and opioid and dependence* and inpatient detoxification and outcome.
*The following balloon terms were added to (dependent, dependency)

Included in review:

37. Buprenorphine for opioid dependence Drug and Therapeutics Bulletin (2007) 45:3 (20-24). Date of Publication: March 2007.

39. Inpatient opiate detoxification in Geneva: Follow-up at 1 and 6 months Broers B. Giner F. Dumont P. Mino A. Drug and Alcohol Dependence (2000) 58:1-2 (85-92). Date of Publication: 1 Feb 2000.

30. Maintenance medication for opiate addiction: The foundation of recovery Bart G. Journal of Addictive Diseases (2012) 31:3 (207-225). Date of Publication: 1 Jul 2012

45. Drug treatment of opiate dependence in primary care - An update MeReC Bulletin (2008) 18:2. Date of Publication: 2008.

1. Substance abuse among adolescents: Current perspectives. Pumariega A.J. Rodriguez L. Kilgus M.D. Addictive Disorders and their Treatment (2004) 3:4 (145-155). Date of Publication: 2004.
   Rational for exclusion: focused on adolescents

2. A prospective study on buprenorphine use during pregnancy: Effects on maternal and neonatal outcome Kahila H. Saisto T. Kivitie-Kallio S. Haukkamaa M. Halmesmaki E. Acta Obstetricia et Gynecologica Scandinavica (2007) 86:2 (185-190). Date of Publication: 2007.
   Rational for exclusion: focused on drug use and pharmacotherapy in pregnancy.

3. A preliminary investigation of outcome following gradual or rapid buprenorphine detoxification Amass L. Bickel Higgins S.T. Hughes J.R. Journal of Addictive Diseases (1994) 13:3 (33-45). Date of Publication: 1994.
   Rational for exclusion: focused on buprenorphine all patients in PhD study were prescribed methadone. More suitable reference to buprenorphine made.

4. Drug and alcohol addiction: Do psychosocial treatments work? Luty J. Advances in Psychiatric Treatment (2015) 21:2 (132-143). Date of Publication: 1 Mar 2015.
Rational for exclusion: study published 1st March (thesis submitted 1st April).

5. Attendance at Narcotics Anonymous and Alcoholics Anonymous meetings, frequency of attendance and substance use outcomes after residential treatment for drug dependence: A 5-year follow-up study Gossop M. Stewart D. Marsden J. Addiction (2008) 103:1 (119-125). Date of Publication: January 2008. **Rational for exclusion: this paper was reviewed but not included in write up findings from same dataset were reported in PhD.**

6. Cognitive behavioral therapy improves treatment outcome for prescription opioid users in primary care based buprenorphine/naloxone treatment Cutter C.J. Moore B.A. Barry D. Fiellin L.E. Schottenfeld R.S. Fiellin D. O'Connor P.Drug and Alcohol Dependence (2015) 146 (e255). Date of Publication: 1 Jan 2015.
Rational for exclusion: only abstract published 1st Jan.

7. Exercise and physical activity in the therapy of substance use disorders Zschucke E. Heinz A. Strhle A.The Scientific World Journal (2012) 2012 Article Number: 901741. Date of Publication: 2012.
Rational for exclusion: study did not look at opioid dependence rather SU broadly.

8. The influence of coping and depression on abstinence from illicit drug use in methadone-maintained patients Avants S.K. Warburton L.A. Margolin A. American Journal of Drug and Alcohol Abuse (2000) 26:3 (399-416). Date of Publication: 2000.
Rational for exclusion: study was not immediately relevant to PhD review.

9. Buprenorphine versus methadone for opioid dependence: Predictor variables for treatment outcome Gera G. Borella F. Zaimovic A. Moi G. Bussandri M. Bubici C. Bertacca S.Drug and Alcohol Dependence (2004) 75:1 (37-45). Date of Publication: 15 Jul 2004.
Rational for exclusion: this paper was reviewed but not included in write up other ref deemed more appropriate (e.g. refs 30, 46, 51 and 199).

10. Buprenorphine versus methadone in the treatment of opioid dependence: Self-Reports, urinalysis, and addiction severity index Strain E.C. Stitzer M.L. Liebson I.A. Bigelow G.E. Journal of Clinical Psychopharmacology (1996) 16:1 (58-67). Date of Publication: 1996.
Rational for exclusion: this paper was reviewed but not included in write up later paper by same authors included (199).

11. Opioid antagonists, partial agonists, and agonists/antagonists: The role of office-based detoxification Helm II S. Trescot A.M. Colson J. Sehgal N. Silverman S. Pain Physician (2008) 11:2 (225-235). Date of Publication: March/April 2008.

Rational for exclusion: study was not immediately relevant to PhD review.

12. Profile of infants born to drug-using mothers: A state-wide audit Abdel-Latif M.E. Oei J. Craig F. Lui K. Journal of Paediatrics and Child Health (2013) 49:1 (E80-E86). Date of Publication: January 2013. **Rational for exclusion: study was not relevant to PhD review.**

13. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: A randomized controlled trial Sees K.L. Delucchi K.L. Masson C. Rosen A. Clark H.W. Robillard H. Banys P. Hall S.M. Journal of the American Medical Association (2000) 283:10 (1303-1310). Date of Publication: 8 Mar 2000 **Rational for exclusion: this paper was reviewed but not included in write up focused on long-term community detoxification.**

14. Drug use and HIV risk outcomes in opioid-injecting men in the Republic of Georgia: Behavioral treatment+naltrexone compared to usual care Otiashvili D. Kirtadze I. O'Grady K.E. Jones H.E. Drug and Alcohol Dependence (2012) 120:1-3 (14-21). Date of Publication: 01 January 2012. **Rational for exclusion: study was not immediately relevant to PhD review.**

15. Drug misuse in pregnancy: The impact of a specialist treatment serviceDay E. Porter L. Clarke A. Allen D. Moselhy H. Copello A. Psychiatric Bulletin (2003) 27:3 (99-101). Date of Publication: 1 Mar 2003. **Rational for exclusion: study was not relevant to PhD review.**

16. Efficacy of maintenance treatment with naltrexone for opioid dependence: A meta-analytical review Johansson B.A. Berglund M. Lindgren A. Addiction (2006) 101:4 (491-503). Date of Publication: April 2006 **Rational for exclusion: study reviewed but was not included as was not immediately relevant to PhD review.**

17. Predictors for completing an inpatient detoxification program among intravenous heroin users, methadone substituted and codeine substituted patients.
Backmund M. Meyer K. Eichenlaub D. Schutz C.G.Drug and Alcohol Dependence (2001) 64:2 (173-180). Date of Publication: 1 Oct 2001. **Rational for exclusion: study reviewed but was not included focused on completing detoxification programme – post-detoxification was considered.**

18. Pregnancy and substance dependency Kraigher D. Schindler S. Ortner R. Fischer G. Gesundheitswesen (Bundesverband der Arzte des Offentlichen Gesundheitsdienstes (Germany)) (2001) 63 Suppl 2 (S101-105). Date of Publication: Aug 2001. **Rational for exclusion: study was not relevant to PhD review focused on pregnancy.**

19. Chronic opioid use during pregnancy: Maternal and fetal implications Stanhope T.J. Gill L.A. Rose C.Clinics in Perinatology (2013) 40:3 (337-350). Date of Publication: September 2013. **Rational for exclusion: study was not relevant to PhD review.**

20. Engaging hospitalized heroin-dependent patients into substance abuse treatment Aszalos R. McDuff D.R. Weintraub E. Montoya I. Schwartz R. Journal of Substance Abuse Treatment (1999) 17:1-2 (149-158). Date of Publication: July/September 1999

21. Opioid addicts at admission vs. slow-release oral morphine, methadone, and sublingual buprenorphine maintenance treatment participants Giacomuzzi S. Kemmler G. Ertl M. Riemer Y. Substance Use and Misuse (2006) 41:2 (223-244). Date of Publication: 2006. **Rational for exclusion: study reviewed but was not included focused on stabilization**

22. Chronic opiate use during methadone detoxification: Effects of a dose increase treatment Stitzer M.L. McCaul M.E. Bigelow G.E. Liebson I.A. Drug and Alcohol Dependence (1984) 14:1 (37-44). Date of Publication: 1984. **Rational for exclusion: this paper was reviewed but not included in write up later paper by same authors included (199).**

23. 'Topping up' methadone: An analysis of patterns of heroin use among a treatment sample of Scottish drug users Bloor M. McIntosh J. McKeganey N. Robertson M. Public Health (2008) 122:10 (1013-1019). Date of Publication: October 2008 **Rational for exclusion: this paper was reviewed but not included in write up focused on maintenance.**

24. Treatment of addiction in the elderly Clay S.W.Aging Health (2010) 6:2 (177-189). Date of Publication: April 2010. **Rational for exclusion: study was not relevant to PhD review.**

25. Methadone detoxification: Effects of methadone dose versus time in treatment McCaul M.E. Stitzer M.L. Bigelow G.E. Liebson I.A. NIDA Research Monograph Series (1984) NO. 49 (269-274). Date of Publication: 1984. **Rational for exclusion: this paper was reviewed but not included in write up later paper by same authors included (199).**

26. Successful treatment of chronic hepatitis C virus infection in severely opioid-dependent patients under heroin maintenance Schulte B. Schutt S. Brack J. Isernhagen K. Deibler P. Dilg C. Verthein U. Haasen C. Reimer J.Drug and Alcohol Dependence (2010) 109:1-3 (248-251). Date of Publication: June 2010.**Rational for exclusion: this paper was reviewed but not included in write up was not immediately relevant to PhD review.**

27. Biomarkers for the development of new medications for cocaine dependence Bough K.J. Amur S. Lao G. Hemby S.E. Tannu N.S. Kampman K.M. Schmitz J.M. Martinez D. Merchant K.M. Green C. Sharma J. Dougherty A.H. Moeller F.G. Neuropsychopharmacology (2014) 39:1 (202-219). Date of Publication: January 2014. **Rational for exclusion: study was not relevant to PhD review.**

28. Predictors of outcome after short-term stabilization with buprenorphine Hillhouse M. Canamar C.P. Ling W. Journal of Substance Abuse Treatment (2013) 44:3 (336-342). Date of Publication: April 2013. **Rational for exclusion: study was not immediately relevant to PhD review focused on stabilsation.**

29. Perinatal toluene use: Associated risks and considerations Clark C.T. Richards E.M. Antoine D.G. Chisolm M.S. Addictive Disorders and their Treatment (2011) 10:1 (1-5). Date of Publication: March 2011. **Rational for exclusion: study was not relevant to PhD review.**

31. On drug treatment and social control: Russian narcology's great leap backwards Elovich R. Drucker E. Harm Reduction Journal (2008) 5 Article Number: 23. Date of Publication: 24 Jun 2008. **Rational for exclusion: study was not immediately relevant to PhD review focused on harm reduction.**

32. The impact of ongoing illicit drug use on methadone adherence in illicit drug users receiving treatment for HIV in a directly observed therapy program Raffa J.D. Grebely J. Tossonian H. Wong T. Viljoen M. Khara M. Mead A. McLean M. Duncan F. Petkau A.J. DeVlaming S. Conway B.Drug and Alcohol Dependence (2007) 89:2-3 (306-309). Date of Publication: 10 Jul 2007. **Rational for exclusion: study was not immediately relevant to PhD review focused on harm reduction.**

33. Buprenorphine tapering schedule and illicit opioid use Ling W. Hillhouse M. Domier C. Doraimani G. Hunter J. Thomas C. Jenkins J. Hasson A. Annon J. Saxon A. Selzer J. Boverman J. Bilangi R. Addiction (2009) 104:2 (256-265). Date of Publication: February 2009. **Reviewed. Rational for exclusion: study was not relevant immediately to PhD review question focus was on pharmacotherapy**

34. A controlled trial of buprenorphine treatment for opioid dependence Johnson R.E. Jaffe J.H. Fudala P.J. Journal of the American Medical Association (1992) 267:20 (2750-2755). Date of Publication: 1992. **Reviewed. Rational for exclusion: study was not immediately relevant to PhD review question.**

35. Drug addiction during pregnancy: Correlations between the placental health and the newborn's outcome Elaboration of a predictive scoreDomenici C. Cuttano A. Nardini V. Varese L. Ghirri P. Boldrini A.Gynecological Endocrinology (2009) 25:12 (786-792). Date of Publication: December 2009. **Rational for exclusion: study was not relevant to PhD review.**

36. Withdrawal from heroin in three or six weeks. Comparison of methadyl acetate and methadone Sorensen J.L. Hargreaves W.A. Weinberg J.A. Archives of General Psychiatry (1982) 39:2 (167-171). Date of Publication: 1982. **Rational for exclusion: study was not relevant to PhD review focus was on cessation of withdrawal.**

38. Management of drug misuse in pregnancy Day E. George S. Advances in Psychiatric Treatment (2005) 11:4 (253-261). Date of Publication: Jul 2005. 37. Buprenorphine for opioid dependence Drug and Therapeutics Bulletin (2007) 45:3 (20-24). Date of Publication: March 2007. **Rational for exclusion: study was not relevant to PhD review.**

40. Treatment interventions-looking towards the millennium Crome I.B.Drug and Alcohol Dependence (1999) 55:3 (247-263). Date of Publication: 1 Jul 1999. **Rational for exclusion: this paper was reviewed but not included in write up.**

41. Proportional hazards frailty models for recurrent methadone maintenance treatment Nosyk B. MacNab Y.C. Sun H. Fischer B. Marsh D.C. Schechter M.T. Anis A.H. American Journal of Epidemiology (2009) 170:6 (783-792). Date of Publication: September 2009. **Rational for exclusion: study was not immediately relevant to question under review.**

42. Practice-based buprenorphine maintenance treatment (BMT): How do French healthcare providers manage the opiate-addicted patients? Vignau J. Duhamel A. Catteau J. Legal G. Huynh A. Grailles I. Beauvillain J. Petit P. Beauvillain P. Parquet P.J. Journal of Substance Abuse Treatment (2001) 21:3 (135-144). Date of Publication: 2001 **Rational for exclusion: study was not immediately relevant to question under review.**

43. ICU management of severe poisoning with medications or Illicit substances Megarbane B. Donetti L. Blanc T. Cheron G. Jacobs F. Reanimation (2006) 15:5 (343-353). Date of Publication: Oct 2006 **Rational for exclusion: study was not relevant to PhD review**

44. Amphetamines, the pregnant woman and her children: A review Oei J.L. Kingsbury A. Dhawan A. Burns L. Feller J.M. Clews S. Falconer J. Abdel-Latif M.E.Journal of Perinatology (2012) 32:10 (737-747). Date of Publication: October 2012. **Rational for exclusion: study was not relevant to PhD review.**

46. Alcohol use and psychopathology in opioid addicts on methadone maintenance Roszell D.K. Calsyn D.A. Chaney E.F. American Journal of Drug and Alcohol Abuse (1986) 12:3 (269-278). Date of Publication: 1986 **Rational for exclusion: study was not immediately relevant to PhD review focused on alcohol.**

47. Factors affecting the outcome of methadone maintenance treatment in opiate dependence. Kamal F. Flavin S. Campbell F. Fagan J. Behan C. Smyth R. Irish Medical Journal (2007) 100:3. Date of Publication: March 2007. . **Rational for exclusion: study was reviewed but not included in write up of PhD focused on continued use while on methadone maintenance.**

48. Methadone transition treatment: A treatment model for 180-day methadone detoxification. Reilly P.M. Banys P. Tusel D.J. Sees K.L. Krumenaker C.L. Shopshire M.S.International Journal of the Addictions (1995) 30:4 (387-402). Date of Publication: 1995

49. Utilizing . Buprenorphine-naloxone to treat illicit and prescription-opioid dependence Mauger S. Fraser R. Gill K. Neuropsychiatric Disease and Treatment (2014) 10 (587-598). Date of Publication: 7 Apr 2014. **Rational for exclusion: study was not immediately relevant to PhD review**

50. Organic mood syndrome associated with detoxification from methadone maintenance Kanof P.D. Aronson M.J. Ness R.American Journal of Psychiatry (1993) 150:3 (423-428). Date of Publication: 1993. **Rational for exclusion: study was reviewed but not included in write up of PhD.**

51. Buprenorphine treatment for hospitalized, opioid-dependent patients: A randomized clinical trial Liebschutz J.M. Crooks D. Herman D. Anderson B. Tsui J. Meshesha L.Z. Dossabhoy S. Stein M. JAMA Internal Medicine (2014) 174:8 (1369-1376). Date of Publication: August 2014. **Rational for exclusion: duplicate sees earlier comment.**

52. Treating homeless opioid dependent patients with buprenorphine in an office-based setting Alford D.P. LaBelle C.T. Richardson J.M. O'Connell J.J. Hohl C.A. Cheng D.M. Samet J.H.Journal of General Internal Medicine (2007) 22:2 (171-176). Date of Publication: February 2007. **Rational for exclusion: duplicate see earlier comment.**

53. Aripiprazole plus topiramate in opioid dependent patients with schizoaffective disorder: Evidence from a pilot study Cordova F. Bruno A. Romeo V.M. Pandolfo G. Scimeca G. Muscatello M.R.A. Zoccali R.A. European Neuropsychopharmacology (2013) 23 SUPPL. 2 (S577). Date of Publication: October 2013. **Rational for exclusion: study was not relevant to PhD review.**

54. Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: A randomized clinical trial Fiellin D.A. Schottenfeld R.S. Cutter C.J. Moore B.A. Barry D.T. O'Connor P.G. JAMA Internal Medicine (2014) 174:12 (1947-1954). Date of Publication: 1 Dec 2014. **Rational for exclusion: study was not immediately relevant to question under review focus.**

55. Pain management prescribing by race/ethnicity in a level 1 Trauma emergency departmentRiley D.C. Burkes K.B. Aldahir S.Pharmacotherapy (2014) 34:10 (e287). Date of Publication: October 2014. **Rational for exclusion: study was not relevant to PhD review.**

56. Primary care buprenorphine detoxification vs. Maintenance for prescription opioid dependence Fiellin D. Cutter C.J. Moore B.A. Barry D. O'Connor P. Schottenfeld R.S. Drug and Alcohol Dependence (2015) 146 (e277). Date of Publication: 1 Jan 2015

57. Discontinuation of buprenorphine maintenance therapy: Perspectives and outcomes. Bentzley B.S. Barth K.S. Back S.E. Book S.W.Journal of Substance Abuse Treatment (2015) 52 (48-57). Date of Publication: 1 May 2015. **Rational for exclusion: study published 1st March (thesis submitted 1st April).**

58. Buprenorphine initiation and linkage to outpatient buprenorphine treatment does not reduce frequency of injection drug use for inpatient opioid-dependent injection drug users: Results of a randomized clinical trialCushman P.A. Anderson B.J. Moreau M. Stein M.D. Liebschutz J.M. Journal of General Internal Medicine (2015) 30 SUPPL. 2 (S114-S115). Date of Publication: April 2015. **Rational for exclusion: study published 1st March (thesis submitted 1st April).**

59. The Leeds Evaluation of Efficacy of Detoxification Study (LEEDS) project: An open label pragmatic randomised control trial comparing the efficacy of differing therapeutic agents for primary care detoxification from either street heroin or methadone - ISRCTN07752728 Oldham N.S. Wright N.M.J. Adams C.E. Sheard L. Tompkins C.N.E.BMC Family Practice (2004) 5 Article Number: 9. Date of Publication: 29 Apr 2004. **Rational for exclusion: study was not included focused on community based detoxification.**

60. Access to treatment for opioid dependence in rural america: Challenges and future directions Sigmon S.C. JAMA Psychiatry (2014) 71:4 (359-360). Date of Publication: April 2014. **Rational for exclusion: study was reviewed but not included.**

61. Buprenorphine implants for treatment of opioid dependence: A randomized controlled trial. Ling W. Casadonte P. Bigelow G. Kampman K.M. Patkar A. Bailey G.L. Rosenthal R.N. Beebe K.L. JAMA - Journal of the American Medical Association (2010) 304:14 (1576-1583). Date of Publication: 13 Oct 2010.

62. Advances in the treatment of opioid dependence: Continued progress and ongoing challenges O'Connor P.G. JAMA - Journal of the American Medical Association (2010) 304:14 (1612-1614). Date of Publication: 13 Oct 2010. **Rational for exclusion: study was reviewed but not included.**

63. Moderate- vs high-dose methadone in the treatment of opioid dependence: A randomized trial Strain E.C. Bigelow G.E. Liebson I.A. Stitzer M.L. Journal of the American Medical Association (1999) 281:11 (1000-1005). Date of Publication: 17 Mar 1999. **Rational for exclusion: study was reviewed but not included in PhD write up.**

64. Low (40 mg) versus high (80 mg) dose methadone in a 180-day heroin detoxification program. Banys P. Tusel D.J. Sees K.L. Reilly P.M. Delucchi K.L. Journal of Substance Abuse Treatment (1994) 11:3 (225-232). Date of Publication: 1994. **Rational for exclusion: study was reviewed but not included in PhD write up.**

65. Improving treatment outcome in pregnant opiate-dependent women Chang G. Carroll K.M. Behr H.M. Kosten T.R. Journal of Substance Abuse Treatment (1992) 9:4 (327-330). Date of Publication: 1992. **Rational for exclusion: study was not relevant to PhD review**

66. Methadone maintenance dosing guideline for opioid dependence, a literature review Fareed A. Casarella J. Amar R. Vayalapalli S. Drexler K. Journal of Addictive Diseases (2010) 29:1 (1-14). Date of Publication: January 2010. **Rational for exclusion: study was reviewed but was not included in PhD review.**

67. Abuse liability measures for use in analgesic clinical trials in patients with pain: IMMPACT recommendations O'Connor A.B. Turk D.C. Dworkin R.H. Katz N.P. Colucci R. Haythornthwaite J.A. Klein M. O'Brien C. Posner K. Rappaport B.A. Reisfield G. Adams E.H. Balster R.L. Bigelow G.E. Burke L.B. Comer S.D. Cone E. Cowan P. Denisco R.A. Farrar J.T. Foltin R.W. Haddox J.D. Hertz S. Jay G.W. Junor R. Kopecky E.A. Leiderman D.B. McDermott M.P. Palmer P.P. Raja S.N. Rauschkolb C. Rowbotham M.C. Sampaio C. Setnik B. Smith S.M. Sokolowska M. Stauffer J.W. Walsh S.L. Zacny J.P.Pain (2013) 154:11 (2324-2334). Date of Publication: November 2013. **Rational for exclusion: study was not relevant to PhD review**

68. Methadone maintenance was more effective for treatment retention for opioid dependence than psychosocially enriched detoxification Sees K.L. Delucchi K.L. Masson C. Hall S.M. Evidence-Based Medicine (2000) 5:6 (180). Date of Publication: 2000. **Rational for exclusion: this paper was reviewed but not included in write up focused on long-term community detoxification.**

69. Pain intolerance in opioid-maintained former opiate addicts: Effect of long-acting maintenance agent Compton P. Charuvastra V.C. Ling W. Drug and Alcohol Dependence (2001) 63:2 (139-146). Date of Publication: 1 Jul 2001. **Rational for exclusion: study was not relevant to PhD review**

70. A comparison of patients relapsing to addictive drug use with non-relapsing patients following residential addiction treatment in Antigua Martin T.C. Josiah-Martin J.A. Kosakoski J. Norton K. Sinnott T. West Indian Medical Journal (2005) 54:3 (196-201). Date of Publication: 2005. **Rational for exclusion: this paper was reviewed but not included in write up focused on several substances.**

71. Treating prescription opioid dependence Ruetsch C. JAMA - Journal of the American Medical Association (2014) 312:11 (1145-1146). Date of Publication: 17 Sep 2014. **Rational for exclusion: study was not relevant to PhD review**

72. Pharmacological issues in the management of people with mental illness and problems with alcohol and illicit drug misuse Hilton T.Criminal Behaviour and Mental Health (2007) 17:4 (215-224). Date of Publication: 2007. **Rational for exclusion: study was not relevant to PhD review**

73. The effect of motivational status on treatment outcome in the North American Opiate Medication Initiative (NAOMI) study. Nosyk B. Geller J. Guh D.P. Oviedo-Joekes E. Brissette S. Marsh D.C. Schechter M.T. Anis A.H. Drug and Alcohol Dependence (2010) 111:1-2 (161-165). Date of Publication: September 2010. **Rational for exclusion: study was reviewed but not included in PhD write up focused on maintenance**

74. Heroin or conventional opioid maintenance? the patients' perspective Bald L.K. Bermpohl F. Heinz A. Gallinat J. Gutwinski S. Journal of Addiction Medicine (2013) 7:6 (401-404). Date of Publication: November-December 2013. **Rational for exclusion: study was reviewed but not included in PhD write up focused on maintenance.**

75. Buprenorphine prescription, misuse and service provision: A global perspective Ho R.C.M. Chen K.Y. Broekman B. Mak A. Advances in Psychiatric Treatment (2009) 15:5 (354-363). Date of Publication: September 2009. **Rational for exclusion: study was not relevant immediately to PhD review question.**

76. Impact of Methadone Program Philosophy Changes on Early Treatment Outcomes Brands B. Blake J. Marsh D. Journal of Addictive Diseases (2003) 22:3 (19-38). Date of Publication: 2003. **Rational for exclusion: study was reviewed but not included in PhD write up.**

77. Prolonged dexmedetomidine infusion to facilitate drug detoxification and withdrawal in patients with multiple drugs addiction Upadhyay S.P. Mallick P.N. Elmatite W.M. Singh R.K. Critical Care and Shock (2011) 14:3 (84-88). Date of Publication: 2011. **Rational for exclusion: study was not relevant immediately to PhD review question.**

78. Cost-Effectiveness of Buprenorphine and Naltrexone Treatments for Heroin Dependence in Malaysia Ruger J.P. Chawarski M. Mazlan M. Ng N. Schottenfeld R. PLoS ONE (2012) 7:12 Article Number: e50673. Date of Publication: 4 Dec 2012. **Rational for exclusion: study was not relevant immediately to PhD review question focus was on pharmacotherapy.**

79. Rapid admission and retention on methadone Maddux J.F. Desmond D.P. Esquivel M. American Journal of Drug and Alcohol Abuse (1995) 21:4 (533-547). Date of Publication: 1995. **Rational for exclusion: study was reviewed but not included in PhD write up focus on stabilisation.**

80. The use of narcotics and street drugs during pregnancy Lindsay M.K. Burnett E. Clinical Obstetrics and Gynecology (2013) 56:1 (133-141). Date of Publication: March 2013. **Rational for exclusion: study was not relevant to PhD review.**

81. Treatment outcome in methadone detoxification: Relationship to initial levels of illicit opiate use Stitzer M.L. McCaul M.E. Bigelow G.E. Liebson I. Drug and Alcohol Dependence (1983) 12:3 (259-267). Date of Publication: 1983. **Rational for exclusion: study was reviewed but not included in PhD write up focus outpatient detoxification.**

82. Acupuncture and spirituality-focused group therapy for the treatment of HIV-positive drug users: A preliminary study Margolin A. Avants S.K. Arnold R. Journal of Psychoactive Drugs (2005) 37:4 (385-390). Date of Publication: December 2005. **Rational for exclusion: study was not relevant to PhD review**

83. Clinical efficacy of buprenorphine: Comparisons to methadone and placebo. Ling W. Wesson D.R. Drug and Alcohol Dependence (2003) 70:2 SUPPL. (S49-S57). Date of Publication: 21 May 2003. **Rational for exclusion: study was reviewed but not included in PhD write up.**

84. Short-term outcomes of five heroin detoxification methods in the Australian NEPOD Project. Digiusto E, Lintzeris N, Breen C, Kimber J, Mattick RP, Bell J, Ali R, Saunders JB;

NEPOD Research Group. Addict Behav. 2005 Mar;30(3):443-65.

PMID: 15718062 [PubMed - indexed for MEDLINE]. This paper was reviewed but later excluded as it focused on completion of herion detoxification. The outcome of interest was initiation of post-detoxification pharmacotherapy (methadone, buprenorphine, or naltrexone).

Cochrane Systematic literature search via Cochrane database

Search: illicit and ('opioid'/exp or opioid) and depend*(ence, dent, ency) and detoxification and outcome.

1. The following was Cochrane reviews were included in PhD thesis:

Cochrane Record #1 of 10ID: CD004580 Day Ed, Ison Julie, Strang John. **Inpatient versus other settings for detoxification for opioid dependence.** Cochrane Database of Systematic Reviews 2005 2 John Wiley & Sons, Ltd Hospitalization; Methadone [therapeutic use];Narcotics [therapeutic use];Opioid-Related Disorders[rehabilitation];Humans[checkword] ADDICTN. DOI: 10.1002/14651858.CD004580.pub.
US:http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004580.pub2/abstract

Record #4 of 10 ID: CD005031. Amato Laura, Minozzi Silvia, Davoli Marina, Vecchi Simona

Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. Cochrane Database of Systematic Reviews 2011. John Wiley & Sons, Ltd. Buprenorphine [therapeutic use];Combined Modality Therapy [methods];Methadone [therapeutic use];Narcotics [therapeutic use];Opioid-Related Disorders [rehabilitation] [therapy];Psychotherapy [methods];Randomized Controlled Trials as Topic;Adult[checkword];Female[checkword];Humans[checkword];Male[checkword]

CC: ADDICTN. DOI: 10.1002/14651858.CD005031.pub4

US: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005031.pub4/abstract

2. The following was Cochrane reviews were excluded

Record #2 of 10 CD002209. Mattick Richard P Breen Courtney Kimber JoDavoli Marina

Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database of Systematic Reviews 2009John Wiley & Sons, Ltd

KY: Inactivation, Metabolic; Methadone [therapeutic use];Narcotics [therapeutic use];Opioid-Related Disorders [rehabilitation];Randomized Controlled Trials as Topic;Humans[checkword] ADDICTN

DOI: 10.1002/14651858.CD002209.pub2

US: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002209.pub2/abstract

Rational for exclusion: review focused on methadone maintenance.

Record #3 of 10 CD006749 Minozzi Silvia, Amato Laura, Bellisario Cristina, Davoli Marina

Detoxification treatments for opiate dependent adolescents. Cochrane Database of Systematic Reviews 2014 PB: John Wiley & Sons, LtdBuprenorphine [therapeutic use];Clonidine [therapeutic use];Naltrexone [therapeutic use];Narcotic Antagonists [therapeutic use];Opioid-Related Disorders [rehabilitation];Adolescent[checkword];Humans[checkword]ADDICTN

DOI: 10.1002/14651858.CD006749.pub3

US: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006749.pub3/abstract

Rational for exclusion: review focused on adolescents.

Record #5 of 10 ID: CD001333. Minozzi Silvia, Amato Laura, Vecchi Simona, Davoli Marina, Kirchmayer Ursula, Verster Annette. **Oral naltrexone maintenance treatment for opioid dependence**. Cochrane Database of Systematic Reviews 2011

John Wiley & Sons, Ltd. Administration, Oral;Benzodiazepines [administration & dosage];Buprenorphine [administration & dosage];Naltrexone [administration & dosage];Narcotic Antagonists [administration & dosage];Opioid-Related Disorders [rehabilitation];Randomized Controlled Trials Female[checkword];Humans[checkword];Male[checkword]ADDICTN

DOI: 10.1002/14651858.CD001333.pub4

US: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001333.pub4/abstract

Rational for exclusion: review focused on maintenance of dependence.

Record #6 of 10ID: CD007775. Rahimi-Movaghar Afarin, Amin-Esmaeili Masoumeh, Hefazi Mitra, Yousefi-Nooraie Reza. **Pharmacological therapies for maintenance treatments of opium dependence**. Cochrane Database of Systematic Reviews 2013. John Wiley & Sons, Ltd

KY: Baclofen [administration & dosage];Buprenorphine [administration & dosage];Drug Administration Schedule; Maintenance Chemotherapy [methods];Narcotic Antagonists

[administration & dosage];Opioid-Related Disorders [drug therapy];Randomized Controlled Trials as Topic;Substance Withdrawal Syndrome [drug therapy];Humans[checkword]

CC: ADDICTN

DOI: 10.1002/14651858.CD007775.pub2

US: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007775.pub2/abstract

Rational for exclusion: review focused on maintenance treatments of dependence.

Record #7 of 10ID: CD003409. Amato Laura, Davoli Marina, Minozzi Silvia, Ferroni Eliana, Ali Robert, Ferri Marica. **Methadone at tapered doses for the management of opioid withdrawal**. Cochrane Database of Systematic Reviews. 2013. John Wiley & Sons, LtdMethadone [administration & dosage];Narcotics [administration & dosage] [adverse effects];Opiate Substitution Treatment [methods];Opioid-Related Disorders [rehabilitation];Randomized Controlled Trials as Topic;Substance Withdrawal Syndrome [rehabilitation];Humans[checkword]

CC: ADDICTN

DOI: 10.1002/14651858.CD003409.pub4

US: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003409.pub4/abstract

Rational for exclusion: review focused on management of withdrawal.

Record #8 of 10 ID: CD007210 Minozzi Silvia, Amato Laura, Bellisario Cristina, Davoli Marina

Maintenance treatments for opiate-dependent adolescents. Cochrane Database of Systematic Reviews. 2014. John Wiley & Sons, Ltd. Buprenorphine [therapeutic use];Methadone [therapeutic use];Methadyl Acetate [therapeutic use];Naloxone [therapeutic use];Narcotics [therapeutic use];Opioid-Related Disorders [rehabilitation];Randomized Controlled Trials as Topic;Adolescent[checkword];Humans[checkword];Young Adult[checkword]

CC: ADDICTN. DOI: 10.1002/14651858.CD007210.pub3

US: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007210.pub3/abstract

Rational for exclusion: review focused on maintenance of dependence and was limited to adolescents.

Record #9 of 10 ID: CD002024. Gowing Linda, Farrell Michael F, Ali Robert, White Jason M

Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane Database of Systematic Reviews. 2014. John Wiley & Sons, Ltd

Acute Disease;Adrenergic alpha-2 Receptor Agonists [therapeutic use];Controlled Clinical Trials as Topic;Methadone [therapeutic use];Opiate Substitution Treatment [methods];Opioid-Related Disorders [complications];Randomized Controlled Trials as Topic;Substance Withdrawal Syndrome [rehabilitation];Humans[checkword]

CC: ADDICTN. DOI: 10.1002/14651858.CD002024.pub4

US: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002024.pub4/abstract

Rational for exclusion: review focused on management of withdrawal.

Record #10 of 10 ID: CD004332. Rösner Susanne, Hackl-Herrwerth Andrea, Leucht Stefan, Lehert Philippe, Vecchi Simona, Soyka Michael. **Acamprosate for alcohol dependence**. Cochrane Database of Systematic Reviews. 2010. John Wiley & Sons, Ltd

Alcohol Deterrents [adverse effects] [therapeutic use];Alcohol-Related Disorders [drug therapy];Diarrhea [chemically induced];Placebo Effect;Randomized Controlled Trials as Topic;Taurine [adverse effects] [analogs & derivatives] [therapeutic use];Adult[checkword];Humans[checkword]

CC: ADDICTN. DOI: 10.1002/14651858.CD004332.pub2

US: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004332.pub2/abstract

Rational for exclusion: review focused on alcohol dendepence.

THE DRUG TREATMENT CENTRE BOARD

PRIVATE & CONFIDENTIAL
STRICTLY ADDRESSEE ONLY
Ms. Jo-Hanna Ivers,
Researcher Department of Public
Health & Primary Care,
Trinity College Centre for Health Sciences,
Adelaide & Meath Hospital Dublin,
Incorporating the National Children's Hospital,
Tallaght,
Dublin 24.

1st February, 2012

Re: Predictions of Outcomes in Opiate Dependent Patients Post detoxification

Dear Ms. Ivers,

Thank you for your response dated 25th January, 2012. The Ethics Committee have now approved the above proposal.

We would ask that you inform us regarding the outcome of the study with a summary of the conclusions and if it is published could you send us the reference of same.

Can you please clarify the commencement date? We would like to wish you the best of luck with your study.

Yours sincerely,

Seamas Noone
Seamas Noone
Vice Chairman
Ethics Committee

p.p. Deirdre Daly
Dr. John O'Connor
Consultant Psychiatrist/
Clinical Director

BORD AN LÁRIONAID CÓIREÁLA DRUGAÍ
Lárionad Mhic Cárthaigh, 30-31 Sráid an Phiarsaigh, Baile Átha Cliath 2
Teileafóin: +353 1 6488600 Facs: +353 1 6488700
Ríomhphost: info@dtcb.ie Láithreán: www.addictionireland.ie

THE DRUG TREATMENT CENTRE BOARD
McCarthy Centre, 30-31 Pearse Street, Dublin 2.
Telephone: +353 1 648 8600 Fax: +353 1 648 8700
E-mail: info@dtcb.ie Website: www.addictionireland.ie

Participant Information Sheet

Title of Project: Predictions of Outcomes in Opiate Dependent Patients Post-detoxification.

Introduction

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

We are a group of researchers studying chosen pathways to rehabilitation in opiate dependent patients. We want to better understand exactly why some patients choose a particular pathway to rehabilitation. To further understand what factors affect patient's choices, are these informed by factors that are: biological, psychological or social. In order to understand choices that are based on biological/psychological we are using a brain scanner – a functional Magnetic Resonance Imaging (fMRI) system. This will require a visit to our brain imaging research centre in the Trinity Centre, St James Hospital. fMRI can tell us the structure of your brain, and which regions of the brain are activated by the visual tasks we are interested in. We will do this by asking participants to watch a short video clip perform simple tasks involving either hand or eye movements in response to visual stimuli

presented on a computer screen and measuring the speed and accuracy with which they respond. In this experiment we shall use a non-invasive technique called functional Magnetic Resonance Imaging (fMRI) to study which brain areas are involved in these tasks. This technique uses a magnetic field to produce high quality images of the brain without the use of harmful radiation.

Why have I been chosen?

You have been chosen because you successfully completed a residential detoxification programme. We believe your participation can provide us with useful information about the choices patients make in relation to their rehabilitation. Because of the nature of the experiment the following persons will NOT be able to take part: patients that are pregnant or any patient that does not have a G.P.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

You will first be asked to fill in a questionnaire to ensure there are no contraindications to your having a FMRI scan. Although fMRI is a widely used and safe technique you should not have a scan if you have any metal implanted in your body. The scan involves being placed in

a large magnetised machine while images of the brain are taken. During the scan you will be asked to respond to a video clip briefly projected on a mirror positioned above your head. You will be asked to respond to the image either by pressing a button or by moving your eyes. If eye movement responses are required the position of your eyes will be monitored by a small infra-red tracker positioned at the opening of the scanner. The tracker only looks at the eyes and does not record a video image of any part of your face.

Once the scanning process begins there will be a loud "knocking" noise from the magnetic coils changing pulse direction. This is normal and you will be given ear plugs to keep the noise to a minimum. The fMRI scan will last less than 60 minutes. Full instructions about the task will be given to you before the beginning of the experiment. At the end of the experiment you will be asked a few simple questions about your symptoms and asked to make some simple movements in order to assess your condition clinically.

What are the potential risks of taking part in this study?

There are no risks attached to your participation in this study.

What are the possible benefits of taking part?

Taking part is of no direct benefit to you. The information we get from this study may help us to treat future patients accessing the Addiction Services. Please note the fMRI scan is not a medical screening procedure and that the researchers are not qualified to provide a clinical diagnosis or identify potential abnormalities. However, if the researchers are concerned that there may be a potential abnormality on the scan, they will disclose the scan to your nominated General Practitioner.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the Detoxification Unit will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

The results of this study are likely to be published in scientific journals. You may request a copy of the published results if you wish. No personally identifiable information will be published.

Who has reviewed the study?

The ethic committee at the Drug Treatment Centre Board have reviewed the study and considered and granted permission for it to be carried out.

Contact for further information

Jo-Hanna Ivers,

Dept. Of Public Health & Primary Care,

Trinity College Dublin

01-8961087

jivers@tcd.ie

Thank you for considering contributing to our study.

Consent Form

The research study has been fully explained to me. I have had opportunities to ask questions concerning the project and procedures involved. I am aware that participation is voluntary and that I am free to withdraw my consent at any time. I am aware that my decision not to participate or to withdraw from the study will not restrict my access to health services normally available to me. I understand that my clinical treatment records and or information held ón mé ón the Central Treatment List (CTL) may be accessed by researchers. I am aware that I may be asked to undergo a Magnetic Resonance Imaging scan in my final week of detoxification and again at 6, 12 and 18 months post detoxification. I am happy for the information gathered about my experience of the addiction services, without my name or an identifying information to be managed by the research team. Confidentiality of records concerning my involvement in this project will be maintained in an appropriate manner.I consent to be followed up and am aware that I made be asked to take part in an interview at a later stage.

a. I, the undersigned, hereby consent to participate in the described study as outlined in the participant information sheet.

b. I understand and agree that the fMRI scan is not a medical screening procedure and that the researchers are not qualified to provide a clinical diagnosis or identify potential abnormalities. However, if the researchers are concerned that there may be a potential abnormality on the scan, I consent to them disclosing the scan results to my General Practitioner.

c. I understand that I will be followed up for twelve months post-detoxification I give the researcher permission to contact me at the telephone number and address provided and or the alternative number of name:(_____)

number: (_____) relationship (_____). Should you fail to reach me through either of these contacts I consent to be followed up through the following named services:

I. _____

II. _____

III. _____

_____ (Please sign here)

_____ (Please print your name here)

Date: _____ Time:_____

Statement of interviewer's responsibility: I believe that the participant understands my explanation and has freely given permission for their information to be anonymised and passed onto the research team.

Interviewer's Name: _____ (Please print your name here)

Interviewer's signature: _____ (Please sign here)

Date: _____ Time:_____

APPENDIX 5: DEMOGRAPHIC QUESTIONNAIRE

Programme Details

Date of completion _____ DDU Id _____

No. Weeks in programme_____ Planned date of D/C _____

Specified pathway Residential

Day programme

No formal aftercare

How long until you move on to this programme _____

Start date_____

Personal Details

Name _____

Address _____

Telephone number_____

Gender

Male ◯

Female ◯

Date of birth

Highest level of education? _____

Highest level of training? _____

General Practitioner Details

Name _____

Address _____

Telephone number_____

Q1. Is your GP aware of your addiction issues?

Yes

No

If yes

a. Are they aware that you are currently detoxifying

Yes

No

If no can we contact them in case of need to follow up on your brain scan or to track you for the study? Yes

No

Name (if different from above)_____

Address _____

Telephone number_____

Drug History:

Q2. Age of first alcohol use ☐

First drug used _____

a. Route of use Oral ☐ Snort ☐ avenous ☐ scular ☐

b. Age of initiation _____

c. Progression

drugs:_____

_____

_____

d. (if IV user)When first injected and how long

injecting_____

_____

e. Why_____

_____

_____

Q3. Primary drug of choice_____

I. Number of years using ☐

Treatment History:

Q4. Number of previous opiate detoxification commenced ☐

- Of these how many were:

I. Inpatient ☐ Outpatient ☐

II. Structured ☐ Unstructured ☐

☐

Number of previous opiate detoxification Completed

- Date of last attempt ☐
- Longest time drug free ☐
- How long ago was this ☐

Number of previous attempts at Rehabilitation

(Rehabilitation: A person is said to be engaging in rehabilitation if he/she is detoxified or has stabilised their drug use and has engaged in structured developmental process involving a continuum of care (range of services) aimed at maximising their quality of life and enabling their re-integration (making them part of) into communities (in a way that is meaningful to them).

- Of these how many were abstinence based

III. Inpatient ☐ Outpatient ☐

- Date of last attempt ☐
- Length of treatment ☐

Q5. Longest time drug free from opiates since initiation ☐

a. How long ago was this ☐

Q6. Were you receiving a methadone maintenance programme prior to this detoxification?

Yes

No

If yes, How many mls ☐

- *If yes* Community Clinic

GP

- Prior to detoxification were you receiving any non-clinical intervention(s)

Counselling

Special CE Schemes

Re-integration/rehabilitation(n)

Programme(e)

Other (specify).....

Q7. How many mls did you reduce per week? ☐

a) Over how many weeks ☐ months ☐

Q8. Where you on a waiting list for detoxification? Yes(s) No(o)

1. *If yes* How long did you wait? weeks ☐ months ☐
2. Why do you think you had to wait so long?

You were not ready(y) Needed to do preparatory work (with professional)

Personal issue(e) (specify) _____ Facility didn't have a bed(d)

Other(r) (specify)_____

3. Was this time beneficial? Yes(s) No(o)

Why_____

_____

_____

_____

4. How many meetings did you have (Inc assessment) with the Unit prior to commencing detox? ☐

Q9. Did you engage in preparatory work prior to detoxification?

Yes(s)

No

a. *If yes* Structured

Unstructured

b. With whom Psychiatrist

GP

Counsellor

Key-worker

Day programme

Other.....

c. For how long (No. weeks) prior to entry ☐

d. Number of hours per week ☐

e. Did you a clear plan regarding aftercare PRIOR to commencing detox?

1. No plan

2 Had some vague ideas re aftercare options

3/ had some quite definite ideas re options

4/ had a definite preference for one aftercare option

(and had identified route into same)

Psychiatric History

Q10. Were you ever linked in with the psychiatric or mental health services, for issue other than addiction? Yes

No

I. *If yes, date* ☐

Q11. Did you receive a diagnosis? Yes

No

If yes, (specify).....

Q12. Did you receive psychiatric treatment? Yes

No

If yes Residential

Community Clinic

Q13. Are you prescribed any medications to assist your mood or wellbeing (antidepressants, antipsychotics etc)? Yes

No

1. *If yes,* name).....
2. *How long have you been prescribed?* .....

Q14. Length of time with psychiatric services

a. If no longer attending, why? Completed Treatment

Dropped Out

Terminated by Facility

Transferred

Other (specify).....

Q15. What are the three most important reasons you have for detoxification at this time?

1.....

2. .....

3.....

Q 16. Apart from yourself, who would you say has been most important in getting you to come to detoxification at this time (this can include anyone who encouraged you to come here or referrer)?

1.....

2. .....

3.....

Living Situation:

(Prompt residential patient group to answer post residential rehabilitation, ifknown).

Q17	In which one of these places will you be living post-detoxification?	Tick Yes (most appropriate)
A	Own house/flat	
B	Rent house/flat	
C	Bedsit/hotel/ boarding house	
D	Hostel/shelter	
E	Squat	
G	House/home of friends	

H	House/home of relatives	
I	Supported housing	
J	Don't know	
K	Other, specify	

Q16. Do you currently have any of the following housing problems?

Homelessness ◯

Eviction notice ◯

Arrears ◯

Other (specify) .....

Q17. With whom will you live when you are drug free?

Partner & children ◯

Partner ◯

Child(ren) ◯

Parent(s) ◯

Parent(s) & Child(ren) ◯

Sibling(s) ◯

Other family ◯

Friend(s) ◯

Alone ◯

Other (specify) .....

Q18. Will there be anyone in this accommodation using illegal drugs or using prescription drugs to get high or for other non-medical effects?

Yes ◯

No ◯

Relation (parent, sibling etc).....

Q19. Will there be anyone in this accommodation receiving alcohol or drug treatment

(Including A.A or N.A.)?

Yes ◯

No ◯

Relation (parent, sibling etc).....

Q20. Does the area where you plan to stay have any of the following?

Anti-social neighbours ◯

Vandalism ◯

Burglary/theft ◯

Drug dealing ◯

Assaults/muggings ◯

Gang violence ◯

Intimidation ◯

Other (specify) .....

Q21. Do you have any children younger than 18 years? (Yes) (No)

No. of Children	Gender				Age (years & months)	Live with you? (Y/N)	Part-time/fulltime (F/P)
1	M		F				
2	M		F				
3	M		F				
4	M		F				
5	M		F				
6	M		F				

Q22. Are any of your children using drugs or alcohol?

No. of Children	Yes	If yes, is he/she receiving necessary tx	Is this causing problems	Alcohol	If yes, is he/she receiving necessary tx	Is this causing problems

1						
2						
3						
4						
5						
6						

Q23. How do you expect to occupy yourself post-detoxification?

Engage in structured programme (Rehabilitation)

Engage in structured programme (Training/Education)

Focus on household duties

Return to previous activities

(specify).....

.....

.....

.....

.....

.....

Other(specify).....

.....

.....

.....

.....

.....

MAUDSLEY ADDICTION PROFILE (MAP)

SECTION A: MANAGEMENT INFORMATION

Include the study specific information as required (e.g. participant identification, programme codes; interview point)

SECTION B: SUBSTANCE USE

CARD 1

None	1 day only	2 days only	3 days only	1 day a week	2 days a week	3 days a week	4 days a week	5 days a week	6 days a week	Every day	Some other number
0	1	2	3	4	9	13	17	21	26	30	

CARD 2

Oral	Snort/sniff	Smoke/chase	Intravenous	Intramuscular
1	2	3	4	9

a. Enter number of days used in past 30 days (Card 1) – enter '0' for no use
b. Enter amount used on a typical day in the past 30 days (verbatim)
c. Record route(s) of administration (Card 2)

SUBSTANCE	DAYS USED	AMOUNT USED ON TYPICAL DAY	ROUTE(S)
B1. Alcohol			
B2. Heroin			
B3. Illicit methadone			
B4. Illicit benzodiazepine		Drug:	
B4. Cocaine powder			
B5. Crack cocaine			
B6. Amphetamine			
B7. Cannabis			
B8. Other:			

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SECTION C: HEALTH RISK BEHAVIOUR

If no illicit drugs injected in the past 30 days, skip to sexual behaviour questions

C1. Days injected drugs in the past 30 days [card 1] _____ Days

C2. Times injected on a typical day in the past 30 days _____ Times

C3. Times injected with a needle/syringe already used by someone else _____ Times

If no penetrative sex in the past 30 days, skip to Section D

C4. Number of people had sex with and not used condom _____ People

C5. Total number of times had sex with and not used condom _____ Times

SECTION D: HEALTH SYMPTOMS

CARD 3

Never 0 | Rarely 1 | Sometimes 2 | Often 3 | Always 4

D1. How often experienced the following physical health symptoms

	Never (0)	Rarely (1)	Sometimes (2)	Often (3)	Always (4)
a. Poor appetite	☐	☐	☐	☐	☐
b. Tiredness/fatigue	☐	☐	☐	☐	☐
c. Nausea (feeling sick)	☐	☐	☐	☐	☐
d. Stomach pains	☐	☐	☐	☐	☐
e. Difficulty breathing	☐	☐	☐	☐	☐
f. Chest pains	☐	☐	☐	☐	☐
g. Joint/bone pains	☐	☐	☐	☐	☐
h. Muscle pains	☐	☐	☐	☐	☐
i. Numbness/tingling	☐	☐	☐	☐	☐
j. Tremors/shakes	☐	☐	☐	☐	☐

E7. Number of days of paid work in past 30 days **[card 1]** [redacted] Days

E8. Days missed from work because of sickness or unauthorised absence in the past 30 days [redacted] Days

E9. Days formally unemployed in the past 30 days [redacted] Days

---

CARD 4

Selling drugs	Fraud/forgery	Shoplifting	Theft from a property	Theft from a vehicle	Theft of a vehicle	Other crimes

E10. Crimes committed in the past 30 days **[card 4 and card 1]**

	Days committed [card 1]	Number of times committed on a typical day [card 2]
a. Selling drugs	[redacted]	[redacted]
b. Fraud/forgery	[redacted]	[redacted]
c. Shoplifting	[redacted]	[redacted]
d. Theft from a property	[redacted]	[redacted]
e. Theft from a vehicle	[redacted]	[redacted]
f. Theft of a vehicle	[redacted]	[redacted]
Other crimes: ----------	[redacted]	[redacted]

END OF INTERVIEW

WHOQOL-BREF

The following questions ask how you feel about your quality of life, health, or other areas of your life. I will read out each question to you, along with the response options. **Please choose the answer that appears most appropriate.** If you are unsure about which response to give to a question, the first response you think of is often the best one.

Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life **in the last four weeks.**

		Very poor	Poor	Neither poor nor good	Good	Very good
1.	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2.	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last four weeks.

		Not at all	A little	A moderate amount	Very much	An extreme amount
3.	To what extent do you feel that physical pain prevents you from doing what you need to do?	5	4	3	2	1
4.	How much do you need any medical treatment to function in your daily life?	5	4	3	2	1
5.	How much do you enjoy life?	1	2	3	4	5
6.	To what extent do you feel your life to be meaningful?	1	2	3	4	5

		Not at all	A little	A moderate amount	Very much	Extremely
7.	How well are you able to concentrate?	1	2	3	4	5
8.	How safe do you feel in your daily life?	1	2	3	4	5
9.	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about how completely you experience or were able to do certain things in the last four weeks.

		Not at all	A little	Moderately	Mostly	Completely
10.	Do you have enough energy for everyday life?	1	2	3	4	5
11.	Are you able to accept your bodily appearance?	1	2	3	4	5
12.	Have you enough money to meet your needs?	1	2	3	4	5
13.	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
14.	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

		Very poor	Poor	Neither poor nor good	Good	Very good
15.	How well are you able to get around?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
16.	How satisfied are you with your sleep?	1	2	3	4	5
17.	How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
18.	How satisfied are you with your capacity for work?	1	2	3	4	5
19.	How satisfied are you with yourself?	1	2	3	4	5

20.	How satisfied are you with your personal relationships?	1	2	3	4	5
21.	How satisfied are you with your sex life?	1	2	3	4	5
22.	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23.	How satisfied are you with the conditions of your living place?	1	2	3	4	5
24.	How satisfied are you with your access to health services?	1	2	3	4	5
25.	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to how often you have felt or experienced certain things in the last four weeks.

		Never	Seldom	Quite often	Very often	Always
26.	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	5	4	3	2	1

Do you have any comments about the assessment?

_____

_____

[The following table should be completed after the interview is finished]

		Equations for computing domain scores	Raw score	Transformed scores*	
				4-20	0-100
27.	**Domain 1**	(6-Q3) + (6-Q4) + Q10 + Q15 + Q16 + Q17 + Q18 ☐ + ☐ + ☐ + ☐ + ☐ + ☐ + ☐	a. =	b:	c:
28.	**Domain 2**	Q5 + Q6 + Q7 + Q11 + Q19 + (6-Q26) ☐ + ☐ + ☐ + ☐ + ☐ + ☐	a. =	b:	c:
29.	**Domain 3**	Q20 + Q21 + Q22 ☐ + ☐ + ☐	a. =	b:	c:
30.	**Domain 4**	Q8 + Q9 + Q12 + Q13 + Q14 + Q23 + Q24 + Q25 ☐ + ☐ + ☐ + ☐ + ☐ + ☐ + ☐ + ☐	a. =	b:	c:

* See Procedures Manual, pages 13-15

The Trait Hope Scale

Directions: Read each item carefully. Using the scale shown below, please select the number that best describesYOU and put that number in the blank provided.

1. = Definitely False
2. = Mostly False
3. = Somewhat False
4. = Slightly False
5. = Slightly True
6. = Somewhat True
7. = Mostly True
8. = Definitely True

___ 1. I can think of many ways to get out of a jam.

___ 2. I energetically pursue my goals.

___ 3. I feel tired most of the time.

___ 4. There are lots of ways around any problem.

___ 5. I am easily downed in an argument.

___ 6. I can think of many ways to get the things in life that are important to me.

___ 7. I worry about my health.

___ 8. Even when others get discouraged, I know I can find a way to solve the problem.

___ 9. My past experiences have prepared me well for my future.

___10. I've been pretty successful in life.

___11. I usually find myself worrying about something.

___12. I meet the goals that I set for myself.

Note. When administering the scale, it is called The Future Scale. The agency subscale score is derived by summing items 2, 9, 10, and 12; the pathway subscale score is derived by adding items 1, 4, 6, and 8. The total Hope Scale score is derived by summing the four agency and the four pathway items.

CLINICAL OUTCOMES in ROUTINE EVALUATION

OUTCOME MEASURE

Site ID ☐☐☐☐ Age ☐☐ Male ☐ Female ☐

letters only ☐☐ numbers only ☐☐☐☐☐☐☐

Client ID

Therapist ID ☐☐☐ numbers only (1) ☐☐☐ numbers only (2) ☐☐☐

Sub codes

D D M M Y Y Y Y

☐☐ / ☐☐ / ☐☐☐☐

Date form given

Stage Completed

S Screening
R Referral
A Assessment
F First Therapy Session
P Pre-therapy (unspecified)
D During Therapy
L Last therapy session
X Follow up 1
Y Follow up 2

Stage ☐

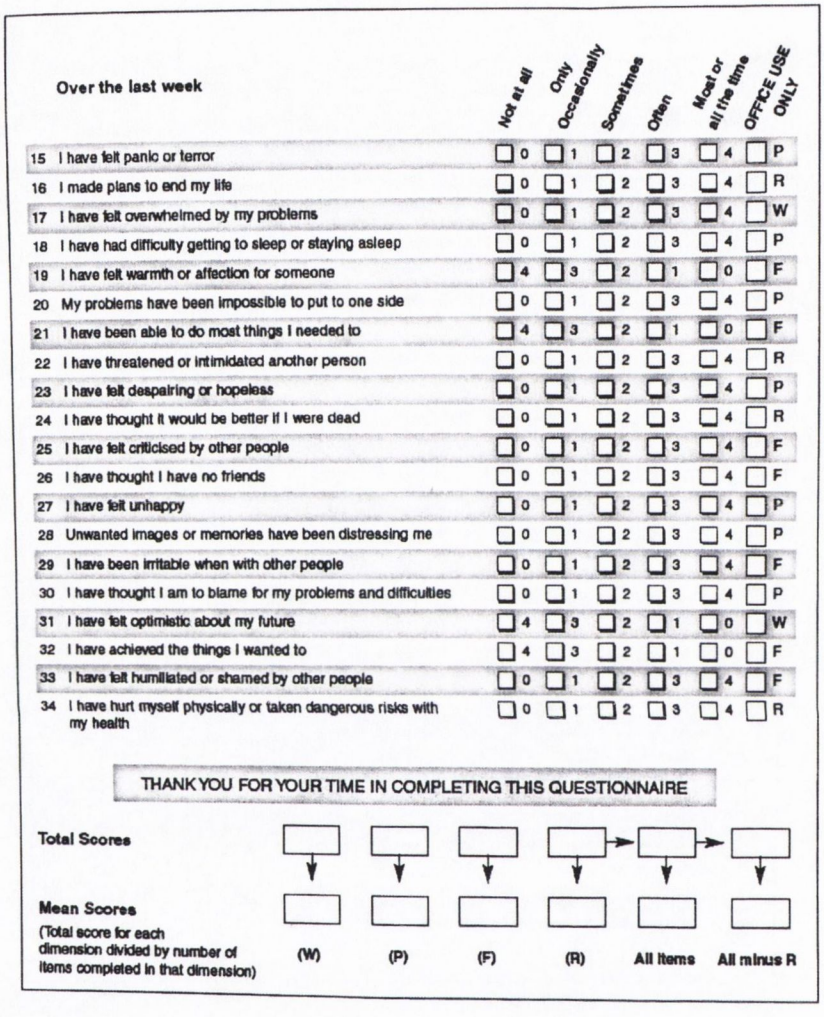
Episode ☐

IMPORTANT – PLEASE READ THIS FIRST

This form has 34 statements about how you have been OVER THE LAST WEEK.
Please read each statement and think how often you felt that way last week.
Then tick the box which is closest to this.
Please use a dark pen (not pencil) and tick clearly within the boxes.

Over the last week	Not at all	Only Occasionally	Sometimes	Often	Most or all the time	OFFICE USE ONLY
1 I have felt terribly alone and isolated	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ F
2 I have felt tense, anxious or nervous	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ P
3 I have felt I have someone to turn to for support when needed	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0	☐ F
4 I have felt O.K. about myself	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0	☐ W
5 I have felt totally lacking in energy and enthusiasm	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ P
6 I have been physically violent to others	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ R
7 I have felt able to cope when things go wrong	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0	☐ F
8 I have been troubled by aches, pains or other physical problems	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ P
9 I have thought of hurting myself	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ R
10 Talking to people has felt too much for me	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ F
11 Tension and anxiety have prevented me doing important things	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ P
12 I have been happy with the things I have done	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0	☐ F
13 I have been disturbed by unwanted thoughts and feelings	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ P
14 I have felt like crying	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ W

Please turn over



Over the last week	Not at all	Only Occasionally	Sometimes	Often	Most or all the time	OFFICE USE ONLY
15 I have felt panic or terror	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ P
16 I made plans to end my life	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ R
17 I have felt overwhelmed by my problems	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ W
18 I have had difficulty getting to sleep or staying asleep	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ P
19 I have felt warmth or affection for someone	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0	☐ F
20 My problems have been impossible to put to one side	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ P
21 I have been able to do most things I needed to	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0	☐ F
22 I have threatened or intimidated another person	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ R
23 I have felt despairing or hopeless	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ P
24 I have thought it would be better if I were dead	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ R
25 I have felt criticised by other people	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ F
26 I have thought I have no friends	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ F
27 I have felt unhappy	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ P
28 Unwanted images or memories have been distressing me	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ P
29 I have been irritable when with other people	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ F
30 I have thought I am to blame for my problems and difficulties	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ P
31 I have felt optimistic about my future	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0	☐ W
32 I have achieved the things I wanted to	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0	☐ F
33 I have felt humiliated or shamed by other people	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ F
34 I have hurt myself physically or taken dangerous risks with my health	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ R

THANK YOU FOR YOUR TIME IN COMPLETING THIS QUESTIONNAIRE

	(W)	(P)	(F)	(R)	All items	All minus R
Total Scores	☐	☐	☐	☐	☐	☐
Mean Scores (Total score for each dimension divided by number of items completed in that dimension)	☐	☐	☐	☐	☐	☐

Interview Topic Guide Qualitative Interviews

Drug History:

Current drug use [prior to, during, and after treatment]

Nature of drug use (type of drugs used)

History/map of drug use in chronological order

Length of addiction

Impact of addiction on relationships, education, employment

Rehabilitation/Treatment History:

Current Status [treatment prior to, during, and after detoxification]

Stage of recovery/readiness for treatment

Number of previous times in treatment

Patterns of drug abuse, service utilization, and outcomes over time

Nature of treatment (type of treatment, residential, day-care, community based)

History/map of drug use in chronological order

Length of treatment

Impact of addiction on relationships, education, employment

Changes in mental health indicators during treatment

The role of their psychological factors in treatment

Factors related to their treatment retention/maintenance

Experience of services and process in different types of treatment settings

Influence of Rehabilitation Pathway:

Relationship between patient, chosen program, and treatment factors, and treatment effectiveness

How has life changed since detoxification?

Influence on choice of a number of variables such as age, gender, ethnicity and social class

Influence of significant others on choice, such as advice and guidance workers, peers, relatives and employers

Has patients' perception of rehabilitation changed

Influences on choice of available provision, ie HSE funded centre/HSE funded place/bed

Future

Aspirations, Hopes for the future, [relationships, education, training, employment] Projection of self in 12 months time

How have these changed since detoxification?

What are you doing now that you doing now that you could not have done prior to detox.