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Optimising opioid assisted therapy outcomes for opioid use disorder treatment using personalised care and therapeutic drug monitoring

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OPTIMISING OPIOID ASSISTED THERAPY: OUTCOMES FOR OPIOID USE
DISORDER TREATMENT USING PERSONALISED CARE AND THERAPEUTIC
DRUG MONITORING

A THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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ABSTRACT

Background and aim

This thesis (incorporating three publications in peer-reviewed journals) investigates the clinical effectiveness of Medication Assisted Treatment (MAT) for opioid use disorder (OUD) with buprenorphine/naloxone film (BUP/NX-F) medication (Suboxone®). In a randomised controlled trial, take-home (i.e. unsupervised patient self-administered) prescriptions BUP/NX-F were made available contingent of medication adherence by Therapeutic Drug Monitoring (TDM) and drug use abstinence by Urine Drug Screen (UDS).

MAT with buprenorphine (BUP) containing medications is an evidence-based treatment for OUD. Clinical effectiveness of BUP is affected by several moderators, including medication misuse and diversion, medication non-adherence, sub-optimal clinical care, and poor treatment retention. While Directly Observed Treatment (DOT) can minimise the likelihood of poor medication adherence and limit diversion, this practice is associated with high treatment discontinuation and high cost. Contingency Management (CM) using medication take-home prescriptions is an effective behavioural adjunct to MAT that enhances retention, but there may be a continued risk of medication diversion. In the Middle-East countries, provision of MAT is limited due to concern over diversion. There is a world-wide call to develop sensitive and specific tools to detect misuse and diversion. Therapeutic Drug Monitoring (TDM) has been recommended to monitor adherence with BUP, but there has been no research trials on integrating feasibility of TDM and integration in clinical practice. The aim of the thesis was to determine the effectiveness of a TDM and CM manualised medication management (MM) to enhance the effectiveness of BUP/NX-F for OUD.

Design and method

This was a single-centre pragmatic randomised controlled trial of MAT (BUP/NX-F; buprenorphine/naloxone ratio 4:1) with TDM and CM (in a manual guided medication management (MM) protocol; Incentivised Abstinence and Adherence Monitoring; IAAM) was the experimental condition. This was compared to BUP/NX-F as usual (the control group) using intention-to-treat analysis. Participants ($n=141$) adults with OUD, all stabilised on BUP/NX-F) were randomised to receive 16-weeks outpatient treatment in the experimental ($n = 70$) and control ($n = 71$) groups. The primary outcome measure was the percentage of negative opioid UDS recorded during the 16-week follow-up

(with missed appointments imputed as positive for opioids). The secondary outcome was the rate of completion of the 16-week outpatient treatment without interruption (retention in treatment) in each condition. On an exploratory basis, the buprenorphine elimination rate (BUP EL. R) was examined for association with the percentage of negative UDS and retention to examine if this would predict outcomes. Several measures of patient characteristics were explored for their associations with outcomes.

Findings

The experimental group achieved 76.7% (*SD* 25.0) negative UDS and the control group achieved 63.5% (*SD* 34.68) (mean difference = 13.26% [95% CI 3.19–23.31; $p = 0.01$; effect size [ES] = 0.44 [95% CI 0.09–0.76]). The difference in study completion rate between the experimental and control group was not significant (i.e. 57.14% in the experimental and 46.4% in the control group; odds ratio [OR] 1.54, 95% CI 0.78–2.97). To achieve higher percentage negative UDS, the adjusted Incidence Rate Ratio (IRR) in the experimental group compared to the control group was 1.15 (95% CI 1.01 – 1.30). For the secondary outcome, 40 participants in the experimental group and 33 in the control group completed the trial without significant difference ($\chi^2 = 1.605$, $p=0.21$). Buprenorphine elimination rate (BUP EL. R) was negatively associated with the percentage of UDS (Spearman's rho = -0.274, $p < 0.05$) and predicted the primary outcome (R^2 0.265, $p=0.001$). No other sociodemographic factor nor the dose of BUP/NX-F correlated with either the primary or the secondary outcome.

Conclusions

The clinical effectiveness of BUP/NX-F for OUD can be, enhanced by integrating TDM with medication management applying two contingencies for take home prescriptions. This treatment modality can facilitate access to MAT with minimal concern over diversion and possibly optimize cost-effectiveness. In contrast, BUP EL.R is a promising predictor of response to buprenorphine/naloxone measured by opioid use, and can contribute to implement precision medicine and personalised treatment.

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ABBREVIATIONS AND ACRONYMS

ALT	Alanine Aminotransferase Test
AST	Aspartate Aminotransferase Test
Alt-D	Alternate Day Dosing
ASI	Addiction Severity Index
BIS-11	Barratt Impulsiveness Scale
BPD	Borderline Personality Disorder
BMI	Body Mass Index
BUP	Buprenorphine
BUP/NX	Buprenorphine/ Naloxone (Suboxone [®])
BUP/NX-F	Buprenorphine/ Naloxone Film (Suboxone [®] Film)
CYP	Cytochrome
CM	Contingency Management
CI	Confidence Interval
COWS	Clinical Opioid Withdrawal Scale
CV	Coefficient of Variance
DEC	Disposable Extraction Column
DOT	Directly Observed Treatment
DSM	Diagnostic Statistical Manual
DW	Disability Weight
EL. R	Elimination Rate
GAD-7	Generalised Anxiety Disorder 7-items screen
HIV	Human Immunodeficiency Virus
ICD	International Classification of Diseases
IRR	Incidence Rate Ratio
LoD	Limit of Detection
LoQ	Limit of Quantitation
MAT	Medication Assisted Treatment using buprenorphine
MCC (O) S	Minnesota Cocaine (Opioid) Craving Scale
MET	Methadone/ Methadone maintenance

MM	Medication Management used interchangeably Medical Treatment Management (MTM).
NRC	National Rehabilitation Center- UAE
N-BUP	Nor-buprenorphine
NNT	Number Needed To Treat
OAT	Medication Assisted Treatment using partial or full opioid receptor agonists
OR	Odds Ratio
ODU	Opioid Use Disorders
PDS	Personality disorders Screener
PHQ-9	Patient health questionnaire, 9 items
PSQI	Pittsburgh Sleep Quality Index
PI	Principal Investigator/ Candidate: Hesham Elarabi
POCT	Point-of-Care-Test
RR	Relative Risk
SD	Standard Deviation
SPE	Solid Phase Extraction
SUD	Substance Use Disorders
TDM	Therapeutic Drug Monitoring
TIW	Three Times Weekly
UAE	United Arab Emirates
UNODC	United Nations Office on Drug and Crime
UDS	Urine Drug Screens
WHO	World Health Organisation
WSAS	Work and Social Adjustability Scale

Dedication

I dedicate this work and every success and achievement in my life to my family. My late beloved father who was and is still my inspiration, mentor and soul mate , and mother were true partners in completing this work. They have lived every moment of the endeavour. I cannot thank them enough.

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Declaration

This declaration is to certify that:

- (i) the thesis contains only my original work,**
- (ii) due acknowledgement has been made,**
- (iii) the thesis is less than 100,000 words in length,**



Hesham Farouk Elarabi

Publications arising from this study (Appendix A)

My thesis is categorised at King's College London as a 'thesis incorporating publications'. Three articles were published in the following peer reviewed academic journals and are presented in separate chapters. The original articles are placed in the appendices:

Elarabi, H., Elrasheed, A., Ali, A., Shawky, M., Hasan, N., Gawad, T. A., Adem, A., & Marsden, J. (2019). Suboxone Treatment and Recovery Trial (STAR-T): Study Protocol for a Randomised Controlled Trial of Opioid Medication Assisted Treatment with Adjunctive Medication Management Using Therapeutic Drug Monitoring and Contingency Management. *Journal of addiction*, 2019, 2491063.

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CHAPTER 1 INTRODUCTION

This thesis is presented in seven chapters and was prepared following the reporting convention of the Consolidated Standards of Reporting Trials (CONSORT) (Shultz, Altman, Moher, 2010). The CONSORT checklist is presented in **Appendix B.1**.

In **Chapter 1**, I provide an overview on Substance Use Disorders (SUD), the prevalence and associated harms, the extent and challenge of co-occurring mental health disorders, the evidence-based treatments applied in Opioid Use Disorders (OUD), and challenges associated with providing Opioid Assisted Treatment (OAT) using opioid agonists and partial agonists. The chapter closes with a summary on the need for developing interventions that optimises both medication adherence and treatment retention.

In **Chapter 2**, I provide a description of the Buprenorphine/Naloxone (BUP/NX) clinical pharmacology, and how it is used in OUD treatment and why is it a candidate for Therapeutic Drug Monitoring (TDM). I also provide an overview on TDM, the requirements for reliable TDM, and current evidence to support its application in BUP/BUP/NX treatment. The summary of **Chapters 1 and 2** incorporate the background and introduction sections of the published protocol and the published study results. **Chapter 2** concludes with an outline gaps in published literature, the primary aim of the study and the study hypotheses.

In **Chapter 3**, I present the clinical study conducted and published to examine the clinical feasibility of TDM in the first 15 participants recruited to Clinical Trial (Suboxone Treatment and Recovery Trial; START) and stabilised on BUP/NX-F. The study further describes the procedures applied to optimise and validate the precision of the laboratory method applied for BUP detection and quantitation.

Chapter 4 incorporates the published clinical study protocol and presents the overall methods and materials used to conduct the randomised clinical trial that contributed to this thesis. In **Chapter 4**, a detailed description of the inpatient procedures conducted for all participants prior to randomisation to the 16-week study period, the specific procedures for the experimental and control groups, the governance framework for the study, and the analyses plan.

Chapter 5 incorporates the main publication of the study that includes the baseline characteristics of the participants, clinical data including the psychosocial and addiction severity measures, craving and pupil reflexes. This chapter presents the study findings addressing hypothesis 1, 2 and 4 of the study. In contrast, **Chapter 6** examines the exploratory hypothesis number 3 and closes with the finding for performed to address all the hypotheses set for this thesis. In the final **Chapter 7**, I provide a summary of the main results and discuss them in the context of the published literature. The strengths and limitations of the study and the clinical and policy implications of the findings are, presented. Suggestions for enhancing outcomes of the current services and further data analyses and future research questions are, outlined. **Chapter 7** closes with the main conclusions.

1.1 OVERVIEW

The aim of this thesis is to determine the clinical effectiveness of Opioid Use Disorder (OUD) treatment using buprenorphine/naloxone film (BUP/NX-F) medication (Suboxone[®]) in ‘take-home’ prescriptions adjusted contingent of medication adherence according to Therapeutic Drug Monitoring (TDM) and drug use abstinence according to Urine Drug Screens (UDS). The content of the thesis provides the background, rationale, clinical feasibility of TDM in monitoring adherence with BUP/NX-F, methods, results, and implications of a 16-week, phase III/IV, parallel group, and randomised controlled trial (the Suboxone[®] Treatment and Recovery Trial; STAR-T). STAR-T was conducted at the National Rehabilitation Centre (NRC), Abu Dhabi-United Arab Emirates (UAE; www.nrc.ae). The NRC is the national addiction response centre for the UAE and is a World Health Organisation (WHO) Collaborating Centre. The trial was developed and completed during the candidate’s PhD programme.

The UAE is a confederate of seven states, or emirates, the largest of which is Abu Dhabi, with a population of approximately 9.5 million. Abu Dhabi is composed of three main regional cities, namely Abu Dhabi, Alain, and AIDhafra. Traveling to Abu Dhabi from these cities or any other emirate would requires a minimum drive of 90 minutes. The NRC established in 2002 as part of the balanced drug response policy, and operates in a suburb of Abu Dhabi city. The UAE adopts a balanced supply and demand reduction drug policy with strict law enforcement component and a facilitation of treatment provision. Part of the NRC’s mandate is providing a multi-modality treatment

service with inpatient and community treatment interventions for psychoactive substance use disorders (SUDs). A sequential, continuing care approach is provided, linking assessment/intake, inpatient care (detoxification and stabilisation, early recovery), and outpatient programme and a day care. A multi-disciplinary team delivers all therapeutic programmes at the NRC, including psychiatrists, physicians, psychologists, nurses, social workers, clinical pharmacists, a clinical pathologist–toxicologist, a dietician, and patient service coordinators.

The substance use landscape of patients presenting to the NRC has significantly changed over the past two decades. In a retrospective study of individuals admitted for treatment prior to 2010, majority of patients were aged 30–40 years (Elkashef et al., 2013). A cross-sectional study in 2015 by Albalooshi and colleagues (2016) reported that the predominant age bracket had fallen to 20–30 years. The presented substance use problem also changed from a predominant use of alcohol (41.3%), followed by opioids (16.3%) to a predominantly ‘opioid and polysubstance use’ presentation (84.4%).

In 2002, the NRC introduced Opioid Assisted Treatment (MAT) using BUP for OUD. BUP, rather than methadone (MET) was chosen due to prevailing concerns about safety, diversion risk, and perceived social stigma associated with MET. In 2009, the combination of BUP and naloxone (BUP/NX) in tablet formulation was introduced to the NRC formulary to replace BUP monotherapy. Treatment has been offered to people with illicit OUD but is not available to those with pharmaceutical/prescription OUD. Directly Observed Treatment (DOT) was not available in outpatient care due to the concerns over patient discontinuation and higher cost. Alternatively, ‘take-home’ prescriptions (i.e. unsupervised patient self-administered) was the medication dispensing method.

At that time, there was no objective means of monitoring BUP/NX adherence. In 2013, the NRC restricted providing MAT using buprenorphine containing medications to patients already enrolled in the MAT programme, i.e. no new patients were prescribed MAT using BUP. This restriction was introduced in response to reports by local drug enforcement identifying local diversion of BUP for non-medical use. Additionally, the decision to limit MAT to recurrent patients seems to be justified by regional reports suggesting a rise in non-authorised use of BUP (Oraby, 2013). Clinically, there was recognition that these response measures were suboptimal to a significant OUD problem in the UAE population and acted as the main motivation for the present study.

In order to address this motivation, and conscious of concerns over medication diversion and abuse –that has limited the provision of MAT in the gulf countries (Alam-meherjerdi et al., 2016; Elkashef et al, 2019), a complex medication management protocol was developed and examined against treatment as usual (STAR-T). The main objective of STAR-T was to provide optimal BUP/NX treatment via monitoring for abstinence from opioid use and adherence with BUP/NX.

1.2 PREVALENCE AND DIAGNOSIS OF SUBSTANCE USE DISORDER

In 2019, the United Nations Office on Drugs and Crime estimated that 247 million people (5% of the global general population aged 15 to 64 years) used psychoactive substances, and 15.6 and 11 million respectively using opioids or illicit heroin (UNODC, 2019).

In the Diagnostic Statistical Manual Fifth Edition (DSM-5) (American Psychiatric Association, 2013) SUDs requires that the individual has experienced two or more of 11 criteria (listed in **Table 1.1**) at the same time in the past 12 months, compared to three or more criteria under DSM-IV-TR (Hasin et al., 2013). These criteria are grouped under four categories: 1) impaired control, 2) social impairment, 3) risky use and 4) pharmacological indicators. Under the DSM-5, SUD severity is classified based on number of symptoms as Mild (2–3 symptoms), Moderate (4–5 symptoms), and Severe (6–11 symptoms). In addition, the “legal consequences” item was, removed from the DSM-5 due to international differences in legal controls.

Table 1.1 The DSM 5 categories and criteria for diagnosis of substance use disorders

Category	Impaired Control	Social impairment	Risky use	Pharmacological indicators
Criteria	Use of larger quantities than intended	Neglect major roles to use	Hazardous use	Tolerance Withdrawal
	Much time spent in use Repeated attempts to quit	Hazardous use Interpersonal or social problems	Physical and psychological problems	Craving

The prevalence of SUD and co-occurring mental health disorders was reported at 45% to 55% (Davis et al., 2005). Prevalent co-occurring disorders include Major Depressive Disorder, General Anxiety Disorder (GAD), Personality Disorders, and Post-Traumatic Stress Disorders (Cottler et al., 1992). In contrast, impulsiveness is a personality trait defined as acting without thinking or planning with maladaptive behaviour despite of pertinent harm (Jentsch et al., 2014). Impulsiveness is characterised by three main constructs: sensation seeking, dis-inhibition, and impulsive decision-making and can be classified to three sub-types—attentional, motor, and non-planning behaviours (Snowden & Gray, 2011). Impulsiveness has reported associations with the initiation, maintenance, and progression of SUD (Allen et al., 1998; Brady et al., 1998). In users of illicit opioids, Baldacchino, Balfour, and Matthews (2015) reported high levels of impulsiveness, particularly impairments in strategic planning and motor impulsiveness. In contrast, personality disorders associated with SUD and has a prevalence of over 50% in the SUD population. Specifically, the prevalence of Borderline Personality Disorders (BPD) is ranges from 5% to 32% in individual with SUD (Trull et al., 2010). Available evidence indicates that individuals with BPD tend to initiate substance use at a younger age and have a poor SUD prognosis (Haro et al., 2004; Sher & Trull, 2002). Emotional dysregulation and other symptoms of BPD were associated with functional changes in the endogenous opioid system, particularly the kappa receptor (Bandelow et al., 2010).

The prevalence of sleep disorders in the SUDs population was reported at 80.2%, compared to 24.5% in non-substance use population (Liao et al., 2011; Putnins et al., 2012). Tang and colleagues (2015) compared the sleep profile of 2,178 drug users (including 1,012 heroin users) to 2,236 non-drug users using the Pittsburgh Quality Sleep Index (PSQI). The drug user group reported a sleep latency of 38.6 minutes, compared to 18.4 minutes among non-drug users. Although total sleep duration did not differ between the two groups, the drug use group had poorer sleep quality and higher daytime dysfunction. Less than half (44%) of the drug users had a total PSQI score exceeding eight (the cut-off score for poor sleep disorders defined in the study), compared to 5.2% for the non-drug users. Heroin users had the highest percentage (55.2%) of individuals with a score above this cut-off, followed by methamphetamine users (33.6%). The need for sleep medications was also higher among the drug users compared to non-drug users.

This co-occurrence of mental disorders and SUDs is likely to reflect common developmental pathways and shared biological and environmental risk factors. Such co-occurrence can be diagnostically challenging to determine whether the SUD or the mental health disorder is the primary problem disorder (Davis et al., 2010; Davis et al., 2012). Therefore, careful diagnosis and coordination of treatment interventions is required (Regier et al., 1990).

1.3 TREATMENT

Treatment usually commences with the evaluation of physical and mental health status and establishment of patient's substance use profile, followed by the patient placement in an appropriate level of care guided by the ASAM Patient Placement Criteria (American Society of Addiction Medicine, 2001). Medically supervised withdrawal (detoxification) is usually the first level of care and involves the stabilisation of patients who are severely intoxicated and the management of withdrawal symptoms (ASAM, PPC-II, 2001). The early phases of treatment can include a motivation enhancement (psychosocial) intervention that sets the stage for an integrated psychosocial, behavioural, biological, and spiritual programme. Following detoxification, the patient transits into a continuum of care that includes short or extended inpatient treatment followed by outpatient and ambulatory care.

Evidence-based psychosocial interventions for SUD include Cognitive Behavioural Therapy (CBT), Relapse Prevention skills training, Contingency Management (CM), Motivational Interviewing, Family Therapy, and the Community Reinforcement Approach (Miller, Zweben, & Johnson, 2005). It is important to highlight that achieving optimal treatment outcomes requires appropriate selection of interventions, understanding how these interventions interact towards developing an integrated comprehensive personalised treatment plan (Elarabi et al., 2014).

Providing pharmacotherapy for SUD extends beyond medical detoxification and acute treatment towards integration with psychosocial care to achieve optimal recovery outcomes (Litten, 1996). For OUD detoxification, the opioid agonist methadone (MET) the opioid partial agonist buprenorphine (BUP) BUP and naloxone in a 4:1 ratio (BUP/NX), and the alpha 2 agonists Clonidine and Lofexidine have all been used for opioid detoxification in addition to symptomatic medications. Opioid Assisted Treatment (OAT) using MET or BUP/BUP/NX is an essential front-line intervention for

OUD (World Health Organization [WHO], 2009). Whether delivered through specialty clinics or community pharmacies, MAT comprises of elements aimed at monitoring treatment outcomes and minimising diversion (Thomas et al., 2013). MAT combines specific psychological and pharmacological interventions intended to reduce opioid use and its related harm, and to enhance quality of life (WHO, 2009). However, as MAT provision can be limited due to several barriers comprised of social stigma, and suboptimal clinical practices, fear from diversion (Elkashaf et al., 2019) and high cost, only 10% of patients in need of treatment are currently receiving MAT (Nosyk et al., 2013).

The rationale for using full opioid agonists and partial agonists in MAT is explained neuro-biologically by reduction in the up-regulation of the opioid receptors and dynorphins. This up-regulation caused by chronic opioid use is assumed to persist after periods of abstinence and is associated with increased dysphoria and anxiety that drive drug use negative reinforcement (Blum et al., 2000). Cross-tolerance is another rationale for the use of full and partial opioid agonists. This feature facilitate opioid agonist action to occur without any additional euphoric effect and is explained by pharmacodynamics and pharmacokinetics principles. From a pharmacodynamics perspective, the lack of euphoria is driven by a complex homeostatic and cellular change resulting in receptor down-regulation and desensitisation, and delayed receptor recovery (AlHasani & Bruchas, 2011). In contrast, cross-tolerance, from a pharmacokinetic perspective, entails displacement of opioids by a higher-affinity opioid, such as BUP.

The value of providing MAT may extend beyond reduction in drug use. The effect of MAT on enhancing psychological functioning was reported in a study of adolescents with OUD enrolled in MAT (MET or BUP). In this study, reduction in depression, anxiety and anger symptoms with a medium effect size [Cohen's d 0.40–0.60] was achieved after four months of treatment (Smyth, Ducray, & Cullen, 2016). In another study, BUP was associated with an improvement in depressive symptoms, as well as reduction in suicidal ideation and feelings of social rejection (Bershad et al., 2015). BUP was reported to reverse sleep disturbance and reduce sleep latency associated with opioid withdrawal (Lukas et al., 1996). Zheng and colleagues (2016) reported significant reductions in the severity of sleep disorders measured over 90 days in patients receiving BUP treatment.

The impact of adjunctive psychosocial interventions was, evaluated in a Cochrane Collaboration meta-analysis of 11 studies with 1,592 participants (Amato et al., 2011a). The authors of this comprehensive review concluded that adding psychosocial treatment to MET- or BUP- significantly reduces opioid use (Relative Risk [RR] 0.82; 95% CI 0.71 – 0.93) and treatment drop out (RR 0.71; 95% CI 0.59–0.85). Another systematic review of 35 studies of Opioid Assisted Treatment (OAT) with a total 4,319 participants, Amato and colleagues (2011b) found no benefit of adding psychosocial interventions to MET or BUP maintenance compared to medication alone on negative drug screens (RR 1.12; 95% CI 0.92–1.37) or retention in treatment (RR 1.03; 95% CI 0.98 – 1.07). The authors noted that the comparator groups in these studies were offered standard counselling as part of the OAT (Amato et al., 2011b).

Although it would appear that no single psychosocial intervention is effective in addressing all relevant SUD manifestations; Contingency Management (CM) has been widely studied and deserves focused attention. CM is a behavioural intervention underpinned by the principles of positive reinforcement (operant conditioning). It is the most widely studied adjunct in MAT (Stitzer & Petry, 2006). CM is described as an intervention that “*organises treatment delivery, sets specific objective behavioural goals, and attempts to structure patient’s environment in a manner conducive to change*” (Stitzer, Bigelow, & Gross, 1989). Contingency rewards take several forms, including financial (e.g., vouchers that can be exchanged for services or commodities), and MAT medication-related (e.g., ability to increase dose and/or earn ‘take-home’ prescriptions for self-administration (Higgins et al., 1994).

Following their meta-analysis of 30 CM studies focusing on MAT using MET; Griffith and colleagues (2000) concluded that CM is associated with a mean effect size of 0.25 in achieving abstinence. These findings underscore the importance of providing CM reinforcement within 24 hours of the UDS in motivating abstinence (reflecting a learning principle that reinforcement should quickly follow the target behaviour). Indeed, this meta-analysis found that CM focusing on increasing MET doses and providing ‘take-home’ prescriptions achieved the largest effect size. The effect of CM was mediated by several factors, including number of drugs targeted (a single drug was associated with a larger effect size) and the number of UDS performed (a higher number of samples was associated with a larger effect size). These findings were replicated in a meta-analysis of 34 studies of different psychosocial interventions among patients with various SUD conducted by Dutra and colleagues (2008). Here, the authors concluded

that CM was the most effective psychosocial intervention, although effect sizes varied considerably by type of substance use.

Another adjunctive intervention for MAT is Medical/Medication Management (MM). This is an integrated patient-centred intervention designed to optimise treatment outcomes by providing safe and effective medication and individualising treatment plans and goals (Cipolle, Strand, & Morley, 2004; Patient-Centered Primary Care Collaborative, 2012). MM aims to maximise patient compliance through collection of clinical information gathered by clinical and biological investigations (American Pharmacists Associations and National Association of Drug Chain Stores Foundation, 2008). Monitoring treatment outcomes and referral to additional interventions is integral to MM (American Pharmacists Associations and National Association of Drug Chain Stores Foundation, 2008).

Fiellen and colleagues (1999) developed a MM manual for BUP maintenance treatment in prescription opioid dependence. This manual is composed of structured psychosocial interventions with emphasis on building rapport with the patient, reviewing medical and psychiatric diagnoses, delivering patient education on achieving and maintaining abstinence, and engaging the patient in treatment. MM was compared to CBT in a randomised controlled trial conducted by Fiellin and colleagues (2013) involving 141 BUP/NX maintained participants. In this study, the approximate duration of the MM session was 15 to 20 minutes, and the duration for the CBT session was 50 minutes. In both groups, opioid use declined from 5.3 days per week at baseline to 0.4 days per week at the end of the study.

1.4 CHALLENGES ASSOCIATED WITH PROVIDING EFFECTIVE OPIOID ASSISTED TREATMENT

The value of retention stems from its contribution to longer abstinence, fewer relapses, lower severity of legal offenses, and enhanced employability (French, Popovici, & Tapsell, 2008). Therefore, various efforts to enhance treatment retention were, explored including frequent drug testing, which resulted in longer retention periods (Hser et al., 2014). In this study, participants receiving frequent drug testing reported a mean retention of 411 days compared to 207 days for those who did not receive the frequent drug testing. Using treatment enrolment as a definition of retention, Lin and colleagues (2013) found an inverse relationship between retention and duration of follow-up (i.e.,

74.8%, 61.5%, and 41.6% retained at 3, 6, and 12 months, respectively). These rates were, based on an analysis of a Taiwanese community sample and were comparable to a sample in Scotland, where Peters and Reid (1998) reported 39% retention at 12-months of follow-up.

Retention appears to be, influenced by patient characteristics, type of SUD, and treatment intervention and the type of medication used in MAT. In a secondary analysis of 1,267 participants randomised to a MET or BUP/NX group, Darke and colleagues (2007) found that 74% of the MET group completed the 6-month treatment at follow-up, compared to 46% of those in the BUP/NX group. Moreover, greater retention was noted for those receiving higher doses (i.e., 60 mg/day for MET and 32 mg/day for BUP/NX), and the BUP/NX group had a significantly smaller number of opioid-positive UDS. Similarly, different types of BUP/NX formulation (Sublingual Tablet and Film) generated different outcomes. There was a longer time to discontinuation, a lower hospitalisation rate, and a greater number of outpatient visits reported for those prescribed the BUP/NX film compared to the BUP/NX tablet (Clay et al., 2014).

As with all chronic illnesses, SUD treatment is associated with medication non-adherence (WHO, 2003). The significance of treatment adherence is, demonstrated by a 10-fold increase in relapse reported in non-BUP adherent individuals (Tkacz et al., 2017). Treatment discontinuation or disengagement from treatment vary across different levels of care. At the inpatient detoxification, discontinuation ranges from 22% to 43%, while 17% to 57% is typical for inpatient rehabilitation programmes. This rate increases to 32% to 67% when MAT is, delivered in an outpatient setting (Specka et al., 2011). Factors associated with high discontinuation rates include polysubstance use, multiple treatment episodes, and criminal behaviour (Gossop et al., 2003; Harvard et al., 2006). Younger individuals suffering from psychiatric disorders with low distress intolerance and high impulsiveness were more likely to discontinue treatment prematurely (Mancino et al., 2010). Similarly, severe psychiatric illness or social harms caused by SUD are associated with treatment discontinuation (Lin et al., 2013). Nevertheless, the impact of depression and anxiety on treatment retention remains equivocal. For example, results obtained in a longitudinal study conducted by Teesson and colleagues (2006) show that depressed patients are more likely to discontinue from treatment than those without depression. This finding was, not replicated in a study involving 2,300 participants, as a part of which the researchers analysed the association between depression or anxiety and retention in treatment (Mancino et al., 2010).

Misuse of BUP/BUP/NX includes using doses or routes different from those prescribed to achieve mood changes. Misuse is rationalised by difficult and progressive non-adherence occurring in the early stages of treatment or is ascribed to possible therapeutic failure occurring later in treatment (Weiss, 2014). Diversion and illegal distribution may lead to overdose and fatalities (WHO, 2009) and is marked by significant social and medical hazards (Yokell, Zaller, Green, & Rich, 2011). Misuse and diversion of BUP/BUP/NX is a common challenge not limited to a particular geographic location or culture according to an international review of studies examining BUP/BUP/NX misuse and diversion (Lowfall et al, 2014). The authors of this review called on ongoing and future research to develop sensitive and specific methods to detect misuse and diversion (Lowfall et al., 2014).

The level of concern over diversion and abuse of BUP/BUP/NX among addiction psychiatrists and non-prescribing clinicians practicing in the United States (US) was the subject of the survey conducted by Schulman-Olivier and colleagues (2013). Their results showed that 40% of the 369 responding clinicians perceived BUP and BUP/NX diversion as dangerous and related this practice with the occurrence of accidental overdose. Another common belief that emerged from this survey was that BUP/NX diversion worsens the opioid epidemic. In the middle-east and Arabian Gulf countries, providing MAT is limited (Alam-Mehrjerdi et al, 2016) due ‘fear’ from medication diversion (Oraby et al, 2013; Elkashef et al., 2019)

Supervised dosing is suggested to limit diversion and enhance retention was reported by Wright et al. 2015 to be associated with high effectiveness and ease of implementation. However, diversion of supervised doses has been reported in a post-marketing surveillance of MAT with 12% for BUP, 9% for BUP/NX, and <1% for MET (Larance et al., 2011). In contrast, supervised treatment is associated with increased costs, particularly those related to staff, and lower retention in treatment (Gerra et al., 2011; SAMHSA, 2015). Supervised and unsupervised doses showed no difference in reducing opioid use or enhancing retention in treatment (Bell et al, 2007; Holland et al., 2014). A systematic review of studies focusing on supervised dosing versus ‘take-home’ prescriptions of BUP/BUP/NX failed to provide evidence to support the effectiveness of supervised dosing related to retention, diversion, or opioid use. The authors evaluated the quality of evidence (rated as low) and called for further studies (Saulle, Vecchi, & Gowing, 2017).

It would appear that the increasing concern over abuse and diversion has led to the development of measures to minimize diversion and detect non-adherence (Hall & Degenhardt, 2011). These include “*real-time*” prescription monitoring systems (in order to avoid doctor-shopping practices), along with the registration of prescribing physicians and a structured policy of random “tablet / medication counts” and urine drug checks (SAMHSA, 2015). No published data on effectiveness of medication counts in enhancing adherence or minimising diversion is available. It is widely believed that regulatory monitoring activities may significantly limit treatment accessibility, and hence explain why only 10% of individuals in need of MAT treatment do actually end up receiving it (Nosyk et al, 2013). Tight control and limiting access to BUP/BUP/NX treatment might contribute to inadequate care and poor adherence leading to the use of BUP-containing medications via non-medical routes (i.e., injecting and snorting). Therefore, facilitating treatment accessibility and availability may actually contribute to curbing diversion and limiting misuse of BUP containing medications (Yokell et al., 2011).

1.5 SUMMARY

OUD is a prevalent, chronic, but treatable disorder that is associated with mortality and a high global disease burden (Martin et al., 2015; Peacock et al., 2018). The increase in the global prevalence of OUD and opioid-related overdose has led to a priority call for expanding treatment services (Volkow et al., 2014). MAT using sublingual buprenorphine (BUP; also available in a 4:1 formulation with naloxone; BUP/NX), is a first-line pharmacotherapy for OUD (WHO, 2009). Patients who adhere to MAT are likely to have more suppression of opioid use and increased periods of abstinence (Mattick et al., 2015; Darke et al., 2007), along with a reduced risk of opioid overdose (White et al., 2015), and a reduced risk of relapse (Tckaz et al., 2012).

Effective MAT includes providing opioid agonists or partial agonists within a structured and integrated framework of motivational interviewing and CBT, as well as response and adherence monitoring. CM is recommended as adjunct behavioural treatment to MAT (National Institute for Health and Care Excellence, 2007) and is the most studied adjunct treatment in MAT (Stitzer & Petry, 2006). Providing ‘take-home’ prescriptions or unsupervised doses is reported to be the most preferred reward among MAT patients (Griffith et al., 2000). However, ‘take-home’ prescriptions or unsupervised doses are,

considered as a source of diversion and abuse. To monitor adherence while on unsupervised doses, self-report and medication counts are, applied with no published evaluations to date (SAMHSA, 2015). These methods may contribute to monitor whether the medication is being taken or not but does not provide information on whether the medication is used as prescribed nor whether it is misused or diverted.

Therefore, developing a treatment modality that optimises medication adherence with minimal concern over diversion or abuse may facilitate access to the provision of opioid assisted treatment in OUD. Demonstrating the effectiveness of this modality by evidence from randomised controlled trials would contribute to its integration into mainstream treatment.

In this chapter, the clinical pharmacology of BUP and its clinical application for the treatment of OUD and the applications of Therapeutic Drug Monitoring (TDM) and the requirements for performing reliable TDM are, described. The chapter closes with the literature search strategy and gaps in reviewed literature, the aim of the study and hypotheses.

2.1 BUPRENORPHINE CHARACTERISTICS

Pharmacologically, BUP exhibits partial agonist activity at opioid mu receptors with low intrinsic activity, high affinity, and low dissociation constant. These characteristics result in the extended duration of action and safety due to ceiling effect. At the kappa receptor, BUP acts as an antagonist with minimal dysphoria, whereas it has no activity at delta receptors (Greenwald et al., 2003; Walsh et al., 1994).

Absorption: Administered orally, BUP has poor bioavailability, with an extensive first-pass effect, and an approximate absorption rate of 14%. Similarly, naloxone's oral bioavailability is 10% (Mendelson et al., 1997). In contrast, the bioavailability of BUP sublingual solution is 28% to 51%, while the bioavailability of a BUP sublingual tablet or cellulose filmstrip is 49% to 63% (relative to solution). Bioavailability data for the continued administration of BUP tablets or solution shows no difference at 28 days (Cowan, 2003).

The time taken for BUP to achieve maximum or peak concentration in plasma depends on the route of administration and the pharmaceutical dosage form and formulation. The reported time to reach peak plasma concentration is 45 minutes for a sublingual tablets, 30–90 minutes for solutions, and 40 minutes for the film formulation (Elkader & Sproule, 2005). Peak concentration increases non-proportionally with dose and due to the large inter-subject variability, no accurate population estimates for dose and concentration can be established (Chiang and Hawks, 2003). Food consumption can also influence the BUP concentration following sublingual administration. Elkader and Sproule (2005) published review on the pharmacokinetics of sublingual BUP and BUP/NX reported significant differences in mean BUP concentrations before and after

food consumption. BUP is 96% bound to alpha and beta globulin while naloxone is only 40% bound to albumin (Mendelson et al., 1997; Micromedex, 2011).

Metabolism: BUP is 100% metabolised by the liver, with a hepatic extraction fraction of 0.6–0.9 (Elkader & Sproule, 2005). BUP is metabolised to N-BUP, which demonstrates 20% of the activity of the parent compound. In the liver, the major metabolic pathway for BUP is the enzyme cytochrome 3A4 (CYP 3A4) (65%), followed by CYP 2C8 (30%). The remaining 5% of BUP is metabolised by CYP2C9, CYP2C18, and CYP2C19 isoforms. Given this metabolic pathway, it is important to monitor liver function in patients diagnosed with liver disease. The elevation of Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) three times above baseline in individuals with hepatitis receiving BUP has been reported (Petry et al., 2000). This is of particular importance for patients with non-viral hepatitis –possibly caused by alcohol use- and those receiving antipsychotics or other mood stabilising agents known to affect liver function (Elkader & Sproule, 2005; Micromedex, 2011).

Elimination: BUP elimination has a first-order kinetic profile. BUP plasma concentration can be estimated by the following equation (Fischer, Jönsson, & Hjelmström, 2013):

$$C(t) = C_0 \cdot e^{-kt}$$

where:

t: Time interval between the maximum concentration and the time of sample drawing

k: Elimination rate constant

C₀: Peak concentration or concentration after achieving steady state

C_t: Concentration at the time point after steady state

Elimination of BUP depends on the route of administration. For example, a mean half-life duration of 5.2 hours is reported for intravenous administration and 40 hours for sublingual administration (Elkader & Sproule, 2005). Authors of single-dose sublingual tablet and 7-day administration consistently report a mean half-life of 20 hours (Ciraulo et al., 2006; Elkader & Sproule, 2005). In-vivo, BUP and N-BUP form an inactive gluco-urate. Up to 30% (10% to 30%) of the BUP and N-BUP is excreted by the kidneys as a gluco-urate conjugate. The remainder is excreted via bile into the intestine, where it is hydrolysed back to the free form, followed by enterohepatic

recirculation, and faecal excretion. Available reports based on small samples and low-dose intravenous BUP suggest no major physiological impacts of BUP among patients with renal disease (McAleer et al., 2003). However, the effect of renal function on plasma levels of BUP and N-BUP remains insufficiently studied.

Drug-drug interaction: BUP is a substrate and a potent inhibitor of CYP3A4 and a potent inhibitor (but not a major substrate) of CYP2D6 (Micromedex, 2011). Therefore, BUP will influence the metabolism of CYP3A4 and CYP2D6 substrates, and is influenced by compounds that induce or inhibit CYP3A4 (Zhou et al., 2007). Hence, care should therefore be taken when prescribing anti-retroviral medications, antidepressants, mood stabilising agents, and antipsychotics. In contrast, BUP exhibits drug–drug interaction through pharmacodynamics with benzodiazepines and alcohol. The extent of benzodiazepine use with MAT was, evaluated in a cross-sectional study of 250 individuals receiving or had received MET or BUP (Nielsen et al., 2007). Results showed that 67% of the participants reported concomitant use of benzodiazepines with a mean daily dose of 30 mg diazepam equivalent via intravenous route. This relatively high prevalence of benzodiazepine use was reported to significantly decline during the first year of MAT (Gossop et al., 2003)

Studying the interaction with benzodiazepines is therefore important, given the high prevalence of Benzodiazepine use among patients receiving MAT and reported fatalities. In a Norwegian study, Bramness and Kornor (2003) reported a 40% prevalence of benzodiazepine prescribing in patients enrolled in MAT, which is about eight times higher than the prevalence of benzodiazepine prescribing in general population. Fatal events due to CNS sedation (indicated by pulmonary oedema and deep cyanosis) were reported in post-mortem evaluation of 20 individuals previously enrolled in BUP maintenance and were using benzodiazepines (Tracqui, Kintz, & Ludes, 1998). The authors attributed fatalities to the use of psychoactive substances with benzodiazepines found in the viscera in 19 of these cases, and BUP injection in 8 cases. The authors further identified 5 ng/mL as the toxic BUP level associated with death.

Diazepam at 10 and 20 mg doses had no effect on the assessed psychological measures (e.g., reaction time, cancellation tasks), or psychological factors such as pulse, blood pressure, peripheral SpO₂, respiratory rate, and pupil size (Lintzeris et al., 2006). In contrast, diazepam at a 10 mg or 20 mg dose caused minimal effects on physiological and psychological parameters in participants stabilized on BUP/BUP/NX or MET. A higher diazepam dose of 40 mg given in conjunction with BUP or MET decreased

psychological parameters (e.g., pulse, blood pressure, peripheral oxygen saturation, respiratory rate, and pupil size) (Lintzeris et al., 2006; Lintzeris et al., 2007). Thus, it is not recommended to prescribe BUP to persons with a recent history (past 30 days) of benzodiazepine use equivalent to a daily dose of 20 mg diazepam (Lintzeris et al., 2007; Lintzeris & Neilson, 2010).

The recognised routes of BUP administration are sublingual, mucosal, and transdermal. The available formulations for OUD treatment are sublingual and mucosal, a subcutaneous depot and an implant. Sublingual buprenorphine/naloxone (BUP/NX) is available in a sublingual film and tablet formulation. The sublingual film formulation was developed with the primary objective of improving patient experience, limiting diversion and abuse, and facilitating supervised dosing (Lintzeris et al., 2013). The capacity of the film formulation to limit diversion from supervised treatment is facilitated by its ability to quickly form a gel aggregate that is difficult to be removed after sublingual application (Lintzeris et al., 2013). Data collected from surveillance systems, prison centres, and MAT programmes indicates that the risk of BUP/NX-F diversion is lower than that associated with BUP/NX tablet use (Lavonas et al., 2014). However, the findings of a small-scale exploratory qualitative study of 16 participants indicate that BUP/NX-F may be injected in solution (Larance et al., 2016).

2.2. CLINICAL USE OF BUPRENORPHINE

BUP as monotherapy (Orman & Keating, 2009) and in combination with naloxone are used in medically supervised withdrawal (detoxification) and in relapse prevention during maintenance treatment of OUD. According to a meta-analysis conducted by Mattick, Kimber, Breen & Davoli (2003), the use of BUP and BUP/NX has been contrasted for low, high, and fixed doses; and in both prescription illicit opioid use against MET. Different BUP-containing preparations and formulations (i.e., BUP tablet vs BUP/NX tablet; and BUP/NX tablet vs BUP/NX-F) were compared. Treatment outcomes included primary measures of abstinence (i.e., consecutive opioid-negative UDS; percentage of opioid-negative UDS across total samples collected; self-reported opioid use during the past 30 days) and treatment retention.

Detoxification of opioids with the alpha-2 agonist clonidine is considered the standard of care in several countries. Ziedonis and colleagues (2009) contrasted clonidine to BUP/NX in 344 participants with OUD attending an inpatient ($n = 113$) and an

outpatient ($n = 231$) care. In this study, two opioid withdrawal scales (the Clinical Opioid Withdrawal Scale—COWS and the Adjective Rating Scale for Withdrawal—ARSW) were applied. Effectiveness was measured by (1) UDS; (2) retention; (3) change in withdrawal and craving scales; and (4) use of ancillary medications. Regardless of the level of care, withdrawal symptoms and craving were significantly lower in the BUP/NX group compared to the clonidine group. Participants allocated to BUP/NX treatment had a higher percentage of opioid negative screens i.e. lower opioid use, compared to those allocated to the clonidine group (76% vs 22%). The mean retention rate at both inpatient and outpatient care was higher in the BUP/NX group compared to the clonidine group (inpatient: 12.6 days versus 6.7 days; outpatient 11.3 days versus 7.1). For ancillary medications, BUP/NX treatment required significantly lower dose supplementation compared to clonidine (mean of 1.7 doses of ancillary compared to a mean of 3.2 doses).

Similar results were replicated in a 5-day outpatient detoxification of 114 adults with OUD comparing BUP with clonidine and symptomatic treatment (Ling et al., 2005). At day-5, participants randomised to the BUP group demonstrated a higher retention of 86% compared to 57% for those allocated to clonidine. Regarding opioid use, 21% of the BUP participants provided negative opioid screens compared to 4% of the clonidine group. During the 28-day follow-up period, participants allocated to the BUP group reported fewer days of drug use (median 6.5 days versus 14 days in the clonidine group)

In contrast, strong evidence supporting the efficacy of BUP maintenance for relapse prevention in OUD exists. For example, in a 17-week randomised controlled trial conducted by Johnson et al. (2000), 220 participants were randomised to receive either: (1) BUP 16–32 mg; (2) MET 60–100 mg; (3) Levomethadyl acetate 75–111 mg; or (4) MET 20 mg. Abstinence was assessed by self-reported drug use and the percentage of opioid-negative UDS. The provision of 12 consecutive opioid-negative UDS was similar for the BUP (26%) and the higher dose MET (28%). Mean retention in treatment was comparable between the groups (95 days for BUP versus 105 days for high-dose MET).

These findings were replicated by Kakko et al. (2007) in a study of 96 subjects randomised to receive flexible doses of either MET or BUP 16 mg (stepped up to 32 mg). Participants requiring additional dose increase in the BUP group beyond 32 mg were offered a transfer to MET. Retention in treatment at six months (76%) and percentage of opioid-negative UDS (80%) in the two groups were similar. However, 20

of the 37 participants completing the 6-month follow-up in the BUP group chose to switch to MET.

2.3. BUPRENORPHINE DOSE

In BUP pharmacokinetics and efficacy studies, the BUP dose ranged of 16mg/70kg to 44 mg/70kg was examined (Chawarski et al., 1999). The maximum daily dose of BUP that demonstrates a ceiling pharmacological effect in healthy adults is 32mg (Walsh et al., 1994). However, the maximum recommended daily dose for BUP/NX-F (Suboxone[®]) is 24mg (Reckit Beckneiser, 2012).

Participants who were stabilised on daily doses of 4-16 mg for 21 days demonstrated a higher abstinence of 64.7% compared to 24.3% in participants stabilized on 4mg (Schottenfeld, et al., 1993). According to a systematic review, the dose range of 8-16mg is effective, but the range 12-24mg is generally preferred for maintenance treatment (Mattick et al., 2003). In contrast, findings from a clinical trial comparing higher dose BUP (i.e., >16 mg) and moderate dose (8–16 mg) on UDS and treatment retention outcomes, indicated that participants stabilised on higher mean dose of 27.5mg (*SD* 4.8) reported higher reduction in opioid use compared to those stabilised on a moderate mean dose (11.5mg (*SD* 4.8) (Fareed et al., 2011). The authors concluded that flexible dosing at ≤ 32 mg optimised treatment outcomes.

The association between dose size, the percentage occupancy of mu receptors, BUP plasma levels, and withdrawal symptoms was examined using Positron Emission Tomography (PET) in a study of 13 participants maintained on BUP 0, 2, 16 and 32 mg/day for a period of 12 days (Greenwald et al., 2003). The findings revealed that total brain mu receptor occupancy varied with the BUP dose. Specifically, 40 %, 80%, and 84% occupancy was achieved at 2 mg, 16 mg, and 32 mg, respectively. The occupancy rates were homogenous across all brain regions for all doses except BUP 32 mg. A time-dependent association between the plasma concentration and opioid occupancy was observed (i.e., higher doses directly correlated with higher peak plasma concentrations and higher receptor occupancy). Over time, the plasma concentration declined and receptor occupancy increased.

In a related study, Greenwald, Comer, and Fiellin (2014) assessed the relationship between mu receptor availability and the clinical effectiveness of BUP. The authors

observed that 50% receptor occupancy corresponded to a minimum of 1 ng/mL plasma concentration needed to control withdrawal symptoms. However, the authors further noted that avoiding objective effects of opioid agonists in “usual doses” required mu receptor occupancy above 80%, and at “higher than usual doses” of full agonists, the required mu receptor occupancy of more than 90%. These findings suggest that fixed doses are not advised and BUP dose should be tailored to each patient.

According to the BUP/NX prescribing information, a single daily dose is the recommended frequency (Suboxone[®] PI, 2012). Dividing daily doses during maintenance is an identified practice in the Australian assessment report on BUP/NX (Department of Health and Ageing-Australia, 2012). Dose administration at lower frequencies (less than once daily) is suggested given the pharmacokinetics and pharmacodynamics characteristics of BUP (Orman & Keating, 2009). Alternate day dosing (Alt-D) was found to be equally effective to daily dosing in a study of 26 participants stabilised on daily 8 mg BUP/NX and randomised to receive either: (1) 8 mg daily, (2) 8 mg on alternate days, or (3) 16 mg on alternate days for 21 days (Amass, Kamien, & Mickulich, 2000). No differences in drug use, patient retention, treatment adherence, or patient and observer rating of withdrawal signs were found. However, pupil diameter readings for participants on the 8 mg alternate day regimen were significantly higher than in the other two groups. In this study, 12 participants (46%) failed to complete treatment, with no significant reasons reported. This group of non-completers had higher Addiction Severity Index (ASI) scores compared to the participants who completed treatment.

Another example of a non-daily dosing schedule is three times weekly (TIW) dosing, which was, compared with daily doses of BUP in a 12-week trial conducted by Schottenfeld and colleagues (2000). Participant (n= 94) were randomised to receive supervised doses of: (1) 16 mg daily dose or (2) 112 mg, the weekly equivalent of 16 mg/day given as two doses of 34 mg and one dose of 44 mg. The groups had similar baseline characteristics and reported similar 1) retention rates (71% for daily and 77% for TIW), 2) medication adherence (91% for daily and 92% for TIW) and 3) reduction in opioid use (57% and 58%). The findings suggest that, when similar efficacy is attained, it is reasonable to expect that participants will prefer fewer visits to the clinic and would opt for TIW.

2.4 THERAPEUTIC DRUG MONITORING AND BUPERNORPHINE TREATMENT

Therapeutic Drug Monitoring (TDM) is a patient centered and precision medicine tool that involves quantitation and interpretation of medication blood concentrations to optimise treatment outcomes (Hiemke et al., 2017). It has been applied in neuropsychiatry to enhance outcomes of anti-epileptics (Stepnova & Beran, 2015) antipsychotics (Patteet et al., 2012), mood stabilizers (Collins et al., 2010) and for monitoring drug-drug interactions (Paulzen et al., 2016).

TDM is recognised by the American Psychiatric Association as a tool in the management of psychiatric disorders yet clinical guidelines on patient management using TDM are lacking (Hiemke et al., 2017). The clinical applications of TDM include managing adverse events, optimising treatment response, assessing drug–drug interactions, and monitoring adherence. Despite such a broad scope, TDM is not a standard of care in pharmacopsychiatry (Hiemke et al., 2017). This may be because 1) not all drugs are candidates for TDM, 2) the clinical utility and feasibility of TDM is evident in some but not all indications and sub-populations, and that 3) sophisticated and reliable assay methods and platforms are often lacking.

According to a 22-item scale developed by Brunen and colleagues (2011) in which a higher score suggests that a drug is eligible for TDM, BUP was rated a candidate for TDM. Scores of 12, 14, and 15 were generated for lithium, nortriptyline, and clozapine, respectively, which are considered reference drugs with TDM applications in use. In contrast, the generated scores for BUP, naltrexone, and MET were 11, 10, and 17, respectively. An expert panel on the use of TDM in pharmacopsychiatry recommended TDM when prescribing mood stabilisers, antidepressants, antipsychotics, and medications prescribed in SUD (Hiemke et al., 2017). Four levels of recommendation were developed, namely “strongly recommended,” “recommended,” “useful,” and “potentially useful.” The panel “recommended” TDM for BUP, naltrexone, and MET. This recommendation positioned TDM for dose titration, and in special indications or in solving clinical problems.

In order to implement TDM, adopting a reliable laboratory test (assay) that detects and accurately quantitates the target analyte is imperative. Detection and quantitation of BUP requires high precision, accuracy, and selectivity across a wide range of concentrations reflecting individual variations. Quantitation of BUP and N-BUP in

urine may not be accurate as clearance of BUP in urine is erratic and accounts for less than 30% of total BUP. In contrast, BUP displays linear kinetics in blood and there is an established reference time to achieve peak and trough concentrations (Elkader & Sproule, 2005). No specific recommendation for the use of total blood, over plasma or serum was made (Hiemke et al., 2017). Therefore, plasma or serum (rather than a complex matrix, such as hair) is the biological matrix of choice, because it is least associated with interfering matrices (Marque & Kintz, 2004). Finally, it is the only matrix producing the required kinetics for TDM (Hiemke et al., 2017).

2.5 SUMMARY AND RESEARCH HYPOTHESIS

The literature reviewed as a part of this study (See Appendix B.2 for search strategy and data base search form) revealed that the suitability of TDM in BUP treatment was, evaluated. No studies were, retrieved on the clinical feasibility of TDM in monitoring the adherence with BUP/BUP/NX nor on how to integrate TDM in BUP-based treatment. Furthermore, the association of BUP elimination rate (EL.R) with illicit opioid use, or retention in treatment was not the subject of any studies identified in the literature search. No studies were retrieved on the effectiveness of CM using ‘take-home’ BUP/NX-F as a reward for both abstinence and adherence.

Therefore, to address the gaps in the current knowledge, STAR-T was designed, aiming to establish whether manual guided medication management of BUP/NX-F integrated with TDM informed ‘take-home’ prescriptions is more effective than BUP/NX-F alone in achieving a higher percentage of opioid-negative UDS and higher treatment retention rates. Accordingly, the following four null-hypotheses were developed:

H1. There will be no statistically significant difference in the percentage of opioid-negative drug screens over a 16-week period between BUP/NX-F (the control group) and BUP/NX-F + medication management guided by TDM (Incentivised Abstinence and Adherence Monitoring (IAAM); the experimental group).

H2. There will be no statistically significant difference in completion of the 16-week study period and rate of retention of participants within the 16-week period between participants in the experimental group and those in the control.

H3. There will be no statistically significant associations between patient characteristics, buprenorphine elimination rate and the dose of buprenorphine/naloxone

film and (1) the percentage of negative opioid screens (primary outcome), (2) the completion of the 16-week study period (secondary outcome).

H4. There will be no statistically significant difference in the change from baseline to 16-week study endpoint in the measures of psychosocial functioning and addiction severity between participants in the experimental group and those in the control group.

NB: Data for an exploratory estimation of the OUD burden at the patient level required to estimate the cost-benefit of treatment conditions was included in the study protocol but are not presented in this thesis following advice from supervisors.

CHAPTER 3 STUDY 1 THERAPEUTIC DRUG MONITORING IN BUPRENORPHINE/NALOXONE TREATMENT FOR OPIOID USE DISORDER: CLINICAL FEASIBILITY AND OPTIMIZING ASSAY PRECISION

3.1 DESCRIPTION OF THE STUDY IN THE CONTEXT OF THE THESIS

This chapter presents the study conducted to assess the clinical feasibility of implementing TDM in 15 adults with OUD stabilised on BUP/NX-F at the inpatient care. Participants in the present study were recruited to the randomised clinical trial presented by this thesis. This study also presents on the preclinical procedures to optimise the precision of detecting and quantitating BUP in plasma.

This study served as an internal pilot to the randomised clinical trial presented by this thesis. Establishing the clinical feasibility of TDM in monitoring adherence with BUP in all 15 participants was required to proceed to definitive recruitment for the randomised clinical trial. Results for participants in the clinical feasibility study were included in the analyses of the randomised clinical trial if TDM feasibility was established in all participants.

This study has been published (Appendix A.1):

Elarabi, H., Hasan, N., Marsden, J., Radwan, D., Adem, A., Almamari, S., Elrasheed, A. (2019). Therapeutic Drug Monitoring in Buprenorphine/Naloxone Treatment for Opioid Use Disorder: Clinical Feasibility and Optimizing Assay Precision. *Pharmacopsychiatry*. 2020; Doi: 10.1055/a-1083-6842

3.2 ABSTRACT

Introduction: Compliance with Sublingual Buprenorphine/Naloxone (SL-BUP/NX) is associated with higher abstinence from illicit opioid use. Therapeutic Drug Monitoring (TDM) has been recommended for adherence monitoring of buprenorphine (BUP) maintenance treatment for opioid use disorder (OUD), but to date there have been no reported clinical applications. In this TDM feasibility study, we investigated BUP assay precision in 15 adults with OUD who had been stabilized on buprenorphine/naloxone.

Methods: Using solid phase extraction, BUP recovery was contrasted at 100 mMol and 1 Molar of acetic acid wash solution. Precision was determined by applying the condition generating highest recovery using 0.2 ng/mL and 10 ng/mL standards. Four blood samples were drawn to examine the BUP peak and trough plasma concentrations and BUP elimination rate was estimated. BUP recovery was examined again in a random sample and contrasted with the concentration predicted applying first-order kinetics.

Results: Higher BUP recovery was achieved with 1 Molar wash (94.3%; $p = 0.05$). Precision ranged from 15% to 20%. The estimated Limit of Detection (LoD) and Limit of Quantitation (LoQ) were 0.02 ng/mL and 0.069 ng/mL, respectively. BUP peak and trough concentrations were successfully examined and BUP trough concentrations were replicated confirming steady state. BUP concentrations were predicted at a variance of -7.20% to 1.54%.

Conclusions: TDM for BUP maintenance treatment of OUD, is feasible and simple adjustment of the assay conditions enhances BUP recovery.

3.3 INTRODUCTION

Opioid use disorder (OUD; DSM-5, 2013) is a prevalent and chronic psychiatric disorder that is associated with a high burden of global disease (Degenhardt et al., 2010) and substantial social costs (Baumberg, 2006). Medication Assisted Treatment (MAT) with full and partial mu opioid receptor agonists including buprenorphine [BUP] and buprenorphine/naloxone [BUP/NX] is the first line, evidence-based pharmacotherapeutic intervention for people with OUD (WHO, 2009). BUP/NX is associated with abstinence from opioids (Blum et al., 2018) and a 10-fold reduced risk of relapse (Tckaz et al., 2012). However, patient non-compliance, medication diversion (Nosyk et al, 2013) and inappropriate treatment discontinuation (Gerra et al., 2011) all limit the effectiveness of MAT.

Traditionally, medication compliance has been assessed in different ways, including patient self-report, pill count, and urine drug screening to detect drug compounds and metabolites. These can provide useful information, but there is an alternative method that provides greater precision. Therapeutic Drug Monitoring (TDM) is a procedure to determine the concentration of a target medication in blood to inform dose adjustment to increase the likelihood of the desired clinical response (Hiemke et al., 2017). TDM has been recommended for monitoring adherence to BUP treatment (Hiemke et al., 2017), but to date it has not been implemented in routine clinical practice (Laib, 2016), due to a lack of data on clinical feasibility, cost-effectiveness (Brunen et al., 2011), and perhaps the complexity of the procedure and the laboratory expertise required for accurate detection and quantitation of target medication (Sargent, 2013).

The opportunity to implement TDM in treatment clinics has been facilitated by recent advances in the sensitivity of analytical methods to detect and quantify lower blood levels of BUP (Laib, 2016). Enhancing the accuracy and precision of BUP assay using Solid Phase Extraction (SPE) would strengthen the reliability of TDM. Several different sample preparation methods and instruments have been evaluated for their sensitivity and selectivity to detect BUP, but Solid Phase Extraction (SPE) is the method of choice for extracting BUP from biological matrices (Sargent, 2013). SPE sensitivity is influenced by several factors, including the type of Disposable Extraction Column (DEC); the type and concentration of the solvent; pH; and sample volume. Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) remains the instrument of choice for BUP detection and quantitation (Sargent, 2013; Moody et al., 1997).

The aim of this article was to contribute to the integration of TDM in the treatment of OUD by conducting a feasibility evaluation of TDM to monitor adherence with BUP as part of the Suboxone Treatment and Recovery Trial (STAR-T) a randomized controlled open-label trial of the sublingual film formulation of BUP/NX (BUP/NX-F) at a specialist addictions treatment clinic in the United Arab Emirates (ISRCTN41645723) (Elarabi et al., 2019)

3.4 METHOD

3.4.1 Materials

Clinical data for the study was obtained from the first 15 adults with OUD recruited as participants in the STAR-T study. External and internal standards of BUP and its major active metabolite nor-buprenorphine (N-BUP), along with blank samples, were purchased from ‘Cerilliant Analytical Standards’ (SIGMA-ALDRICH).

Two Disposable Extraction Columns (DECs) examined for SPE namely CSDAU® 206 manufactured by United Chem, and Isolute HXC® 130 mg/10 mL (part number 902-0013-H) manufactured by Biotage. The CSDAU® 206 is composed of a long-chain non-polar reverse phase sorbent, while the Isolute HXC® is composed of co-polymeric non-polar (C8) and a strong cation exchange retention component (SO₃⁻). The acetic acid wash solution was examined at 1 Molar and 100 mM concentrations.

Accuracy and precision are determined according to the mean Coefficient of Variance (CV) from the target value for the within-run and between-run results. Limit of Detection (LoD) and Limit of Quantitation (LoQ) are estimated using the signal-to-noise ratio. Lower LoD and LoQ reflect higher selectivity and sensitivity, whereas a higher recovery rate (the ratio of obtained BUP concentration to the BUP standard concentration) indicates higher sensitivity (Brunen et al., 2011; Sargent, 2013).

Detection and quantitation of BUP and N-BUP was performed using Liquid Chromatography Tandem Mass Spectrometry (LC-MS-MS 400; Shimadzu Scientific Instruments) at 20 µL injection volume, 0.2 mL/min flow rate, and 45 °C. Electron Spray Ionization was the interface and the analytical column used was Raptor C18 (Restek 9304A12). **Table 3.1** summarizes the detector conditions set for optimal ion production.

Table 3.1 Detector conditions for optimal ion production for buprenorphine and Nor buprenorphine (m/z)

Target analyte	Ion production (m/z)
Buprenorphine	468.4/55.1 B-902
Nor-buprenorphine	414.3/83.1 N-912
Buprenorphine D-4	472.4/59.1 B-901
Nor-buprenorphine D-3	417.4/55.1 N-920

M/z: mass-to-charge-ratio; D-4: Deuterated buprenorphine; D: Deuterated nor buprenorphine

3.4.2 Sample preparation and extraction

The method published by the manufacturer of CSDAU[®] 206 DEC was adopted (United Chem, n.d) referred herein as the ‘original method’. **Appendix D.1.1 and D.1.2** describe the original method in detail and the procedures for preparing the reagents, respectively.

3.4.3 Method optimization

The accuracy of the original method was optimized by determining the highest BUP recovery rate for combinations of two types of DEC and acetic acid wash solution at two concentrations (**Table 3.2**). All optimization procedures, BUP, and N-BUP assay were performed at the National Rehabilitation Centre Laboratory in Abu Dhabi.

Table 3.2 Disposable extraction columns and concentration of wash solution

Method	Disposable extraction column	Acetic acid concentration
Original method	CSDAU 206	100 mmol
Test trial 1	CSDAU 206	1 Molar
Test trial 2	Isolute HCX	1 Molar.

CSDAU: <https://www.unitedchem.com>; Iso-solute HCX: (<https://www.biotage.com>)

3.4.4 Method validation

The US Food and Drug Administration criteria for selectivity, limits and carry-over were applied (European Medicine Agency, 2011). For selectivity, six blank samples were injected after 10 samples of BUP and N-BUP standards. Under the assay settings,

any interferences from other drugs or the matrix were analysed. For determining accuracy and precision, duplicate samples of standard BUP and N-BUP concentrations at 0.2 ng/mL and 10 ng/mL were measured over five days, i.e. at 10 samples. A CV of 15%–20% from standard concentration was deemed acceptable (European Medicine Agency, 2011). The LoQ parameter was accepted if the Signal-to-Noise ratio was greater than 5 (European Medicine Agency, 2011). Signals for BUP and N-BUP standards and deuterated standards were contrasted at an internal standard of 5 ng/mL. Daily calibration was performed with zero and six standard BUP and N-BUP concentrations (0.2, 0.5, 1, 5, 10, and 20 ng/mL) using plasma of a healthy volunteer who was not consuming any BUP-containing medications (European Medicine Agency, 2011).

3.4.5 Clinical feasibility

All participants were stabilized on BUP/NX-F – defined as receiving the same dose for two weeks without change – were assumed to have reached a BUP Steady State Concentration (SSC) (Compton, 2007). At SSC, four blood samples for BUP peak and trough concentrations were collected over a four-day period. Two samples were drawn 40 minutes after administering the BUP/NX-F dose on Day 1 and 3 (to represent the BUP peak concentration) and the remaining two samples were drawn 30 minutes prior to the BUP/NX-F dose (i.e. 23.5 hours after administering the last BUP/NX-F dose) on Day 2 and 4 (to represent the trough concentration). We determined that the replication of two BUP trough concentrations would indicate that SSC was verified. Alternatively, additional samples were collected until SSC was confirmed, and BUP elimination rate (EL.R) was estimated using the following first order kinetics

$$C_{pss} = C_o \cdot e^{-kt}$$

Where:

- C_o denotes the peak plasma concentration of BUP
- C_{pss} is the trough concentration measured at steady state or at any subsequent point in time
- k represents the EL.R constant
- t is time in hours between collecting peak and trough concentrations

Solving for k:

$$\ln(C_{pss}) = \ln(C_o) - kt$$

Therefore:

$$-k = \ln(C_{pss}/C_o)/t$$

A further blood sample for each participant was randomly drawn and the exact time of withdrawal was recorded. The BUP concentration for the random sample was measured at the laboratory (herein referred to as the ‘examined concentration’) and BUP level was predicted by applying first-order kinetics (herein referred to as the ‘predicted concentration’). The examined and predicted concentrations were contrasted and accuracy was confirmed if the variance was within 20%. The reliability of the first-order pharmacokinetics in estimating BUP concentrations at any time point was confirmed if prediction was accurate in all participants.

3.5. RESULTS

3.5.1. Method optimization

The mean recovery rates generated for the five BUP standard concentrations using the combinations of DEC and acetic acid concentrations ranged from 87.5% to 94.3%.

Table 3.3 summarizes the recovery rate for each of the tested conditions. The combination of the CSDAU 206 DEC and 1 M acetic acid wash solution generated significantly higher BUP recovery rates compared to the CSDAU 206 DEC and 100 mM acetic acid used in the ‘original method’ (94.3% versus 87.5%, $t = 2.41$; $df = 14$, $p = 0.05$).

Table 3.3 Mean recovery rates and actual concentrations for buprenorphine

Buprenorphine concentration	CDSAU and 1 Molar acetic acid	CDSAU and 100mmol acetic acid	HCX and 1 Molar acetic acid
Blank	0	0	0
0.2	71.80 (0.14)	61.70 (0.12)	68.40 (0.13)
0.5	81.70 (0.40)	71.70 (0.35)	87.90 (0.44)
1	118.0 (1.18)	97.90 (0.97)	102.50 (1.02)
5	99.20 (4.90)	106.20 (5.30)	102.60 (5.12)
20	100.0 (20.0)	99.60 (19.90)	99.80 (19.98)
Mean recovery percentage (SD)	94.26 (6.10)	87.46 (6.47)	92.26 (6.23)

CSADU: United Chem Disposable Extraction Column; HCX: Biotage Disposable Extraction Column; SD: Standard deviation

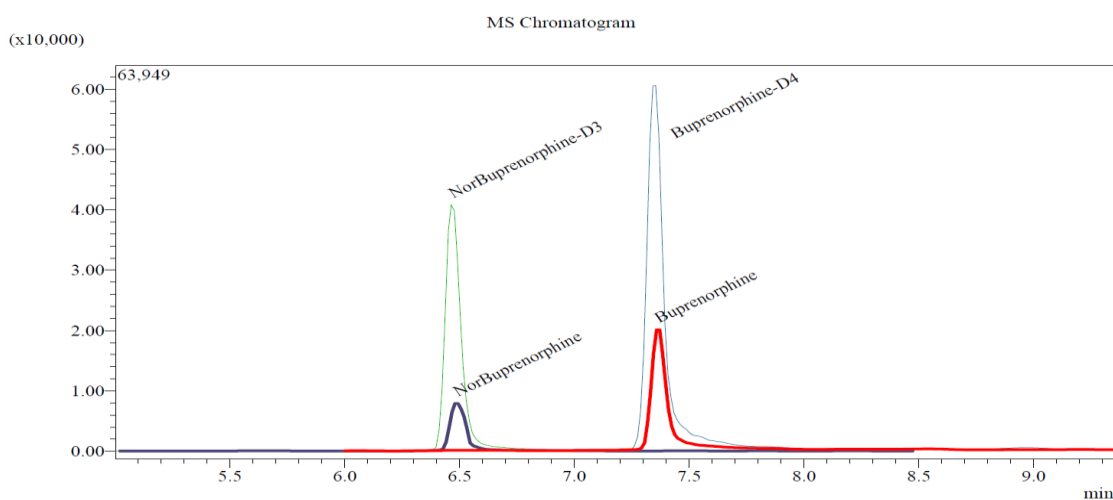
3.5.1. Accuracy and precision

The actual measures for BUP and N-BUP standards at 0.2 ng/mL and 10 ng/mL are presented in **Table 3.4** for duplicate samples assayed over five days. The estimated CV for ‘within-run’ and ‘between-run’ measurements was 9.6% and 12%, respectively. Linearity was established for these samples ($R^2 = 0.999$ for BUP and $R^2 = 0.999$ for N-BUP; **Appendix D.2**). Chromatograms for BUP and N-BUP standards and deuterated standards showed almost superimposable signals using an internal standard of 5 ng/mL (**Figure 3.1**).

Figure 3.1 Chromatogram for buprenorphine, nor buprenorphine and deuterated standards using buprenorphine internal standard at 5 ng/mL

```

Patient Name      :
NRC Number       : Matrix spike@0.2ppb-1
Tray#            : 1
Vial#            : 8
Injection Volume  : 20
Data File        : Matrix spike@0.2ppb-1_5.lcd
Method File      : BUP_NORBUP_Blood.lcm
Original Method   : BUP_NORBUP_Blood.lcm
Report Format     : REPORT.lsr
Tuning File      : Tuning_23.06.2019.lct
Location         :
  
```



MS Quantitative Table

ID#	Name	Ret. Time	m/z	Conc.	Area	Unit
1	NorBuprenorphine-D3	6.468	417.00>101.05	5.000	197343	ng/mL
2	NorBuprenorphine	6.487	414.00>101.15	0.232	37970	ng/mL
3	Buprenorphine-D4	7.348	471.90>59.10	5.000	334612	ng/mL
4	Buprenorphine	7.365	468.10>55.10	0.243	97332	ng/mL

No carry-over of BUP or N-BUP was detected with the blank samples (**Appendix D.3.1**) and no interferences from other drugs or the matrix were observed. The signal-to-noise ratio for buprenorphine was estimated at 9.5 (**Appendix D.3.2**), and the estimated LoQ for BUP and N-BUP was estimated at 0.069 ng/mL and 0.039 ng/mL, respectively, while the corresponding LoD was estimated at 0.02 ng/mL and 0.012 ng/mL.

Table 3.4 Buprenorphine and nor buprenorphine concentrations measured against standard concentration of 0.2 ng/mL and 10 ng/mL

Concentration ng/mL	Assay results									
	Day 1		Day 2		Day 3		Day 4		Day 5	
BUP 0.2 ng/mL	0.235	0.224	0.185	0.20	0.196	0.22	0.215	0.212	0.220	0.234
BUP 10 ng/mL	10.02	10.539	9.898	9.980	10.01	11.45	11.787	11.776	9.217	9.306
N-BUP 0.2 ng/mL	0.226	0.229	0.232	0.232	0.228	0.234	0.230	0.234	0.238	0.236
N-BUP 10 ng/mL	9.590	9.359	9.461	9.461	9.174	9.154	9.727	10.325	9.217	9.306

BUP: Buprenorphine; N-BUP: Nor-buprenorphine

3.5.2. Clinical feasibility

In all participants, the variance between the measured BUP trough concentrations ranged from -6.3% to 13.9%. As the variance between the examined and predicted concentrations in all 15 participants was within 20% (-7.20% to 1.54%) the reliability of the first-order pharmacokinetic model in predicting the BUP plasma concentrations was confirmed (**Table 3.5**). Data for the peak and trough plasma, nor buprenorphine concentrations are, presented in **Appendix D.4**

Table 3.5 Examined and predicted buprenorphine concentrations at different time intervals from administering buprenorphine/naloxone film

Pt	BUP/NX-F dose (mg/day)	Cmax BUP (ng/mL)	Cmin (1) BUP (ng/mL)	Cmin (2) BUP (ng/mL)	Time of random sample (hours post BUP/NX dose)	Examined BUP Concentration	BUP EL.R ng.mL hr⁻¹	Predicted BUP Concentration.	% Difference between Examined and Predicted BUP concentrations ϕ
1	14	5.84	2.84	2.86	(20)	3.14	0.03	3.14	0.00
2	14	1.31	0.55	0.55	(10)	0.71	0.04	0.74	-4.23
3	16	1.83	0.55	0.56	(7)	1.30	0.05	1.28	1.54
4	16	1.15	0.48	0.50	(20)	0.50	0.04	0.51	-2.00
5	14	3.85	2.57	2.74	(5)	3.55	0.02	3.53	0.56
6	16	11.97	1.68	1.58	(7)	5.89	0.1	6.11	-3.74
7	14	30.33	11.65	11.65	(20)	13.63	0.04	13.43	1.47
8	16	21.61	0.262	0.253	(8)	4.82	0.19	4.81	0.21
9	12	23.95	1.16	1.34	(12)	4.83	0.13	5.01	-3.73
10	12	7.22	1.23	1.43	(11)	3.18	0.07	3.16	0.63
11	14	16.56	1.0	0.97	(11)	4.86	0.11	4.93	-1.44
12	12	1.98	1.12	1.17	(20)	1.20	0.02	1.22	-1.67
13	12	65.63	3.23	3.37	(18)	6.11	0.13	6.55	-7.20
14	12	1.82	1.30	1.34	(14)	1.48	0.01	1.49	-0.68
15	16	1.03	0.42	0.42	(8)	0.74	0.04	0.73	1.35

Pt: Participant, BUP/NX-F: Cmax: peak concentration; Cmin: trough concentration; BUP EL.R: Buprenorphine Elimination Rate Constant

Buprenorphine/ Naloxone daily dose: The mean daily stabilization dose of BUP/NX-F was 14 mg (range 12 mg to 16 mg).

Buprenorphine Elimination Rate: The mean estimated BUP EL.R constant was 0.068 ng.mL hr⁻¹ (SD = 0.056; range 0.01 to 0.19).

Buprenorphine trough concentration: At steady state, in the 15 participants, the examined BUP trough concentration ranged from 0.26 ng/mL to 11.65 ng/mL. In 9 participants, the BUP trough concentration at steady state ranged from 1–3 ng/mL, while in 5 participants, BUP trough concentrations were below 1 ng/mL.

In one participant only –stabilized on a daily BUP/NX-F dose of 14 mg – a BUP trough concentration of 11.65 ng/mL was detected, which is above the 10 ng/mL laboratory level. No signs of intoxication or clinical symptoms were observed or reported by this participant.

3.6 DISCUSSION

In this TDM for BUP feasibility study among 15 adults with OUD stabilized on BUP/NX-F, simple adjustment in the sample preparation conditions (method optimization) resulted in higher mean BUP recovery rate compared to those obtained applying the original method and those previously reported for standard SPE (Moody et al., 1997). The assay precision and accuracy for the optimized method was confirmed.

When applying the optimized method, the estimated LoD and LoQ were lower than those reported for the original method (United Chem, n.d). The estimated LoQ is lower than the value reported by Luthi and colleagues (0.1 ng/mL) (2013). Similarly, the sensitivity of the optimized method appeared to be lower than the value obtained by Regina and Karash (2013). All BUP peak and trough plasma concentrations were successfully examined according to the published BUP kinetics data reporting peak concentrations at 40 minutes after medication administration (Elkader & Sproule, 2005). BUP trough concentrations were replicated in all participants, confirming BUP SSC.

The reliability of the first-order pharmacokinetic model in predicting BUP concentrations (Hiemke et al., 2017) strongly supports the clinical feasibility of TDM in monitoring adherence with BUP. Quantifying BUP trough concentrations over a wide range supports the clinical reliability of the assay method in the presence of reported

inter-individual differences (Brunen et al., 2011). A majority of the participants (9 out of 15) had BUP trough concentrations at steady state within 1–3 ng/mL reported as the therapeutic range (Hiemke et al., 2017) and no participant had a BUP concentration below 0.2 ng/mL.

Given these results, there may not be a strong clinical need in routine practice to use methods capable of detecting BUP at very low concentrations since none of the detected BUP concentrations were below 0.1 ng/mL. It should be noted, however, that this method was developed for total rather than free BUP; hence, complete liberation of BUP from the gluco-uronidate conjugate was required. Such liberation contributes to minimal variance of measurement over time and higher assay sensitivity, as well as minimizes the potential impact of the source of β -glucouridase enzyme on the hydrolysis rate (Huang et al., 2006). In order to achieve complete liberation, extended hydrolysis conditions were adopted, i.e., overnight hydrolysis at 55 °C instead of 37 °C for less than an hour (Wang et al., 2006).

A key strength of the present work stems from the feasibility of successful measurement of the peak and trough BUP concentrations at steady state and accurate prediction of BUP concentration at any time point. The study provides empirical data on clinical applications of TDM in monitoring BUP in blood and hence monitoring treatment adherence. Unlike the methods currently applied to verify compliance with BUP, quantitative measurement of BUP provides the clinician with accurate verification of BUP adherence.

Successful matching of the extraction conditions with the BUP physicochemical characteristics (a weak basic compound with a pK_b of 8) may have contributed to the enhanced recovery rate. Unlike the wash solution concentration, no impact of DEC on the BUP recovery was noted. The cationic exchange component of the Isolute HCX[®] did not enhance the recovery despite setting the pH at two units below the pK_b to charge BUP and facilitate cationic exchange. The impact of adjusting the wash solution supports the previously reported significance of the wash step in the recovery outcomes (Sargent, 2013).

The results of this study should also be considered in the light of some limitations. We must stress the importance of accurately drawing blood samples representing BUP peak and trough concentrations. In particular, determination of the BUP peak concentration required close coordination between the laboratory and the addiction clinic nursing staff

due to the narrow time period within which samples had to be obtained to measure peak concentration.

3.7 CONCLUSIONS

We have demonstrated that TDM is clinically feasible for estimating BUP concentrations and monitoring adherence with BUP MAT for OUD. Sensitivity and precision of BUP detection and quantitation can be optimized by simple adjustments in the wash step conditions of the solid phase extraction. For further studies, we suggest applying this procedure using BUP monotherapy preparations, given the lower cost of BUP tablets compared to BUP/NX-F preparations.

CHAPTER 4 METHODS

This chapter describes the study design and setting, clinical population, materials, clinical procedures performed at the inpatient care and for each of the randomised groups, the trial governance framework, and the analyses plan for the trial. The chapter incorporates the published protocol for the clinical trial as follows (**Appendix A.2**):

Elarabi, H., Alrasheed, A., Ali, A. Shawky, M., Hasan, N., Gawad, T.A., Adem, A., Marsden, J. (2019). Suboxone Treatment and Recovery Trial (STAR-T): Study protocol for a randomised controlled trial of opioid medication assisted treatment using buprenorphine together with adjunctive medication management using therapeutic drug monitoring and contingency management. *Journal of Addiction*
<https://doi.org/10.1155/2019/2491063>

4.1 DESIGN AND SETTING

The STAR Trial (STAR-T) was a pragmatic, single-centre, parallel group, 16-week-long outpatient randomised controlled superiority trial as a part of which BUP/NX-F + Medication Management integrated with TDM (Incentivised Abstinence and Adherence Monitoring; the experimental group) was compared to BUP/NX-F only (the control group). Study interventions were provided in the open label mode.

BUP/NX-F was selected over the tablet formulation for this study to facilitate Directly Observed Treatment (DOT), given its shorter dissolution time and patient preference (Lintzeris et al., 2013). BUP/NX-F in 2 mg, 4 mg and 8 mg doses, but not 12 mg, were imported, further to an import permit issued by the UAE Ministry of Health. The UAE import permit was mailed to the manufacturer to issue the export permit. This procedure was performed for each shipment and was closely supervised by the candidate who was the Principal Investigator (PI) of the study.

STAR-T was conducted at the NRC's inpatient and outpatient care services. The NRC's voluntary inpatient programme has a 45-bed capacity extends for four weeks. It is differentiated to two levels of care: an acute care unit (for detoxification) and a step-down early recovery unit for rehabilitation. Individuals who completed the inpatient phase were randomised to receive the 16-week study interventions at the outpatient

care. All study interventions were performed by licensed health care workers and providers including psychiatrists, nurses, psychologists, social workers, clinical pharmacists, and clinical pathologists.

An application for research ethical approval was, submitted by the candidate and senior investigators in March 2014 to the official Institutional Review Board (IRB) regulated by the Department of Health in Abu Dhabi. The IRB recommended that the study should be, made available to male and female patients, with pregnancy as one of the exclusion criteria. The IRB also recommended that a pilot study should be, conducted to secure evidence on the clinical feasibility and precision of TDM prior to definitive recruitment. An internal pilot of 15 patients was recommended. Progression from the pilot study was allowable if the clinical feasibility was, confirmed in 100% of the pilot sample.

During the initial protocol development, the research committee at the NRC recommended a 24-week outpatient treatment. However, the PhD upgrade committee at the Institute of Psychiatry, Psychology and Neurosciences at King's College London (IOPPN) expressed concern that this would be too long for the candidate's work programme, and recommended that the outpatient treatment period to be limited to 12 weeks. A final decision was, made and agreed by all parties to set the outpatient period at 16 weeks, with a maximum of 36 weeks of follow up. The PhD upgrade committee at the IOPPN also recommended that the protocol should be, amended to include a random UDS and BUP level assay. All of the above were included in the amended version of the ethical application and approval was granted on April 30th, 2014 (**Appendix B.3: IRB approval letter; Appendix B.4: Upgrade approval letter**).

The study was registered under the Bio-Central ISRCTN registry (number ISRCTN 41645723) and was conducted at the National Rehabilitation Center (NRC) - United Arab Emirates (UAE). The Scholarship Office at the Ministry of Presidential Affairs–United Arab Emirates supported doctoral study educational expenses and activities.

4.2 PARTICIPANTS

As this was a pragmatic study, the exclusion criteria were minimal to maximise the generalisability of the findings.

Table 4.1 Participant Inclusion and exclusion criteria

Inclusion criteria

For a participant to be enrolled into the study he must fulfil all the following inclusion criteria:

- (1) Aged 18 and above with no upper limit (usually 64 years);
 - (2) Current diagnosis of OUD;
 - (3) Voluntarily seeking MAT;
 - (3) Resident in the UAE;
 - (4) Evidence of stable accommodation.
-

Exclusion criteria

Otherwise, eligible patients will be excluded from the study for any of the following:

- (1) Benzodiazepine use in excess of 20 mg daily diazepam equivalent in the past 28 days;
 - (2) Known naloxone or BUP hypersensitivity;
 - (3) Pregnancy;
 - (4) Hepatic impairment (elevation of liver function tests three times normal);
 - (5) Suicide attempt in past 12 months;
 - (6) Involvement in criminal justice system, which is likely to result in arrest and incarceration;
 - (7) Uncontrolled severe mental or physical illness judged to compromise safety;
 - (8) Mini Mental State Examination [MMSE] score < 17 indicating cognitive dysfunction. (Folstein, & McHugh, 1975; Tombaugh & McIntyre, 1992).
-

4.3 STUDY OUTCOMES

4.3.1 Primary outcome

The primary outcome measure was the count of negative opioid urine drug screens (UDS) for opioids during 16 weeks of outpatient treatment. Conservatively, if the

participant failed to attend the clinic for a scheduled UDS, this missed test would be recorded as an opioid-positive UDS. At the study endpoint, the outcome was computed as a percentage of the total scheduled UDS as follows:

$$[(\text{total number of scheduled UDS}) - (\text{number of observed positive opioid UDS results} + \text{missed appointments}) / (\text{total number of scheduled UDS})] \times 100$$

4.3.2 Secondary outcome

The secondary outcome measure was completion of the 16-week outpatient treatment programme. A participant was classified as a study completer if he/she attended all scheduled clinic appointments without interruption, and his/her final appointment was on or after 16 weeks (i.e. were enrolled for 16 weeks of treatment). Study non-completers are participants who: 1) discontinued outpatient treatment before the 16 weeks endpoint, or did not attend three consecutive appointments at the outpatient clinic (i.e. interruption in treatment), or lost contact with the clinic for one month. Participants discontinued were, re-engaged only after completing an in-depth assessment.

The completion rate was, calculated as the percentage of randomised participants as follows:

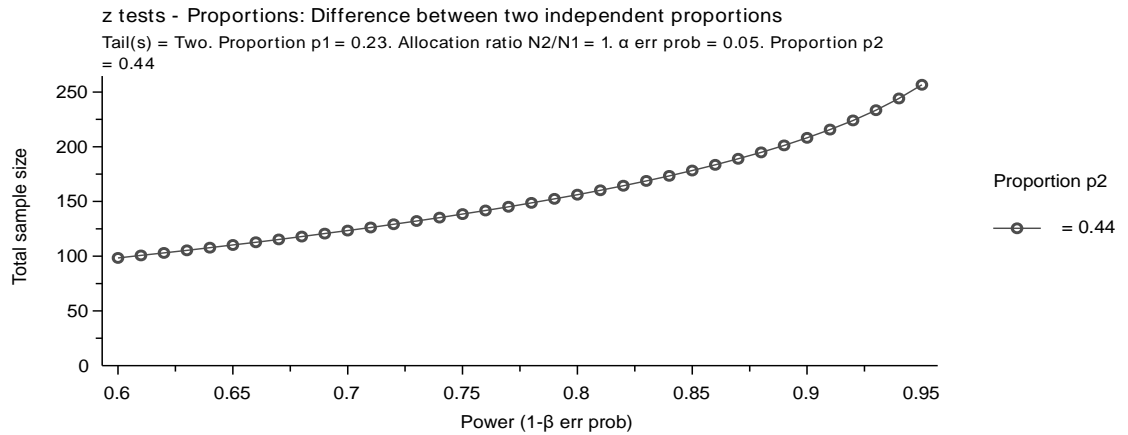
$$[(\text{number of participants completing the 16-week programme without interruption}) / (\text{total number of participants randomised})] \times 100.$$

4.4 SAMPLE SIZE

A target sample size for the study was determined in accordance with the approach adopted in the 2007 meta-analysis of psychosocial interventions conducted by the National Institute for Clinical Excellence (NICE CG51, 2007). From **Appendix 15** (page 14), taking an outcome of 3 weeks abstinence achieved during treatment based on three trials among 266 participants in the experimental group and 262 participants in the control group, 118 experimental group members achieved this outcome compared to 62 participants in the control group, with an odds ratio (OR) of 1.96 (95% confidence interval, CI 1.76–3.72).

Taking these proportions in a two-tailed power calculation (i.e., 0.44 for the experimental group versus 0.23 for the control group), with Type I error set to 5% and the power of 80% and with 15% added for attrition, a sample size of 182 participants was targeted (with 91 allocated to each group, see **Figure 4.1**).

Figure 4.1 Sample size estimation (experimental; control)



4.5 MATERIALS

4.5.1 Measures

Drug toxicology assessment and buprenorphine quantitation. Participant UDS data were collected under-supervision and analysed by an immunoassay, drug toxicology point-of-care-test (POCT: Invitro Diagnostic Device) approved by the US Food and Drug Administration. The POCT used is waived by Clinical Laboratory Improvement Amendments (CLIA) for opioids (morphine for illicit heroin), propoxyphene, tramadol, oxycodone, benzodiazepines, tricyclic antidepressants, psychostimulants (*d*-amphetamine, methyl-amphetamine, MDMA, cocaine), cannabinoids, phencyclidine, and BUP. Fentanyl and pregabalin were, initially tested by a separate kit/device until included in a single kit. All positive UDS results were subject of confirmatory testing by Gas Chromatography and Mass Spectrometry. BUP levels were detected and quantified by a Liquid Chromatography Tandem Mass Spectrometry 400 (Schimadzu Scientific Instruments) with a Raptor C18 analytical column (Restek Corp. 9304A12).

Clinical Opioid Withdrawal Scale (COWS). The COWS (Wesson & Ling, 2003) is an 11-item clinician-administered rating scale that assesses signs and symptoms of opioid withdrawal (with a higher score indicating more severe opioid withdrawal). In STAR-T, induction with Sublingual BUP/NX-F commenced at a minimum COWS score of **10** to avoid precipitating withdrawal symptoms. Participants with a COWS

score of ' ≤ 5 ' were assumed to have mild or no withdrawal signs and were transferred to the early recovery unit.

Pupil reflexes. A hand-held pupilometer camera (PLA Inc. 2000) was used to capture pupil reflexes to provide a non-conscious measure of opioid withdrawal (Demberg, 2013), and as a proxy for craving during different phases of the trial. To establish baseline measures, the pupil reflexes were, captured at intake and before onset of withdrawal. The reflexes captured are: (1) maximum pupil diameter reading before exposure to light (before contraction); (2) minimum pupil diameter reading after exposure to light (after contraction); and (3) maximum and average constriction velocity, dilation velocity, and time to 75% recovery of the pupil diameter.

Patient Health Questionnaire (PHQ-9). The PHQ-9 (Kroenke, Spitzer, & Williams, 2001) is a well-validated, self-administered nine-item scale recording the frequency of depression-related symptoms according to the DSM-IV depression criteria. Responses pertaining to the period spanning the preceding two weeks were rated using four frequency levels ("not at all," "a few days," "more than half of the days," and "almost every day," which were scored on a 0–3 scale, resulting in the total score range of 0–27). A score between 5 and 9 indicates mild depression; a score between 10 and 14 indicates moderate depression, whereas a score of 15–19 indicates moderately severe depression with 20 or more being indicative of severe depression. To screen for major depression, at least five criteria have to be present for more than half of the days in the preceding two weeks, if one of the symptoms is depressed mood or lack of interest in pleasurable activities, and that suicidal thoughts are not reported. The PHQ-9 validated Arabic Near East Area version was used in the present study.

Generalised Anxiety Disorder (GAD-7). The GAD-7 (Spitzer, Kroenke, Williams, & Lowe, 2006) is a well-validated self-administered seven-item scale recording anxiety-related symptoms experienced in the preceding two weeks, which are rated using three frequency levels ("never," "sometimes," and "always," which are scored on a 0–3 scale, giving the total score range of 0–21). The GAD-7 screens for mild, moderate, and severe anxiety at the cut-offs of 5, 10 and 15, respectively. The validated Near East Arabic version for GAD-7 was used in the present study.

Barratt Impulsiveness Scale (BIS-11). The BIS-11 (Barratt, Coller, & Somogyi, 2006) is a validated 30-item self-administered questionnaire that assesses three sub-traits of impulsiveness: non-planning, motor, and attention. Items are rated using a four-point

scale (ranging from 0 = “never” to 4 = “always,” with the total score range of 0–120). A higher score on the BIS-11 indicates higher impulsiveness. Translation of the BIS-11 to Arabic was performed at the NRC considering the available Arabic translation of this tool (Ellouze et al., 2013).

Personality Disorder Screener (PDS). The PDS (Kessler et al., 1998) is a well-validated clinician-administered tool comprising of 34 questions extracted from the Composite Diagnostic Index to which the participant responds by choosing “true,” “false,” or “don’t know.” PDS scoring follows the ICD-10 criteria (WHO, 2003) of three clusters of personality disorders Cluster A (Paranoid), Cluster B (Borderline Personality & Antisocial), and Cluster C (Anxious-Avoidant & Obsessive-Compulsive).

Addiction Severity Index (Lite version). The ASI-Lite (Cacciola, Alterman, McLellan, Lin, & Lynch, 2006) is a well-validated semi-structured clinician-administered outcome evaluation instrument developed from the full version of the Addiction Severity Index (McLellan et al., 1992). The ASI-Lite assesses seven domains of addiction severity (medical, employment and social status, alcohol use, drug use, family conflicts, legal, and mental health status) rated based on the responses pertaining to the preceding 30 days. A composite score for each domain ranging from 0 to 1 is generated with higher scores indicating higher problem severity.

Work and Social Adjustment Scale (WSAS). The WSAS (Mundt, Marks, Shear, & Greist, 2002) is a validated five-item self-reported tool that measures perceived personal, social, and occupational impairment caused by a clinical problem (for example, OUD in the present study). Each item is rated using an eight-point scale (ranging from 0 [no impairment] to 8 [full impairment]), with the total score range of 0–40. A score lower than 10 indicates no clinical impairment, a score in the 10–20 range indicates significant impairment and a score in the 21–40 range indicates severe impairment.

Pittsburgh Sleep Quality Index (PSQI). The PSQI (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) is a well-validated self-administered tool that evaluates sleep quality across seven categories: subjective evaluation of sleep quality, sleep latency, sleep duration, sleep efficiency, use of sleep medication, daytime dysfunction, and sleep disturbance. Each item is rated on a three-point scale (ranging from 0–3) with the total score ranging from 0–21. A higher score on the PSQI reflects worse sleep quality, with five as the cut-off for diagnosing sleep disorders or poor sleep quality.

Minnesota Cocaine Craving Scale (MCCS). The MCCS (Halikas, Kuhn, Crosby, Carlson, & Crea, 1991) is a validated five-item scale measuring the following aspects of cocaine craving: intensity, duration, frequency, change from last week/day, and how the medication has helped in craving reduction. The MCCS was adapted to ‘opiates’ (**MOCS**) for the present study.

Translation to Arabic. Measures that have no Arabic validation (e.g. COWS, BIS-11, PDS, ASI-Lite, WSAS, PSQI, MOCS) were translated to Arabic by a team of bilingual (Arabic–English) mental health professionals at the NRC (two PhD-level clinical psychologists, one PhD researcher, two consultant psychiatrists, and the candidate). The candidate produced a first draft using semantic translation that was circulated to the translation team for revisions. Next, a focus group discussion inclusive of the translation team and all investigators was conducted to generate a consensus for the second version. The consensus version back translated by an external translator. Minor discrepancies were adjusted and the final version was tested in the first 15 participants recruited to the study.

The decision to translate the BIS-11 to ‘classical Arabic’ despite the presence of a validated dialectal Arabic version (Ellouze et al., 2013) was made, as the validated dialect (North African) was difficult to interpret by citizens of the lower gulf region. A non-validated Arabic version of the PSQI developed by Suleiman, Yates, and Burger (2010) was, considered while generating the Arabic version of the PSQI in the present study.

4.5.2 Medication Management Manual.

This manual was adapted from the COMBINE Medical Management Manual (MM) and the POATS Medical Manual (Fiellen et al., 1999). All materials were adapted for BUP/NX-F and approved by the Institutional Scientific Committee (mandated to review and approve all health promotion and education material) and the IRB. The MM manual provide a full guide to implement the experimental intervention using TDM. This manual includes forms to structure MM foundation and follow up sessions, to evaluate medication adherence (**Appendix C.1–Appendix C.3**), and counselling text to guide the clinical response according to the participant’s condition. The manual includes medication education material, a counselling checklist, a participant recovery passport (diary) and an emergency card as described below.

BUP/NX-F education material (Appendix C.4). Developed using the BUP prescribing information together with the Clinical Practice Guideline for Buprenorphine (SAMHSA, 2004) according to the standards of providing medication education (Pantalon et al., 2004). This material covered (1) a description of the prescribed medication and why it was, (2) expectations from the treatment, (3) how to use the medication and what is expected from the patient while on BUP/NX-F, (4) how to monitor response, (5) the anticipated adverse events and alarming signs necessitating help, (6) what to do in case of missed doses and suggestions for minimising forgetfulness, (7) how to store the medication, and (8) any medication or food interactions.

Two bilingual psychiatrists revised the content, developed by the candidate in Arabic, prior to being a subject of a review carried by the Institutional Scientific Committee at the NRC, mandated to review any scientific publication. The material used ‘simple’ Arabic language in a question-and-answer format and was approved by the IRB. A guide for counselling text was developed (**Appendix C.5**).

Buprenorphine/Naloxone counselling checklist (Appendix C.6). This is a 19-item checklist to guide medication counselling developed by the Prince Edward Island Pharmacy Board (2005). Items 1–15 are medication related, while the remaining four items summarize the counselling session.

Emergency card (Appendix C.7). This wallet-sized hard card was developed for healthcare professionals attending to unconscious participants in case of emergency, and informed them that the patient was receiving BUP/NX-F. The information presented on the card (in both English and Arabic) included the patient’s name, BU/NX-F dose, date of commencing BUP/NX-F treatment, and the expected date of treatment completion.

‘Recovery Passport’ (Appendix C.8). A passport-sized participant diary was developed to enhance patient and family engagement in treatment and was based on the patient health engagement model (Barello and Grafinga, 2015; Grafinga & Barello, 2018) and self-management (Newman, 2008).

The passport design applied the principles of CM available in three colours - light blue, navy blue, and red - corresponding to the colours of the national passports (temporary, normal, and diplomatic). These coloured passports were provided at different stages of treatment according to recovery milestones. For example, light blue is valid for the first

month in recovery, after which the patient is eligible for the navy blue passport. The ultimate goal for the patient is obtaining the red-coloured passport requiring successful completion of the 16-week study period.

The ‘participant passports’ (diaries) is composed of the following:

- Patient identification and target goal for recovery, purpose in life.
- Baseline scores for MCOS, PSQI, PHQ-9, and GAD-7.
- A record of medications (other than BUP/NX-F) received, including dose, start and end date of use.
- Weekly day-by-day schedule for recording BUP/NX-F doses administered¹.
- MCOS, PSQI, PHQ-9, and GAD-7 measures to be self-completed by participants.
- UDS log.
- Recovery visa pages (participants who continue to be adherent and abstinent would receive one stamp of “recovery visa” valid towards the next level of recovery).

4.6 PROCEDURES

Patient screening, initial history taking, and other clinical assessments were, completed with input from different disciplines (psychiatry, psychology, social work, and nursing). Patients were, screened for study eligibility at the intake assessment by the attending psychiatrist and the PI. Patients meeting the STAR-T criteria were, admitted to a 4-week inpatient care with a recommendation to be recruited for STAR-T. At this stage, a blood sample was withdrawn for a complete blood picture and liver function tests.

Eligible individuals were, invited to participate in the study by the PI or the attending psychiatrist following the patient’s endorsement of the ‘therapeutic contract’ as required by the standard procedures at the NRC. This contract outlines the patient rights and responsibilities and includes items related to participating in clinical research. The social workers performed the contracting process independent of the study consent process.

Patient consent to participate in the study was completed on admission by the PI or the attending psychiatrist using the study consent form (**Appendix B.7**). Before seeking informed consent, the investigator/s ensured that the patient was coherent and able to

¹ In this section, the participant and a family member sign against the date and time for each dose.

provide consent. The consent process required that the patient be informed about and has understood the content of the form. This consent form was, completed in a triplicate copy, one provided to the patient, the second was, kept in the patient’s file, and the third was, retained for audit/review purposes. The consent process encompassed explanation of the (1) the nature of the study and its provisions, including collection of blood samples, and assessments to be performed; (2) the confidentiality of information, including access to patient clinical data, use of results and storing patient data; (3) the benefits from participating in the study; and (5) the freedom of participation and withdrawal from the study.

If the patient agreed to participate, the investigator signed and dated the form, and asked the patient to provide his/her full name, and sign and date the form. Alternatively, patients requested time to respond to the consent or decline to enter the study. In such cases, the investigator reassured the patient that there would be no impact on their treatment provision, and treatment would proceed according to the developed treatment plan. The PI/investigator further explained that participants might be withdrawn from the study if any serious adverse reactions or clinical deteriorations were observed.

A projection of the potential monthly patient recruitment was developed according to the number of OUD patients who presented to treatment in the preceding years (2013 and 2014). The monthly forecast for patient recruitment was adjusted considering seasonal changes affecting patient flow. For example, the number of patients tends to decline during summer and the holy month of Ramadan (the fasting month in the Muslim faith). Actual patient recruitment versus the target was reviewed monthly and the forecasts were adjusted accordingly (**Table 4.2**).

Table 4.2 Forecast for participant recruitment and actual number and difference.

Number of participants	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7
Target number	8	10	12	12	15	14	15
Actual recruited	10	8	4	4	4	14	12
Difference	+2	-2	-8	-8	-11	-1	-2

4.6.1 Management of opioid withdrawal and induction on Buprenorphine/Naloxone film

Completed at the detoxification unit, management of withdrawal syndrome was guided by the self-reported drug use documented at the initial assessment, UDS results and the clinical picture. Pupil reflexes captured before the emergence of withdrawal symptoms served as the baseline for monitoring response to BUP/NX-F and withdrawal status, alongside the COWS scores. Induction on BUP/NX-F commenced at the first sign of withdrawal, quantified by a COWS score of >10 (SAMHSA, 2004). Participants with primary heroin or morphine use disorders went through a 3-day BUP/NX-F dose induction, while participants with predominant prescription opioid use underwent a 5-day induction, according to the following procedures.

On day one, induction was carried out by administering BUP/NX-F 2–4 mg, depending on: (1) severity of withdrawal, e.g. low doses of 2 mg were warranted for mild withdrawal symptoms (COWS score of <12); (2) concomitant drug use, e.g. low doses of 2 mg were warranted in the presence of benzodiazepine or alcohol use history; and (3) concurrent medical conditions and medications e.g. low doses of 2 mg for participants with history of hepatic disease or currently using medications known to affect liver function.

During the first four hours post-induction, the nursing team carried close observation for ‘precipitated withdrawal’. Response to BUP/NX-F was assessed by the COWS score generated at 4-hour intervals in addition to the daily measurement of pupil reflexes. A BUP/NX-F dose was increased by 2 mg or 4 mg if signs of withdrawal were observed, with a total daily dose not exceeding 8 mg on day one. Induction on BUP/NX-F was postponed for three days in participants presenting with intricate polysubstance use and signs of intoxication with benzodiazepine and/or prescription drug use. In this case, opioid withdrawal symptoms were managed symptomatically.

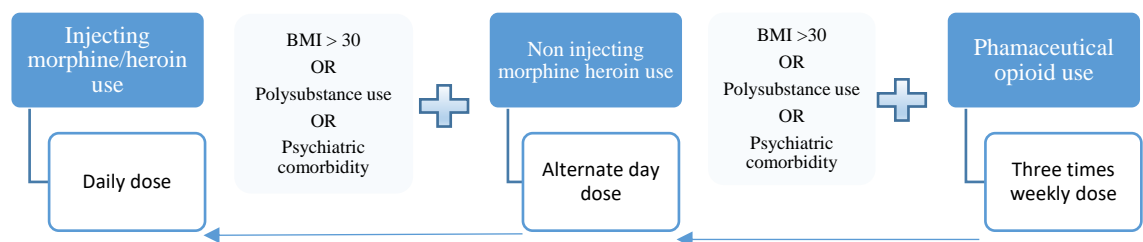
On day two and day three, BUP/NX-F dose was increased by 4 mg to 6 mg to achieve a COWS score below ‘5’. For users of opioid prescription drugs who experienced signs of withdrawal on days two or three, BUP/NX-F induction was, extended for five days. At eight-hour intervals, COWS was, administered and participants were, transferred to the early recovery unit (a step-down inpatient care) at a COWS score below five. The total 24-hour BUP/NX dose required to achieve a COWS score below ‘5’ served as the daily dose and functioned as the basis for determining the stabilisation and maintenance

dose. During the subsequent inpatient care, BUP/NX-F was, administered under supervision at the same time each day.

4.6.2. Stabilisation on Buprenorphine/Naloxone film

After successful induction at the inpatient detoxification unit and upon transfer to early recovery unit (step down inpatient care), participants were assigned to either daily, Alt-D, or TIW dose according to the criteria illustrated in **Figure 4.3**. For example, participants who used pharmaceutical opioids only, have no psychiatric comorbidity or polysubstance use, and with a BMI <30, were placed on the TIW dose schedule. If they continued to experience a distressing opioid craving or did not satisfactorily tolerate their dosing, dose adjustments were made with a possible transfer to the next more frequent schedule.

Figure 4.2 Buprenorphine/naloxone dose assignment criteria



Dose adjustment was guided by self-reports of comfort, sleeping and craving or any documented signs of withdrawal and confirmed by readings of pupil reflexes.

Figure 4.3 and 4.4 illustrate changes in pupil diameter readings before and after induction with BUP/NX-F. Details of dose assignment and adjustments are outlined in **Appendix C.1**.

Figure 4.3 Pupil diameter reading before induction on buprenorphine/naloxone (Max 5.8, Min 4.3)

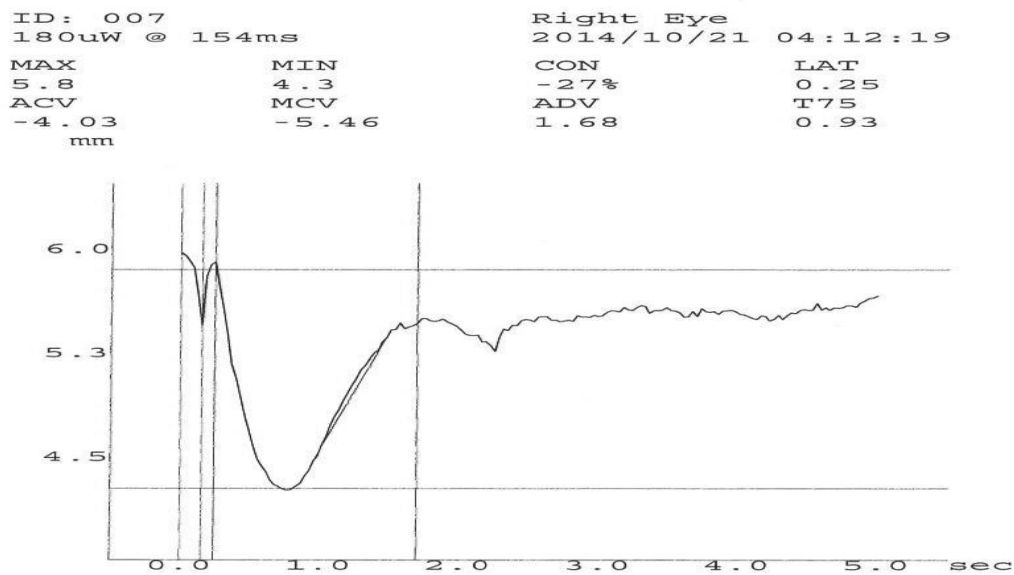
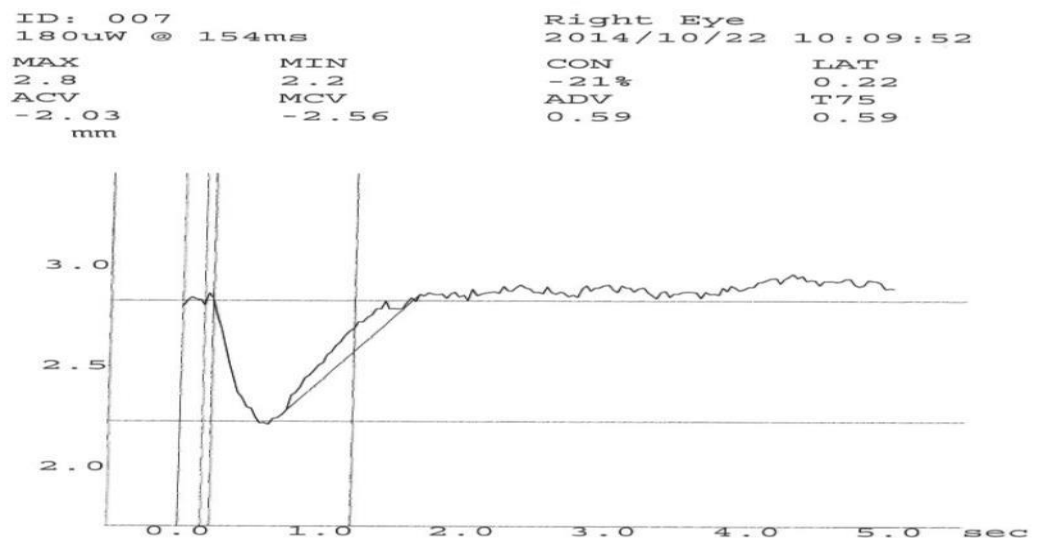


Figure 4.4 Pupil diameter reading at Day 1 of induction on BUP/NX (Max 2.8, Min 2.2)



For participants with poor quality of sleep, opioid withdrawal was ruled out by administering the COWS, and measuring pupil reflexes. Participants with poor quality of sleep unrelated to withdrawal and in the absence of a co-occurring disorder were prescribed non-pharmacological interventions (e.g., Cognitive Behavioural Therapy for insomnia including sleep hygiene, limiting caffeine intake after 16:00, walking for 30 minutes) and hydroxyzine 10 mg for one week, followed by evaluation. If poor quality of sleep persisted, and major depressive disorder or anxiety disorder were confirmed and pharmacotherapy was recommended, mirtazapine 15 mg was suggested for

treatment initiation. If other affective disorders (e.g. bipolar) were diagnosed quetiapine (50–100 mg) or olanzapine (5 mg) once at bedtime were, recommended.

4.6.3. Data Collection

The PI and study investigators administered the study measures, according to the schedule outlined in **Table 4.3**. On transfer to the early recovery unit, baseline cognitive functioning was evaluated using the MMSE in participants with clinically observed cognitive impairment, or in those demonstrating difficulty-understanding instructions, or reporting a history of high-dose benzodiazepine use. Participants with MMSE scores ≤ 17 were, removed from the study, and assessment was, deferred for one week in participants with MMSE scores in the 18–24 range. If cognitive impairment or challenges persisted, a recommendation to remove the participant from the study due to a medical condition was, made.

For participants with no observed cognitive challenges, baseline assessments were, administered over two days, to minimize burden to the participant, optimize patient focus, and hence ensure reliability of the assessments. The GAD-7, BIS-11, and WSAS were, administered on the first day, while the ASI, PD screener, PHQ-9, and PSQI were, completed on the second day. Participants with scores indicative of anxiety and depression were, referred to psychiatry for comprehensive assessment and subsequent treatment planning.

Medication education and counselling was offered to each participant at the beginning of the inpatient treatment, and during the last week prior to transfer to outpatient care. For participants reporting problems with memory or cognitive difficulties, indicated by a MMSE score of 18-24, patient education was deferred until their cognitive functioning was recovered, i.e. clinically validated by the attending psychiatrist and confirmed by MMSE scores above 24.

Table 4.3 Schedule for administering study measures

Tool/ Screen	Baseline	Inpatient	16-week outpatient study period					
	Intake	detoxification (Daily)	Stabilisation (Weekly)	Week 1 to 4	Week 5 to 8	Week 9 to 12	Week 13 to 16	Week 16 End of study
Eligibility Screen	X							
MCCS	X	X	X*	x	x			
Pupil Reflexes	X	X	X*	x	x		x	x
COWS	X	X	X	x				
PHQ-9	X			x		x		x
GAD-7	X			x		x		x
BIS-11	X			x				x
PSQI	X		X	x	x	x	x	x
WSAS	X			x				x
PDS	X			x				x
ASI-Lite	X			x				x

MCCS, Minnesota Cocaine Craving (adapted for opioids); PHQ-9, Patient Health Questionnaire; COWS, Clinical Opioid Withdrawal Scale; Patient Health Questionnaire; GAD-7, Generalised Anxiety Disorder; BIS-11, Barrett Impulsiveness Scale; WSAS, Work and Social Adjustability Scale; PDS, Personality Disorder Screen; ASI-Lite, Addiction Severity Index-Lite.*: Daily for the first week.

4.6.4 Randomisation and Transfer to Outpatient Care

Prior to discharge to the outpatient programme, participants were allocated to the experimental group or the active control comparator on a 1:1 basis, according to a simple non-stratified randomisation procedure. An online software² was used to generate two-group randomisation for up to 200 participants.

During the final week of inpatient treatment at the early recovery unit, the PI ensured that all participants received: (1) counselling on BUP/NX-F according to the medication counselling checklist; (2) the BUP/NX-F education handout; and (3) the BUP/NX-F emergency card and (4) that medication reconciliation was performed.

4.7 EXPERIMENTAL AND CONTROL INTERVENTIONS AT THE OUTPATIENT CARE

This section describes the procedures applied for the experimental and control groups.

4.7.1 Experimental

Participants randomised to the experimental group were invited to participate in a 16-week MM outpatient treatment. The MM was delivered by the PI or a psychiatrist at the outpatient clinic and was structured to provide BUP/NX-F ‘take-home’ prescriptions contingent on adherence and abstinence from drugs. The framework for the ‘take-home’ prescriptions and the MM used stepped ‘take-home’ prescriptions whereby participants moved up and down the steps according to their medication adherence and drug abstinence data. For example, if a participant was considered abstinent and compliant with BUP/NF-F, ‘take-home’ prescriptions of longer duration were provided, whereas shorter durations were offered to non-abstinent and or non-adherent participants.

All participants in the experimental group commenced with an initial one-week DOT according to their assigned dosing schedule (Daily, Alt-D, or TIW). During the DOT week, participants were required to provide a minimum of three urine samples for toxicological screens (the default is five samples). If all appointments were attended without evidence of drug use (i.e., no positive UDS), participants were given a one-week ‘take-home’ prescription. Alternatively, participants continued on DOT for another week. Participants who received one-week ‘take-home’ prescription were required to provide a urine sample on returning to the clinic. If participants continued to

² available at www.randomization.com

be abstinent, they were given a two-week ‘take-home’ prescription. Alternatively, participants were stepped down to one week DOT.

Participants who received a two-week ‘take-home’ prescription were advised *not* to take the BUP/NX-F dose on the day they return to the clinic. This was further accounted for in the prescription refill by the dispensing pharmacist. At this visit, a blood sample was drawn for BUP quantitation, and urine was collected for drug screening. The exact timings for drawing the blood sample and the time of last BUP/NX-F dose were recorded to predict the BUP concentration using the pharmacokinetics model. The predicted BUP concentration was contrasted with that reported by the laboratory and participants were considered non-adherent if the difference was not within the 20% range.

Participants who were non-adherent or non-abstinent were moved a level down on their ‘take home’ prescriptions, i.e. from two to one-week ‘take-home’ prescription. In contrast, those who were abstinent and considered as medication adherent were stepped up to a three-week ‘take-home’. For participants receiving three-week ‘take-home’ prescription and found to be non-adherent to BUP/NX-F according to the TDM results or those with a positive UDS for any drug, the ‘take-home’ prescription was stepped down to two-weeks. Alternatively, participants who remained abstinent and adherent to the treatment received extended ‘take-home’ prescriptions, with the maximum set to four weeks. In the event that the participant was considered non-adherent and non-abstinent, he/she was reset to 5-day DOT regardless of the level achieved on the ‘take-home’ dose. Finally, a check of abstinence and adherence was performed for participants receiving at least three-week ‘take-home’ by random recalling these participants to provide a urine and a blood sample. Social workers who advised the participant not to take the BUP/NX-F dose on appointment day coordinated these random checks.

The Medication Management (MM) manual was developed to help and support participants achieve optimal and safe treatment with BUP/NX-F. During the first week of outpatient treatment, two MM sessions were delivered. The first –foundation session– was delivered on the first appointment at the outpatient clinic after transfer from inpatient care with a duration of approximately 40 minutes. On arrival to the clinic, UDS was performed, and the results were documented by the nursing. The PI then captured the pupil reflexes and asked the participant to complete the MOCS. A full review of the assessments’ results administered during the inpatient care and their

relevant to the recovery process was, conducted. The participant was invited to provide his/her reflections. The PI reviewed the consequences for drug use with the participant and assessed his/her motivation to change, before the participant was invited to provide two main goals expected from the treatment.

Next, the PI/investigator asked the participant to identify their major craving cues and suggested two relapse prevention strategies. The participant and the PI/investigator agreed on what 'craving' meant and discussed the most suitable strategies to curb it. The PI/investigator explained the diagnosis of OUD, why BUP/NX-F was prescribed, and the dose size and frequency and reinforced the importance of regularly taking the prescribed dose at the same time each day to obtain optimal response. The PI/investigator confirmed that the participant had received and understood the medication counselling and was fully aware of the importance of medication adherence (**Appendix C.7 Medication counselling checklist**). The PI/investigator summarised and concluded the session by providing the recovery passport (participant diary) and the necessary counselling to complete the passport. The participant was encouraged to ask questions, and the PI/investigator documented the intervention using the MM foundation session form (**Appendix C.1**). Finally, the PI scheduled the participant for the second session at the end of the first 5-day DOT week.

In contrast, the second session was delivered the end of the first week and extended for approximately 15 minutes. In this session, the PI/investigator explained the TDM procedure and its aim to monitor medication adherence, and invited the participant to reflect on their first outpatient week. Next, the PI/investigator reviewed the completed sections of the recovery passport with the participant. The PI/investigator documented the pupil reflexes to confirm whether the participant is experiencing withdrawal or craving. For participants found to observe cravings supported by pupil reflexes, the PI/investigator recommended BUP/NX-F dose adjustment, after addressing uncontrolled symptoms of anxiety and/or depression.

In the subsequent MM sessions, UDS and TDM results were reviewed, and the interventions were provided in response to one of the four outcomes: (1) the participant was abstinent and medication-adherent; (2) the participant was non-abstinent but was medication-adherent; (3) the participant was non-abstinent and medication non-adherent; or (4) the participant was both non-abstinent and medication non-adherent (**Appendix C.2 MM Follow up session form and guide**). These interventions are briefly outlined as follows:

Outcome 1. Participant was abstinent and adherent to BUP/NX-F: The PI/investigator praised and complimented the patient on his/her ability to adhere to treatment and maintain abstinence. The PI/investigator further explained that most participants experience difficulty achieving this outcome and encouraged the participant to share his/her strategies used to achieve this outcome. Furthermore, the PI/investigator discussed common mistakes, such as dropping out of the treatment as soon as the participant feels better, and reinforced that recovery is more likely to be sustained if ‘treatment as prescribed’ is maintained for at least six months. The PI/investigator also discussed the participant’s treatment goals and ways to promote their recovery, and concluded the session by motivating the participant to sustain abstinence and medication adherence. Finally, the PI/investigator moved the participant’s ‘take-home’ prescription one level up, according to the protocol, and scheduled the next appointment.

Outcome 2. Participant was non-abstinent but adherent to BUP/NX-F: If this situation occurred early in treatment, the PI/investigator advised the participant that non-abstinence is both challenging and common in treatment all substance use disorders. The PI/investigator further explained that this outcome might be attributed to medications not achieving optimal effect yet or to the potential effect of co-occurring disorders.

The PI/investigator encouraged the participant to continue taking BUP/NX-F as prescribed and reinforced that abstinence is a gradual process requiring adherence to both medication and behavioural treatment. The PI/investigator also praised any steps taken towards recovery and highlighted that achieving and maintaining abstinence usually becomes easier over time. The PI/investigator and the participant collaboratively generated a plan on how abstinence could be achieved. In response to this outcome, the PI/investigator stepped down the participant’s ‘take-home’ prescription by one level down, according to the protocol, and scheduled the next appointment.

Outcome 3. Participant was abstinent but non-adherent to BUP/NX-F: The PI/investigator congratulated the participant for being abstinent and inquired on the abstinence-related benefits observed by the participant. The PI/investigator checked whether the participant experienced other problems or challenges linked to poor adherence, probed on reasons for non-adherence, and attempted to address any problems, including adverse events.

Next, the PI/investigator counselled the participant that medication adherence increases the likelihood of sustained improvement and reduces the probability of relapse. The PI/investigator concluded the session by reviewing the medication adherence plan and stepped down the 'take-home' prescription by one level, and scheduled the next appointment.

Outcome 4. Participant was non-abstinent and non-adherent to BUP/NX-F: The PI/investigator complimented the participant on any steps taken towards achieving abstinence and evaluated the level of motivation. Next, the PI/investigator, reminded the participant of his/her identified treatment goals, and reiterated that abstinence contributes to achieving these goals. The PI/investigator highlighted to the participant that recovery is a gradual process facilitated by medication adherence.

Next, the participant was, probed on the reasons for non-adherence and the PI/investigator addressed those problems likely to be associated with poor adherence, such as adverse events. The PI/investigator referred the participant to the appropriate discipline according to the identified problem. For example, if psychological disorders were, observed, a referral was made to psychology and similarly a referral to the attending psychiatrist was made if unresolved psychiatric disorders were identified. Finally, the PI/investigator transferred the participant to the initial 5-day DOT BUP/NX-F and UDS protocol.

4.7.2 Control

Unlike the experimental group, participants in the Control group were entitled to BUP/NX-F 'take-home' prescriptions from the first week of outpatient treatment. Outpatient visits were, scheduled as once, twice weekly or once every two weeks contingent on UDS results only, and according to the convenience of the participant (e.g. proximity of residence to the NRC). Providing 'take-home' prescriptions did not follow a structured protocol. Similarly, outpatient management sessions did not follow the MM manual implemented in the experimental group.

The procedures for the control and experimental groups are contrasted in **Table 4.4**.

Table 4.4 Study procedures by group

Study procedures	Study group	
	Experimental	Control
Induction and stabilisation	Yes	Yes
Baseline assessments	Yes	Yes
Establishing BUP SSC	Yes	Yes
Medication education	Yes	Yes
Outpatient 5-Day DOT with UDS	Yes	No
Outpatient medication management manualised intervention	Yes	Not delivered according to a defined manual
UDS at outpatient visit	Yes	Yes
Take-home prescriptions	Contingent on UDS & TDM (abstinence & adherence)	Contingent on UDS results only
Stepped take-home prescriptions	Yes	No
Maximum take home prescriptions	4 weeks	2 weeks
Blood sample for TDM	Yes After 2 weeks, 3 weeks and 4 weeks, every other month	No

BUP/NX-F: Buprenorphine/naloxone film; DOT: Direct Observed Treatment; SSC: Steady State Concentration; TDM: Therapeutic Drug Monitoring; UDS: Urinary Drug Screens

In both study conditions, assessment of relapse and the need for inpatient treatment was performed at each relapse event defined by multiple uncontrolled substance use. Intoxicated participants, regardless of the substance used, were offered a short period of inpatient treatment. Functional analyses of the relapse event was performed and interventions were individualized. After the study period was concluded, all randomised participants received the NRC's standard of care with efforts to maintain follow-up for up to 36 weeks.

4.8 TRIAL GOVERNANCE

To ensure the safe, unbiased, and timely delivery of STAR-T, a governance structure consisting of two ‘governance’ committees—Management and Safety Committee and Trial Management Group—as well as regular supervision, and internal and external audits, was developed.

The governance committees were structured according to Good Clinical Practice. As an independent committee, the Management and Safety Committee included representatives of the sponsor/clinical site -not involved in the study- and the PI, and met every 3 months to monitor the study and review emerging safety data. In contrast, the Trial Management Group comprised of members of the trial investigators and was responsible for day-to-day management of the study, and reported to the Management and Safety Committee on study progress and patient safety. The Trial Management Group met bimonthly to review study updates and discuss operational matters. The PI documented meetings and ‘meeting minutes’ were circulated to all members within a maximum of 3 days. At each meeting, the group reviewed the recommendations and follow-up actions generated from the previous meeting. Any observed challenges in the service delivery found to affect the study progress was shared with the director of treatment and rehabilitation (Medical Director) and suggestions to address these responses were shared with the Management and Safety Committee/

All clinical research files were stored as paper files in a locked filing cabinet, with a single key access in the custody of the PI. No other keys were available and losing the key would require the cabinet lock to be broken. The paper files included sections for assessments/screens, MM forms, and pharmacotherapy consults. Additionally, the scales/measures generating composite scores (e.g., PSQI, BIS-11, ASI-Lite) were entered on the digitally automated scoring template developed for each scale with composite scores (e.g. ASI, BIS-11, PSQI, PHQ-9, GAD-7). A digital version of the participants’ data using a coded participant number and randomisation group was uploaded to a shared folder on a secured server with restricted access limited to the study investigators.

4.8.1. Participant safety and withdrawal from the study

All non-fatal or non-life threatening events were reported within 15 days upon discovering the event. Fatal or life-threatening events were reported immediately and additional information was submitted within eight days. The PI and the attending psychiatrist

assessed adverse events for the level of seriousness, and possible association with BUP/NX-F. Results were recorded using the adverse event form (**Appendix C.10**). The PI, chief psychiatrist, and medical director removed participants from the study for safety reasons according to a joint decision. A decision to prematurely stop the study was possible based on data gathered by the Management and Safety Committee. For participants who elected to withdraw from the study at any time, reasons for withdrawal were clarified and recorded by the PI.

4.8.2 Data Audit and Quality Assurance

The following describes the audit performed for the data and the quality assurance carried out during the study period. This included an internal and independent audit followed by an audit completed by the first supervisor. No budget was available for an external audit.

The internal data audit was completed at two levels, the first aimed to verify and validate the study outcomes (UDS and retention), and was completed by the attending psychiatrist at the inpatient care (NH). At this level, NH validated UDS results, retention periods, and completion rates on the participant data file with that retrieved from the patient electronic medical records. Discrepancies were verified and adjusted subject to an independent review performed by two medical-record officers and a medical secretary representing the NRC (clinical site) before the final data set was available for audit by the first supervisor.

Prior to writing up this thesis, an audit was, carried by the first supervisor between January 16 and 20, 2017, and was completed for 100% of the cases over 26 working hours. The first supervisor reviewed and verified: (1) the randomisation procedure, (2) number of scheduled clinical appointments with expected UDS, (3) number of actual appointments attended by the participants and the number of UDS performed, (4) positive opioid screens confirmed by Gas Chromatography Mass Spectrometry, (5) participant end-of-study assessments, (6) retention (days to discontinue, days to endpoint) for each participant, (7) laboratory procedures and TDM data, (8) all study interventions made and documented in the clinical research files, (9) adverse events reports, (10) consent procedures and consent forms, (11) the data management process, and (12) the documentations for the Trial Management Group. Finally, a report summarising the audit was generated, highlighting the study outcomes (**Appendix B.6**).

In addition to regular supervision, eight field visits were, undertaken by the first supervisor and second supervisor during the course of the study. The visits entailed provision of training, review of study progress, review of the study documentations, and assessment of the delivery of the study interventions, and quality assurance.

Appropriate coaching and recommendations for the study were, also provided.

Recommendations generated from the field visits for optimal clinical management were, discussed with the Trial Management Group. Examples recommendations to minimize treatment discontinuation by participants were, induction on BUP/NX-F upon admission as quickly as possible; minimise likelihood of patient discharge during the weekends, secure outpatient appointments for the first two weeks post-discharge from inpatient care to avoid ‘bottlenecks’; refer participants relapsing on pregabalin to psychology for assessment and management of anxiety; assessment of previous treatment responses and risks of treatment non-adherence or failure; functional assessment of relapse/lapse; and early engagement of social workers in following up with participants who miss appointments.

To ensure the quality the delivery of the MM sessions, the PI conducted at least two random checks for each psychiatrist delivering the MM sessions. The PI observed the delivery of the MM sessions for concordance with the MM manual, completion of MM forms, and implementation of the ‘take-home’ prescription protocol. The PI provided the necessary feedback and no specific checklists or evaluation forms were completed.

4.9 TRAINING

To ensure that all investigators were prepared to deliver BUP/NX-F treatment and perform study-related assessments and interventions, several training sessions were delivered.

Two international experts in addiction medicine and addiction psychology delivered the first training over three days in January 2014 to all investigators. The training focused on patient assessment and clinical management of OUD along the full continuum of care. The training content was benchmarked against the standard training required to license BUP/BUP/NX prescribers in the US, and covered psychosocial and pharmacological treatments, the challenges and opportunities associated with delivering effective MAT, specific guidelines for BUP/NX pharmacotherapy, and the STAR-T study protocol and materials.

The PI delivered the second training in September 2014 before commencing with the patient recruitment. This training, attended by all investigators, focused on the study protocol and the procedures required for performing TDM. The third training was delivered by the PI and two psychiatrists (investigators) and was tailored to the nursing and pharmacy disciplines. The training curriculum focused on the importance of accurate timing for collection of blood samples representing peak and trough BUP concentrations (**Appendix B.7. Nursing training program**). All but one inpatient nurse attended the training, and a one-on-one session was delivered for this nurse. The fourth training was, delivered by the PI to all social workers and nurses involved in coordinating the outpatient care. This training focused on methods to administer the end-of-study assessments to all randomised participants including those who discontinued treatment. Since the social workers were, blinded to the randomisation, bias towards any of the study approaches was, minimal.

4.10 ANALYSES PLAN

All statistical analyses performed under the present investigation were pragmatic and based on the 'Intention-to-Treat' population. Significance was set at 95% confidence (i.e., 5% level of uncertainty, $\alpha = 0.05$). The Statistical Package for Social Sciences (SPSS) version 24.0 and was used for the descriptive and inferential statistics and STATA version 15 was used for secondary analysis of the primary outcome.

Baseline patient characteristics (sociodemographic and clinical data) for each the randomised groups were analysed for mean (M) and range, as well as standard deviation (SD) or 95% confidence interval (CI). For between-group differences, assuming the data were normally distributed evaluated by a non-significant homogeneity test of variances, a two-sample t-test was used to compare the means. If data did not follow normal distribution, the median with interquartile range (IQR) were calculated and a Mann-Whitney test was performed to compare the two medians. For categorical data, e.g. the secondary outcome, a Chi-squared (Pearson χ^2) test was conducted to compare the study groups.

Significant difference observed in the primary outcome was analysed adjusting for covariates by applying a fixed-effects linear regression model using STATA version 15 with Bootstrapping for the Incident Rate Ratio (IRR). The selected covariates (age, days to measure outcome, and ASI-Drug use) were reported or assumed to have an impact on

opioid use, e.g. age (Hser et al., 2014) and retention in treatment (Weiss et al., 2011). The difference between groups was explored after testing for homogeneity using the appropriate test. For the secondary outcome, the OR (and associated 95% confidence interval) and the Number-Needed-To-Treat (NNT) to complete the study period was completed. For this outcome, secondary analysis a Kaplan-Meier test was conducted to estimate the difference in time in days to measure the primary outcome.

The mean change between baseline and the end of study or within subject change in scores of the PHQ-9, GAD-7, PSQI, WSAS, ASI, and BIS-11 was examined using a paired samples t-test for normally distributed data, or the Wilcoxon Signed Ranks test for paired data not following normal distribution. Between subject, analysis for the magnitude of change in measures was also performed to evaluate if the change is driven by the intervention. For categorical data (personality disorders), within-subject analysis was conducted using a McNemar's test

Bivariate associations between the study outcomes and sociodemographic characteristics, BUP/NX-F dose and BUP EL.R were determined using Pearson's association for continuous normally distributed data and Spearman's rho association for data not normally distributed or for categorical data. Statistically significant associations were then adjusted for the study allocation and a best-fit regression model was applied to examine the predictive power of the variables showing significant associations.

CHAPTER 5 STUDY 2 EFFECTIVENESS OF INCENTIVISED THERAPEUTIC DRUG MONITORING IN BUPRENORPHINE MAINTENANCE TREATMENT: A PRAGMATIC, RANDOMISED CONTROLLED TRIAL

5.1. DESCRIPTION OF THE STUDY IN THE CONTEXT OF THE THESIS

This chapter presents the publication on the study reporting the primary and secondary outcomes addressing hypothesis 1 and 2. In this chapter, the change in psychosocial measures from baseline at the end of the study is briefly covered with detailed analyses presented in **appendix 1**.

This study has been published as

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Effectiveness of incentivised adherence and abstinence monitoring in buprenorphine maintenance: a pragmatic, randomised controlled trial

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Incentivised adherence and abstinence monitoring in buprenorphine maintenance

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DECLARATIONS OF INTERESTS

In the past three years, J.M. declares research grants to King's College London (KCL) from: (1) the National Institute for Health Research (NIHR) for a multi-centre RCT of acamprosate for alcohol use disorder; (2) the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Mental Health Foundation Trust (SLaM) for a pilot RCT of novel cognitive therapy for cocaine use disorder; and (3) an unrestricted grant from Indivior to KCL and SLaM from Indivior for a multi-centre, RCT of extended-release injectable buprenorphine for OUD. He has part-time employment as Senior Academic Advisor for the Alcohol, Drugs, Tobacco and Justice Division, Health Improvement, Public Health England. He is a clinical academic consultant for the US National Institute on Drug Abuse, Centre for Clinical Trials Network. He holds no stocks in any company.

All other authors state they have no declarations of interests.

ABSTRACT

BACKGROUND AND AIM: Buprenorphine (BUP) maintenance treatment for opioid use disorder (OUD) begins with supervised daily dosing. We estimated the clinical effectiveness of a novel incentivised medication adherence and abstinence monitoring protocol in BUP maintenance to enable contingent access to increasing take-home medication supplies.

DESIGN: Two-arm, single-centre, pragmatic, randomised controlled trial of outpatient BUP maintenance, with during-treatment follow-ups at 4 weeks, 8 weeks, 12 weeks and 16 weeks.

SETTING: Inpatient and outpatient addictions treatment centre in the U.A.E

PARTICIPANTS: Adults with OUD, voluntarily seeking treatment.

INTERVENTIONS: The experimental condition was 16 weeks BUP maintenance with incentivised adherence and abstinence monitoring (I-AAM) giving contingent access to 7-day, then 14-day, then 21-day, and 28-day medication supply. The control, treatment-as-usual (TAU) was 16 weeks BUP maintenance, with contingent access to 7-day then 14-day supply.

MEASUREMENTS: The primary outcome was number of negative urine drug screens (UDS) for opioids, with non-attendance or otherwise missed UDS, imputed as positive for opioids. The secondary outcome was retention in treatment (continuous enrolment to the 16-week endpoint).

FINDINGS: Of 182 patients screened, 171 were enrolled and 141 were randomly assigned to I-AAM (70 [49.6%]) and to TAU (71 [50.4%]). Follow-up rates at 4 weeks, 8 weeks, 12 weeks and 16 weeks were 91.4%, 85.7%, 71.0%, 60.0% respectively in I-AAM and 84.5%, 83.1%, 69.0%, 56.3% in TAU. By intention-to-treat, the absolute difference in percentage negative UDS for opioids was 76.7% (SD 25.0%) in I-AAM versus 63.5% (SD 34.7%) in TAU (mean difference 13.3%; 95% confidence interval [CI] 3.2%–23.3%; Cohen's *d* 0.44; 95% CI 0.10–0.87). In I-AAM, 40 participants (57.1%) were retained versus 33 (46.4%) in TAU (odds ratio 1.54; 95% CI 0.79–2.98).

CONCLUSIONS: Buprenorphine maintenance with incentivised therapeutic drug monitoring to enable contingent access to increasing take-home medication supplies increased abstinence from opioids compared with buprenorphine maintenance treatment-as-usual, but it did not appear to increase treatment retention.

Keywords: opioid use disorder; buprenorphine; therapeutic drug monitoring; adherence; abstinence; effectiveness.

INTRODUCTION

Opioid use disorder (OUD) is a global public health problem associated with a high disease burden (Peacock et al., 2008). Retention-oriented medication maintenance treatment with methadone or buprenorphine (BUP), or combined BUP and naloxone, are the first-line pharmacotherapies. Patients who engage in OUD treatment have a marked reduction in overdose mortality and use of opioids (White et al., 2015; Mattick et al., 2014). However, many patients struggle to adhere to treatment and discontinue prematurely. In a systematic review of four randomised controlled trials [RCT] and 63 observational studies (294,592 participants in total), the median retention rate was approximately 57% at 12 months (O'Connor et al., 2020). Non-adherent patients are substantially more likely to relapse to opioid use (Tckaz et al., 2011).

Driven by safety concerns, national clinical guidelines for OUD maintenance treatment recommend that patients should receive all, or the majority of their medication, by supervision for several months, with access to take-home supplies (to a typical maximum of 14-days at a single dispensing event) granted to those who can attend and take their medication as directed (Ajay, 2008); SAMHSA, 2015). Clinicians favour access to unsupervised dosing for adherent patients (Lowfall & Walsh, 2014; Shuman-Olivier, 2013) and it would appear that most patients endorse this as well (Griffith et al., 2000). Some patients believe supervised dosing is stigmatising and this may motivate the decision to leave treatment (Gerra et al., 2011)

Typically, prescription adherence during OUD maintenance treatment is monitored through a combination of non-attendance alerted by the dispensing pharmacy and monitoring of point-of-care urine drug screening (UDS) at the clinic. The UDS is a qualitative test which gives an indication of recent medication use (at a level of detection sensitivity) but it cannot show whether the prescribed dose has been taken as prescribed. There have been several clinical effectiveness studies of supervised and unsupervised dosing. A meta-analysis of 6 such studies in methadone, BUP and combined BUP and naloxone maintenance (4 RCTs and 2 prospective observational cohort studies; 7,999 participants in total) judged that there was insufficient evidence for a robust difference in retention (relative risk 0.99, 95% CI 0.88–1.12); or endpoint abstinence (67% versus 60%); or medication diversion (5% versus 2%) (Saulle et al., 2017). However, the quality of these studies was rated as 'low–very low', so further evidence is likely to change this conclusion.

Is there a better way to monitor adherence during BUP maintenance and help patients receive increasing take-home supplies? One promising set of procedures is Therapeutic Drug Monitoring (TDM). TDM is defined as the “quantification and interpretation of drug concentrations in blood to optimize pharmacotherapy” (Hiemke et al., 2017). Clinical applications involve repeated measurements of the plasma concentration of a medicine to reach a dose that is well tolerated, minimises the risk of adverse drug reactions, and achieves the desired effect. Unlike UDS, TDM can provide a precise indication that medication has been taken as directed. Two decades ago, TDM was predicted to become the standard-of-practice for OUD maintenance pharmacotherapy (Wolff & Strang, 1999). However, TDM has not been implemented to any significant extent, and there have been no trials applying TDM procedures during BUP maintenance.

Accordingly, this study as a contribution towards closing this gap. As a precursor, we optimised a laboratory quantification method for BUP monitoring, demonstrating that this was feasible during routine clinical operations (Elarabi et al., 2020). Including TDM procedures, we developed a novel incentivised medication adherence and abstinence monitoring (I-AAM) protocol. The aim of I-AAM was to enable BUP dose-optimised patients who could provide ongoing evidence of adherence and abstinence from opioids, access to increasing take-home supplies of their medication. The aim was to estimate the clinical effectiveness of BUP maintenance with I-AAM versus BUP maintenance treatment-as-usual.

METHODS

Setting

The study was done at the inpatient and outpatient service of the National Rehabilitation Centre (NRC), Abu Dhabi, United Arab Emirates (UAE). The NRC is the only national provider of BUP maintenance treatment in the UAE. The centre receives referrals from metropolitan Abu Dhabi with 50% of patients attending from other cities and remote areas. In the UAE, heroin, morphine, and tramadol are the most common illicit and non-medical prescription opioids reported by populations with OUD. Locally, BUP is not available at community retail pharmacies, so medication is dispensed by the NRC’s outpatient pharmacy.

The NRC commenced BUP maintenance treatment in 2002. Patients who took their medication as directed and were abstinent from opioids were received up to 14-days take-home supply (this limit set by the centre's dispensing policy). A decade later, and in the context of anecdotal reports of BUP diversion and non-adherent dosing behaviours among some patients, the NRC suspended treatment for people with no treatment history of BUP maintenance, while granting maintenance treatment to new patient episodes enrolled in this study.

Design

This was a single-centre, two-arm, open-label, parallel group, pragmatic RCT of BUP I-AAM (the experimental group) versus BUP TAU (the control group) during 16-weeks of outpatient maintenance treatment. During-treatment follow-ups were at 4 weeks, 8 weeks, 12 weeks, and 16 weeks. The NRC's Institutional Review Board approved the protocol (reference: NRC/2/2014). The study was retrospectively registered with the ISRCTN registry (number ISRCTN416 45723) and the study protocol was published (Elarabi et al., 2019). In this article, methods and findings are reported by CONSORT (Shultz, Altman, Moher, 2010). Medication management and other participant materials can be access on the Open Science Framework (<https://osf.io/t9rp4/quickfiles>).

The study was conducted in accordance with the ethical principles of the World Medical Association's Declaration of Helsinki for research involving human subjects, good clinical practice, and the Abu Dhabi Department of Health's guidelines for medical research. Study participants received study medication without charge and did not receive any compensation for completing research measures. After participants completed the study, they continued to receive BUP maintenance according to their preference and clinic policy.

Contingent on evidence of adherence (attendance and contrasting BUP measured and concentrations) and abstinence (from opioids by UDS), participants allocated to the I-AAM condition had access to increasing take-home supplies of BUP. Dispensing increased from 7-days, to 14-days, to 21-days to a maximum of 28-days supply. Participants allocated to TAU had no blood testing for BUP concentration measurement and had access to a 7-days then 14-days maximum.

An online randomisation service (www.randomization.com) was used to allocate participants to the two groups (1:1 ratio; no stratification). Given the open-label design, it was not feasible to mask participants and study investigators. A planned, exploratory health economic analysis will be reported elsewhere.

Inpatient withdrawal management and BUP stabilisation

At the NRC, medically supervised opioid withdrawal and BUP dose induction is done at an onsite inpatient programme prior to outpatient treatment. During inpatient stay, dose stabilisation was carried out with the objective of settling on a maintenance dose that was personalised for each participant informed by signs and symptoms of opioid withdrawal and their feedback.

Outpatient maintenance medication treatment

Participants were maintained on BUP-naloxone (4:1 ratio) sublingual film formulation (Suboxone™; Indivior; BUP herein). This product was developed to limit risk of diversion and dissuade injection. All medication was bought commercially. The outpatient maintenance treatment endpoint was 16-weeks (112 days). This was pragmatic and judged reasonable to estimate clinical benefit. During treatment, all participants were offered general counselling and case management support.

For each scheduled clinic visit, the participant was asked to return opened medication packaging, and take a UDS test. We used commercial point-of-care UDS product (www.cliawaived.com). The test cup was configured to detect morphine (detection limit 300ng/mL), heroin (6-acetylmorphine 20ng/mL), codeine (100ng/mL), propoxyphene and hydrocodone (300ng/mL), tramadol (200ng/mL), oxycodone (100ng/mL), fentanyl (1000ng/mL), and BUP (10ng/mL). With the exception of BUP, all test results were required to be negative for the UDS to be recorded 'opioid negative'. All positive opioid test results were confirmed by Gas Chromatography Tandem Mass Spectrometry.

Study participants

Participants were adults (18 years and over). All had current OUD and voluntarily seeking treatment (**Table 5.1** shows the inclusion and exclusion criteria). Consecutive referrals were screened in person and all participants provided their informed written

consent. All adverse events were reviewed by the senior investigators and the data monitoring committee.

Table 5.1: Participant inclusion and exclusion criteria

Inclusion criteria

1. Aged 18 and above (no upper limit);
2. Current diagnosis of OUD;
3. Voluntarily seeking BUP maintenance treatment;
4. Resident in the UAE;
5. Evidence of stable accommodation.

Exclusion criteria

1. Benzodiazepine use in excess of 20mg/day daily diazepam equivalent in the past 28 days;
 2. Known naloxone or BUP hypersensitivity;
 3. Pregnancy;
 4. Hepatic impairment (elevation of liver function tests three times normal);
 5. Suicide attempt in past 12 months;
 6. Involvement in criminal justice system which is likely to result in arrest and incarceration;
 7. Uncontrolled severe mental or physical illness judged to compromise safety;
 8. Mini Mental State Examination score <17 (indicating cognitive dysfunction).
-

Note:

OUD, opioid use disorder;
UAE, United Arab Emirates;
BUP, buprenorphine.

Study procedures

After enrolment, participants were admitted to the NRC's onsite inpatient service for up to 4 weeks for medically supervised withdrawal, BUP induction, and dose stabilization. As soon as they were comfortable, participants completed a structured interview recording demographic characteristics and baseline measures. Each participant was administered BUP daily under supervision at the same time. In an effort to personalise each participant's dosing interval, those who consumed illicit opioids by an injection (or

with a Body-Mass Index of 30 and polysubstance use) commenced daily dosing. Those with prescription OUD were recommended to receive alternate-day dosing (i.e. every 48-hours). Our protocol also included the option for this patient group to attempt stabilisation with three-times weekly dosing (to the dose maximum of 32mg/day). Alongside patient preference, clinical signs and symptoms (using the Clinical Opiate Withdrawal Scale [COWS]) (Wesson & Ling, 2003); pupil reflexes (www.neurooptics.com), and craving using the Minnesota Cocaine Craving Scale adapted for opioids (MCCS-O; scored: 0-100%) (Halikas et al., 1991) informed decisions about commencing, achieving a dosing interval, or reverting to a more frequent dosing interval.

When the participant was comfortably stable on the same BUP dose for 2 weeks, we assumed BUP's steady-state concentration had been achieved. An on-site laboratory, computed the BUP elimination rate (EL.R) from three blood samples: the first drawn 30 minutes prior to administration of the participant's BUP dose (to estimate the BUP trough concentration); the second drawn after 40 minutes (peak concentration); and the third after 48 hours prior to the next BUP dose (for a second trough concentration to confirm steady-state concentration if replicated). The inpatient episode was then judged completed once the EL.R had been calculated and the participant had a COWS score of 0–4 (no active opioid withdrawal). Prior to transfer to the outpatient programme, a member of the study team accessed the randomisation service and the participant was allocated to the I-AAM or TAU condition.

I-AAM procedure and take-home dosing schedule

(1) For the first 5 days of BUP maintenance treatment, the participant was asked to attend the clinic daily for supervised dosing and to take a UDS test at each visit (or a minimum of 3 UDS). If they adhered (i.e. all doses taken; at least three negative UDS; all UDS positive for BUP), participants were dispensed with 2 doses to take that weekend and a 7-day supply. They were given instructions on how to take their medication (i.e. daily, alternate-day and thrice weekly regimens) and asked to return to the clinic 1 week later.

(2) If participants returned as directed, and reported following their prescription, gave an opioid negative UDS that was positive for BUP, they were dispensed with a 14-day

supply. Participants were asked to not take their BUP dose on the day of their next appointment because this was given by the dispensing pharmacy. On arrival, they were given their dose of BUP, they took a UDS, and had a blood sample drawn. A pharmacokinetic model was applied to predict BUP concentration (Elarabi et al., 2020). If the UDS confirmed abstinence for opioids and was positive for BUP, the participant was given a further 14-day supply (with same directions) and asked to return to the clinic 2 weeks later.

(3) On return to the clinic, the procedure was repeated and the predicted BUP concentration (estimated from the previous visit) was contrasted with the BUP concentration on the day. If the concentration difference was $<20\%$, and the UDS was negative, participants were given a 21-day supply and asked to return 3 weeks later. As a safety measure, participants given 21-days supply were contacted randomly and asked to attend for UDS and blood testing.

(4) On return to the clinic, and with evidence of continued adherence and clinical benefit (i.e. difference in BUP concentration $<20\%$; UDS negative), participants were given 28-days supply and asked to return 1 month later for a further monthly supply. Adherence and abstinence were then randomly monitored every other month to the endpoint.

Those not adhering to the above procedure at the outset or for the requirements of the 7-day supply, were held at a 5-day supervised dosing requirement pending evidence of adherence and abstinence. Those receiving 14-days who were non-adherent *or* non-abstinent were 'reset' to receive a 7-day supply. Those receiving a 21-day and 28-day supply who were non-adherent *or* non-abstinent were reset to a 14-day or 21-day supply, respectively. At any point, a participant who was non-adherent *and* non-abstinent was held in a 5-day supervised dosing and UDS testing regimen. During this process, patients discussed their scores on the COWS (week 1-4), and MCCS-O (week 1-4 and week 5-8), and pupil reflexes (weeks 5-8 and 13-16) and asked if they wanted their dose adjusted.

TAU procedure and take-home dosing schedule

(1) In the first 5 days of maintenance, participants were asked to attend the clinic at least once for supervised BUP dosing and to take a UDS at each visit. Between visits participants were dispensed with take-home doses. If they adhered (i.e. all doses taken; all UDS negative; all UDS positive for BUP), they were dispensed with a 7-day supply including 1 dose to take on each day of weekend. Participants were given instructions on how to take their medication and were asked to return to the clinic one week later.

(2) If participants returned, reported following their prescription, provided an opioid negative UDS that was positive for BUP, they were dispensed with a 14-day take-home supply.

Participants who did not adhere to the above procedure at the outset or for the requirements of the 7-day supply, were held in 5-day supervised dosing (with 2 take-home doses for the weekend) until there was evidence of abstinence. At any point, a participant who was non-adherent *and* non-abstinent was reset to 5-day supervised dosing and UDS testing. During treatment, there was discussion of withdrawal symptoms, craving and dose adequacy, as described above for the experimental group.

Outcome measures

The primary outcome was the number (percentage) of scheduled and biochemically-verified (UDS and laboratory confirmed) tests negative for opioids during 16-weeks of outpatient BUP maintenance treatment. Conservatively, non-attendance for scheduled UDS was recorded as positive for opioids (Mcpherson et al., 2012). The secondary outcome measure was retention in outpatient treatment, defined as completion of 16-weeks of treatment (with no more than three missed consecutive clinic appointments).

The five exploratory outcome measures (end-of-study group comparison), were: The Addiction Severity Index-*Lite* – drug use sub-scale (*ASI-Lite*) (Cacciola et al., 2007); the nine-item Patient Health Questionnaire (PHQ-9) (Kroenke, Spitzer, Williams, 2001); the Generalized Anxiety Disorder scale (GAD-7) (Spitzer et al., 2006); the Barratt Impulsiveness Scale (BIS-11) (Patton, Stanford, Barratt, 1995) and the Work and Social Adjustability Scale (WSAS; score range: 0-40; higher scores reflecting more social impairment attributed to OUD) (Mundt et al., 2002). No changes were made to the outcomes after the trial commenced.

Statistical analysis

To guide the target sample size, we used a measure of sustained (three-week) abstinence between treatment and comparison groups in a meta-analysis of incentivised OUD treatment (44% versus 23%; odds ratio [OR] 1.96) (NICE, 2007). With type I error at 5%, and a 15% increase in the sample to offset withdrawal attrition, we estimated that 182 participants (91 in each group) would give 80% statistical power for detection of a treatment effect.

The analysis was done by intention-to-treat in Stata 15. The primary outcome was analysed as the absolute difference in the percentage of negative UDS tests for opioids, reporting the mean and standard deviation (SD) for each group, the mean difference on this measure with a 95% confidence interval (CI); and the Cohen's *d* effect size with a 95% CI.

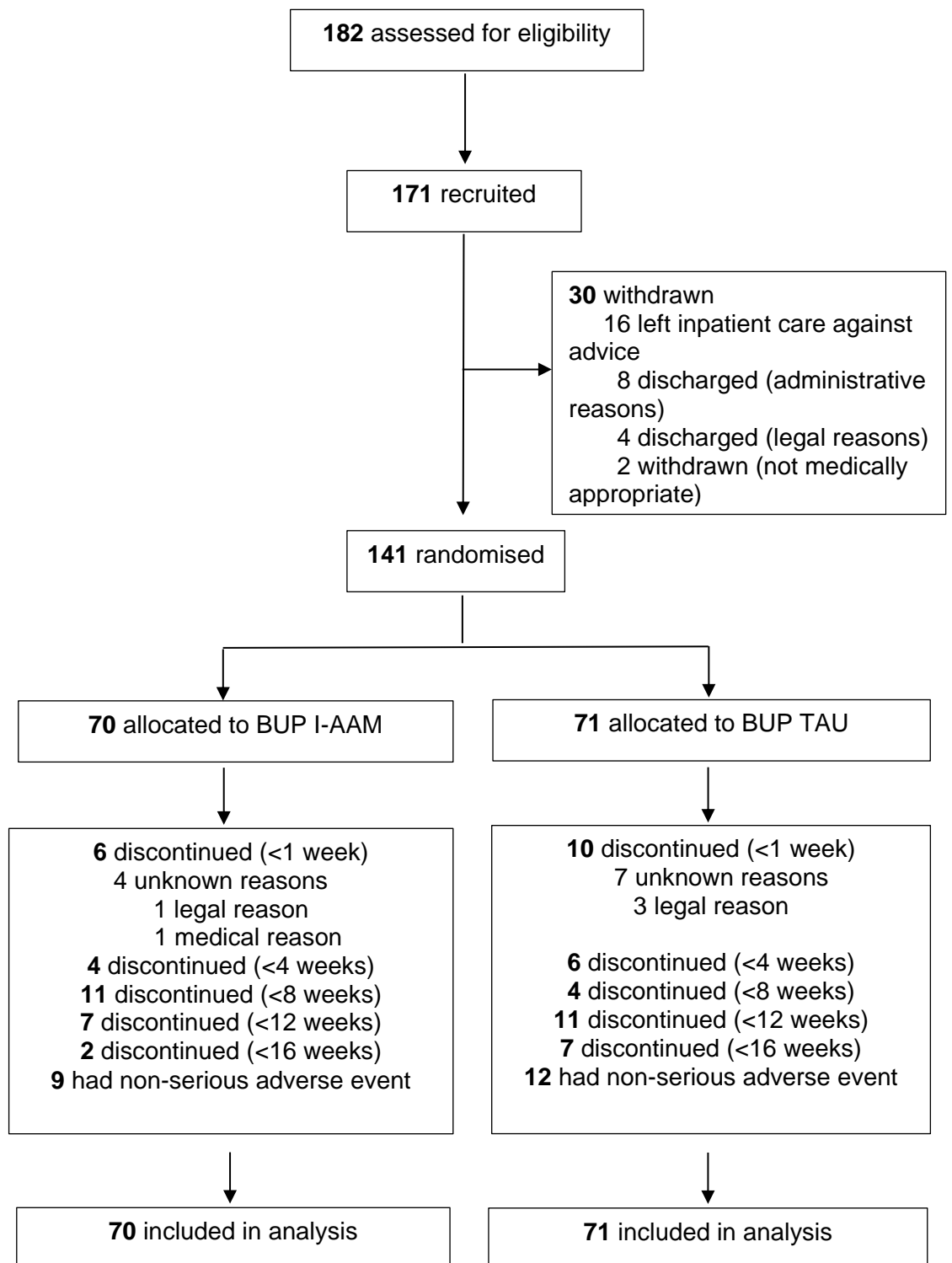
There were two sensitivity checks: an adjusted treatment effect estimated by a bootstrapped Poisson regression (incident rate ratio [IRR]) with the following covariables: age, baseline *ASI-Lite* drug use, and time (days) to discontinuation or completion of treatment. We also calculated the primary outcome as a complete case measure using only observed (non-imputed) UDS data. The secondary outcome measure was analysed by OR and Kaplan-Meier test. Exploratory outcomes were analysed by group mean difference at the study endpoint. The incidence of all adverse events was reported for both study groups.

RESULTS

Characteristics of the participants

The first participant was enrolled on 15 September 2014, and the last follow-up contact was on 16 September 2016. The trial database was locked on 19 January 2017. A total of 182 patients were screened for eligibility and 171 were enrolled into the study. Thirty participants (17.5%) withdrew before randomisation, and 141 (82.4%) were randomised (70 [49.6%] to the I-AAM group and 71 [50.4%] to the TAU group (**Figure 5.1** shows the study profile and reasons for exclusion). We were unable to extend the participant recruitment phase due to restrictions on the time permitted for the study.

Figure 5.1: Study profile



Note:

BUP I-AAM, BUP maintenance with incentivised adherence and abstinence monitoring;
 BUP TAU, BUP maintenance treatment-as-usual.

On admission to the inpatient service, the majority of participants received daily dosing at the outset, with just 4 accepting our recommendation for alternate-day dosing. A single participant was inducted onto thrice-weekly dosing. The two groups were well-balanced on demographic and clinical characteristics (upper section of **Table 5.2**). After randomisation, all participants were transferred to commence BUP maintenance at the outpatient clinic. In the first week, 16 participants left treatment (6 in the I-AAM group and 10 in the TAU group).

Between randomisation and the endpoint, a total of 30 (42.9%) participants in the I-AAM group and 38 (53.5%) participants in the TAU group discontinued treatment. All participants agreed to take UDS, provide blood samples, return opened BUP packaging, and all consented for their data to be used for the analysis. Follow-up rates at 4-week, 8-week, 12-week and 16-weeks were 91.4%, 85.7%, 71.0%, 60.0% respectively in the I-AAM group and 84.5%, 83.1%, 69.0%, and 56.3% respectively in the TAU group.

BUP maintenance treatment

Table 5.2 (lower section) shows the mean BUP dose for the participants retained at each follow-up week and their access to take-home supplies. On average, the BUP dose was 15mg/day in the I-AAM group and 16mg/day in the TAU group at each follow-up. Almost all study participants remained on their stabilisation dose during maintenance (138/141; 97.9%).

Three participants increased their dose, as follows: after three weeks, a participant in the I-AAM group reported distressing craving, and informed by measures of pupil reflexes (particularly measures of maximum pupil diameter) their dose was increased from 14–16mg/day; a TAU participant – with a long history of tramadol use – reported opioid withdrawal symptoms in the second week of treatment and dose was increased from 12–14mg/day; the other participant – a member of the TAU condition – had presented for treatment with severe OUD involving intravenous use of morphine, and tramadol – reported craving and withdrawal symptoms during the second week of treatment and dose was increased from 12–16mg/day.

During treatment, 18 participants in the I-AAM group (29.0%) were determined to be non-adherent to BUP and non-abstinent. All were reset to 5-day supervised dosing. Among 62 participants in the I-AAM group who received at least one 14-day supply of medication, a total of 109 blood samples were drawn with 37 samples estimated to have

BUP concentrations outside the 20% range for adherence (33.9% non-adherent). In the TAU group, 20 participants (28.2%) were able to receive no more than a total of 7 day take-home doses, and 51 (71.8%) received no more than a 14-day take-home supply.

In the I-AAM group, among 62 participants who received at least 2-weeks take-home supply, 109 blood samples were drawn (mean 1.8 (SD 0.77) per participant). The non-adherence rate was 34% (i.e. 37 samples had BUP concentrations outside the 20% range). Eighteen participants in the I-AAM group (29.0%) were evaluated as BUP non-adherent and non-abstinent and were reset to 5-day directly supervised dosing.

In the TAU group, 20 participants (28.2%) received no more than a 7-day take-home doses, and 51 (71.8%) received no more than 14-day take-home doses. There was no statistically significant difference in the mean number of scheduled UDS: 16.2 (SD 9.0) in the I-AAM group versus 14.1 (SD 8.9) in the TAU group (p-value 0.10).

During treatment, participants in both groups returned opened BUP packaging to the pharmacy very sporadically. Patients failing to return opened packaging were reminded to do so, but full compliance was rare. In the group of participants completing the 16 weeks of maintenance treatment, 1 participant in the I-AAM group was fully adherent according to TDM data and remained abstinent; 17 (42.5%) were adherent, but not abstinent. Among the non-adherent, 18 (45.0%) were also non-abstinent, and 4 (10.0%) were abstinent.

Table 5.2: Participant characteristics (n=141)

Characteristic	I-AAM (n=70)	TAU (n=71)
Demographic and clinical characteristics at baseline	30.4 (8.70)	27.7 (7.30)
Age – years ¶		
Sex – male	69 (98.6%)	70 (98.6%)
Married	36 (51.4%)	46 (63.3%)
Employed – full or part-time	28 (40.0%)	21(29.6%)
Resident in Metropolitan Abu Dhabi	36 (52.8%)	30 (42.2%)
Heroin/morphine OUD	55 (78.6%)	55 (77.5%)
Prescription/mixed OUD	15 (21.4%)	16 (22.5%)
Duration of OUD – median years	9.9 (5.7–17.3)	8.9 (5.4–14.7)
MCCS-O – maximum intensity in week before admission	88.6% (23.7%)	83.9% (31.5%)
ASI (drug use scale score) ¶	0.2 (0.1–0.4)	0.2 (0.1–0.4)
PHQ-9	12.9 (6.6)	13.6 (6.9)
GAD-7	10.0 (4.0–15.0)	10.0 (5.0–15.0)
WSAS	22.1 (9.8)	24.2 (9.2)
Inpatient withdrawal and stabilisation (ng/ml)		
BUP trough concentration after 2 weeks – mean	1.73 (1.47)	1.81 (2.47)
EL.R prior to transfer to outpatient treatment – median	0.05 (0.03–0.09)	0.05 (0.02–0.10)
Maintenance treatment week – BUP dose (mg/day) †		
Week 1	14.51 (4.63)	15.71 (3.60)
Week 4	14.68 (4.58)	15.60 (3.51)
Week 8	15.08 (4.50)	15.72 (3.52)
Week 12	15.02 (4.57)	15.72 (3.58)
Week 16	14.75 (4.45)	15.36 (3.22)
Take-home supplies (total dispensing events)		
No more than 7-days	1 (1)	20 (20)
No more than 14-days	55 (402)	51 (387)
No more than 21-days	7 (81) §	- #
No more than 28-days	1 (8) ‡	- #

Note:

Numbers in parentheses standard deviation, interquartile range, or as shown.

I-AAM, BUP maintenance treatment with incentivised adherence and abstinence monitoring;

TAU, BUP maintenance treatment-as-usual;

OUD, opioid use disorder; MCCS-O, Minnesota Cocaine Craving Scale, adapted for opioids, maximum intensity in week before admission (0-100%); PHQ-9, Patient Health Questionnaire; GAD-7, Generalized Anxiety Disorder; WSAS, Work and Social Adjustability Scale; ASI-*Lite*, Addiction Severity Index; EL.R, elimination rate (ng.mL/hr -1).

† all participants enrolled at follow-up;

§ 5 participants were dispensed this supply once, and 2 each received this supply twice;

‡ this participant received 2 successive 21-day supply prior to the single 28-day supply;

Prohibited under local treatment system policy.

Primary outcome

Although the obtained sample was smaller than that was targeted (post-study sample size calculation using the expected effect and obtained sample size indicated that statistical power was 75%), there was a statistically significant effect for the I-AAM condition on the primary outcome (**Table 5.3**).

For the two sensitivity analyses, I-AAM effectiveness (including age, baseline ASI-Lite drug use, and time to discontinuation or completion of treatment) was observed (adjusted IRR 1.15; 95% CI 1.02–1.32); and using observed UDS data only, the percentage of UDS negative for opioids was 90.5% (SD 19.8%) in the I-AAM group and 71.8% (SD 36.7) in the TAU group (mean difference 18.7%; 95% CI 8.9–28.5; d 0.63; 95% CI 0.29–0.97). There was no statistically significant difference in the mean number of scheduled UDS tests (16.2 [SD 9.0] in the I-AAM group versus 14.1 [SD 8.9] in the TAU group; p -value 0.10).

Table 5.3: Summary of scheduled and imputed urine drug screen tests and primary outcome measure (n=141)

Measure	I-AAM (n=70)	TAU (n=71)
UDS testing		
A. Mean number of scheduled UDS (SD)	16.2 (9.0)	14.1 (8.9)
B. Mean number of UDS positive for opioids (SD)	1.0 (1.8)	1.9 (3.2)
C. Mean number of UDS, missed, imputed positive (SD)	2.3 (2.4)	2.2 (2.4)
Efficacy		
Primary outcome measure †	76.7% (25.0%)	63.5% (34.7%)
Mean difference (95% CI)	13.3% (3.2%–23.3%)	
d (95% CI)	0.44 (0.10–0.87)	

Note:

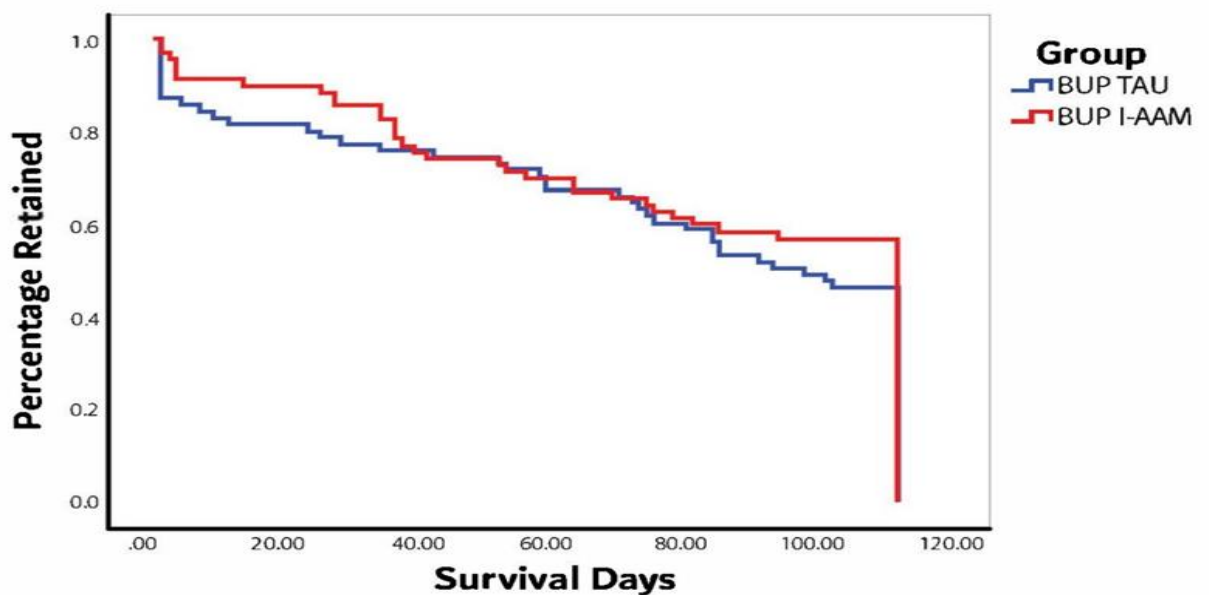
I-AAM, incentivised adherence and abstinence monitoring;
TAU, treatment-as-usual;
UDS, urine drug screen;
CI, confidence interval.

† Computed as $(A-B+C)/(A*100)$ (SD)

Secondary outcome

Forty participants (57.1%) in the I-AAM group were retained continuously in maintenance treatment to the endpoint versus 33 participants (46.4%) in the TAU group (OR 1.54; 95% CI 0.79–2.98). The I-AAM group was retained for a mean of 81.7 days (SD 42.3), and TAU participants were retained for a mean of 76.6 days (SD 39.9; mean difference 5.1 days; 95% CI -8.6–18.8). **Figure 5.2** displays a survival chart for time-to-discontinuation by group (log rank test p -value 0.26).

Figure 5.2: Survival analysis for retention over 16 weeks (log rank p -value 0.26)



Exploratory outcomes

End-of-study group differences on the exploratory outcome are shown in the article's supplementary material (**Table S5.2**). There was an I-AAM effect on the WSAS indicating fewer social impairments associated with OUD at the endpoint (a 6-point mean difference; d 0.53; 95% CI 0.19–0.87).

Table S5.2: Exploratory outcomes at study endpoint by group (n=141)

Measure	I-AAM (n=70)	TAU (n=71)	Mean difference (95% CI)	p-value
ASI-Lite (drug use)	0.1 (0.1)	0.1 (0.2)	0.15 (0.1–0.2)	0.14
PHQ-9	7.9 (6.5)	9.1 (7.5)	1.2 (-1.2–3.6)	0.30
GAD-7	7.3 (5.6)	6.5 (6.0)	0.8 (-2.8–1.8)	0.42
BIS-11	64.5 (14.2)	63.8 (12.6)	0.7 (-5.2–3.8)	0.76
WSAS	10.3 (10.9)	16.9 (13.7)	6.6 (2.5–10.7) ¶¶	0.01

Note:

Numbers in table are number of participants, mean (standard deviation);

I-AAM, incentivised adherence and abstinence monitoring;

TAU, treatment-as-usual; ASI-Lite, Addiction Severity Index–Lite version;

PHQ-9, Patient Health Questionnaire; GAD-7, Generalized Anxiety Disorder;

BIS-11: Barratt Impulsiveness Scale; WSAS, Work and Social Adjustability Scale;

¶¶ Cohen’s *d* 0.53; 95% CI 0.19–0.87.

Adverse events

There were no serious adverse events requiring hospitalisation and there was a similar profile of adverse events in both groups (**Table S5.3**). The adverse event with the highest reported incidence was sweating. This was rated severe by 3 participants in the I-AAM group and 4 participants in TAU group and judged to have a possible association with BUP.

Table S5.3: Adverse events during BUP maintenance treatment over 16-weeks by severity likelihood of association and group (n=141)

Report	Likely association with treatment	BUP I-AAM (n = 70)	BUP TAU (n = 71)
Metallic taste	Possible	-	1 (1.4)
Hiccoughs	Unrelated	-	1 (1.4)
Sweating	Possible	3 (4.2)	4 (5.6)
Constipation	Definite	2 (2.8)	4 (5.6)
Nausea/vomiting	Probable	3 (4.2)	1 (1.4)
Sexual dysfunction	Unrelated	-	1 (1.4)
Pedal oedema	Unrelated	1 (1.4)	-

Note:

Numbers in table are number of participants (%);

I-AAM, BUP maintenance treatment with incentivised adherence and abstinence monitoring;

TAU, BUP maintenance treatment-as-usual;

DISCUSSION

In the I-AAM group, slightly more participants achieved dispensing of 14-days supply compared with TAU (55 versus 51). Within the I-AAM group, a minority achieved dispensing supplies above this: 7 receiving dispensing of 21-days supply and 1 attaining maintenance dispensing of 28-days supply. In terms of the primary outcome, there was significant variability between the two groups, but we believe that the I-AAM condition was associated with a clinically important effect. There was a single exploratory outcome on the WSAS suggested that I-AAM participants had the additional benefit of fewer social problems attributed to OUD.

Although the randomisation procedure did not include any stratification, the sensitivity including patient demographic, baseline drug use, and time in treatment showed an adjusted treatment effect that was statistically significant. Furthermore, comparison of the conservatively imputed versus observed primary outcome measure (13.3% versus 18.7%, respectively), suggests that true effect for I-AAM is bracketed within these two estimates. Nevertheless, there remains considerable scope to increase clinical

effectiveness. Among participants in the I-AAM group who completed 16-weeks of treatment, 22 (55%) were completely adherent. This is comparable to an Australian surveillance study, where a third of patients enrolled in BUP-naloxone maintenance did not adhere and 34 (85%) of those who stayed in treatment did not abstain from opioids (Larance et al., 2011).

In the present study, I-AAM was not significantly associated with a higher rate of completion for the 16-week active treatment period or duration of enrolment (57% versus 46%). These rates are comparable with other studies of BUP maintenance. For example, in a US dose comparison trial over 16 weeks of BUP maintenance, completion rates were 52% for patients receiving 8mg/day, and 61% for those allocated to 16mg/day (Ling et al., 1998). Another US trial of 17 weeks of maintenance treatment reported a 58% completion for patients receiving higher-doses of 16–32mg/day (Johnson et al., 2000).

Study limitations

Our findings must be considered in the light of several limitations. Firstly, the sample was 23% smaller than planned so the analyses had reduced statistical power by 5%. The study took longer to complete than we envisaged due to a lower rate of recruitment. During the recruitment phase there was a reduction in opioid use in the UAE and an increase in amphetamine-type stimulant use (Al Ghaferi et al., 2017). This may have reduced OUD treatment demand.

Second, the sample was almost exclusively male, with just two female participants. We had no control over the referral process, and it remains an important priority to study sex as a factor in OUD treatment delivery and outcomes (Jones, Fitzgerald, Johnson, 2005).

Third, the BUP induction and stabilisation was done in an inpatient facility which is typically available in the healthcare systems in UAE and states in the Eastern Mediterranean, but dose induction is most commonly done in an outpatient setting elsewhere. A 24-hour medically supervised setting makes it more convenient to collect blood samples, but our discontinuation rate in this phase of the study (30/171; 17.5%) was comparable to the discontinuation rate reported for an 8-day outpatient study in Australia (14% for patients assigned to BUP for withdrawal management) (Lintzeris et

al., 2002). We contend that outpatient services based in locations with reasonably good local transport options, collection of three blood samples for BUP EL.R should be acceptable to most patients.

Clinical and research importance of the findings

The I-AAM protocol included a quantitative TDM procedure (BUP plasma concentration criterion) to monitor adherence. TDM procedures to inform changes in maintenance dosing were rarely used with the majority of the group remaining on their stabilisation dose. We also found that almost all participants accepted daily dosing.

It is important to consider how the primary and secondary outcomes were defined in this study. At present, there is no common outcome set for OUD pharmacotherapy trials. It is not uncommon to define the primary outcome as a count of consecutive negative UDS. This can give valuable insight into periods of stability. This was a pragmatic and study among patients who presented for treatment as usual, so we believe our findings are generalisable. Our I-AAM protocol has promise as a clinically effect method helping patients access increasing supplies of take-home medication. Relatively few participants (8/40; 20%) were able to provide evidence of sustained adherence and abstinence to receive supplies above the comparator. Overall, participants in the I-AAM condition received 20% more take-home supplies for more or equal to 7-days (492 total dispensing events versus 407 among the TAU group).

There remains a priority need to discover better ways of encouraging patients to stay in optimised treatment. While efforts to increase retention are crucial, it should be recognised that retention is a proxy measure of clinical benefit since some patients stay in treatment but continue to use opioids. This has been observed in other treatment systems. For example, in an English national study of 12,745 patients enrolled for 12–26 weeks in OUD maintenance pharmacotherapy, 64% reported using opioids on 10 or more days in the month before follow-up (Marsden et al., 2009). One option is to include an adjunctive psychosocial intervention targeting patients who struggle to adhere or abstain (Marsden et al., 2019). Extended-release (depot injection) BUP products are now becoming increasingly available and this may reduce concerns about diversion and provide potential opportunities to apply TDM for dose optimisation during stabilisation and dose adjustment during maintenance.

Although we had direct access to a clinical toxicology laboratory, it typically took 48 hours to process blood samples and receive test results for BUP plasma levels. This was longer than anticipated and it did hamper our efforts to make timely clinical decisions with study participants. In other areas of psychiatry, there is active research and development on non-invasive technologies such as small, portable sensing or test strips for capture of capillary blood to detect antipsychotic medication concentration (Kalaria & Kelly, 2019). Rapid point-of-care diagnostics to facilitate medication adherence monitoring during BUP treatment would be welcome. Monitoring BUP plasma concentration may be added to measures of craving, drug use and withdrawal symptoms to optimise treatment as part of measurement-based care for OUD (Marsden et al., 2019).

ACKNOWLEDGEMENTS

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SUPPLEMENTARY MATERIAL

Summary of study procedures by arm

Phase/procedure	Study arm	
	I-AAM	TAU
4-week inpatient withdrawal and BUP stabilisation	Yes	Yes
Provision of pharmacotherapy education	Yes	Yes
Induction (BUP-naloxone) by COWS	Yes	Yes
<ul style="list-style-type: none"> • Daily blood sample 1 for trough concentration (30 mins < dose) • Daily blood sample 2 for peak concentration (40 mins > dose) • Daily blood sample 3 for concentration (48 hours > dose) 	Yes	Yes
EL.R has been calculated, and patient has COWS score of 0–4	Yes	Yes
16-week outpatient BUP maintenance	Yes	Yes
Attendance for first 5 days for supervised dosing	Yes	No
Scheduled UDS at clinic visit for dosing/pick up of take-home supply	Yes	Yes
Blood sampling at clinic visit	Yes	No
Ability to receive 1-2 weeks take-home supply (via UDS)	Yes	Yes
Ability to receive 3-4 weeks take-home supply (via UDS and blood test)	Yes	No
COWS for monitoring of withdrawal symptoms (weeks 1–4)	Yes	Yes
Minnesota Cocaine Craving Scale – adapted for opioids (weeks 5–8)	Yes	Yes
Pupillary reflex (weeks 13-16)	Yes	Yes

Note:

I-AAM, incentivised adherence and abstinence monitoring;

TAU, treatment-as-usual;

BUP, buprenorphine;

COWS, Clinical Opiate Withdrawal Scale;

EL.R, BUP elimination rate;

UDS, urine drug screen.

CHAPTER 6 ASSOCIATIONS WITH OPIOID USE AND RETENTION IN TREATMENT

This Chapter is dedicated to report on the results of the exploratory analyses set by hypotheses 3 on the associations between the primary and the secondary study outcomes with participant characteristics. This chapter closes with the summary of results for all study hypotheses.

6.1. Association with percentage of negative opioid screens (primary outcome)

Age: In the total sample randomised, a significant association was established between the percentage of negative opioid screens (primary outcome) and age at presentation to treatment (Pearson correlation coefficient = 0.18, $p = 0.03$). In other words, higher percentage of negative opioid screens correlated with older age (>30 years). Otherwise, there was no significant association found between the percentage of negative opioid screens and (1) age at first use (Pearson correlation coefficient 0.08, $p = 0.32$) nor with the (2) duration of illness (Spearman's rho 0.10, $p = 0.99$). Adjusting the association of age with percentage negative opioid screens for the study group showed no statistically significant association (Standardized Coefficient Beta =0.604, $p=0.052$, 95% CI -0.007–1.21).

City of residence: No significant association was established between the percentage of negative opioid screens and residing in Abu Dhabi city (Spearman's rho -0.12, $p = 0.15$).

Primary type and route of opioid use: No significant association was established between the primary type of opioid whether illicit or prescription opioid or the route of use i.e. whether injecting or non-injecting (Spearman's rho 0.11; $p = 0.17$) with the percentage of negative screens for any opioid. In other words, whether the participants were heroin users (injecting or non-injecting) or were using tramadol at baseline, this preference did not significantly affect their use of any opioids while on BUP/NX-F.

Measures of psychosocial functioning: No significant associations were, established between any of the measures of psychosocial functioning and ASI at baseline and the percentage negative opioid screens.

Buprenorphine/naloxone dose: No significant association was established between BUP/NX-F dose and percentage negative opioid screens (Pearson correlation coefficient 0.07, $p=0.40$).

Buprenorphine elimination rate: A significant negative association was established between BUP EL. R and the percentage negative screens (Pearson correlation coefficient -0.29, $p < 0.05$). In other words, an increase in BUP EL. R was associated with a decrease in percentage of negative opioid screens or an increase in opioid use. Adjusting for the study group showed statistically significant association with a small predictive power (Standardized Coefficient Beta = - 89.95, R^2 0.216, $p < 0.01$, 95% CI -154.20 – - 25.70).

Buprenorphine plasma trough concentration: No significant association was established between BUP plasma trough concentration and the percentage negative opioid screens (Pearson correlation coefficient -0.007, $p=0.95$).

Body Mass Index: No significant association was established between BMI and percentage of negative opioid screens (Pearson correlation coefficient 0.12, $p=0.28$).

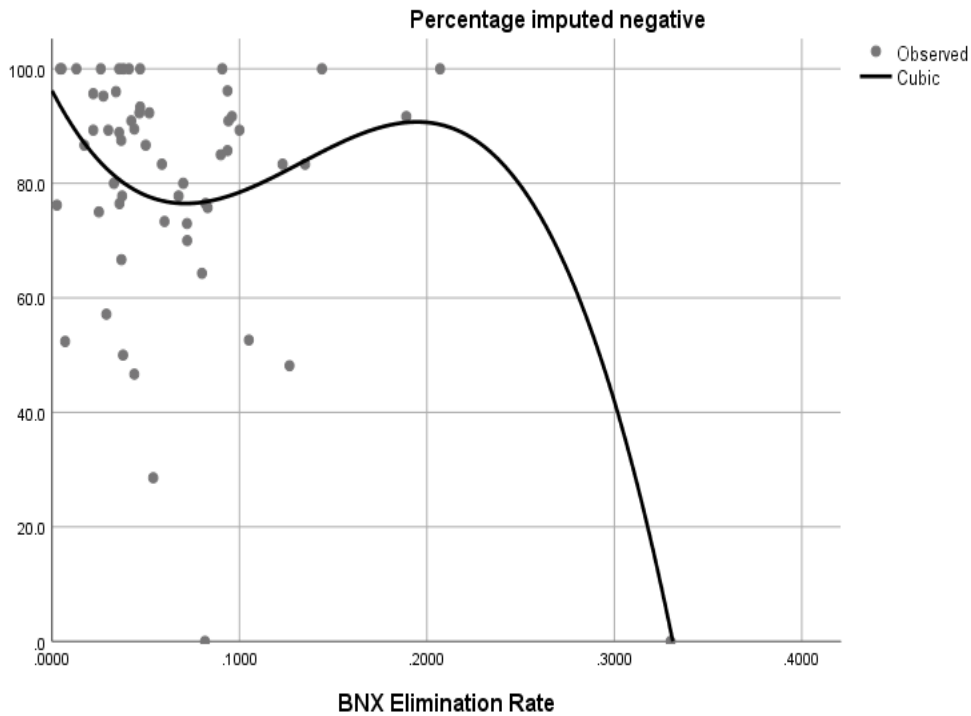
Table 6.1 Associations with percentage of negative opioid screens

Variable	Association	Significance (p-value)
Age at first use	Pearson correlation coefficient 0.08	0.32
Age at presentation	Pearson correlation coefficient 0.17	0.03
Duration of illness	Spearman's rho 0.10	0.99
City of residence (Abu Dhabi)	Spearman's rho -0.12	0.15
Family history of substance use	Spearman's rho 0.03	0.74
Primary type and route of opioid use	Spearman's rho 0.11	0.17
PHQ-9	Pearson correlation coefficient -0.14	0.11
GAD-7	Pearson correlation coefficient 0.06	0.50
PSQI	Pearson correlation coefficient 0.08	0.39
BIS-11	Pearson correlation coefficient -0.01	0.91
WSAS	Pearson correlation coefficient -0.03	0.74
ASI-Medical	Pearson correlation coefficient 0.06	0.43
ASI-Social	Pearson correlation coefficient 0.03	0.70
ASI-Alcohol	Pearson correlation coefficient -0.02	0.83
ASI-Legal	Pearson correlation coefficient 0.14	0.12
ASI-Drug Use	Pearson correlation coefficient -0.15	0.98
ASI-Family	Pearson correlation coefficient -0.06	0.48
ASI-Mental Health	Pearson correlation coefficient 0.03	0.68
BPD	Spearman's rho 0.42	0.67
OCPD	Spearman's rho 0.05	0.63
APD	Spearman's rho 0.09	0.34
OCPD	Spearman's rho 0.07	0.45
DPD	Spearman's rho 0.12	0.22
Anxious PD	Spearman's rho 0.03	0.72
BUP EL. R	Pearson correlation coefficient -0.29	<0.05
BUP trough concentration	Pearson correlation coefficient -0.007	0.95
BUP/NX-F dose	Pearson correlation coefficient 0.07	0.40
	Pearson correlation coefficient 0.12	0.28

PHQ-9: Patient Health Questionnaire 9 items, GAD-7: Generalized Anxiety Disorder 7 items; BIS-11: Barratt Impulsiveness Scale 11th version; ASI: Addiction Severity Index; EL. R: Elimination Rate

Prediction of the percentage of negative opioid screen using buprenorphine elimination rate: The association of BUP EL. R with percentage negative opioid screens was, found to be significant for cubic association (**Figure 6.1**). A cubic regression was fit to model BUP EL. R to predict the percentage of negative opioid screens showed an R^2 of 0.265, $p < 0.01$.

Figure 6.1 Association plot between the buprenorphine elimination rate and percentage of negative opioid screens with cubic curve superimposed



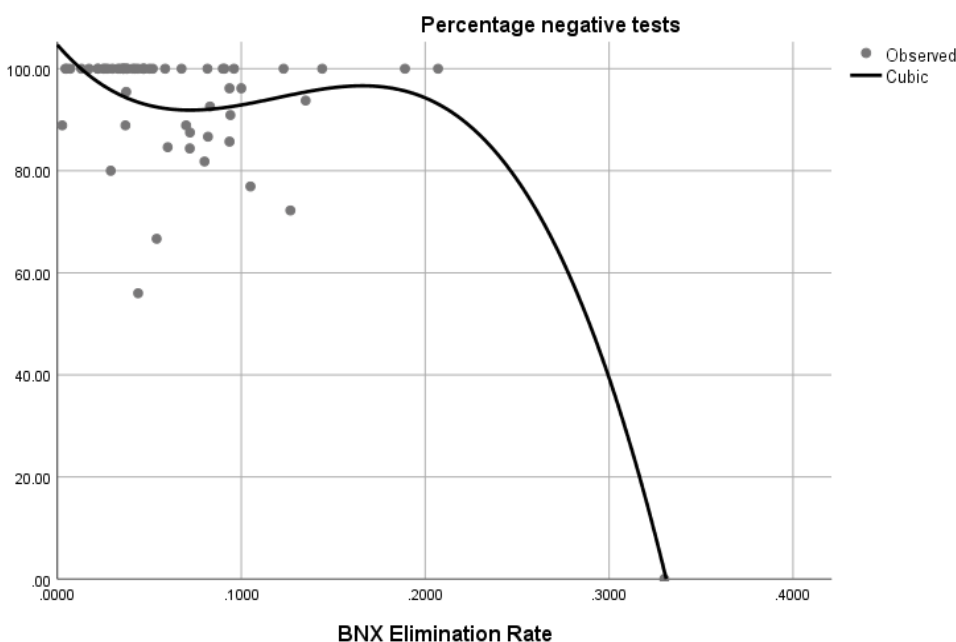
In other words, the primary outcome can be predicted in 26.5% of the cases by the following mathematical expression:

$$\begin{aligned} & \textit{Percentage of imputed negative opioid screens} \\ & = 96.1 - 629.2 \textit{ BUP EL. R} - 6037.3 \textit{ BUP EL. R}^2 - 15137.5^3 \end{aligned}$$

This analysis was extended to the actual percentage of opioid negative screens which showed a similar cubic association (**Figure 6.2**). The power of the prediction was considered high (R^2 of 0.649, $p < 0.001$). In other words, 64.9% of the actual percentage negative opioid screens can be predicted by the following mathematical expression:

$$\begin{aligned} & \textit{Percentage of actual negative opioid screens} \\ & = 104.6 - 415.32 \textit{ BUP EL. R} - 4132.8 \textit{ BUP EL. R}^2 - 11580.2^3 \end{aligned}$$

Figure 6.2 Association of buprenorphine elimination rate and actual percentage negative opioid screens with cubic curve superimposed



6.2. Associations with study completion (Secondary outcome)

The associations with the rate of study completion rate are, displayed in **Table 6.2**. None of the variables showed a significant association with the rate of study completion.

Age and duration of illness: No significant associations were found between the completion rate and: 1) age at first use (Spearman's rho 0.10, $p=0.22$), 2) age at presentation to treatment (Spearman's rho 0.03, $p=0.70$) and 3) duration of illness (Spearman's rho -0.17, $p=0.80$).

City of residence: Residing in or outside the city of Abu Dhabi demonstrated no significant association with the completion rate (Spearman's rho 0.005, $p=0.95$).

Primary type and route of opioid use: No significant association was found between the study completion rate and the type and route of opioid use (Spearman's rho = -0.09; $p = 0.26$).

Body Mass Index: No significant association was found between BMI and study completion rate (Spearman's rho 0.14; $p = 0.08$).

Measures of psychosocial functioning: No significant association was found between completion rate and any of the measures of psychosocial functioning.

BUP elimination rate: No significant association was found between BUP EL. R and study completion rate (Spearman’s rho 0.085; $p = 0.49$).

BUP trough plasma concentrations: No significant association was found with study completion rate (Spearman’s rho -0.007; $p = 0.95$).

BUP/NX-F dose: No significant association was found between BUP/NX-F dose and study completion rate (Spearman’s rho 0.15; $p = 0.08$).

Table 6.2 Associations with completing the 16-week study period

Variable	Associations (Spearman’s rho)	Significance (p-value)
Age at first use	0.10	0.22
Age at treatment	0.03	0.69
Duration of illness	-0.17	0.80
Family history of substance use	-0.01	0.93
Primary type and route of opioid use	-0.09	0.26
PHQ-9	-0.15	0.09
GAD-7	0.04	0.61
PSQI	0.14	0.88
BIS-11	-0.03	0.71
WSAS	-0.39	0.71
ASI-Medical	0.12	0.15
ASI-Social	-0.01	0.80
ASI-Legal	0.06	0.51
ASI-Alcohol	0.02	0.79
ASI-Drug use	-0.10	0.51
ASI-Family	0.13	0.13
ASI-Mental health	0.02	0.80
BPD	0.15	0.12
OCPD	0.02	0.78
APD	0.08	0.41
DPD	0.12	0.23
Anxious PD	0.01	0.89
BUP/NX-F dose	0.15	0.08
BUP EL. R	0.08	0.49
BUP trough concentration	-0.007	0.95

PHQ-9: Patient Health Questionnaire 9 items, GAD-7: Generalized Anxiety Disorder 7 items; BIS-11: Barratt Impulsiveness Scale 11th version; ASI: Addiction Severity Index; EL. R: Elimination Rate;* Significant positive association

6.3. SUMMARY OF RESULTS FOR HYPOTHESES OF THE THESIS

H1. There will be no statistically significant difference in the percentage of opioid-negative drug screens over a 16-week period between BUP/NX-F (the control group) and BUP/NX-F + medication management guided by TDM (Incentivised Abstinence and Adherence Monitoring, the experimental group).

The null hypothesis for this outcome (H1) was rejected.

H2. There will be no statistically significant difference in completion of the 16-week study period and rate of retention of participants within the 16-week period between participants in the experimental group and those in the control.

The null hypothesis for this outcome (H2) was retained.

H3. There will be no statistically significant associations between patient characteristics, BUP EL.R, and BUP/NX-F dose and: (1) the percentage of negative opioid screens (primary outcome), (2) the completion of the 16-week study period (secondary outcome).

The null hypothesis [H3] was, retained for all sociodemographic characteristics, BUP dose, and BUP trough plasma concentrations and rejected for buprenorphine elimination rate.

H4. There will be no statistically significant difference in the change from baseline to 16-week study endpoint in the measures of psychosocial functioning and addiction severity between participants in the experimental group and those in the control group.

The null hypothesis [H4] was retained for both groups.

CHAPTER 7 DISCUSSION AND CONCLUSIONS

7.1. OVERVIEW

In this final chapter of the thesis, the results generated by the study are consolidated, before proceeding with the critical interpretations of the main findings in relation to the current knowledge of the medication assisted treatment using buprenorphine for OUD, as derived from the literature search.

This chapter is, structured as 1) summary of findings, 2) strengths and limitations, 3) clinical and policy implications, 4) further analyses, 5) future research questions and 6) conclusions.

7.2. SUMMARY OF FINDINGS

Developed and implemented as a doctoral research programme for the candidate, the Suboxone[®] Treatment and Recovery Trial (STAR-T) was a novel single-centre pragmatic randomised controlled trial. The trial examined the effectiveness of BUP/NX-F + structured MM with incentivised TDM (experimental; incentivised abstinence and adherence monitoring) was compared to that attained by BUP/NX-F+ non-structured MM without TDM (control) as the currently adopted care. At the completion of the inpatient stabilisation phase, 141 adults with OUD stabilised on BUP/NX-F were randomised to receive: (1) the experimental intervention ($n = 70$), or (2) the control (treatment-as-usual; $n = 71$). In this study, personalising treatment was provided in the experimental group through stepped BUP/NX-F ‘take-home’ prescriptions contingent on indicators of abstinence and adherence using TDM data.

7.2.1. Primary outcome

The primary outcome was defined as the percentage of opioid-negative UDS during enrolment in outpatient treatment. A conservative approach was taken to the missed appointments by participants, whereby each missed appointment was recorded as a positive opioid screen. For the primary outcome, the mean percentage of opioid-negative UDS was 76.71% and 63.46% in the experimental and the control group, respectively. This observed difference of 13.25% (95% CI 3.19–23.31) was within the 15% variance anticipated in the sample size estimation, which yielded a relatively wide confidence interval. However, the group differences corresponded to a medium Cohen’s d effect size

(ES 0.44; 95% CI 0.10–0.77) and was statistically significant ($t = 2.60$, $df = 126$, and $p=0.01$). Adjusting this outcome for the age at treatment, days to measure the outcome, ASI-drug use scores resulted in concluding that participants in the experimental group were 1.15 times more likely to achieve higher percentage negative opioid screens compared to participants in the control group.

Hence, there was sufficient evidence for rejecting the first null hypothesis in favour of the experimental intervention.

7.2.2. Secondary outcome

In relation to the secondary outcome measure, one of the aims of STAR-T was to establish whether the proposed experimental intervention would enhance retention in treatment and completion of the 16-week outpatient study period. In the experimental group, with 40 participants, 11% greater completion rate of the 16-week period was observed (57%) compared to 46% for the control group ($n = 33$). This difference was not significant despite that participants in the experimental group completed the study period at an OR of 1.54 (95% CI 0.780–2.97) compared to the control with a NNT of 9. This single digit NNT might be of clinical significance given that the comparator (control) was an active intervention. Furthermore, the difference in the mean number of days to discontinue treatment between the study groups was not significant. Therefore, no evidence exists to support rejecting the second null hypothesis.

7.2.3. Associations with the primary and secondary outcomes

In the randomised total sample, age at presentation to treatment, positively and significantly associated with a percentage of negative opioid screens. In other words, older patients were more likely to use less opioids while on treatment. Adjusting for the study allocation, did not predict percentage negative opioid screens. In contrast, BUP EL. R, showed a significant association with the percentage negative of opioid screens after adjusting for study allocation. The prediction model for the percentage negative of opioid screens imputing missed appointments as positive opioid screens (primary outcome) and percentage of actual percentage negative opioid screens were, generated at different powers. The higher prediction power for actual percentage negative opioid screens is statistically attributed to the higher percentage of actual negative opioid screens.

The established negative association between the percentage negative opioid screens and BUP EL. R, but not with the BUP trough concentration, indicates that participants with

lower BUP EL. R used fewer opioids. This finding aligns with a previous hypothesis correlating craving with the rate of decrease in BUP plasma concentration rather than the actual BUP concentration (Lopatko et al., 2003). One explanation supporting this hypothesis is that effective blocking of mu opioid receptors requires limited fluctuation in plasma concentrations.

Therefore, there was sufficient evidence to reject the third null hypothesis for the primary outcome about BUP EL. R. Otherwise, the null hypothesis was retained for all other participant characteristics and BUP/NX-F dose. In contrast, the null hypothesis was retained for the secondary outcome with all variables.

7.2.4. Change in measures of psychosocial functioning

There was sufficient evidence for significant symptom reduction in both study groups according to the scores of the PHQ-9 (depression), and ASI drug use and mental health domains. However, a significant reduction in the BIS-11 (impulsiveness) scores was noted only for the experimental group and a significant reduction in the GAD-7 (anxiety) scores was noted only for the control group. With respect to the quality of sleep, personality disorders, and other ASI domains (medical, alcohol, legal, family, and social domains), neither group achieved scores indicative of significant improvement over time. Finally, the WSAS scores reflecting social dysfunction attributed to OUD indicated reduction from baseline in both groups. Clinically, the WSAS scores at the end of the study show subclinical impairment in the experimental group and significant impairment in the control group, i.e. clinical improvement was only observed in the experimental group. Despite the significant within group difference, the magnitude of reduction in these measures was not significantly different between groups. In other words, the change in measures from baseline could not be attributed to the interventions applied. Therefore, there was sufficient evidence to accept the fourth null hypothesis.

In contrast, STAR-T successfully optimised and validated a laboratory detection and quantitation of BUP adopted from a published method. The optimised method generated significantly higher mean BUP recovery rate. The coefficient of variance for the ‘within-run’ and ‘between-run’ assay were within the 20% acceptable range for accuracy and precision. The clinical feasibility of applying TDM in monitoring BUP plasma levels and the accuracy of predicting the BUP plasma levels using the PK model were established.

According to the available WHO (2013) estimates, 30–50% of the individuals receiving medications for chronic treatments do not take them as prescribed, or are non-adherent.

In psychiatry, the rate of non-adherence with the prescribed antidepressants was, estimated at 65%, while non-adherence to antipsychotic regimens was estimated at 58% (Cramer & Rosenheck, 1998). Given this evidence, Remien et al. (2003) argued that it is important to conceptualise adherence to treatment as falling along a continuum, which places adherence on one end and non-adherence on the other. In this context, non-adherence develops from partial adherence into total non-adherence. Adherence is as a dynamic behaviour that alters with time because of the patients' efforts to address their health condition (Remien et al., 2003). The value of adherence to treatment has been demonstrated across many chronic illnesses (WHO, 2003) and is not limited to reduction in relapse rates associated with opioid assisted treatment (OAT) (Tkacz et al., 2017).

In order to optimise adherence to MAT using opioid agonists and partial agonists, treatment provision via Directly Observed Treatment (DOT) is recommended however is associated with increased staff costs and high rates of treatment discontinuation (Gerra et al., 2011; SAMHSA, 2015). In contrast, the availability of 'take-home' prescriptions/doses made participants '*feel good*' and was preferred by treatment providers (Amass et al., 2000). Although 'take-home' prescriptions encourage access to treatment, there are concerns related to medication diversion and abuse (SAMHSA, 2015). STAR-T was designed with the aim of striking the balance between optimising adherence and minimising the risk of diversion.

The application of TDM in methadone assisted treatment (MET) clinics to optimise care was studied nearly two decades ago (Wolff & Strang, 2000). Although TDM has been recommended for MET, it is not clear why it has not been adopted in mainstream MET maintenance programmes. Similarly, TDM has been recommended for BUP maintenance programmes, with a focus on adherence monitoring (Hiemke et al., 2018). Again, this has not led to greater adoption of TDM in BUP based treatment, which was one of the guiding reasons for STAR-T to address this gap in the clinical effectiveness literature. A possible reason for this omission could be the specific requirements that need to be met in order to perform reliable TDM, as well as the lack of data on how TDM can be integrated into the drug use reduction. In the present study context, increased concerns about the risk of medication diversion provided support for conducting STAR-T.

Adherence to BUP has been suggested to strengthen relapse prevention (Weiss et al., 2014). In contrast, medication non-adherence was associated with 10-fold increase in the risk of relapse (Tkacz et al., 2017). In STAR-T, possible enhanced medication adherence in the experimental group could have been achieved via the CM framework. In

comparison to the Iguchi and colleagues (1996) protocol, where participants received ‘take-home’ prescriptions contingent on providing three consecutive opioid-negative UDS and the contingency schedule was reset with a positive screen, the STAR-T was designed to provide up to four weeks of ‘take-home’ prescriptions through stepped approach. It thus seems reasonable to conclude that this procedure leveraged behavioural modification (i.e., participants were motivated to receive the benefit of a ‘take-home’ dose and responded by taking their BUP/NX-F as directed). Furthermore, ‘take-home’ prescriptions in the experimental group was, integrated with structured MM unlike the control group. The MM applied shared decision-making between the patient and the therapist. Previous studies showed that shared decision-making was, reported to improve treatment outcomes in other chronic diseases (Wilson et al., 2010).

While medication ‘take-home’ prescriptions, may contribute to enhanced access to treatment it is recognised as a source of medication diversion and abuse (SAMSHA, 2015). In addition to non-adherence and relapse, diversion is a legal offense, adding to the challenges that may hamper recovery. However, no data on the adherence rates with BUP and BUP/NX ‘take-home’ prescriptions were, published. It is noteworthy that Larance and colleagues (2011) reported a 28% abuse via injecting (also considered as a form of non-adherence) and 5% diversion of supervised doses of BUP/NX tablets accounting to a total of 33% non-adherence rate, which is comparable to the 34% non-adherence rate reported by STAR-T. This supports previous evaluation of TDM in monitoring adherence but not in optimising clinical response (Marque & Kintz, 2004). It is suggested that the benefits of the regular monitoring of adherence enhance adherence rates similar to the reported 50% reduction in opioid use achieved by regular UDS monitoring (Dupouy et al., 2013).

Contrasting the opioid use outcome (primary outcome) generated from the present study with those reported internationally may not be straightforward due to several reasons. First, participants in STAR-T received four weeks of inpatient care prior to the 16-week outpatient study period. This inpatient care is, reported to carry additional benefit in reducing drug use compared to outpatient care only (Digiusto et al., 2005). Hence this should be accounted for when contrasting results. Second, opioid use outcome is not consistently defined across literature. In the present study, opioid use outcome was defined as the percentage of opioid-negative UDS, while other studies used consecutive opioid-negative UDS (e.g., Ling et al., 2013) to assess opioid use. While the mean percentage of opioid-negative UDS applied in STAR-T reflects patient performance

during the entire study period, consecutive negative drug screens provides a meaningful indication of the patient's ability to maintain recovery. Similarly, no consensus exists on how to operationalise retention (Krishnan et al., 2014). In STAR-T, participants were considered retained in treatment if they were able to access treatment over different intervals, including end of study, based on which they were classified as completers or non-completers of the study. This definition tends to generate lower retention rates compared to other definitions, such as access to treatment over a pre-set proportion of the treatment period, or access to treatment at the end of the study. In STAR-T, 49.64% of the participants completed the 16-week study period, which lies at the lower range of retention reported in a 16 week outpatient study of BUP/NX (Darke et al., 2007). Finally, population differences like genetics reported to be associated susceptibility for the progression from hazardous or harmful use to dependence, and response to treatment (Goldman, Oroszi, & Ducci, 2005) must be taken into account when contrasting results with international literature.

In the present study, the effect sociodemographic factors and patient characteristics on treatment outcomes was not consistent with findings from previous research. Age at treatment was previously, reported to be associated with opioid use in heroin studies (Backmund et al., 2001; Saxon et al., 1996) or prescription opioids (Dreifuss et al., 2013). Despite that in the present study, age did not have significant effect on the primary outcome after adjusting for the study group, a trend towards providing a greater number of opioid-negative UDS was observed among older participants, particularly those above 30 years. Similarly, the present study did not replicate results reported by Laqueille and colleagues (2001) that concluded that duration of illness under 10 years BUP are more likely use less opioids compared to those with longer duration of illness above 10 years. Similarly, in the present study, no evidence existed to support that injecting drug use predicted treatment attrition contrary to that reported by Dayal and Balhara (2017) suggesting that baseline injecting drug use predicts treatment attrition.

The findings of the present study do not replicate previous data supporting an association between BUP/NX-F dose and opioid use or retention in treatment reported by Mattick and colleagues (2003). The findings on how BMI had no association with any of the study outcomes were similar to those published by Barry and Petry (2009) showing no association between illicit drug use and BMI. However, one study of young males supports a negative association between BMI and illicit drug use, i.e. adults with higher BMI tend to use less illicit drugs (Bluml et al., 2011). Similarly, Li and colleagues (2016)

reported that opioid use is inversely associated with BMI in an American female subpopulation. In contrast, the lack of associations between measures of psychosocial functioning and the study outcomes in the present study suggests that subjects with co-occurring mental health disorders would equally benefit from MAT compared to those without. This is not consistent with previous research showing that treatment outcomes are lower for those with co-occurring SUD and mental health disorders compared to individuals with SUD only (Schuckit, 2006; Ciraulo, Piechniczek-Buczek, Iscan, 2003).

Despite the statistically significant within group reductions observed in some measures, the lack of significance in the magnitude of reductions between groups could be attributed to the statistical power of the small sample. The impact of BUP/NX on co-occurring psychopathology should be further analysed considering that BUP was recognised with possible antidepressant effect (Bershad et al., 2015) and possible confounders like prescribed psychotropics. In contrast, participants still reported from poor quality of sleep at the end of the study. Results in the present study did not replicate the association found between the percentage of opioid-negative UDS and quality of sleep reported by Gerra and colleagues (2004), who concluded that participants with poor quality of sleep tended to achieve lower opioid use. The authors proposed no mechanism for association. Results obtained in the present study suggest that sleep is an independent co-occurring factor rather than being secondary to substance use. In contrast, participants' performance on the social domain of the ASI worsened at end of the study from baseline. One possible explanation is that approximately 30% of the participants seeking treatment were terminated from their jobs prior to study enrolment, which has reflected on the income category of the ASI-social domain (ASI inquires on the income received one month prior to presenting to treatment).

On further analyses, half of the unemployment was found to be due to termination from jobs while the other half was never employed. With a rising rate of unemployment in the UAE, termination further to substance use could pose an added challenge for re-employment, since the government is the major employer for UAE citizens. In contrast, participants who were never employed lacked the minimal occupational/vocational requirements for employment requiring a tailored vocational training. Given this complex and unfavourable employment scene, participants were advised that meaningful changes in the social domain can be achieved by maintaining recovery, and that radical changes in their social status should not be expected in the first six months of treatment. It is thought that change in employment status and improvements in other social aspects

would manifest within longer follow-up periods, if a significant reduction in substance use was, maintained. Similarly, gains in social functioning, employment, and reduction in recidivism may contribute to the sustainability of abstinence. Therefore, extended follow-up periods are recommended, as this allows for a realistic assessment of recovery elements related to social functioning (French & Drummond, 2005).

In this context, early indicators of social change and perceived ability to work and undergo social adjustments may serve as a valuable tool for monitoring recovery. In the present study, early indicators of long-term social function were captured using WSAS, rarely utilised for OUD. Both study groups achieved significant reductions in their mean WSAS scores despite the lack of improvement in their ASI-social domain scores.

The prospective dose assignment algorithm developed for this study resulted in allocating almost all participants to the daily dose schedule except for two participants. Assignment to the daily dose was because majority of the participants had co-occurring mental health disorders, and were injecting drug users with polysubstance use. Therefore, the reliability of the proposed prospective dose assignment criteria could not be, evaluated. A practical alternative to explore the association between the patient characteristics and the dosing schedule would have been random assignment of participants to daily and non-daily doses, followed by retrospective analyses of the participants' characteristics and the corresponding maintenance dose. Exploring these characteristics and contrasting them with those reported in other populations (Dreifuss et al., 2013; Hillhouse et al., 2011) may contribute to better understanding of the factors influencing BUP based treatment dosing.

Evaluation of the safety and tolerability of BUP/NX-F was particularly important for this study because this was the first time the film formulation was used in the UAE. The incidence of adverse events was within the range reported in the BUP/NX product insert (Suboxone[®] PI, 2012). Sweating was the most frequently reported adverse event and was lower than the reported in the BUP/NX-F product prescribing information. It is important to note that quetiapine was, prescribed to all patients who reported sweating. Since quetiapine is, reported to cause body temperature dysregulation (Seroquel XR[®], n.d.), the association of sweating with BUP/NX-F was confounded by the antipsychotic medication. One participant reported 'metallic taste' which may be attributed to the diluents of the film formulation, rather than the BUP/NX active ingredients particularly that this participant previously received BUP/NX tablets and did not report this event.

One participant withdrew from the study due to nausea and vomiting which was not of particular concern. Two participants were removed from the study for medical conditions not related to the study medication one suffered from thalassaemia–sickle cell anaemia and was withdrawn due to concerns over effective management of breakthrough pain. These concerns were warranted despite the fact that BUP was postulated to reduce the intensity and frequency of sickle cell anaemia attacks (Cote & Montgomery, 2014). Interestingly, this participant reported no attacks until week 10 of treatment. However, the members of the governance committees decided to remove the patient in the absence of conclusive evidence on the value of BUP or BUP/NX in similar cases and were further of view that management of breakthrough pain may be hampered by BUP/NX-F. This participant was therefore transferred to psychosocial relapse prevention programme at the NRC. The second participant presented with scabies and was removed due to the concerns of being contagious, and transferred to a specialised facility for scabies treatment.

One case of acute liver toxicity (ALT/AST 400 U/L) was reported on the third day of treatment with BUP/NX-F. This participant received other medications, including quetiapine. In this case, all medications were withheld and the ALT/AST levels returned to normal within five days. On reintroducing the medications one at a time, quetiapine emerged as the causative medication. One participant died after concluding the 16-week study period during the post-study follow up. This participant had been compliant with all treatment provisions and remained abstinent despite a complex and long history of substance use and multiple treatment episodes. No specific cause of death was identified.

7.3. STRENGTHS AND LIMITATIONS

7.3.1. Strengths

To the candidate's knowledge, STAR-T is the first study as a part of TDM to enhance BUP or BUP/NX treatment outcomes in OUD is clinically tested. Implementing a randomised clinical design in a 'naturalistic' environment is a major strength. In this naturalistic environment, participants were not provided with incentives for participating and meeting the study provisions. Another strength associated with STAR-T is expanding the inclusion criteria to include comorbidities, particularly personality disorders known to pose significant challenges for maintaining retention in treatment. Similarly, when recruiting participants for STAR-T, polysubstance use was not an exclusion criterion.

This broad scope actually contributed to the strength of the evidence generated by STAR-T. Finally, given that this was a naturalistic study, the observed barriers to treatment access—including those unrelated to the study interventions, such as transportation—were noted and relevant disciplines were tasked with providing necessary solutions. This adaptive intervention likely minimised the effect of confounders assumed to moderate retention, rather than acting as a source of bias.

The 16-week study duration is optimal for assessing relapse prevention. On one end, it is longer than the 8–12 weeks used in several clinical trials, which may not be enough to assess the robustness of the clinical effectiveness of the intervention. On the other, it is shorter than the 24-week duration associated with higher treatment attrition and lower study power.

7.3.2. Limitations

Given that no study is without limitations, it is essential to discuss those pertaining to STAR-T as well as to outline the challenges observed during the implementation of the study interventions. This section concludes with suggestions that could have mitigated the identified limitations.

A potentially significant limitation is that the study randomised lower than the estimated sample size. While having sufficient number of participants is key in achieving the effect size that would aid in generalising study results, to the best knowledge of the candidate, studies involving interventions similar to that examined in STAR-T were never conducted. Hence, sample size estimation was carried considering data from CM studies endorsing three-week abstinence as the outcome a stringent outcome that may require a large sample size. Randomising lower than the estimated sample size was due to extended participant recruitment duration that conflicted with the time requirements for submission of the thesis. Despite this, a statistically significant difference between the experimental and control arms, with a moderate effect size, was generated. Moreover, the estimated difference in the primary outcome adjusting for covariates was the same as the difference powered for this trial.

This study was open label and participants nor investigators were blinded to the intervention. However, mitigating factors were undertaken including multiple levels of data audit, and random allocation of participants to treating psychiatrists. This meant that

three investigators (specialising in psychiatry) delivered the study interventions other than the PI, hence minimising the bias associated with delivering the interventions. It is noteworthy that, in the outpatient care setting, the same psychiatrist may have provided treatment to participants in both study groups. This could have potentially resulted in ‘contamination’ by extending the provisions of the experimental intervention to those allocated to the control group. Such ‘contamination’ may have actually contributed to minimising the difference between the study groups and can be considered as a strength rather than a limitation.

Another limitation stems from sample homogeneity with respect to gender. While two female participants were recruited, only one completed the inpatient treatment phase and was randomised. It is likely that the pattern and profile of opioid use are gender related, as females were found more likely to be unemployed, use opioids for a shorter period, and demonstrate complex psychiatric presentation when compared to males (Petry & Bikcel, 2000; Schottenfeld, Pakes, & Kosten, 1998). Jones et al.(2005) reported lower drug use in women receiving BUP compared to men in a 24 week study, attributing this finding to several factors such as gender-related differences in the BUP metabolism, pharmacodynamics interaction with female sex hormones, and higher mu receptor sensitivity to BUP (Unger, Jung, Winklbaur, & Fischer, 2010). In contrast, Johnson and colleagues (1995) reported lower drug use in males compared to females receiving BUP in a 14 days study.

Common to all randomised controlled trials, missing data is a universal and non-ignorable phenomenon with a clear need for an appropriate response (McPherson et al., 2012). There is no consensus on how this issue should be, managed. In STAR-T, a conservative approach was taken for the primary outcome, whereby missing UDS results (equivalent to a missed scheduled appointments at the outpatient care) were treated assuming the ‘worst case scenario’ and were (i.e., missing appointments were equated to positive drug screens). One way of addressing this ‘single level imputation’ was to use a statistical prediction model based on all available data for each participant (McPherson et al., 2012). In the present study, single level imputation was mitigated by analysing the observed (actual) UDS results without imputation. This analysis showed significant difference between both groups.

In STAR-T, simple non-stratified randomisation was due to an extended list of stratification factors and number of blocks. These stratification factors include but are not limited to type of opioid use, pattern of opioid use, polysubstance use, age, duration of

illness, city of residence, comorbid depression and anxiety, and comorbid impulsiveness. It is exceedingly rare for a trial to be able to include more than four stratification factors due to the large number of cells generated. While justified by the extended number of stratification blocks, non-stratified randomisation may not have controlled for all possible confounding factors.

In STAR-T, as several measures of different psychosocial attributes were applied, it is important to note that completing one measure is reported to influence the participant response on subsequent measure. For example, Mark et al. (1991) found that completion of a mood scale like Beck Depression Inventory would influence the response to subsequently completed measures of mood. Considering this potential bias, participants in the present study were provided the mood-related screens (depression and anxiety) on two different days. However, the impact of completing these tools on other measures of different attributes, such as craving and impulsiveness, is presently unclear.

Even though measures with good validity and reliability were used to estimate within-subject and between-subject changes, the reliability of these measures in estimating within-subject change, over and above regression to the mean effects, may not be assured. One reason for selecting these measures was their widespread use and free availability. An example of alternative measures to estimate within-subject change is Hamilton Depression Rating Scale 17 items (HAM-D-17; Hamilton, 1960). In fact, HAM-D-17 was used more often than PHQ-9 in depression-related studies and response was defined as a 50% reduction in the baseline scores. It thus remains to be ascertained whether within- and between-group change (contrasting change over time and at the endpoint) would have been observed with alternative measures, but this seems unlikely.

It is also worth noting that STAR-T lacked a framework for defining craving that is of value in selecting appropriate craving scales. For instance, placing craving on a continuum of desire, or limiting craving to a high level of desire associated with intention to use drugs and ‘drug seeking’ behaviours, would strongly favour a scale that differentiates ‘urge,’ ‘desire,’ and ‘craving.’ Furthermore, defining craving as a measure limited to a certain moment or as a relatively stable measure over time would be helpful in determining whether ‘real time’ or ‘recall’ scales would be more appropriate (Sayette et al., 2000). In this study, craving was assessed using the MCCS adapted for opioids (MCOS), which is a multicomponent tool with good face validity and selectivity. Nonetheless, MCOS does not differentiate urge, craving, and desire and does not generate a composite score to facilitate measurement of within-subject change across these

measures. MCOS captures changes in craving over time, and whether medication is helping the patient, allowing the patient to develop self-awareness of the value of medication adherence in craving control.

In contrast, measuring pupil reflexes (mainly pupil diameter) is a quick, non-invasive, and non-verbal measure of craving that is not affected by any form of bias. Capturing pupil reflexes to assess craving is a form of measuring non-conscious psychophysiological responses that may carry additional sensitivity over self-reports (Baker & Brandon, 1990). However, this approach is insufficiently specific. In other words, changes in pupil reflexes may not necessarily lead to or be caused by craving (Tiffany, 1990). Similar to other measures of psycho-physiological responses (e.g., heart rate, salivation, skin temperature, and conduction), pupil reflexes do not reflect the intention to use drugs (Tiffany, 1990). Nevertheless, using the pupil reflexes data during the study period objectively guided assessment of *'real time'* craving and facilitated decisions on fine dose adjustments of BUP/NX-F. Therefore, appropriate selection of the craving scale may improve patient's experience, which would facilitate fine dose adjustments of BUP/NX-F during the stabilisation phase. It is, expected that the mean BUP/NX-F daily dose vary according to the method used in assessing the craving levels. This may be of particular importance, since BUP daily doses were, reported to predict treatment attrition (Dayal & Balhara, 2017).

The timely reporting of BUP concentrations by the laboratory was challenging due to the lack of trained clinical scientists to perform the laboratory detection and quantitation test. This test was performed by the same clinical scientist and was assisted by the candidate hence minimize between sample errors. One working day was required for a batch of approximately 35 samples resulting in a total turn-around time of up to three days hence postponing the *'take-home'* interventions prescriptions to the following clinic visit. Postponing the intervention may have contributed to minimising the benefits of CM, as immediate ramification is reported to be associated with the highest effectiveness in behaviour therapy (Griffith et al., 2000). Therefore, to mitigate the extended turn-around time and avoid interruption in care, priority was given to blood samples collected at the outpatient clinic over those collected at the inpatient care.

Clinical challenges to implement the present study in a *'busy'* setting with well-established practice *'habits'* were encountered. The collection of blood samples corresponding to the peak and trough BUP concentrations at accurate times was initially challenging particularly for the peak concentration due to the short window of 40 minutes

between dose administration and sample withdrawal. Maintaining accuracy in drawing and recording blood samples is integral to delivering TDM-based treatment (Hiemke et al., 2018). To achieve accurate collection of blood samples corresponding to peak BUP concentrations, extensive coordination between the nursing and laboratory staff and monitoring by the candidate was required.

7.4. CLINICAL AND POLICY IMPLICATIONS

The main policy implication generated from the study findings relates to regulating access to MAT. In fact, Hall and Degenhardt (2007) described achieving optimal access and minimal diversion as an ‘overdue’ topic over a decade ago. STAR-T provides empirical evidence to facilitate the provision of BUP-based treatment with minimal concern over diversion regardless of the patient area of residence and co-occurring disorders. Findings from the present study may contribute to the public confidence in the effectiveness of MAT possibly alleviating barriers associated with accessing treatment. In fact, the lack of confidence in the effectiveness of OUD treatment was found to be associated with negative attitudes and lack of willingness to pay for treatment (Matheson, et al., 2014). Expanding access to treatment can further be, achieved by establishing multi-disciplinary BUP/NX-F satellite clinics and community pharmacies with minimal need for providing BUP as DOT. In fact, diversion of supervised BUP doses was detected by pharmacists authorised to provide supervised BUP doses (Winstock et al., 2009) and the pharmacists’ role is described in the broad context of providing pharmaceutical care beyond medication dispensing (Matheson et al. 2014) and in Scotland was integrated in mainstream MAT (Matheson et al., 2014).

Finally, prediction of response to BUP based treatment measured by percentage negative opioid screens may also contribute to cost-effective personalised care. A treatment algorithm to allocate participants to BUP/NX maintenance treatment is, suggested (**Appendix E.2**). This model allocates patients meeting a pre-set threshold of opioid-negative UDS percentage to BUP/NX-F maintenance care. The alternative treatment would be a gradual switch to another pharmacotherapy assisted treatment, e.g. naltrexone while slowly tapering BUP/NX-F. Assessing the effectiveness of this approach on retention in treatment and opioid use is suggested for future research.

7.5. SUGGESTIONS FOR IMPROVING TREATMENT EFFECTIVENESS

Family involvement in treatment may contribute to enhanced treatment (Higgins et al., 1994). Family therapy or family-related interventions that address family stress, strengthen coping capacity were reported to enhance patient engagement in treatment (Copello, et al., 2005; Orford et al., 2009) and reduce the negative stress and strain observed by the patient's family (Daley, 2013). In the UAE, where family related matters are highly valued and respected (Alsayegh, 2013), a great potential exists for developing a culturally oriented family intervention/therapy. Studying the effect of family involvement in treatment and family therapy on both retention and opioid use is suggested. Furthermore, introducing a 'case management' model would aid in early identification and resolution of barriers to access treatment, assist in enhancing adherence to BUP/NX-F and minimise treatment discontinuation -especially when transferring participants along the continuum of care- and as an early intervention when missed appointments or lapses are observed.

Other suggestions to enhance treatment outcomes include introducing assessment tools that facilitate treatment personalisation. For instance, 'Drug-Taking Confidence Questionnaire' (Annis & Martin, 1985) assesses the patient's ability to cope with relapse. This tool is suggested to be administered before transfer to outpatient care. A practical application of this tool is extending the duration of inpatient care for participants who demonstrate low confidence in drug taking or considering cue exposure treatment. Another consideration is in-depth cognitive assessment and integrated response to cognitive deficits, known to contribute to impaired inhibitory control, and lower response to treatment. Delivering a CBT-based treatment to participants with cognitive challenges may contribute to patient discomfort and anxiety, leading to treatment dropout. Therefore, adjusting treatment intensity according to cognitive functioning may enhance retention in treatment. In this respect, a comprehensive tool like the 'Montreal Cognitive Assessment' (MOCA; Nasreddine et al., 2005) is preferred over the MMSE to assess cognition and inform CBT.

7.6. FURTHER RESEARCH

Further analyses on the correlation of city of residence with the type of opioids, i.e. illicit prescription may help identifying ‘hot spots’ or areas where substances are more available or used hence guiding prevention and early intervention programmes.

Exploring the effect of BUP/NX-F on non-opioid substance use and association with opioid use is, also suggested. The clinical use of BUP/NX in individuals reporting non-opioid substance use has not been established. Additionally, performing a qualitative assessment of patient’s and family experience may help provide information relevant to personalizing treatment.

Future research should extend to BUP depot preparations expected to optimize adherence and minimize diversion. In November 2017, the FDA approved the first long-acting BUP injection for the US market. This preparation, branded as Sublocade[®], became the first extended-release BUP preparation given as a subcutaneous injection and is available in two strengths (100 mg and 300 mg). These preparations resulted in a mean BUP plasma concentration of 2 ng/mL, which is comparable to the mean BUP trough concentration of 1.71 ng/mL achieved in the present study. The second long-acting subcutaneous BUP preparation (CAM2038) (FDA, 2017b) is available in weekly and monthly doses. This preparation completed a multiple-dose phase-III randomised controlled parallel study with two phases and powered as a ‘non-inferiority’ treatment to the sublingual BUP treatment. The response set was based on relatively low thresholds for percentage negative opioid screens, i.e., 33% for Phase 1 and 67% for Phase 2. Assuming that these reductions in opioid use are met, depot preparations are yet to provide evidence on treatment retention and the concomitant use of non-opioid substances in contrast to sublingual treatment.

Future research opportunities may exist in developing ‘point of care’ apparatus to monitor BUP levels given the extended turn-around time currently required to obtain the BUP levels. The availability of fast and convenient tests could facilitate TDM-guided BUP treatment and optimise the effect of CM-based ‘take-home’ prescriptions. This ‘point of care’ tool would be similar in concept to the apparatus used in clozapine clinics.³

³ Pharmacist-led clozapine clinics are established to monitor clozapine treatment.

Secondary data analysis is suggested to contrast the characteristics of adults with polysubstance use with single opioid use. In this context, it is suggested to examine the rate of non-opioid substance use and contrast it with the rate of opioid use in this population maintained on BUP/NX-F as a proxy to the effect of BUP on non-opioid use.

7.8. CONCLUSIONS

The findings generated by STAR-T lead to the conclusion that adaptive BUP/NX-F ‘take-home’ prescriptions using TDM and UDS is clinically more effective to providing BUP/NX-F under usual care protocol. TDM is accurate and clinically feasible in monitoring adherence with BUP/NX-F treatment and is reliable detecting and potentially limiting BUP/NX diversion. Hence, providing TDM-based BUP/NX-F ‘take-home’ prescription with adjunctive MM (Incentivised Abstinence and Adherence Monitoring) is more effective in achieving reduction in opioid use compared to usual care. The effect of the experimental intervention is significant on opioid use rather than retention in treatment.

Except for the association of BUP EL.R with opioids use, no other factor correlated with opioid use or retention in treatment. There is no evidence that either treatments is associated with a significant higher reduction in the severity of psychosocial functioning or addiction severity. The estimated BUP EL.R could predict response to BUP/NX-F measured by percentage of opioid-negative UDS.

In conclusion, results from this study would potentially set the stage for adopting ‘precision medicine’ in MAT. One application would be that adults with OUD who meet a cut-off response estimated by the suggested response prediction model are directed to BUP treatment or alternative treatment if the pre-set cut-off levels were not achieved. Reporting on the comparative advantage and cost-effectiveness of personalised medicine is expected to encourage studying biomarkers for disease and treatment outcomes. Adopting the use of biomarkers may contribute to a paradigm shift in managing mental health disorders and provide an objective and ‘empirical’ measure of disease severity and response to treatment. Identifying a reliable biomarker would may further contribute to facilitate patient engagement in treatment and self-management and care. Finally, it is suggested that further research explore factors – particularly modifiable factors- with association with the rate of retention in treatment.

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Appendix. A.1 Published Papers

Paper 1: Elarabi, H., Alrasheed, A., Ali et al. (2019). Suboxone Treatment and Recovery Trial (STAR-T): Study protocol for a randomised controlled trial of opioid medication assisted treatment with adjunctive medication management using therapeutic drug monitoring and contingency management. *J Addict*, <https://doi.org/10.1155/2019/2491063>

Paper 2: Elarabi, H., Hasan, N., Marsden, J et al. (2020). Therapeutic Drug Monitoring in Buprenorphine/Naloxone Treatment for Opioid Use Disorder: Clinical Feasibility and Optimizing Assay Precision. *Pharmacopsychiatry*. Doi: 10.1055/a-1083-6842

Paper 3: Elarabi, H., Shawky, M., Marsden, J et al. (2020). Effectiveness of incentivised adherence and abstinence monitoring in buprenorphine maintenance: a pragmatic, randomised controlled trial. *Addiction*; DOI: 10.1111/add.15394

Supplementary papers:

Elarabi, H.F., Al Ghaferi .H., Gawad, T.A., Hasan, N., Shawky, M., Al Kathiri, H., Al Maamari, S., Radwan, D., Lee, A.J., Adem, A., Marsden, J. Exploratory Economic Evaluation of Buprenorphine Treatment in Opioid Use Disorder. *The Journal of Mental Health Policy and Economics* 24, 89-95

AlGhaferi, H., Hasan, N., Elarabi, H.F., Radwan, D., Shawky, M., Al Mamari, S., Abdelgawad, T., Elrasheed, A., Koder, A., Al Kathiri, H., Wanigaratne, S. (2020). The impact of family engagement in opioid assisted treatment: Results from a randomised controlled trial. *International Journal of Social Psychiatry*. DOI: 10.1177/0020764020979026

Clinical Study

Suboxone Treatment and Recovery Trial (STAR-T): Study Protocol for a Randomised Controlled Trial of Opioid Medication Assisted Treatment with Adjunctive Medication Management Using Therapeutic Drug Monitoring and Contingency Management

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Introduction. Opioid assisted treatment (OAT) with buprenorphine (BUP) is front-line medical maintenance intervention for illicit and prescription opioid use disorder (OUD). In many clinics, opioid medication is dispensed for several days for self-administration. This provides flexibility to the patient but may compromise the effectiveness of OAT because of nonadherence or medication diversion. OAT can be delivered as an entirely supervised intervention, but many patients discontinue treatment under this arrangement and dispensing costs may be prohibitive. An alternative is to enable patients to receive take-home doses contingent on OAT adherence guided by a medication management framework using Therapeutic Drug Monitoring (TDM) alongside negative urine drug screens (UDS) to provide evidence of abstinence. TDM is recommended to monitor adherence with BUP but it has not been applied in OAT programs and evaluation research to date. **Methods.** The Suboxone Treatment and Recovery Trial (STAR-T) is a single site, 16-week, parallel-group, randomised controlled trial. The aim of the study is to determine the effectiveness of a medication management framework including TDM and UDS to enable patients enrolled on outpatient OAT (with buprenorphine/naloxone [sublingual film formulation; BUP/NX-F; Suboxone™]) to receive stepped take-home doses. Following stabilisation during inpatient care, adult participants with illicit or prescription OUD were allocated (1:1) to receive (1) BUP/NX-F plus medication management for take-home doses based on TDM, UDS, and contingency management protocol (the experimental group) or (2) BUP/NX-F plus UDS only (treatment-as-usual, the control group). The primary outcome is the mean percentage of negative UDS over 16 weeks. The secondary outcome is treatment retention defined as completion of 16 weeks of OAT without interruption. There will be an exploratory analysis of the association between participant characteristics, clinical data, and outcomes. **Conclusions.** Providing BUP/NX-F take-home doses contingent on adherence and opioid abstinence may enable OAT to be delivered flexibly and effectively. **Trial Registration.** ISRCTN41645723 is retrospectively registered on 15/11/2015.

1. Introduction

The annual mortality rate among the illicit opioid use population is 1%, a rate 10-fold greater than the general

population [1]. The front-line, evidence-supported pharmacotherapy for opioid dependence [2] or opioid use disorder [3] (OUD herein) is oral methadone or sublingual tablet buprenorphine (BUP) maintenance [4]. On average, this

opioid assisted therapy (OAT) is associated with clinically meaningful suppression of nonmedical opioid use and drug injection [5]. Studies have shown that patients who take buprenorphine/naloxone (BUP/NX) 80% of the time or more have a 10-fold increase in the odds of heroin abstinence [6] and those considered as compliant with BUP medication provide more opioid negative urine screens [7].

The effectiveness of OAT is hampered by treatment non-adherence and diversion, prescribing lower than the doses need [8], and also early discontinuation [9]. The medication dispensing policy may influence these negative outcomes. Medication can be administered either under direct supervision or flexibly, with the patient given the opportunity to receive “take home” doses for self-administration, contingent on medication adherence, and providing evidence of illicit opioid abstinence [10, 11]. A fixed policy of only dispensing medication under supervision substantially reduces the likelihood of medication diversion; but this may prove unpopular among patients and lead to drop out [9]. Medication dispensing costs may also be prohibitive for many clinical services [12]. Patients respond well to a medication management framework using flexible dosing and behavioural reinforcement (contingency management [CM] is associated with good adherence [11]), although there remains a risk of medication diversion [9]. The current evidence shows no difference between the fixed and the flexible OAT prescribing practice in reducing opioid use or enhancing retention in treatment. This evidence however was judged to be of low quality [13].

Several patient characteristics are associated with sub-optimal OAT response. Younger patients [14] and those with unstable housing [15] tend to have a higher risk of treatment discontinuation. Co-occurring mental health disorders have a prevalence of 40 to 55% in this clinical population [16] and may be associated with compromised treatment response [17]. In particular, depression and anxiety disorders are often reported to predict treatment discontinuation [18] and heroin use [18]. Personality disorders (particularly borderline personality disorder) are associated with poor prognosis of substance use treatment [19]). An impulsive personality trait has been observed to predict noncompletion of SUD treatment [20]. Sleep disorders are associated with daytime dysfunction in the heroin using population which may compromise patient engagement in treatment [21].

Buprenorphine and naloxone (BUP/NX; ratio 4:1; and a sublingual film formulation [Suboxone®; BUP/NX-F developed for rapid dissolution]) have been developed for maintenance OAT with the aim of suppressing the likelihood of illicit opioid injecting (because the opioid antagonist naloxone may cause opioid withdrawal) and maximising adherence (because BUP/NX-F is very hard to remove once placed under the tongue). In contrast to BUP mono therapy, there is evidence that these alternative formulations deliver further reduction in diversion [22]. A ‘pill or medication count’ practice has also been recommended as part of the effort to increase medication adherence [23] but, to date, there are no reported randomised controlled trials.

Therapeutic Drug Monitoring (TDM) is a patient centered and precision medicine tool that involves quantitation

and interpretation of medication blood concentrations with necessary dose adjustments to optimise treatment outcomes [24]. It has been applied in neuropsychiatry to enhance outcomes of antiepileptics [25], antipsychotics [26], and mood stabilisers [27] and for monitoring drug-drug interactions [28]. The potential value of TDM in OAT has been recognised as a monitor of compliance [24] yet there is no consensus or guidelines on how it should be clinically implemented and there have been no published clinical trials.

Against this background, the present study will determine the effectiveness of TDM, urine drug screens (UDS), and medication take-home dosing by CM. To our knowledge, there have been no trials that use these adjunctive elements in OAT. In this protocol paper, we describe the design, methods, procedures, and strengths and limitations for a randomised controlled trial to determine the clinical effectiveness of an adjunctive medication management protocol for OAT with BUP/NX-F.

2. Methods

2.1. Study Design, Population, and Setting. The Suboxone Treatment and Recovery Trial (STAR-T) is a single centre, 16-week outpatient intervention, two-arm, pragmatic, phase IV randomised controlled trial of OAT and adjunctive TDM for OUD. The study population is adults (≥ 18 years) with current OUD.

The study setting is the specialist OUD treatment and care programme operated by National Rehabilitation Centre (NRC), Abu Dhabi, United Arab Emirates (UAE; www.nrc.ae). In the UAE, use and combination use of heroin, morphine, and illicit tramadol are the most prevalent [29, 30]. The NRC treatment programme includes an inpatient unit for assessment and management of medical and mental health comorbidities with (poly) substance and alcohol use disorders [29–31]. In 2002, the NRC introduced OAT with BUP with induction and stabilisation procedures conducted in the inpatient unit. However, following concerns about medication diversion in 2011, the NRC suspended all new admissions to OAT pending the development and findings from the present study.

Following a standard of care protocol for OAT, all participants will first complete inpatient care (up to four weeks) to achieve medically supervised withdrawal and stabilisation on BUP/NX-F and to estimate the BUP Elimination Rate (EL.R). After study enrolment and prior to discharge, participants will be randomly allocated (1:1: using an online randomisation service [32] with no stratification) to an experimental group (that immediately received 16 weeks of outpatient BUP/NX-F maintenance, standard case management, and manualised adjunctive medication management with TDM monitoring and CM) or to a treatment-as-usual, control group (that immediately received BUP/NX-F and standard case management and usual medication management only). Using ongoing medication management, TDM, and CM protocol, participants in the experimental group will be able to receive up to four weeks of medication on a take-home basis. All participants will continue to receive ongoing treatment after 16 weeks as usual.

TABLE 1: Participant inclusion and exclusion criteria.

Inclusion criteria

For a participant to be enrolled into the study he must fulfil all the following inclusion criteria:

- (1) Aged 18 and above with no upper limit (usually 64 years);
- (2) Current diagnosis of OUD;
- (3) Voluntarily seeking OAT treatment;
- (3) Resident in the UAE;
- (4) Evidence of stable accommodation.

Exclusion criteria

Otherwise eligible patients will be excluded from the study for any of the following:

- (1) Benzodiazepine use in excess of 20 mg daily diazepam equivalent in the past 28 days;
- (2) Known naloxone or BUP hypersensitivity;
- (3) Pregnancy;
- (4) Hepatic impairment (elevation of liver function tests three times normal);
- (5) Suicide attempt in past 12 months;
- (6) Involvement in criminal justice system which is likely to result in arrest and incarceration;
- (7) Uncontrolled severe mental or physical illness judged to compromise safety;
- (8) Mini Mental State Examination score < 17 indicating cognitive dysfunction.

The trial will follow the ethical principles of the World Medical Association's Declaration of Helsinki for research involving human subjects and is registered with the ISRCTN (number: 41645723). The study will adhere to the medical research guidelines of the Department of Health of Abu Dhabi [33] and the CONSORT guideline extension for pragmatic randomised controlled trials [34]. Good clinical practice training will be provided in the UAE and in the United Kingdom by King's Health Partners Clinical Trials Office (<https://www.khpcto.co.uk>).

The study protocol, participant information sheet (describing the study rationale, design and procedures), participant consent form, and clinical research forms have been approved by the Institutional Review Board of the National Rehabilitation Centre, Abu Dhabi (number: NRC/2/2014; granted April 2014; first participant enrolled on 15.9.2014).

2.2. Study Aims. The primary aim of this pragmatic study is to determine if BUP/NX-F with adjunctive TDM is clinically superior to BUP/NX-F only in terms of reduced opioid use during outpatient treatment.

In addition to determining group differences on OAT retention, there are two exploratory secondary aims: (1) to determine if there are associations between participant demographics, two BUP parameters (elimination rate and dose), and opioid use and treatment retention; and (2) to determine if there are associations between patient psychosocial functioning and opioid use and treatment retention.

STAR-T also includes an exploratory health economic (cost-benefit and cost-effectiveness) evaluation. This component of the study will be described and reported separately.

2.3. Participant Eligibility and Enrolment Procedure. The participant inclusion and exclusion criteria for the study

are summarised in Table 1. Screening of patients for study eligibility was carried at intake before admission to the inpatient detoxification unit.

2.4. Research Assessments. The following measures were recorded prior to randomisation (baseline), during the outpatient treatment phase (as shown in parentheses; see Table 2 for summary)

2.4.1. Urine Drug Screen (with Confirmatory Testing; Baseline and Every Clinic Visit) and BUP Level Determination (See Section 2.7 for Frequency of Administration). A 5-minute, point-of-care immunoassay UDS test will be used that is US FDA approved and Clinical Laboratory Improvement Amendments (CLIA) waived for the following drugs screen in urine: opioids (morphine for illicit heroin), propoxyphene, tramadol, oxycodone, benzodiazepines, tricyclic antidepressants, psychostimulants (d-amphetamine, methyl-amphetamine, MDMA, cocaine), cannabinoids, phencyclidine, and BUP. All urine samples were collected under supervision, and positive screens were sent for confirmatory analysis at the laboratory using Gas Chromatography Tandem Mass Spectrometry. BUP levels were detected and quantified by Liquid Chromatography Tandem Mass Spectrometry (Schimadzu Scientific Instruments) with a Raptor C18 analytical column (Restek Corporation; 9304A12).

2.4.2. Clinical Opioid Withdrawal Scale (COWS [35]; See Table 2). The COWS is an 11-item clinician-administered scale which assesses opioid withdrawal signs and symptoms (a higher score indicates more severe opioid withdrawal).

2.4.3. Pupil Reflexes (PLA Inc. 2000; Neuroptics, <https://neuroptics.com>; See Table 2). A hand-held camera captures three pupil reflexes [36]: (1) maximum pupil diameter reading

TABLE 2: Schedule for administering study measures.

Tool/ Screen	Baseline Intake	Inpatient		16 week outpatient study period				
		Detoxification (Daily)	Stabilisation (Weekly)	Week 1 to 4	Week 5 to 8	Week 9 to 12	Week 13 to 16	Week 16 End of study
Eligibility Screen	x							
MCCS	x	x	x	x	x			
Pupil Reflexes	x	x	x	x	x		x	x
COWS	x	x	x	x				
PHQ-9	x			x		x		x
GAD-7	x			x		x		x
BIS-11	x			x				x
PSQI	x		x	x	x	x	x	x
WSAS	x			x				x
PDS	x			x				x
ASI-Lite	x			x				x

MCCS: Minnesota Cocaine Craving (adapted for opioids); PHQ-9: Patient Health Questionnaire; COWS: Clinical Opioid Withdrawal Scale; GAD-7: Generalised Anxiety Disorder; BIS-11: Barrett Impulsiveness Scale; WSAS: Work and Social Adjustability Scale; PDS: Personality Disorder Screen; ASI-Lite: Addiction Severity Index-Lite.

before exposure to light (before contraction). (2) minimum pupil diameter reading after exposure to light (after contraction), and (3) maximum and average constriction velocity, dilation velocity, and time to 75% recovery of pupil diameter.

2.4.4. Patient Health Questionnaire (PHQ-9 [37]; See Table 2 for Frequency of Administration). The PHQ-9 is a validated, self-administered 9-item scale recording frequency of depression-related symptoms according to the DSM-IV depression criteria using responses over the past two weeks. The PHQ-9 screens for mild, moderate, moderately severe, and severe depression at cut-offs of 5, 10, 15, and 20, respectively. A validated Arabic version downloaded from the PHQ Screeners webpage [www.phqscreener.com] was used in the present study.

2.4.5. Generalised Anxiety Disorder (GAD-7 [38]; See Table 2 for Frequency of Administration). The GAD-7 is a validated, self-administered 7-item scale recording frequency of anxiety-related symptoms according to the DSM-IV anxiety criteria using responses over the past two weeks. The GAD-7 screens for mild, moderate, and severe anxiety at cut-offs of 5, 10, and 15, respectively. A validated Arabic version downloaded from the PHQ Screeners webpage [www.phqscreener.com] was used in the present study.

2.4.6. Barratt Impulsiveness Scale (BIS-11 [39]; See Table 2 for Frequency of Administration). The BIS-11 is a validated, 30-item self-administered questionnaire that assesses three impulsiveness subtraits: nonplanning, motor, and attention. Items are rated over a four-point scale (“never” to always; scored 0 to 4 total score range: 0 to 120). A higher score indicates higher trait impulsiveness.

2.4.7. Personality Disorder Screener (PDS [40]; See Table 2 for Frequency of Administration). The PDS is a validated, clinician-administered 34-item “true”, “false”, or “do not know” checklist. Scoring follows the ICD-10 criteria to screen for three clusters of personality disorders: Cluster A (Odd or Eccentric), Cluster B (Borderline Personality), and Cluster C (Anxious Personality).

2.4.8. Addiction Severity Index (ASI-Lite Version [41]; See Table 2 for Frequency of Administration). The ASI-lite is a validated, semistructured interviewer administered outcome evaluation instrument that assesses seven addiction severity domains over the past 30 days (medical and employment and social status; alcohol use; drug use; family; legal; and mental health). The tool generates a composite score for each domain (ranging from “0 to 1”), with higher scores indicating higher problem severity.

2.4.9. Work and Social Adjustment Scale (WSAS [42]; See Table 2 for Frequency of Administration). The WSAS is a validated, 5-item self-reported scale that measures perceived personal, social, and occupational impairment caused by a clinical problem (OUD in the present study). Each item is rated using an 8-point scale (“0” [no impairment] to “8” [full impairment]; total score range: 0 to 40). A score of “10 to 20” indicates significant impairment and a score of “21 to 40” reflects severe impairment.

2.4.10. Pittsburgh Sleep Quality Index (PSQI [43]; See Table 2 for Frequency of Administration). The PSQI is a validated, self-administered tool that evaluates sleep quality across seven categories with items rated on a 3-point scale (total score 0 to 27). A higher score reflects worse sleep quality and the cut-off score for sleep disorders is “5”. The published

Arabic version by Suleiman and colleagues in 2010 [44] will be utilised.

2.4.11. Minnesota Cocaine Craving Scale (MCCS [45]; See Table 2 for Frequency of Administration). The MCCS is a validated, 5-item scale measuring the following aspects craving: intensity, duration, frequency, change from last week/day, and how the medication has helped. The MCCS was adapted to record “opioids” (MOCS) for the present study.

2.5. Patient Education and Medication Management Materials. The following materials were developed to support trial implementation and fidelity:

(1) *Medication Education Leaflet.* An educational material on how to use BUP/NX-F was developed for patient medication education [46] and following the BUP clinical practice published by the US Department of Health and Human Services-Substance Abuse and Mental Health Services Administration [37];

(2) *Emergency Card.* As a safety measure, a wallet-size hard card was developed for health care professionals who attend participants in the state of emergency specifying the prescription of BUP/NX-F;

(3) *Patient Diary/“Recovery Passport”.* A passport-sized diary was developed based on the patient health engagement model [47], self-management, and principles of CM to include material on self-assessment, a log of BUP/NX-F dosing (validated by the participant and a family member), and a log of clinic visits for UDS and results;

(4) *Patient Counselling Checklist.* A 19-item checklist is developed to guide medication counselling [48]; and

(5) *Medication Management Manual.* A manual was developed to structure the medication management sessions for the experimental group. This was based on material developed for US trials of alcohol [49] and opioid pharmacotherapy [50] and included monitoring forms to individualise interventions and text to guide the clinician’s interactions with the patient.

2.6. Procedures

2.6.1. Buprenorphine/Naloxone Induction and Stabilisation. On the first day of admission to the inpatient unit, participants’ pupil reflexes will be measured to provide a baseline for monitoring craving and medication response. Then, at the first sign of withdrawal, a three-day or five-day supervised BUP/NX-F induction will commence for individuals with morphine/heroin use disorder or pharmaceutical OUD, respectively. The longer induction period for the latter group reflects the relatively longer half-life of these products compared to heroin.

BUP/NX-F will be initiated at a dose of 2 to 4 mg will be used for those with a COWS score of <10. The participant will be closely observed during the first 4 hours to signs of

precipitated withdrawal, together with regular pupil reflex monitoring and COWS assessments. The participant’s dose will be increased by 2 to 4 mg to a maximum of 8 mg in the first 24 hours. On the second day of induction, the dose will be increased by 4 to 6 mg every 4 to 6 hours to a maximum of 24 mg per day.

With an achieved COWS score of <5, the participant will be transferred to an “early recovery unit” a step-down phase to achieve BUP/NX-F stabilisation. Each participant will be assigned to a personalised dosing schedule (i.e., daily, alternate-day [Alt-D] or thrice-weekly [TIW]) followed by further dose adjustment as required. Those who continue to report distressing opioid craving or do not tolerate their dosing schedule satisfactorily will be transferred to another (usually more frequent) schedule. The published correlation of patient characteristics and BUP/BUP/NX maintenance doses [51, 52] will serve as the theoretical basis for this regimen and the daily, or the total 24-hour dose, required to achieve a COWS scores <5 will be used as the reference for estimating non-daily doses.

The Alt-D schedule will be a 3×48 -hour dose and 1×24 -hour dose. The TIW schedule will be a 2×48 -hour dose and 1×72 -hour dose (calculated as 3×24 -hour dose at a maximum of 32 mg) [53, 54]. Clinical determination of the dosing schedule was informed by illicit injecting status (i.e., participants injected street heroin/morphine will receive daily doses and noninjected heroin and morphine users received alternate daily doses) while prescription opioid users (nonpolysubstance users) will receive TIW doses. Additionally, participants with severe psychiatric comorbidity, polysubstance use, or a body mass index (BMI) of ≥ 30 will be placed on the next higher frequency schedule (e.g., from TIW to ALT-D). Fine dose adjustments will be guided by self-report participant comfort, sleeping, craving, and pupil reflexes. Participants continuing to observe craving and or signs of withdrawal will be transferred to the next frequent dosing schedule towards the daily schedule as illustrated by Figure 1.

2.6.2. Estimating the Buprenorphine Elimination Rate Constant. Maintenance of a BUP/NX-F dose without change for two weeks will be taken to indicate that a BUP steady state concentration (SSC) [55] has been achieved for participants receiving a daily or Alt-D dosing schedule. A longer period of 21 days (or an equivalent of 9 doses) will be needed to achieve SSC for participants assigned to TIW. Then, applying the function for first order kinetics (Figure S1), the BUP EL.R will be estimated by

(1) examination of the peak BUP plasma concentration measured 40 minutes after the dose on day 19 and day 22 [peak concentration, C-max]; and

(2) examination of BUP trough levels measured 30 minutes prior administering BUP/NX-F on day 21 and day 24 (trough concentrations, C-min). The replication of two trough concentrations will be taken to confirm that a SSC has been achieved. It is possible that additional samples will need to be drawn until SSC is confirmed. The reliability of the first order pharmacokinetic (PK) model to accurately predict BUP levels will be evaluated in the first 15 participants

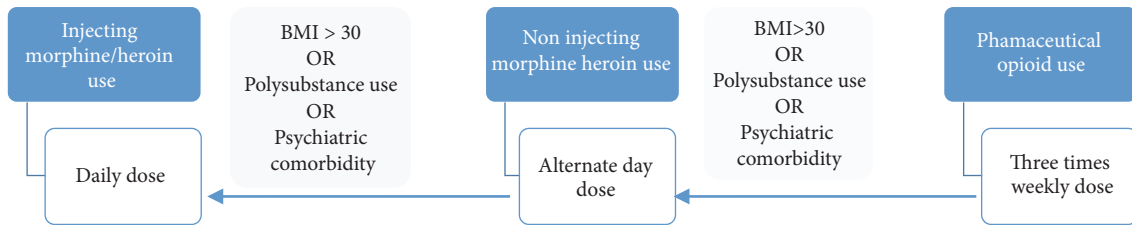


FIGURE 1: Dose assignment and stabilisation.

recruited to the study in the form of an internal pilot study for TDM. After confirming the reliability of the PK model in all 15 participants, the study will proceed to definite recruitment and results from the pilot will be included in the study analysis. Details of the laboratory assay and clinical procedures for this step will be presented separately.

2.6.3. Interventions for Experimental Group. In week one of outpatient care, participants allocated to the BUP/NX-F and TDM (experimental) group will receive directly supervised doses according to their dosing schedule. Participants are required to randomly provide a minimum of three negative UDS during these visits on a random basis. If the participant is able to meet this requirement, a CM protocol will enable them to receive a one-week prescription of medication for self-administration at home. On return for their prescription to be refilled, a negative UDS will enable the participant to receive a two-week prescription and then a three-week prescription. On the other hand, if the participant is not able to meet the initial requirement (i.e., they fail to attend all appointments or provide at least three negative UDS) they will receive supervised dosing for another week (five days for daily dosing schedule and two days of take home for the weekend). At any point, a positive UDS will either hold the participants on five-day supervised dosing or step them down to this arrangement from the two-week or three-week dosing arrangement.

For the TDM element, after the participant has been able to earn a two-week take-home prescription, a blood sample will be collected during a clinic visit for laboratory to measurement of BUP level labelled the “observed concentration”. On the sample collection day, participants will be strictly advised not to take their BUP/NX-F dose and the quantity of medication dispensed will be accounted for by the pharmacy. The exact time of blood sample collection, the time of the last BUP/NX-F dose taken/administered, and the established BUP EL.R will be applied in the function of first order kinetics (Figure S1) to predict the participant’s concentration labelled as “predicted concentration” of BUP. If the observed and predicted concentration values do not differ by more than 15%, the participant will be classified “adherent”. Participants who are adherent will be stepped up to a three-week take-home prescription. All nonadherent participants will be stepped down to a one-week take-home prescription.

On a random basis, all participants who attain the three-week take-home prescription will be invited to visit the clinic between scheduled visits to give a blood sample for BUP

testing and also to take a UDS. Nonadherent or nonabstinent participants will be stepped down to two-week take-home prescription while adherent and abstinent participants will receive a four-week take-home prescription at the next scheduled visit (the maximum permitted for the trial). During outpatient treatment, participants who are assessed as both nonadherent and nonabstinent will be reset to supervised dosing.

During the first week of outpatient care, two medication management foundation sessions will be scheduled to help participants (1) understand the importance of taking BUP/NX-F as prescribed, (2) become aware of BUP/NX-F mechanism of action and ways to monitor withdrawal signs and adverse events, (3) recognise and cope with cravings, and (4) build and sustain motivation for abstinence. Then, medication management maintenance sessions will be offered in response to the following four participant conditions:

Abstinent and Adherent. Discussion is held to reinforce and motivate continued abstinence and medication adherence. Prescription for take-home doses will be extended step-wise to a maximum of four weeks.

Abstinent but Nonadherent. Discussion is held to reinforce and motivate continued abstinence, remind the participants about the value of adherence, identify the source of nonadherence and strategies to improve adherence. A follow-up call on the agreed tasks will be arranged and prescription for take-home doses will be stepped down by one level.

Nonabstinent but Adherent. Discussion is held to reinforce and motivate medication adherence and remind participants about the value of abstinence. The context and triggers for using will be assessed and relapse prevention strategies discussed. Additionally, comorbid conditions and social situations will be evaluated with referral to ancillary services. The prescription for take-home doses will be stepped down by one level.

Nonabstinent and Nonadherent. Functional assessment of relapse/lapse will be performed, with referral to an appropriate service if co-occurring conditions were identified. Engagement of family members and close network will be sought to encourage retention. The participant will be transferred to five-day supervised BUP/NX-F dosing.

2.6.4. Interventions for the Control Group. Participants randomised to the TAU control group will receive BUP/NX-F dosing according to preference of daily, twice weekly, or

TABLE 3: Interventions under study groups (TDM; TAU).

Intervention	Randomisation Group	
	TDM	TAU
Induction	Yes	Yes
Stabilisation	Yes	Yes
Baseline assessments	Yes	Yes
Estimating BUP Elimination Rate	Yes	Yes
Medication education	Yes	Yes
Emergency card	Yes	Yes
<i>Outpatient DOT</i>	Yes	No
<i>Outpatient medication management manualised intervention</i>	Yes	No
UDS at outpatient care	Yes	Yes
Providing prescription take-home doses	Contingent on UDS & TDM (i.e., abstinence & adherence)	Contingent on UDS only
<i>Stepped BUP/NX-F take-home doses</i>	Yes	No
Maximum take BUP/NX-F home doses	4 weeks	2 weeks
<i>TDM</i>	Yes	No
Periodic study assessments	Yes	Yes
End of study assessments	Yes	Yes
Psychosocial support	Yes	Yes

BUP: buprenorphine; DOT: directly observed treatment; UDS: urinary drug screen; TDM: therapeutic drug monitoring.

every two weeks alternatives without a mandatory supervised dosing period. In this group, take-home doses will be provided contingent on provision of negative UDS only without following a fixed protocol. Medication management sessions will not be delivered according to structured manual and no monitoring of BUP levels will be done. Table 3 contrasts the interventions under the experimental and control group.

2.7. Study Outcomes

2.7.1. Primary Outcome. The primary outcome measure for the study will be the count of negative opioid UDS (excluding BUP) over 16 weeks. Scheduled appointments for a UDS that are missed will be conservatively imputed as positive for opioids.

2.7.2. Secondary Outcome. Retention as defined as completion of the 16-week outpatient treatment without interruption. All participants who miss three consecutive appointments will be judged to have discontinued treatment.

2.7.3. Exploratory Outcomes. There is change in psychosocial functioning from baseline at the end of the 16-week treatment. There is correlation of participant demographics, clinical data, BUP EL.R, and BUP/NX-F maintenance dose with the primary and second outcome.

2.8. Sample Size Calculation. Given the novelty of the study, the sample size was estimated indirectly with reference to

the relevant CM literature as reviewed by the UK National Institute of Care Excellence (NICE Clinical Guideline 51; Appendix 15 [56]). The study was powered for 80% to detect a difference of 3 weeks opioid abstinence as evaluated by NICE for three trials (an odds ratio in favour of CM of 2.56; 95% CI 1.76 to 3.72). Using this pooled effect, uplifted by 15% for attrition and with a 5% two-sided alpha, it was estimated that 92 participants should be allocated to the experimental and control group.

2.9. Statistical Analysis of the Primary and Secondary Outcomes. Data for the whole population and by study group will be analysed for mean, standard deviation, 95% confidence interval, and range. With no interim analysis, all statistical analyses will be pragmatically done according to intention-to-treat principle. All analyses will be conducted using two-sided 5% significance test. A fixed-effects logistic model will be applied to analyse the primary outcome. To analyse between group differences, student *t*-test will be conducted for normally distributed data, or a Mann-Whitney test. For the primary outcome, a planned sensitivity analysis will determine the impact of the imputed or complete case [57]. Alternatively, reported observed opioid screens or actual screens without imputation will be analysed between group differences. Secondary outcome will be evaluated using proportional hazards regression model and Chi-Square test will be performed to measure between group differences.

2.10. Analyses for Exploratory Outcome. Bivariate correlation tests to explore correlations with study outcomes will be

performed. Specifically, Pearson's correlation will be applied for continuous and Spearman's rho test for categorical data. Factors demonstrating significant correlation and those with potential impact on the primary outcome will be studied for predictive power using a simple linear regression model. Finally, analysing for the effect of confounders will be done using univariate analyses for factors generating higher correlation (>0.5). The mean change from baseline scales or within group change will be analysed using a generalised linear model framework. A paired t -test will be conducted where normal distribution is assumed or alternatively Kruskal-Wallis test. The magnitude of change from baseline will be estimated using bias corrected Hedge's g effect size. Mean difference between groups will be analysed using student t -test where normal distribution is assumed or a Mann-Whitney test.

3. Treatment Monitoring

The study will be overseen by a Management and Safety Committee (MSC) and a Trial Management Group (TMG). The MSC is an independent committee and will meet quarterly to monitor participant recruitment, safety aspects, and implementation process. Reporting to the MSC, the TMG will meet fortnightly and will focus on day-to-day management of the study. An adverse event form will record the type, severity, start and end dates of each event, likely association to BUP/NX-F, and actions taken and outcome. Response to adverse events will follow the study protocol (Table S.1.). Implementation of the study procedures, data collection and management, and functions of the governance committees will be audited every 6 months. A random 5% audit of the material recorded during the medication management sessions will also be conducted with additional training provided as required.

4. Recruitment and Study Status

STAR-T is an ongoing study that commenced recruiting participants on 15th of September 2014 and data analyses is still in progress.

5. Discussion

This pragmatic study will provide empirical data on the outcomes of personalising OAT in reducing opioid use and enhancing treatment retention. Personalised care was assumed by adjusting BUP/NX-F "take-home" prescriptions according to medication adherence, judged by TDM data, and drug use judged by UDS. This approach was hypothesised to optimise adherence and minimise diversion. This study evaluates the integration of TDM to provide stepped BUP/NX-F "take-home" against usual treatment. Findings from this study would contribute to the expanding OAT currently limited by poor compliance, concerns over diversion, and high cost supervised treatment [12] associated with high treatment dropout rates [6].

A practical alternative to prospectively assigning participants to BUP/NX-F dose schedules would be random

assignment and stabilisation of participants followed by analysis of participant characteristics associated with each dose schedule. On the other hand, contrasting the level of medication adherence concluded by TDM with that generated by UDS would have strengthened the justification of using TDM considering the cost of both methods.

Although EQ-5D [58] is the approved tool for health utility calculations by the National Institute for Clinical Excellence (NICE) in the UK, EQ-5D does not offer the required sensitivity to assess mental health disorders of nonacute presentations. This has encouraged the authors to explore WSAS as a brief and self-administered measure of disability and inversely utility to estimate changes in quality of life (QOL). For future research we suggest the validation of WSAS against a standard tool measure of QOL like Short Form Health Survey-Arabic version (SF-36, [59]).

Blood is the biological matrix identified by the TDM consensus guidelines for quantitation of BUP [24]. In blood, BUP demonstrates linear kinetics and time to peak concentration has been established [24, 60]. In contrast, detection of BUP in urine is performed but quantitation was not recommended due to erratic clearance with approximately 30% of BUP excreted in urine. Equally important, time to achieve BUP peak concentration was not established in urine unlike blood [60].

The identified strengths allowing for generalisability of results include expanded inclusion criteria and exclusion of factors reported to minimise retention, e.g., unstable housing arrangements [15]. The 16-week period could be optimal for evaluating relapse prevention. On the other hand, the extended turn-around time to report BUP levels might influence the effectiveness of CM based interventions shown to be most effective when provided within 24 hours of the behaviour [11]. Other possible limitations include applying nonstratified randomisation due to the extended stratification factors and blocks include city of residence; type and pattern of opioid use; polysubstance use; and comorbid anxiety, depression, and impulsiveness. Categorical reporting of retention limits assessing the potential value of partial completion. In the absence of consensus on defining treatment retention, we chose the most stringent definition of retention which is maintaining access to treatment at different treatment points including the end of the study [61].

Data Availability

Data supporting the findings of this study are available from the NRC (www.nrc.ae) but restrictions apply to the availability of data used under license for the current study. Public availability of materials is not applicable due to concerns of violating patient confidentiality. However, data are available from the corresponding author upon reasonable request and permission of the NRC.

Additional Points

Changes Made to the Protocol. The EQ-5D was excluded from the list of tools implemented in the study and was reported to the IRB in December 2014.

Safety Reporting, Participant Withdrawal, and Treatment Stopping Rules. All adverse reactions are recorded. Nonfatal or life threatening events are reported within 15 days of discovering the reaction. Fatal or life-threatening events are immediately reported with additional information reported within eight days. Adverse events managed according to the provisions of Table S1 are assessed for level of seriousness and likely association with study interventions. Participants can withdraw from treatment at any time, and the reason for withdrawal is recorded. Participants may also withdraw from the study for safety reasons (e.g., in the event of serious adverse events and reactions, or medical conditions which require acute or intensive hospital procedures). Finally, a decision to stop the trial prematurely might be taken further to emerging data.

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Consent

Not applicable as the manuscript does not contain any individual person's data whether details, videos or images). However, the consent to participate in the study includes the use of study data in scientific publication and presentations in conferences (Figure S3: Consent form in Arabic).

Disclosure

The study has not received funding from any commercial entity and no grants have been awarded by a major funding body. The National Rehabilitation Centre (NRC) is the study site and is independently funding the study. The NRC received no support for the supply of the study materials (medications, point-of-care testing), or for overheads related to laboratory assay. The Scholarship Office of the Ministry of Presidential Affairs in the UAE funded educational costs.

Conflicts of Interest

In the past three years, John Marsden declares research grants from the NHS England and the English Department of Health and Social Care (prison setting maintenance medication for opioid use disorder [OUD]), the National Institute for Health Research (NIHR: randomised controlled trial of depot naltrexone for OUD, and a randomised controlled trial of acamprosate for alcohol use disorder), and the NIHR

Biomedical Research Centre for Mental Health at South London and Maudsley NHS Mental Health Foundation Trust (SLaM: randomised controlled trial of novel cognitive therapy for cocaine use disorder). He has part-time employment as Senior Academic Advisor for the Alcohol, Drugs, Tobacco, and Justice Division, Health and Wellbeing Directorate, Public Health England (PHE), and is a clinical academic consultant for the US National Institute on Drug Abuse, Centre for Clinical Trials Network. John Marsden declares an unrestricted research grant at IoPPN and SLaM from Indivior via Action on Addiction for the present study and unrestricted research grant funding at IoPPN and SLaM from Indivior for a three-year, multicentre, randomised controlled trial of injectable depot buprenorphine (from 2019). He has received honoraria and travel support from Merc-Serono (2015: oncology medical education) and Reckitt-Benckiser (2016: treatment of OUD and PCM Scientific and Martindale for the Improving Outcomes in Treatment of Opioid Dependence conference (2015-2018: contributions and chairing)). He holds no stocks in any company. All other authors declare that they have no conflicts of interest in relation to this protocol.

Authors' Contributions

The original idea for the study intervention was conceived by Hesham Elarabi. The study protocol was written by Hesham Elarabi and John Marsden with input from all authors. The statistical analysis plan was developed by Hesham Elarabi and John Marsden. Hesham Elarabi and John Marsden wrote the first draft of the manuscript and following input from all authors Hesham Elarabi took the decision to submit for publication.

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Supplementary Materials

Table S1. Management of adverse events. Figure S1. Elimination rate equation. (*Supplementary Materials*)



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Effectiveness of incentivised adherence and abstinence monitoring in buprenorphine maintenance: a pragmatic, randomised controlled trial

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ABSTRACT

Background and Aim Buprenorphine (BUP) maintenance treatment for opioid use disorder (OUD) begins with supervised daily dosing. We estimated the clinical effectiveness of a novel incentivised medication adherence and abstinence monitoring protocol in BUP maintenance to enable contingent access to increasing take-home medication supplies. **Design** Two-arm, single-centre, pragmatic, randomised controlled trial of outpatient BUP maintenance, with during-treatment follow-ups at 4 weeks, 8 weeks, 12 weeks and 16 weeks. **Setting** Inpatient and outpatient addictions treatment centre in the United Arab Emirates. **Participants** Adults with OUD, voluntarily seeking treatment. **Interventions** The experimental condition was 16 weeks BUP maintenance with incentivised adherence and abstinence monitoring (I-AAM) giving contingent access to 7-day, then 14-day, then 21-day and 28-day medication supply. The control, treatment-as-usual (TAU) was 16 weeks BUP maintenance, with contingent access to 7-day then 14-day supply. **Measurements** The primary outcome was number of negative urine drug screens (UDS) for opioids, with non-attendance or otherwise missed UDS, imputed as positive for opioids. The secondary outcome was retention in treatment (continuous enrolment to the 16-week endpoint). **Findings** Of 182 patients screened, 171 were enrolled and 141 were randomly assigned to I-AAM (70 [49.6%]) and to TAU (71 [50.4%]). Follow-up rates at 4 weeks, 8 weeks, 12 weeks and 16 weeks were 91.4%, 85.7%, 71.0%, 60.0% respectively in I-AAM and 84.5%, 83.1%, 69.0%, 56.3% in TAU. By intention-to-treat, the absolute difference in percentage negative UDS for opioids was 76.7% (SD = 25.0%) in I-AAM versus 63.5% (SD = 34.7%) in TAU (mean difference = 13.3%; 95% CI = 3.2%–23.3%; Cohen's d = 0.44; 95% CI = 0.10–0.87). In I-AAM, 40 participants (57.1%) were retained versus 33 (46.4%) in TAU (odds ratio = 1.54; 95% CI = 0.79–2.98). **Conclusions** Buprenorphine maintenance with incentivised therapeutic drug monitoring to enable contingent access to increasing take-home medication supplies increased abstinence from opioids compared with buprenorphine maintenance treatment-as-usual, but it did not appear to increase treatment retention.

Keywords abstinence, adherence, buprenorphine, effectiveness, opioid use disorder, therapeutic drug monitoring.

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INTRODUCTION

Opioid use disorder (OUD) is a global public health problem associated with a high disease burden [1].

Retention-oriented medication maintenance treatment with methadone or buprenorphine (BUP), or combined BUP and naloxone, are the first-line pharmacotherapies. Patients who engage in OUD treatment have a marked

reduction in overdose mortality and use of opioids [2,3]. However, many patients struggle to adhere to treatment and discontinue prematurely. In a systematic review of four randomised controlled trials (RCT) and 63 observational studies (294 592 participants in total), the median retention rate was approximately 57% at 12 months [4]. Non-adherent patients are substantially more likely to relapse to opioid use [5].

Driven by safety concerns, national clinical guidelines for OUD maintenance treatment recommend that patients should receive all, or the majority of their medication, by supervision for several months, with access to take-home supplies (to a typical maximum of 14-days at a single dispensing event) granted to those who can attend and take their medication as directed [6,7]. Clinicians favour access to unsupervised dosing for adherent patients [8,9] and it would appear that most patients endorse this as well [10]. Some patients believe supervised dosing is stigmatising and this may motivate the decision to leave treatment [11].

Typically, prescription adherence during OUD maintenance treatment is monitored through a combination of non-attendance alerted by the dispensing pharmacy and monitoring of point-of-care urine drug screening (UDS) at the clinic. The UDS is a qualitative test that gives an indication of recent medication use (at a level of detection sensitivity) but it cannot show whether the prescribed dose has been taken as prescribed. There have been several clinical effectiveness studies of supervised and unsupervised dosing. A meta-analysis of six such studies in methadone, BUP and combined BUP and naloxone maintenance (four RCTs and two prospective observational cohort studies; 7999 participants in total) judged that there was insufficient evidence for a robust difference in retention (relative risk = 0.99, 95% CI = 0.88–1.12); or endpoint abstinence (67% vs 60%); or medication diversion (5% vs 2%) [12]. However, the quality of these studies was rated as 'low–very low', thus further evidence is likely to change this conclusion.

Is there a better way to monitor adherence during BUP maintenance and help patients receive increasing take-home supplies? One promising set of procedures is therapeutic drug monitoring (TDM). TDM is defined as the 'quantification and interpretation of drug concentrations in blood to optimize pharmacotherapy' [13]. Clinical applications involve repeated measurements of the plasma concentration of a medicine to reach a dose that is well tolerated, minimises the risk of adverse drug reactions and achieves the desired effect. Unlike UDS, TDM can provide a precise indication that medication has been taken as directed. Two decades ago, TDM was predicted to become the standard-of-practice for OUD maintenance pharmacotherapy [14]. However, TDM has not been implemented to any significant extent, and there have

been no trials applying TDM procedures during BUP maintenance.

Accordingly, this study is a contribution toward closing this gap. As a precursor, we optimised a laboratory quantification method for BUP monitoring, demonstrating that this was feasible during routine clinical operations [15]. Including TDM procedures, we developed a novel incentivised medication adherence and abstinence monitoring (I-AAM) protocol. The aim of I-AAM was to enable BUP dose-optimised patients who could provide ongoing evidence of adherence and abstinence from opioids, access to increasing take-home supplies of their medication. The aim was to estimate the clinical effectiveness of BUP maintenance with I-AAM versus BUP maintenance treatment-as-usual (TAU).

METHODS

Setting

The study was done at the inpatient and outpatient service of the National Rehabilitation Centre (NRC), Abu Dhabi, United Arab Emirates (UAE). The NRC is the only national provider of BUP maintenance treatment in the UAE. The centre receives referrals from metropolitan Abu Dhabi with 50% of patients attending from other cities and remote areas. In the UAE, heroin, morphine and tramadol are the most common illicit and non-medical prescription opioids reported by populations with OUD. Locally, BUP is not available at community retail pharmacies, so medication is dispensed by the NRC's outpatient pharmacy.

The NRC commenced BUP maintenance treatment in 2002. Patients who took their medication as directed and were abstinent from opioids received up to 14-days take-home supply (this limit set by the centre's dispensing policy). A decade later, and in the context of anecdotal reports of BUP diversion and non-adherent dosing behaviours among some patients, the NRC suspended treatment for people with no treatment history of BUP maintenance, although granting maintenance treatment to new patient episodes enrolled in this study.

Design

This was a single-centre, two-arm, open-label, parallel group, pragmatic RCT of BUP I-AAM (the experimental group) versus BUP TAU (the control group) during 16-weeks of outpatient maintenance treatment. During-treatment follow-ups were at 4 weeks, 8 weeks, 12 weeks and 16 weeks. The NRC's Institutional Review Board approved the protocol (NRC/2/2014). The study was retrospectively registered with the ISRCTN registry (number ISRCTN416 45 723) and the study protocol was published [16]. In this article, methods and findings are reported by Consolidated Standards of Reporting Trials (CONSORT)

[17]. Medication management and other participant materials can be accessed on the Open Science Framework (<https://osf.io/t9rp4/quickfiles>).

The study was conducted in accordance with the ethical principles of the World Medical Association's Declaration of Helsinki for research involving human subjects, good clinical practice and the Abu Dhabi Department of Health's guidelines for medical research. Study participants received study medication without charge and did not receive any compensation for completing research measures. After participants completed the study, they continued to receive BUP maintenance according to their preference and clinic policy.

Contingent on evidence of adherence (attendance and contrasting BUP measured and concentrations) and abstinence (from opioids by UDS), participants allocated to the I-AAM condition had access to increasing take-home supplies of BUP. Dispensing increased from 7 days, to 14 days, to 21 days to a maximum of 28 days supply. Participants allocated to TAU had no blood testing for BUP concentration measurement and had access to a 7 days then 14 days maximum.

An online randomisation service (www.randomization.com) was used to allocate participants to the two groups (1:1; no stratification). Given the open-label design, it was not feasible to mask participants and study investigators. A planned, exploratory health economic analysis will be reported elsewhere.

Inpatient withdrawal management and BUP stabilisation

At the NRC, medically supervised opioid withdrawal and BUP dose induction is done at an onsite inpatient programme before outpatient treatment. During inpatient stay, dose stabilisation was carried out with the objective of settling on a maintenance dose that was personalised for each participant informed by signs and symptoms of opioid withdrawal and their feedback.

Outpatient maintenance medication treatment

Participants were maintained on BUP-naloxone (4:1) sublingual film formulation (Suboxone; Indivior; BUP herein). This product was developed to limit risk of diversion and dissuade injection. All medication was bought commercially. The outpatient maintenance treatment endpoint was 16 weeks (112 days). This was pragmatic and judged reasonable to estimate clinical benefit. During treatment, all participants were offered general counselling and case management support.

For each scheduled clinic visit, the participant was asked to return opened medication packaging and take a UDS test. We used commercial point-of-care UDS product (<https://www.cliawaived.com>). The test cup was

configured to detect morphine (detection limit 300 ng/mL), heroin (6-acetylmorphine 20 ng/mL), codeine (100 ng/mL), propoxyphene and hydrocodone (300 ng/mL), tramadol (200 ng/mL), oxycodone (100 ng/mL), fentanyl (1000 ng/mL) and BUP (10 ng/mL). With the exception of BUP, all test results were required to be negative for the UDS to be recorded 'opioid negative'. All positive opioid test results were confirmed by gas chromatography tandem mass spectrometry.

Study participants

Participants were adults (18 years and over). All had current OUD and voluntarily seeking treatment (Table 1 shows the inclusion and exclusion criteria). Consecutive referrals were screened in person and all participants provided their informed written consent. All adverse events were reviewed by the senior investigators and the data monitoring committee.

Study procedures

After enrolment, participants were admitted to the NRC's onsite inpatient service for up to 4 weeks for medically supervised withdrawal, BUP induction and dose stabilisation. As soon as they were comfortable, participants completed a structured interview recording demographic characteristics and baseline measures. Each participant was administered BUP daily under supervision at the same time. In an effort to personalise each participant's dosing

Table 1 Participant inclusion and exclusion criteria.

Inclusion criteria	
1.	Aged 18 and above (no upper limit)
2.	Current diagnosis of OUD
3.	Voluntarily seeking BUP maintenance treatment
4.	Resident in the UAE
5.	Evidence of stable accommodation
Exclusion criteria	
1.	Benzodiazepine use in excess of 20 mg/day daily diazepam equivalent in the past 28 days
2.	Known naloxone or BUP hypersensitivity
3.	Pregnancy
4.	Hepatic impairment (elevation of liver function tests three times normal)
5.	Suicide attempt in past 12 months
6.	Involvement in criminal justice system, which is likely to result in arrest and incarceration
7.	Uncontrolled severe mental or physical illness judged to compromise safety
8.	Mini Mental State Examination score <17 (indicating cognitive dysfunction)

OUD = opioid use disorder; UAE = United Arab Emirates; BUP = buprenorphine.

interval, those who consumed illicit opioids by an injection (or with a body mass index of 30 and polysubstance use) commenced daily dosing. Those with prescription OUD were recommended to receive alternate-day dosing (i.e. every 48 hours). Our protocol also included the option for this patient group to attempt stabilisation with thrice-weekly dosing (to the dose maximum of 32 mg/day). Alongside patient preference, clinical signs and symptoms (using the Clinical Opiate Withdrawal Scale [COWS]) [18]; pupil reflexes (<https://www.neuroptics.com>) and craving using the Minnesota Cocaine Craving Scale adapted for opioids (MCCS-O; scored: 0–100%) [19] informed decisions about commencing, achieving a dosing interval or reverting to a more frequent dosing interval.

When the participant was comfortably stable on the same BUP dose for 2 weeks, we assumed BUP's steady-state concentration had been achieved. An on-site laboratory, computed the BUP elimination rate (ELR) from three blood samples; the first drawn 30 minutes before administration of the participant's BUP dose (to estimate the BUP trough concentration), the second drawn after 40 minutes (peak concentration), and the third after 48 hours before the next BUP dose (for a second trough concentration to confirm steady-state concentration if replicated). The inpatient episode was then judged completed once the ELR had been calculated and the participant had a COWS score of 0–4 (no active opioid withdrawal). Before transfer to the outpatient programme, a member of the study team accessed the randomisation service and the participant was allocated to the I-AAM or TAU condition.

I-AAM procedure and take-home dosing schedule

- 1 For the first 5 days of BUP maintenance treatment, the participant was asked to attend the clinic daily for supervised dosing and to take a UDS test at each visit (or a minimum of three UDS). If they adhered (i.e. all doses taken, at least three negative UDS and all UDS positive for BUP), participants were dispensed with two doses to take that weekend and a 7-day supply. They were given instructions on how to take their medication (i.e. daily, alternate-day and thrice weekly regimens) and asked to return to the clinic 1 week later.
- 2 If participants returned as directed, reported following their prescription, and gave an opioid negative UDS that was positive for BUP, they were dispensed with a 14-day supply. Participants were asked to not take their BUP dose on the day of their next appointment because this was given by the dispensing pharmacy. On arrival, they were given their dose of BUP, they took a UDS and had a blood sample drawn. A pharmacokinetic model was applied to predict BUP concentration [15]. If the UDS confirmed abstinence for opioids and was positive for BUP, the participant was given a further 14-day supply (with

same directions) and asked to return to the clinic 2 weeks later.

- 3 On return to the clinic, the procedure was repeated and the predicted BUP concentration (estimated from the previous visit) was contrasted with the BUP concentration on the day. If the concentration difference was <20% and the UDS was negative, participants were given a 21-day supply and asked to return 3 weeks later. As a safety measure, participants given a 21-day supply were contacted randomly and asked to attend for UDS and blood testing.
- 4 On return to the clinic, and with evidence of continued adherence and clinical benefit (i.e. difference in BUP concentration <20%; UDS negative), participants were given a 28-day supply and asked to return 1 month later for a further monthly supply. Adherence and abstinence were then randomly monitored every other month to the endpoint.

Those not adhering to the above procedure at the outset or for the requirements of the 7-day supply were held at a 5-day supervised dosing requirement pending evidence of adherence and abstinence. Those receiving 14 days who were non-adherent or non-abstinent were 'reset' to receive a 7-day supply. Those receiving a 21-day and 28-day supply that were non-adherent or non-abstinent were reset to a 14-day or 21-day supply, respectively. At any point, a participant who was non-adherent and non-abstinent was held in a 5-day supervised dosing and UDS testing regimen. During this process, patients discussed their scores on the COWS (weeks 1–4), and MCCS-O (weeks 1–4 and 5–8), and pupil reflexes (weeks 5–8 and 13–16) and asked if they wanted their dose adjusted.

TAU procedure and take-home dosing schedule

- 1 In the first 5 days of maintenance, participants were asked to attend the clinic at least once for supervised BUP dosing and to take a UDS at each visit. Between visits participants were dispensed with take-home doses. If they adhered (i.e. all doses taken, all UDS-negative and all UDS-positive for BUP), they were dispensed with a 7-day supply including 1 dose to take on each day of weekend. Participants were given instructions on how to take their medication (i.e. daily, alternate-day and thrice weekly regimens) and asked to return to the clinic 1 week later.
- 2 If participants returned, reported following their prescription, and provided an opioid negative UDS that was positive for BUP, they were dispensed with a 14-day take-home supply.

Participants who did not adhere to the above procedure at the outset or for the requirements of the 7-day supply, were held in 5-day supervised dosing (with 2 take-home doses for the weekend) until there was evidence of abstinence.

At any point, a participant who was non-adherent and non-abstinent was reset to 5-day supervised dosing and UDS testing. During treatment, there was discussion of withdrawal symptoms, craving and dose adequacy, as described above for the experimental group.

Table S1 summarizes the Interventions under each arm.

Outcome measures

The primary outcome was the number (percentage) of scheduled and biochemically verified (UDS and laboratory confirmed) tests negative for opioids during 16 weeks of outpatient BUP maintenance treatment. Conservatively, non-attendance for scheduled UDS was recorded as positive for opioids [20]. The secondary outcome measure was retention in outpatient treatment, defined as completion of 16 weeks of treatment (with no more than three missed consecutive clinic appointments).

The five exploratory outcome measures (end-of-study group comparison), were; The Addiction Severity Index-Lite—drug use sub-scale (ASI-Lite) [21], the nine-item Patient Health Questionnaire (PHQ-9) [22], the Generalized Anxiety Disorder scale (GAD-7) [23], the Barratt Impulsivity Scale (BIS-11) [24] and the Work and Social Adjustability Scale (WSAS; score range = 0–40; higher scores reflecting more social impairment attributed to OUD) [25]. No changes were made to the outcomes after the trial commenced.

Statistical analysis

To guide the target sample size, we used a measure of sustained (3-week) abstinence between treatment and comparison groups in a meta-analysis of incentivised OUD treatment (44% vs 23%; OR 1.96) [26]. With type I error at 5%, and a 15% increase in the sample to offset withdrawal attrition, we estimated that 182 participants (91 in each group) would give 80% statistical power for detection of a treatment effect.

The analysis was done by intention-to-treat in Stata 15 (Statacorp 2017). The primary outcome was analysed as the absolute difference in the percentage of negative UDS tests for opioids, reporting the mean and SD for each group, the mean difference on this measure with a 95% CI; and the Cohen's *d* effect size with a 95% CI.

There were two sensitivity checks: (1) an adjusted treatment effect estimated by a bootstrapped Poisson regression (incident rate ratio [IRR]) with the following covariables: age, baseline ASI-Lite drug use, and (2) time (days) to discontinuation or completion of treatment. We also calculated the primary outcome as a complete case measure using only observed (non-imputed) UDS data. The secondary outcome measure was analysed by Odds

Ratio (OR) and Kaplan-Meier test. Exploratory outcomes were analysed by group mean difference at the study endpoint. The incidence of all adverse events was reported for both study groups.

RESULTS

Characteristics of the participants

The first participant was enrolled on 15 September 2014 and the last follow-up contact was on 16 September 2016. The trial database was locked on 19 January 2017. A total of 182 patients were screened for eligibility and 171 were enrolled into the study. Thirty participants (17.5%) withdrew before randomisation and 141 (82.4%) were randomised (70 [49.6%] to the I-AAM group and 71 [50.4%] to the TAU group. Figure 1 shows the study profile and reasons for exclusion. We were unable to extend the participant recruitment phase because of restrictions on the time permitted for the study.

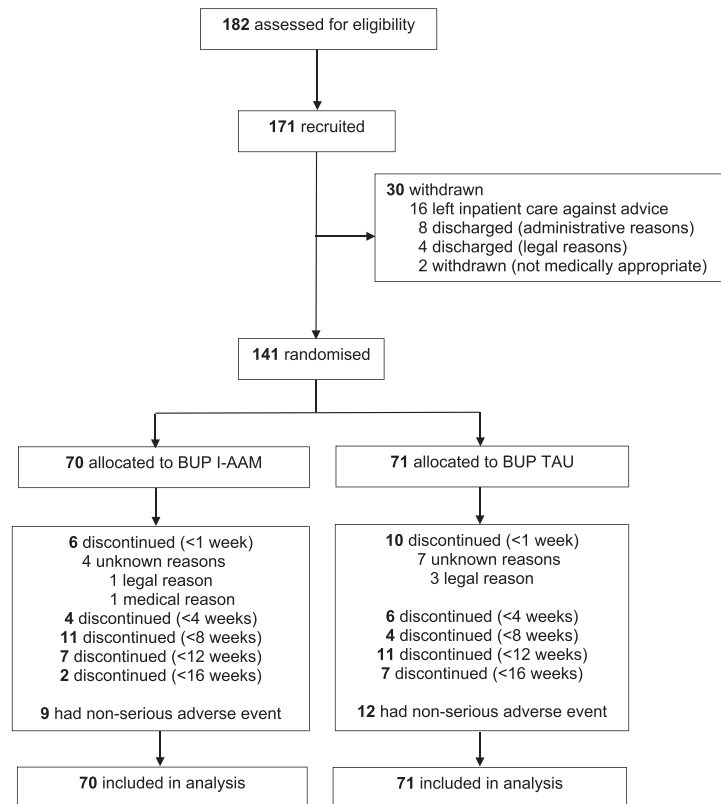
On admission to the inpatient service, the majority of participants received daily dosing at the outset, with just four accepting our recommendation for alternate-day dosing. A single participant was inducted onto thrice-weekly dosing. The two groups were well-balanced on demographic and clinical characteristics (upper section of Table 2). After randomisation, all participants were transferred to commence BUP maintenance at the outpatient clinic. In the first week, 16 participants left treatment (six in the I-AAM group and ten in the TAU group).

Between randomisation and the endpoint, a total of 30 (42.9%) participants in the I-AAM group and 38 (53.5%) participants in the TAU group discontinued treatment. All participants agreed to take UDS, provide blood samples, return opened BUP packaging and all consented for their data to be used for the analysis. Follow-up rates at 4 weeks, 8 weeks, 12 weeks and 16 weeks were 91.4%, 85.7%, 71.0%, and 60.0%, respectively, in the I-AAM group and 84.5%, 83.1%, 69.0% and 56.3%, respectively, in the TAU group.

BUP maintenance treatment

Table 2 (lower section) shows the mean BUP dose for the participants retained at each follow-up week and their access to take-home supplies. On average, the BUP dose was 15 mg/day in the I-AAM group and 16 mg/day in the TAU group at each follow-up. Almost all study participants remained on their stabilisation dose during maintenance (138/141; 97.9%).

Three participants increased their dose, as follows: after 3 weeks, a participant in the I-AAM group reported distressing craving and informed by measures of pupil reflexes (particularly measures of maximum pupil

**Note:**

BUP I-AAM, BUP maintenance with incentivised adherence and abstinence monitoring;

BUP TAU, BUP maintenance treatment-as-usual.

Figure 1 Study profile

diameter) their dose was increased from 14–16 mg/day; a TAU participant—with a long history of tramadol use—reported opioid withdrawal symptoms in the second week of treatment and dose was increased from 12–14 mg/day; the other participant—a member of the TAU condition—had presented for treatment with severe OUD involving intravenous use of morphine and tramadol—reported craving and withdrawal symptoms during the second week of treatment and dose was increased from 12–16 mg/day.

During treatment, 18 participants in the I-AAM group (29.0%) were determined to be non-adherent to BUP and non-abstinent. All were reset to 5-day supervised dosing. Among 62 participants in the I-AAM group who received at least one 14-day supply of medication, a total of 109 blood samples were drawn with 37 samples estimated to have BUP concentrations outside the 20% range for adherence (33.9% non-adherent). In the TAU group, 20 participants (28.2%) were able to receive no more than a total of 7-day take-home doses, and 51 (71.8%) received no more than a 14-day take-home supply.

In the I-AAM group, among 62 participants who received at least 2 weeks take-home supply, 109 blood

samples were drawn (mean 1.8 [SD 0.77] per participant). The non-adherence rate was 34% (i.e. 37 samples had BUP concentrations outside the 20% range). Eighteen participants in the I-AAM group (29.0%) were evaluated as BUP non-adherent and non-abstinent and were reset to 5-day directly supervised dosing.

In the TAU group, 20 participants (28.2%) received no more than 7-day take-home doses, and 51 (71.8%) received no more than 14-day take-home doses. There was no statistically significant difference in the mean number of scheduled UDS: 16.2 (SD = 9.0) in the I-AAM group versus 14.1 (SD = 8.9) in the TAU group (P value = 0.10).

During treatment, participants in both groups returned opened BUP packaging to the pharmacy very sporadically. Patients failing to return opened packaging were reminded to do so, but full compliance was rare. In the group of participants completing the 16 weeks of maintenance treatment, 1 participant in the I-AAM group was fully adherent according to TDM data and remained abstinent; 17 (42.5%) were adherent, but not abstinent. Among the non-adherent, 18 (45.0%) were also non-abstinent, and 4 (10.0%) were abstinent.

Table 2 Participant characteristics (*n* = 141).

Characteristic	I-AAM (<i>n</i> = 70)	TAU (<i>n</i> = 71)
Demographic and clinical characteristics at baseline	30.4 (8.70)	27.7 (7.30)
Age, years		
Sex, male	69 (98.6%)	70 (98.6%)
Married	36 (51.4%)	46 (63.3%)
Employed, full or part-time	28 (40.0%)	21 (29.6%)
Resident in metropolitan Abu Dhabi	36 (52.8%)	30 (42.2%)
Heroin/morphine OUD	55 (78.6%)	55 (77.5%)
Prescription/mixed OUD	15 (21.4%)	16 (22.5%)
Duration of OUD, median years	9.9 (5.7–17.3)	8.9 (5.4–14.7)
MCCS-O, maximum intensity in week before admission	88.6% (23.7%)	83.9% (31.5%)
ASI (drug use scale score)	0.2 (0.1–0.4)	0.2 (0.1–0.4)
PHQ-9	12.9 (6.6)	13.6 (6.9)
GAD-7	10.0 (4.0–15.0)	10.0 (5.0–15.0)
WSAS	22.1 (9.8)	24.2 (9.2)
Inpatient withdrawal and stabilisation (ng/mL)		
BUP trough concentration after 2 weeks—mean	1.73 (1.47)	1.81 (2.47)
ELR before transfer to outpatient treatment—median	0.05 (0.03–0.09)	0.05 (0.02–0.10)
Maintenance treatment week—BUP dose (mg/day) ^a		
Week 1	14.51 (4.63)	15.71 (3.60)
Week 4	14.68 (4.58)	15.60 (3.51)
Week 8	15.08 (4.50)	15.72 (3.52)
Week 12	15.02 (4.57)	15.72 (3.58)
Week 16	14.75 (4.45)	15.36 (3.22)
Take-home supplies (total dispensing events)		
No more than 7 days	1 (1)	20 (20)
No more than 14 days	55 (402)	51 (387)
No more than 21 days	7 (81) ^b	— ^d
No more than 28 days	1 (8) ^c	— ^d

I-AAM = BUP maintenance treatment with incentivised adherence and abstinence monitoring; TAU = BUP maintenance treatment-as-usual; OUD = opioid use disorder; MCCS-O, Minnesota Cocaine Craving Scale, adapted for opioids, maximum intensity in week before admission (0–100%); PHQ-9 = Patient Health Questionnaire; GAD-7 = Generalized Anxiety Disorder; WSAS = Work and Social Adjustability Scale; ASI-Lite = Addiction Severity Index; ELR = elimination rate (ng × mL/hr – 1). Numbers in parentheses = SD, interquartile range, or as shown. ^aAll participants enrolled at follow-up. ^bFive participants were dispensed this supply once and two each received this supply twice. ^cThis participant received two successive 21-day supply before the single 28-day supply. ^dProhibited under local treatment system policy.

Table 3 Summary of scheduled and imputed urine drug screen tests and primary outcome measure (*n* = 141).

Measure	I-AAM (<i>n</i> = 70)	TAU (<i>n</i> = 71)
UDS testing		
A. Mean number of scheduled UDS (SD)	16.2 (9.0)	14.1 (8.9)
B. Mean number of UDS positive for opioids (SD)	1.0 (1.8)	1.9 (3.2)
C. Mean number of UDS, missed, imputed positive (SD)	2.3 (2.4)	2.2 (2.4)
Efficacy		
Primary outcome measure ^a	76.7% (25.0%)	63.5% (34.7%)
Mean difference (95% CI)	13.3% (3.2%–23.3%)	
<i>d</i> (95% CI)	0.44 (0.10–0.87)	

I-AAM = incentivised adherence and abstinence monitoring; TAU = treatment-as-usual; UDS, urine drug screen. ^aComputed as $A - B + C / (A \times 100)$ (SD).

Primary outcome

Although the obtained sample was smaller that was targeted (post-study sample size calculation using the expected effect and obtained sample size indicated that statistical power was 75%), there was a statistically significant

effect for the I-AAM condition on the primary outcome (Table 3).

For the two sensitivity analyses, I-AAM effectiveness (including age, baseline ASI-Lite drug use and time to discontinuation or completion of treatment) was observed (adjusted IRR = 1.15; 95% CI = 1.02–1.32), and using

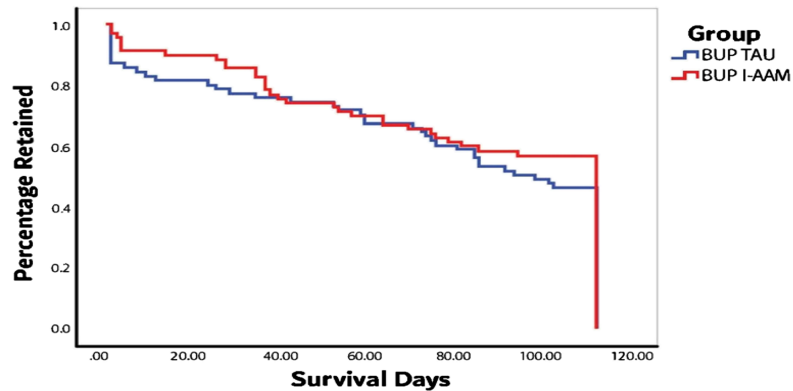


Figure 2 Survival analysis for retention over 16 weeks (log-rank P value = 0.26). BUP = Buprenorphine; I-AAM = incentivised adherence and abstinence monitoring; TAU = treatment-as-usual. [Colour figure can be viewed at wileyonlinelibrary.com]

observed UDS data only, the percentage of UDS negative for opioids was 90.5% (SD = 19.8%) in the I-AAM group and 71.8% (SD = 36.7) in the TAU group (mean difference 18.7%; 95% CI = 8.9–28.5; d = 0.63; 95% CI = 0.29–0.97). There was no statistically significant difference in the mean number of scheduled UDS tests (16.2 [SD = 9.0] in the I-AAM group versus 14.1 [SD = 8.9] in the TAU group; P value = 0.10).

Secondary outcome

Forty participants (57.1%) in the I-AAM group were retained continuously in maintenance treatment to the endpoint versus 33 participants (46.4%) in the TAU group (OR = 1.54; 95% CI = 0.79–2.98). The I-AAM group was retained for a mean of 81.7 days (SD = 42.3), and TAU participants were retained for a mean of 76.6 days (SD = 39.9; mean difference 5.1 days; 95% CI = –8.6–18.8). Figure 2 displays a survival chart for time-to-discontinuation by group (log rank test P value = 0.26).

Exploratory outcomes

End-of-study group differences on the exploratory outcome are shown in the article's supplementary material (Supporting information Table S2). There was an I-AAM effect on the WSAS indicating less social impairment associated with OUD at the endpoint (a 6-point mean difference; Cohen's d = 0.53; 95% CI = 0.19–0.87).

Adverse events

There were no serious adverse events requiring hospitalisation and there was a similar profile of adverse events in both groups (Supporting information Table S3). The adverse event with the highest reported incidence was sweating. This was rated severe by three participants in the I-AAM group and four participants in TAU group and judged to have a possible association with BUP.

DISCUSSION

In the I-AAM group, slightly more participants achieved dispensing of 14 days supply compared with TAU (55 vs 51). Within the I-AAM group, a minority achieved dispensing supplies above this; seven receiving dispensing of 21 days supply and one attaining maintenance dispensing of 28 days supply. In terms of the primary outcome, there was significant variability between the two groups, but we believe that the I-AAM condition was associated with a clinically important effect. There was a single exploratory outcome on the WSAS suggested that I-AAM participants had the additional benefit of fewer social problems attributed to OUD.

Although the randomisation procedure did not include any stratification, the sensitivity including patient demographic, baseline drug use and time in treatment showed an adjusted treatment effect that was statistically significant. Furthermore, comparison of the conservatively imputed versus observed primary outcome measure (13.3% vs 18.7%, respectively), suggests that true effect for I-AAM is bracketed within these two estimates. Nevertheless, there remains considerable scope to increase clinical effectiveness. Among participants in the I-AAM group who completed 16 weeks of treatment, 22 (55%) were completely adherent. This is comparable to an Australian surveillance study, where a third of patients enrolled in BUP-naloxone maintenance did not adhere and 34 (85%) of those who stayed in treatment did not abstain from opioids [27].

In the present study, I-AAM was not significantly associated with a higher rate of completion for the 16-week active treatment period or duration of enrolment (57% vs 46%). These rates are comparable with other studies of BUP maintenance. For example, in a United States dose comparison trial over 16 weeks of BUP maintenance, completion rates were 52% for patients receiving 8 mg/day, and 61% for those allocated to 16 mg/day [28]. Another United States trial of 17 weeks of maintenance treatment reported a 58% completion for patients receiving higher-doses of 16–32 mg/day [29].

Study limitations

Our findings must be considered in the light of several limitations. First, the sample was 23% smaller than planned so the analyses had reduced statistical power by 5%. The study took longer to complete than we envisaged because of a lower rate of recruitment. During the recruitment phase there was a reduction in opioid use in the UAE and an increase in amphetamine-type stimulant use [30]. This may have reduced OUD treatment demand.

Second, the sample was almost exclusively male, with just two female participants. We had no control over the referral process, and it remains an important priority to study sex as a factor in OUD treatment delivery and outcomes [31].

Third, the BUP induction and stabilisation was done in an inpatient facility that is typically available in the healthcare systems in UAE and states in the Eastern Mediterranean, but dose induction is most commonly done in an outpatient setting elsewhere. A 24-hour medically supervised setting makes it more convenient to collect blood samples, but our discontinuation rate in this phase of the study (30/171; 17.5%) was comparable to the discontinuation rate reported for an 8-day outpatient study in Australia (14% for patients assigned to BUP for withdrawal management) [32]. We contend that where outpatient services are based in locations with reasonably good local transport options, collection of three blood samples for BUP EL.R should be acceptable to most patients.

Clinical and research importance of the findings

The I-AAM protocol included a quantitative TDM procedure (BUP plasma concentration criterion) to monitor adherence. TDM procedures to inform changes in maintenance dosing were rarely used with the majority of the group remaining on their stabilisation dose. We also found that almost all participants accepted daily dosing.

It is important to consider how the primary and secondary outcomes were defined in this study. At present, there is no common outcome set for OUD pharmacotherapy trials. It is not uncommon to define the primary outcome as a count of consecutive negative UDS. This can give valuable insight into periods of stability. This was a pragmatic and study among patients who presented for treatment as usual, so we believe our findings are generalizable. Our I-AAM protocol has promise as a clinically effect method helping patients access increasing supplies of take-home medication. Relatively few participants (8/40; 20%) were able to provide evidence of sustained adherence and abstinence to receive supplies above the comparator. Overall, participants in the I-AAM condition received 20% more take-home supplies for more or equal to 7 days (492 total dispensing events vs 407 among the TAU group).

There remains a priority need to discover better ways of encouraging patients to stay in optimised treatment. Although efforts to increase retention are crucial, it should be recognised that retention is a proxy measure of clinical benefit because some patients stay in treatment but continue to use opioids. This has been observed in other treatment systems. For example, in an English national study of 12 745 patients enrolled for 12–26 weeks in OUD maintenance pharmacotherapy, 64% reported using opioids on 10 or more days in the month before follow-up [33]. One option is to include an adjunctive psychosocial intervention targeting patients who struggle to adhere or abstain [33]. Extended-release (depot injection) BUP products are now becoming increasingly available and this may reduce concerns about diversion and provide potential opportunities to apply TDM for dose optimisation during stabilisation and dose adjustment during maintenance.

Although we had direct access to a clinical toxicology laboratory, it typically took 48 hours to process blood samples and receive test results for BUP plasma levels. This was longer than anticipated and it did hamper our efforts to make timely clinical decisions with study participants. In other areas of psychiatry, there is active research and development on non-invasive technologies such as small, portable sensing or test strips for capture of capillary blood to detect antipsychotic medication concentration [34]. Rapid point-of-care diagnostics to facilitate medication adherence monitoring during BUP treatment would be welcome. Monitoring BUP plasma concentration may be added to measures of craving, drug use and withdrawal symptoms to optimise treatment as part of measurement-based care for OUD [35].

Declarations of interests

In the past 3 years, J.M. declares research grants to King's College London (KCL) from: (i) the National Institute for Health Research (NIHR) for a multi-centre RCT of acamprosate for alcohol use disorder; (ii) the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Mental Health Foundation Trust (SLaM) for a pilot RCT of novel cognitive therapy for cocaine use disorder; and (iii) an unrestricted grant from Indivior to KCL and SLaM from Indivior for a multi-centre, RCT of extended-release injectable buprenorphine for OUD. He has part-time employment as Senior Academic Advisor for the Alcohol, Drugs, Tobacco and Justice Division, Health Improvement, Public Health England. He is a clinical academic consultant for the United States National Institute on Drug Abuse, Centre for Clinical Trials Network. He holds no stocks in any company. All other authors state they have no declarations of interests.

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Author contributions

Hesham Elarabi: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; supervision; validation; visualization. **Mansour Shawky:** Data curation; investigation. **Nael Mustafa:** Data curation; investigation; project administration; validation. **Doaa Radwan:** Data curation; investigation. **Abuelgasim Rasheed:** Conceptualization; data curation; methodology. **Ahmed Yousif Ali:** Conceptualization; methodology; project administration. **Mona Osman:** Data curation; project administration; software. **Ahmad Kashmar:** Data curation. **Helal Alkathiri:** Data curation; project administration. **Tarek Gawad:** Project administration. **Ayman Kodera:** Investigation. **Mohammed Aljeneibi:** Data curation; investigation; project administration. **Abdu Adem:** Supervision. **Amanda Lee:** Formal analysis; validation. **John Marsden:** Conceptualization; formal analysis; investigation; methodology; resources; software; supervision; validation.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1: Summary of study procedures by arm

Table S2: Exploratory outcomes at study endpoint by group (n = 141)

Table S3: Adverse events during BUP maintenance treatment over 16-weeks by severity likelihood of association and group (n = 141).

Therapeutic Drug Monitoring in Buprenorphine/Naloxone Treatment for Opioid Use Disorder: Clinical Feasibility and Optimizing Assay Precision

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opioid dependence, therapeutic drug monitoring, validation, feasibility

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ABSTRACT

Introduction Compliance with sublingual buprenorphine/naloxone (SL-BUP/NX) is associated with higher abstinence from illicit opioid use. Therapeutic drug monitoring (TDM) has been recommended for adherence monitoring of buprenorphine (BUP) maintenance treatment for opioid use disorder (OUD), but to date there have been no reported clinical applications. In this TDM feasibility study, we investigated BUP assay precision in 15 adults with OUD who had been stabilized on buprenorphine/naloxone.

Methods Using solid phase extraction, BUP recovery was contrasted at 100 mMol and 1 Molar of acetic acid wash solution. Precision was determined by applying the condition generating highest recovery using 0.2 ng/mL and 10 ng/mL standards. Four blood samples were drawn to examine the BUP peak and trough plasma concentrations, and BUP elimination rate was estimated. BUP recovery was examined again in a random sample and contrasted with the concentration predicted applying first-order kinetics.

Results Higher BUP recovery was achieved with 1 Molar wash (94.3%; $p=0.05$). Precision ranged from 15–20%. The estimated limit of detection (LoD) and limit of quantitation (LoQ) were 0.02 and 0.069 ng/mL, respectively. BUP peak and trough concentrations were successfully examined, and BUP trough concentrations were replicated confirming steady state. BUP concentrations were predicted at a variance of –7.20% to 1.54%.

Conclusions TDM for BUP maintenance treatment of OUD is feasible, and simple adjustment of the assay conditions enhances BUP recovery.



Supporting information for this article is available online at <https://doi.org/10.1055/a-1083-6842>

Introduction

Opioid use disorder (OUD; DSM-5 [1]) is a prevalent and chronic psychiatric disorder that is associated with a high burden of global disease [2] and substantial social costs [3]. Medication-assisted treatment (MAT) with full and partial mu opioid receptor agonists (including buprenorphine [BUP] and buprenorphine/naloxone

[BUP/NX]) is the first line, evidence-based pharmacotherapeutic intervention for people with OUD [4]. BUP/NX is associated with abstinence from opioids [5] and a 10-fold reduced risk of relapse [6]. However, patient non-compliance, medication diversion [7], and inappropriate treatment discontinuation [8] all limit the effectiveness of MAT.

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Traditionally, medication compliance has been assessed in different ways, including patient self-report, pill count, and urine drug screening to detect drug compounds and metabolites. These can provide useful information, but there is an alternative method that provides greater precision. Therapeutic drug monitoring (TDM) is a procedure to determine the concentration of a target medication in blood to inform dose adjustment to increase the likelihood of the desired clinical response [9]. TDM has been recommended for monitoring adherence to BUP treatment [9], but to date it has not been implemented in routine clinical practice [10] due to a lack of data on clinical feasibility, cost-effectiveness [11], and, perhaps, the complexity of the procedure and the laboratory expertise required for accurate detection and quantitation of a target medication [5].

The opportunity to implement TDM in treatment clinics has been facilitated by recent advances in the sensitivity of analytical methods to detect and quantify lower blood levels of BUP [10]. Enhancing the accuracy and precision of BUP assay using solid phase extraction (SPE) would strengthen the reliability of TDM. Several different sample preparation methods and instruments have been evaluated for their sensitivity and selectivity to detect BUP, but SPE is the method of choice for extracting BUP from biological matrices [12]. SPE sensitivity is influenced by several factors, including the type of disposable extraction column (DEC); the type and concentration of the solvent; pH; and sample volume. Liquid chromatography tandem mass spectrometry (LC-MS/MS) remains the instrument of choice for BUP detection and quantitation [12, 13].

The aim of this article was to contribute to the integration of TDM in the treatment of OUD by conducting a feasibility evaluation of TDM to monitor adherence with BUP as part of the Suboxone Treatment and Recovery Trial (STAR-T), a randomized controlled open-label trial of the sublingual film formulation of BUP/NX (BUP/NX-F) at a specialist addiction treatment clinic in the United Arab Emirates (ISRCTN41645723) [14].

Method

Materials

Clinical data for the study was obtained from the first 15 adults with OUD recruited as participants in the STAR-T study. External and internal standards of BUP and its major active metabolite nor-buprenorphine (N-BUP), along with blank samples, were purchased from Cerilliant Analytical Standards (SIGMA-ALDRICH).

Two DECs examined for SPE, namely CSDAU® 206 manufactured by United Chem, and Isolute HCX® 130 mg/10 mL (part number 902-0013-H) manufactured by Biotage. The CSDAU® 206 is composed of a long-chain non-polar reverse phase sorbent, while the Isolute HCX® is composed of co-polymeric non-polar (C8) and a strong cation exchange retention component (SO₃⁻). The acetic acid wash solution was examined at 1 Molar and 100 mM concentrations.

Accuracy and precision are determined according to the mean coefficient of variance (CV) from the target value for the within-run and between-run results. Limit of detection (LoD) and Limit of quantitation (LoQ) are estimated using the signal-to-noise ratio (S/N). Lower LoD and LoQ reflect higher selectivity and sensitivity,

whereas a higher recovery rate (the ratio of obtained BUP concentration to the BUP standard concentration) indicates higher sensitivity [11, 12]. Detection and quantitation of BUP and N-BUP was performed LC-MS/MS 400 (Schimadzu Scientific Instruments) at 20 µL injection volume, 0.2 mL/min flow rate, and 45 °C. Electron spray ionization (ESI) was the interface, and the analytical column used was Raptor C18 (Restek 9304A12). ► **Table 1** summarizes the detector conditions set for optimal ion production.

Sample preparation and extraction

The method published by the manufacturer of CSDAU 206 DEC was adopted [15], referred herein as the “original method.” Supplementary File 1 describes the original method in detail.

Method optimization

The accuracy of the original method was optimized by determining the highest BUP recovery rate for combinations of 2 types of DEC and acetic acid wash solution at 2 concentrations (► **Table 2**). All optimization procedures and BUP and N-BUP assay were performed at the National Rehabilitation Center Laboratory in Abu Dhabi.

Method validation

The U.S. Food and Drug Administration criteria for selectivity, limits, and carry-over were applied [16]. For selectivity, 6 blank samples were injected after 10 samples of BUP and N-BUP standards. Under the assay settings, any interferences from other drugs or the matrix were analyzed. For determining accuracy and precision, duplicate samples of standard BUP and N-BUP concentrations at 0.2 ng/mL and 10 ng/mL were measured over 5 days (i. e., at total of 10 samples). A CV of 15–20 % from standard concentration was deemed acceptable [16]. The LoQ parameter was accepted if the S/N was > 5 [16]. Signals for BUP and N-BUP standards and deuterated standards were contrasted at an internal standard of 5 ng/mL.

► **Table 1** Detector conditions for optimal ion production for buprenorphine and norbuprenorphine (m/z).

Target analyte	Ion production (m/z)
Buprenorphine	468.4/55.1 B-902
Nor-buprenorphine	414.3/83.1 N-912
Buprenorphine D-4	472.4/59.1 B-901
Nor-buprenorphine D-3	417.4/55.1 N-920

m/z: mass-to-charge-ratio; D-4: Deuterated buprenorphine; D: Deuterated norbuprenorphine.

► **Table 2** Disposable extraction columns and concentration of wash solution.

Method	Disposable extraction column	Acetic acid concentration
Original method	CSDAU 206	100 mmol
Test trial 1	CSDAU 206	1 Molar
Test trial 2	Isolute HCX	1 Molar

CSADU: <https://www.unitedchem.com>; Iso-solute HCX: (<https://www.biotage.com>).

Daily calibration was performed with 0 and 6 standard BUP and N-BUP concentrations (0.2, 0.5, 1, 5, 10, and 20 ng/mL) using plasma of a healthy volunteer who was not consuming any BUP-containing medications [17].

Clinical feasibility

All participants who were stabilized on BUP/NX-F—defined as receiving the same dose for 2 weeks without change—were assumed to have reached a BUP steady state concentration (SSC) [18]. At SSC, 4 blood samples for BUP peak and trough concentrations were collected over a 4-day period. Two samples were drawn 40 min after administering the BUP/NX-F dose on day 1 and 3 (to represent the BUP peak concentration), and the remaining 2 samples were drawn 30 min prior to the BUP/NX-F dose (i. e., 23.5 h after administering the last BUP/NX-F dose) on day 2 and 4 (to represent the trough concentration). We determined that the replication of 2 BUP trough concentrations would indicate that SSC was verified. Alternatively, additional samples were collected until SSC was confirmed, and BUP elimination rate (EL.R) was estimated using the first order kinetics as follows:

$$C_{pss} = C_o \cdot e^{-kt}$$

Where:

- C_o denotes the peak plasma concentration of BUP
- C_{pss} is the trough concentration measured at steady state or at any subsequent point in time
- k represents the EL.R constant
- t is time in hours between collecting peak and trough concentrations

Solving for k :

$$\ln(C_{pss}) = \ln(C_o) - kt$$

Therefore:

$$-k = \ln(C_{pss}/C_o) / t$$

A further blood sample for each participant was randomly drawn, and the exact time of withdrawal was recorded. The BUP concentration for the random sample was measured at the laboratory (herein referred to as the “examined concentration”), and BUP level was predicted by applying first-order kinetics (herein referred to as the “predicted concentration”). The examined and predicted concentrations were contrasted, and accuracy was confirmed if the variance was within 20%. The reliability of the first-order pharmacokinetics in estimating BUP concentrations at any time point was confirmed if prediction was accurate in all participants.

► **Table 4** Buprenorphine and norbuprenorphine concentrations measured against standard concentration of 0.2 and 10 ng/mL.

Concentration	Assay results									
	Day 1		Day 2		Day 3		Day 4		Day 5	
BUP 0.2 ng/mL	0.235	0.224	0.185	0.20	0.196	0.22	0.215	0.212	0.220	0.234
BUP 10 ng/mL	10.02	10.539	9.898	9.980	10.01	11.45	11.787	11.776	9.217	9.306
N-BUP 0.2 ng/mL	0.226	0.229	0.232	0.232	0.228	0.234	0.230	0.234	0.238	0.236
N-BUP 10 ng/mL	9.59	9.359	9.461	9.461	9.174	9.154	9.727	10.325	9.217	9.306

BUP: buprenorphine; **N-BUP:** nor-buprenorphine.

Results

Method optimization

The mean recovery rates generated for the 5 BUP standard concentrations using the combinations of DEC and acetic acid concentrations ranged from 87.5% to 94.3%.

► **Table 3** summarizes the recovery rate for each of the tested conditions. The combination of the CSDAU 206 DEC and 1 M acetic acid wash solution generated significantly higher BUP recovery rates compared to the CSDAU 206 DEC and 100 mM acetic acid used in the “original method” (94.3% vs. 87.5%, $t = 2.41$; $df = 14$, $p = 0.05$).

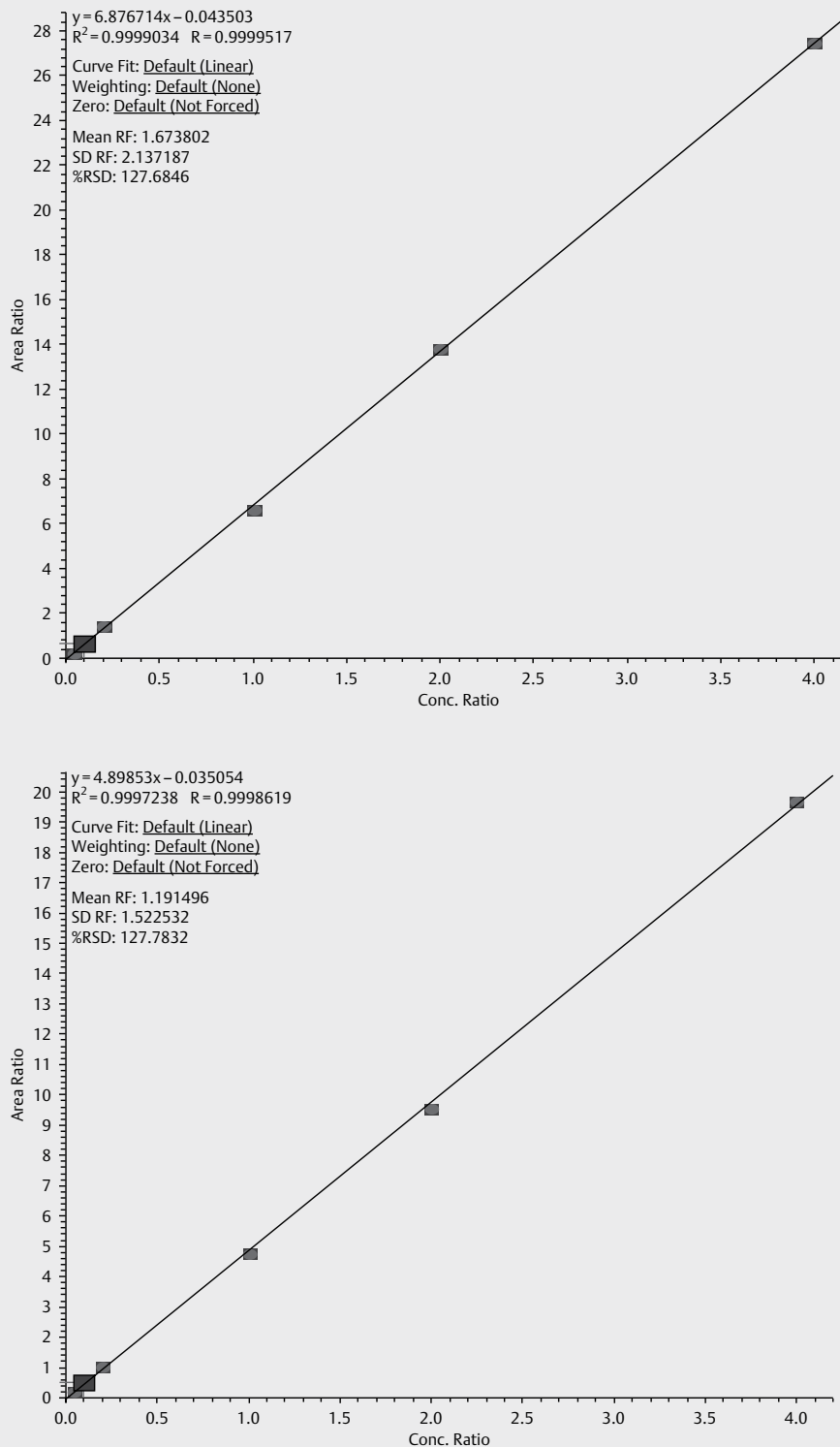
Accuracy and precision

The actual measures for BUP and N-BUP standards at 0.2 ng/mL and 10 ng/mL are presented in ► **Table 4** for duplicate samples assayed over 5 days. The estimated CV for “within-run” and “between-run” measurements was 9.6 and 12%, respectively. Linearity was established for these samples ($R^2 = 0.999$ for BUP and $R^2 = 0.999$ for N-BUP; ► **Fig. 1**). Chromatograms for BUP and N-BUP standards and deuterated standards showed almost superimposable signals using an internal standard of 5 ng/mL (► **Fig. 2**). No carry-over of BUP or N-BUP was detected with the blank samples (► **Fig. 3**), and no interferences from other drugs or the matrix were observed. The S/N for BUP is 9.5 and the estimated LoQ for BUP and N-BUP is 0.069 and 0.039 ng/mL, respectively, while the corresponding LoD is 0.02 and 0.012 ng/mL.

► **Table 3** Mean recovery rates and actual concentrations for buprenorphine.

Buprenorphine concentration	CSDAU and 1 Molar acetic acid	CSDAU and 100 mmol acetic acid	HCX and 1 Molar acetic acid
Blank	0	0	0
0.2	71.80 (0.14)	61.70 (0.12)	68.40 (0.13)
0.5	81.70 (0.40)	71.70 (0.35)	87.90 (0.44)
1	118.0 (1.18)	97.90 (0.97)	102.50 (1.02)
5	99.20 (4.90)	106.20 (5.30)	102.60 (5.12)
20	100.0 (20.0)	99.60 (19.90)	99.80 (19.98)
Mean recovery percentage (SD)	94.26 (6.10)	87.46 (6.47)	92.26 (6.23)

CSDAU: United Chem Disposable Extraction Column; HCX: Biotage Disposable Extraction Column; SD: Standard deviation.



► **Fig. 1** Calibration curve for buprenorphine and norbuprenorphine.

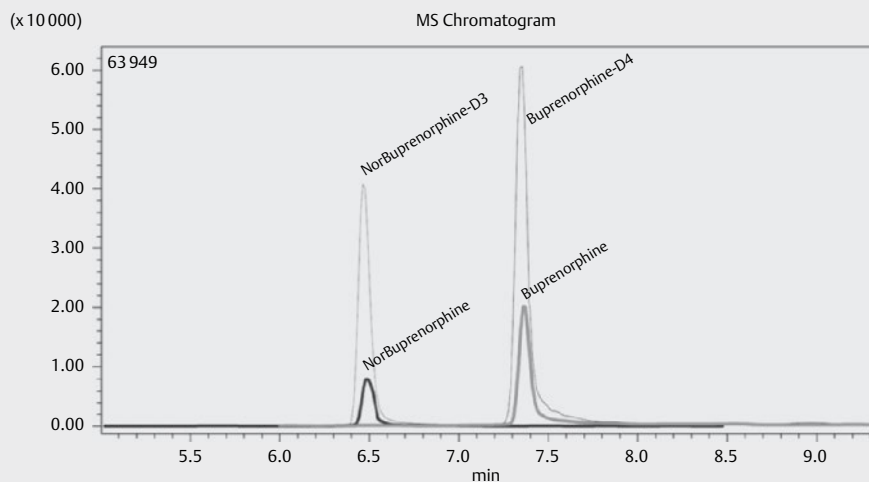
Clinical feasibility

In all participants, the variance between the measured BUP trough concentrations were ranged from -6.3% to 13.9% . As the variance between the examined and predicted concentrations in all 15 par-

ticipants was within $15\text{--}20\%$ (-7.20% to 1.54%), the reliability of the first-order pharmacokinetic model in predicting the BUP plasma concentrations was confirmed (► **Table 5**).

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Patient Name :
 NRC Number : Matrix spike@0.2ppb-1
 Tray# : 1
 Vial# : 8
 Injection Volume : 20
 Data File : Matrix spike@0.2ppb-1_5.1cd
 Method File : BUP_NORBUP_Blood.1cm
 Original Method : BUP_NORBUP_Blood.1cm
 Report Format : REPORT.1sr
 Tuning File : Tunning_23.06.2019.1ct
 Location :



MS Quantitative Table

ID#	Name	Ret. Time	m/z	Conc.	Area	Unit
1	NorBuprenorphine-D3	6.468	417.00 > 101.05	5.000	197 343	ng/mL
2	NorBuprenorphine	6.487	414.00 > 101.15	0.232	37 970	ng/mL
3	Buprenorphine-D4	7.348	471.90 > 59.10	5.000	334 612	ng/mL
4	Buprenorphine	7.365	468.10 > 55.10	0.243	97 332	ng/mL

► Fig. 2 Chromatogram for buprenorphine, norbuprenorphine and deuterated standards using buprenorphine internal standard at 10 ng/mL.

BUP/ NX daily dose

The mean daily stabilization dose of BUP/NX-F was 14 mg (range 12–16 mg).

BUP Elimination Rate

The mean estimated BUP EL.R constant was 0.068 (SD = 0.056; range 0.01–0.19).

BUP trough concentration

At steady state, in the 15 participants, the examined BUP trough concentration ranged from 0.262–11.65 ng/mL. In 9 participants, the BUP trough concentration at steady state ranged from 1–3 ng/mL, while in 5 participants, BUP trough concentrations were below 1 ng/mL.

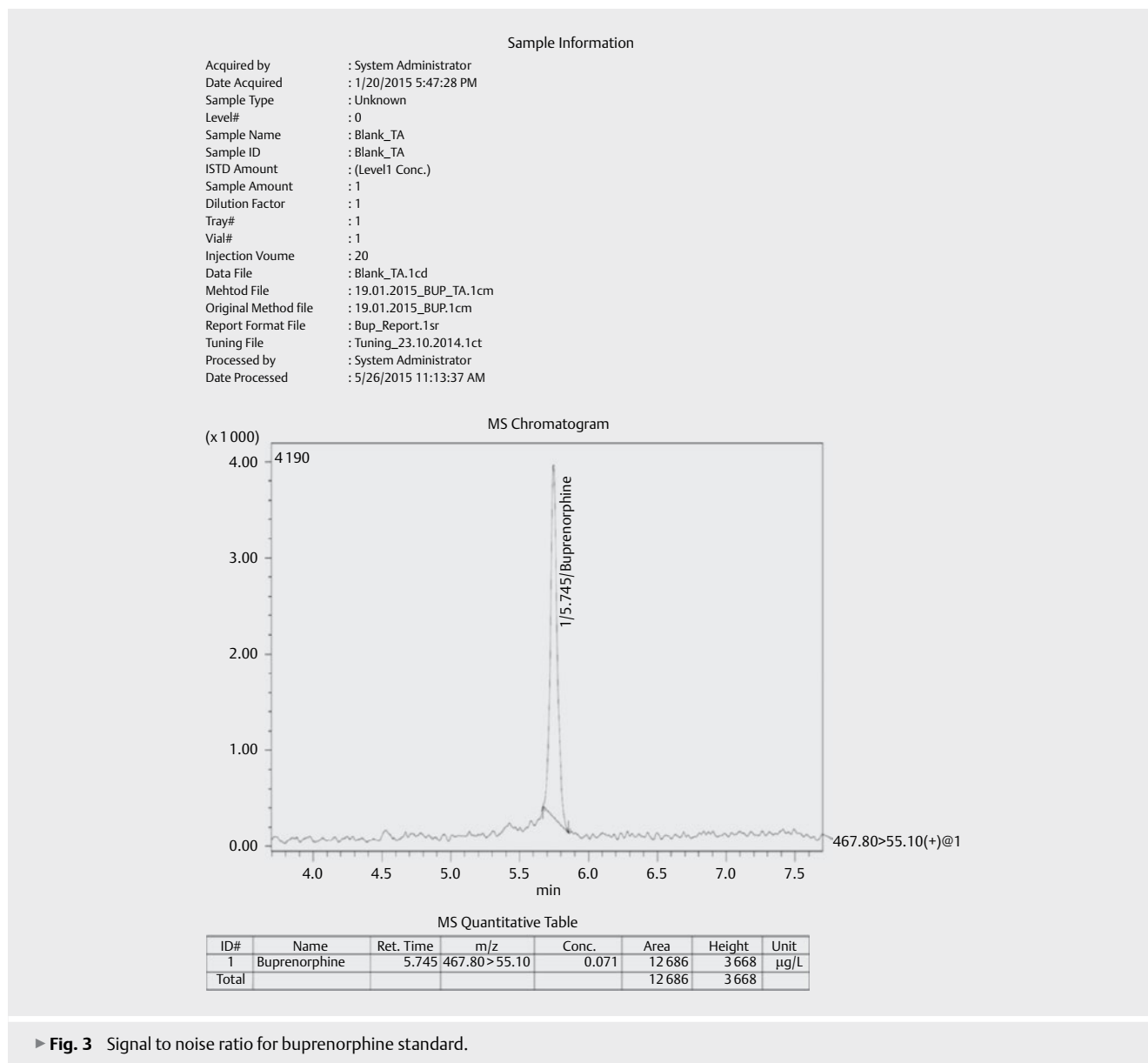
In one participant only—stabilized on a daily BUP/NX-F dose of 14 mg—a BUP trough concentration of 11.65 ng/mL was detected, which is above the 10 ng/mL laboratory level. No signs of intoxication or clinical symptoms were observed or reported by this participant.

Discussion

In this TDM for BUP feasibility study among 15 adults with OUD stabilized on BUP/NX-F, simple adjustment in the sample preparation conditions (method optimization) resulted in higher mean BUP recovery rate compared to those obtained applying the original method and those previously reported for standard SPE [13]. The assay precision and accuracy for the optimized method was confirmed.

When applying the optimized method, the estimated LoD and LoQ were lower than those reported for the original method [15]. The estimated LoQ is lower than the value reported by Luthi and colleagues (0.1 ng/mL) [19]. Similarly, the sensitivity of the optimized method appeared to be lower than the value obtained by Regina and Karash [20]. All BUP peak and trough plasma concentrations were successfully examined according to the published BUP kinetics data, reporting peak concentrations at 40 min after medication administration [21]. BUP trough concentrations were replicated in all participants, confirming BUP SSC.

The reliability of the first-order pharmacokinetic model in predicting BUP concentrations [9] strongly supports the clinical feasibility of TDM in monitoring adherence with BUP. Quantifying BUP trough concentrations over a wide range supports the clinical reliability of the assay method in the presence of reported inter-indi-



► **Fig. 3** Signal to noise ratio for buprenorphine standard.

vidual differences [11]. A majority of the participants (9 out of 15) had BUP trough concentrations at steady state within 1–3 ng/mL reported as the therapeutic range [9], and no participant had a BUP concentration below 0.2 ng/mL.

Given these results, there may not be a strong clinical need in routine practice to use methods capable of detecting BUP at very low concentrations since none of the detected BUP concentrations were below 0.1 ng/mL. It should be noted, however, that this method was developed for total rather than free BUP or buprenorphine-3-glucuronide [22]; hence, complete liberation of BUP from the gluco-uronidate conjugate was required. Such liberation contributes to minimal variance of measurement over time and higher assay sensitivity, as well as minimizes the potential impact of the source of β -glucouridase enzyme on the hydrolysis rate [23]. In order to achieve complete liberation, extended hydrolysis conditions were adopted, (i. e., overnight hydrolysis at 55 °C instead of 37 °C for less than an hour [23]).

A key strength of the present work stems from the feasibility of successful measurement of the peak and trough BUP concentrations at steady state and accurate prediction of BUP concentration at any time point. The study provides empirical data on clinical applications of TDM in monitoring BUP in blood and hence monitoring treatment adherence. Unlike the methods currently applied to verify compliance with BUP, quantitative measurement of BUP provides the clinician with accurate verification of BUP adherence.

Successful matching of the extraction conditions with the BUP physicochemical characteristics (a weak basic compound with a pK_b of 8) may have contributed to the enhanced recovery rate. Unlike the wash solution concentration, no impact of DEC on the BUP recovery was noted. The cationic exchange component of the Isolete HCX[®] did not enhance the recovery despite setting the pH at 2 units below the pK_b to charge BUP and facilitate cationic exchange. The impact of adjusting the wash solution supports the

► **Table 5** Examined and predicted buprenorphine concentrations at different time intervals from administering buprenorphine/naloxone film.

	BUP/ NX-F dose	Cmax BUP	Cmax NBUP	Cmin (1) BUP	Cmin (1) NBUP	Cmin (2) BUP	Cmin (2) NBUP	Time Rand. Samp	Exam BUP Conc.	Exam NBUP Conc.	EL.R	Pred BUP Conc.	Percentage Diff between Exam. & Pred
	mg/day	ng/mL	ng/mL	ng/mL	ng/mL	ng/mL	ng/mL	hrs. post dose	ng/mL	ng/mL	hr ⁻¹	ng/mL	φ
1	14	5.84	8.25	2.84	3.76	2.86	5.32	(20)	3.14	5.96	0.03	3.14	0.00
2	14	1.31	1.61	0.55	0.84	0.55	0.99	(10)	0.71	0.1	0.04	0.74	-4.23
3	16	1.83	1.76	0.55	0.78	0.56	0.85	(7)	1.30	1.28	0.05	1.28	1.54
4	16	1.15	0.55	0.48	0.52	0.50	0.53	(20)	0.50	0.53	0.04	0.51	-2.00
5	14	3.85	6.99	2.57	4.14	2.74	5.27	(5)	3.55	6.11	0.02	3.53	0.56
6	16	11.97	19.74	1.68	6.22	1.58	0.64	(7)	5.89	11.36	0.1	6.11	-3.74
7	14	30.33	28.3	11.65	29.28	11.65	29.3	(20)	13.63	35.92	0.04	13.43	1.47
8	16	21.61	14.19	0.262	1.78	0.253	1.9	(8)	4.82	18.17	0.19	4.81	0.21
9	12	23.95	6.31	1.16	1.01	1.34	1.02	(12)	4.83	8.81	0.13	5.01	-3.73
10	12	7.22	3.56	1.23	1.01	1.43	2.21	(11)	3.18	1.59	0.07	3.16	0.63
11	14	16.56	20.42	1.0	4.67	0.97	3.77	(11)	4.86	12.69	0.11	4.93	-1.44
12	12	1.98	1.37	1.12	1.04	1.17	0.98	(20)	1.20	0.98	0.02	1.22	-1.67
13	12	65.63	13.83	3.23	7.40	3.37	6.37	(18)	6.11	3.37	0.13	6.55	-7.20
14	12	1.82	1.76	1.30	1.28	1.34	1.53	(14)	1.48	1.29	0.01	1.49	-0.68
15	16	1.03	0.83	0.42	0.52	0.42	0.48	(8)	0.74	*****	0.04	0.73	1.35

BUP/NX-F: Cmax: peak concentration; Cmin: trough concentration; Conc: concentration; Rand: random, Samp: sample; Exam: examined; Pred: predicted; hrs: hours; Diff: difference; φ: [(Examined BUP Conc - Pred BUP Conc)/Examined BUP Conc] * 100.

previously reported significance of the wash step in the recovery outcomes [12].

The results of this study should also be considered in the light of some limitations. We must stress the importance of accurately drawing blood samples representing BUP peak and trough concentrations. In particular, determination of the BUP peak concentration required close coordination between the laboratory and the addiction clinic nursing staff due to the narrow time period within which samples had to be obtained to measure peak concentration.

Conclusions

We have demonstrated that TDM is clinically feasible for estimating BUP concentrations and monitoring adherence with BUP MAT for OUD. Sensitivity and precision of BUP detection and quantitation can be optimized by simple adjustments in the wash step conditions of the solid phase extraction. For further studies, we suggest applying this procedure using BUP monotherapy preparations, given the lower cost of BUP tablets compared to BUP/NX-F preparations.

Acknowledgements

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Conflict of Interest

The authors declare that they have no conflict of interest.

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APPENDIX A.2 CHANGE IN MEASURES OF PSYCHOSOCIAL FUNCTIONING

The scores of the measures at the study end-point, the within group difference and magnitude of change from baseline are displayed for PHQ-9, GAD-7, PSQI, BIS-11 and WSAS in **Table A.1**

Depression: In both groups, significant reductions from baseline PHQ-9 scores were observed [experimental 3.0 (*IQR* 0.0-12.0), $Z=-3.22$ $p=0.01$) versus control 4.0 (*IQR* 0.0-10.0), $Z= -2.97$, $p=0.03$). Clinically, participants in both groups changed from ‘severe depression’ to ‘mild depression’.

Anxiety: Participants in the experimental group showed a median of 0.000 (-2.0 –7.75) point reduction in the GAD-7 score at the end of the study that was non-significant ($Z= -1.35$, $p=0.18$). In contrast, participants in the control group showed a median of 4.5 (*IQR* -0.75–9.0) point reduction that was significant ($Z= -2.58$, $p=0.01$).

Quality of sleep: Participants in the experimental group showed a median of 2.0 (*IQR* -1.75–4.0) point reduction in PSQI scores that was non-significant ($Z= -1.69$, $p=0.09$). Similarly, participants in the control group showed a median of 0.000(-1.50 –3.50) point reduction that was non-significant ($Z=-1.43$, $p=0.15$).

Impulsiveness: Participants in the experimental group showed a mean reduction of 9.17 (*SD* 16.2) points in the BIS-11 scores that was found to be significant ($t= 3.04$, $p <0.01$). In contrast, participants in the control group showed a 4.0-point (*SD* 15.7) reduction in the BIS-11 scores that was non-significant ($t=1.41$, $p= 0.17$).

Work and Social Adjustment: At the end of the study period, the experimental group showed a median reduction of 10.50 (*IQR* -7.5 –21.0) points in the WSAS scores that was significant ($p=0.01$). Clinically, the experimental group changed from *severe* to sub-clinical impairment at the end of the study (4.0, *IQR* 0.00-15.0). In contrast, the control group showed a median reduction of 5.0 points (*IQR* -2.0–19.75) that was significant ($p=0.01$). Clinically, participants in the control changed from *sever significant impairment* at the end of the study (19.0, *IQR* 3.25-28.75).

Personality Disorders: Participants in the experimental and control groups showed no significant change in the percentage of personality disorders screened from baseline at the end of the study (Borderline personality disorders: Experimental $p = 0.68$, Control $p=1.0$; Paranoid personality disorders: Experimental $p = 1.0$, Control $p=0.38$; Dependent

personality disorders: Experimental, $p=0.72$, Control $p = 0.45$; Antisocial personality disorders: Experimental $p=1.0$, Control $p=1.0$; OCPD: Experimental $p=1.0$, Control $p=0.58$).

Addiction Severity Index: The ASI scores at the study end point, the within group difference and between group magnitude of change from baseline are displayed in **Table A.2**. In both groups, statistically significant reductions were, observed only in the median scores of the drug use and mental health domains. Otherwise, no significant reduction from baseline was observed at the end of the study in Medical, Social, Alcohol, Legal, and Family domains.

Finally, the magnitude of reduction for between group differences showed no significant difference in *all* measures. In other words, the change in measures from baseline line was not due to the study allocation.

Table A.1 Measures of psychosocial functioning at end-point, within and between group changes from baseline

Measures	Experimental			Control			Magnitude of change between group
	Endpoint	Change from baseline	Within group (p-value)	End point	Change from baseline	Within group (p-value)	(p-value)
PHQ-9	7.90 (6.5)	4.51 (7.0)	0.01	9.12 (7.5)	6.02 (8.1)	<0.01	0.56
GAD-7	5.0 (2 – 10)	0.000 (-2.0 –7.75)	0.18	5.50 (2.25-9.50)	4.50 (-0.75 –9.0)	0.01	0.32
BIS-11	64.50 (14.20)	9.2 (16.3)	<0.01	63.80 (12.60)	4.0 (15.40)	0.17	0.41
PSQI	9.0 (4.0 – 13.0)	2.0 (-1.75–4.0)	0.09	9.0 (6.25–11.75)	0.00 (-1.50 –3.50)	0.15	0.66
WSAS	5.0 (0–15)	10.50 (-7.5 –21.0)	0.01	19.0 (3.25–28.75)	5.0 (-2.0–19.75)	0.01	0.48

Data are Mean (SD); Median (Inter Quartile Range). PHQ-9: Patient Health Questionnaire 9 items, GAD-7: Generalized Anxiety Disorder-7 items; BIS-11: Barratt Impulsiveness Scale 11th version; WSAS: Work and Social Adjustability Scale

Table A.2 Measures of Addiction Severity Index domains at end-point, within and between group change from baseline

ASI Domains	Experimental			Control			Magnitude of change between group (p-val)
	End point	Change from baseline	Within group (p-value)	Endpoint	Change from baseline	Within group (p-value)	
Medical	0.000 (0.000 – 0.380)	0.000 (-0.147 – 0.1528)	0.62	0.000 (0.000 – 0.333)	0.000 (-0.021 – 0.341)	0.29	0.59
Social	0.500 (0.000 – 0.750)	0.000 (-0.187 – 0.185)	0.77	0.5000 (0.500 – 0.750)	0.000 (-0.106 – 0.000)	0.28	0.65
Alcohol	0.000 (0.000 – 0.00)	0.000 (0.000 – 0.097)	0.05	0.000 (0.000 – 0.292)	0.000 (-0.002 – 0.020)	0.52	0.73
Drug use	0.000 (0.000 – 0.005)	0.153 (0.018– 0.301)	<0.01	0.002 (0.000 – 0.150)	0.143 (0.019–0.260)	<0.01	0.27
Legal	0.000 (0.000 – 0.002)	0.000 (-0.022 – 0.193)	0.60	0.000 (0.000- 0.200)	0.000 (0.000 – 0.121)	0.16	0.58
Family	0.3000 (0.100–0.400)	0.000 (-0.100– 0.089)	0.89	0.300 (0.183-0.400)	0.001 (-0.145– 0.257)	0.20	0.47
Mental health	0.395 (0.000–0.624)	0.000 (-0.006– 0.187)	0.04	0.416 (0.142 – 0.585)	0.037 (-0.102– 0.477)	0.03	0.77

Data are Median and (Inter Quartile Range)

Appendix. B. Reports and regulatory documents

Appendix B.1	CONSORT check-list
Appendix B.2	Data base search form
Appendix B.3.	Ethical approval
Appendix B.4	Approval for Ph.D. upgrade
Appendix B.5	End of study audit report
Appendix B.6	Nursing training program
Appendix B.7	Authors' contributions



Appendix B1. CONSORT: Checklist of items CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3 -- 4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	15 --36
	2b	Specific objectives or hypotheses	36
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	52
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	53 & 89
	4b	Settings and locations where the data were collected	51
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	68—74; 89--92
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	54 & 55
	7b	When applicable, explanation of any interim analyses and stopping guidelines	

Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	68; 87
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	68; 87
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	68;87
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	87
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	51;87
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	77—78; 92
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	93
	13b	For each group, losses and exclusions after randomisation, together with reasons	93
Recruitment	14a	Dates defining the periods of recruitment and follow-up	92
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	96
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	97
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	97 & 98
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	98
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	98,99,106--111


Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	100
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	102;123
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	127
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	117
Other information			
Registration	23	Registration number and name of trial registry	40
Protocol	24	Where the full trial protocol can be accessed, if available	87
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	52

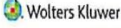
*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Appendix B.2. Data base search form

Ovid: Search Form

Page 1 of 4





[My Account](#)
[Support & Training](#)
[Help](#)
Logged in as Hesham Elarabi at Kings College London
[Logoff](#)

[Search](#)
[Journals](#)
[Books](#)
[My Workspace](#)
[Multimedia](#)
[Mobile](#)

Search History (116) [View Saved](#)

<input type="checkbox"/>	#	Searches	Results	Type	Actions	Annotations
<input type="checkbox"/>	1	Sul opioid addiction.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tx, sh, ct, tc, id, tm]	2679	Advanced	Display Results More	<input type="checkbox"/> Contract
<input type="checkbox"/>	2	Sul opiate addiction.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tx, sh, ct, tc, id, tm]	16362	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	3	Sul heroin addiction.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tx, sh, ct, tc, id, tm]	5467	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	4	Sul morphine addiction.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tx, sh, ct, tc, id, tm]	3710	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	5	Sul tramadol addiction.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tx, sh, ct, tc, id, tm]	23	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	6	Sul opioid dependence.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tx, sh, ct, tc, id, tm]	7699	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	7	Sul opiate dependence.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tx, sh, ct, tc, id, tm]	3146	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	8	Sul tramadol dependence.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tx, sh, ct, tc, id, tm]	56	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	9	Sul heroin dependence.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tx, sh, ct, tc, id, tm]	19171	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	10	Sul morphine dependence.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tx, sh, ct, tc, id, tm]	5159	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	11	Sul opioid use*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tx, sh, ct, tc, id, tm]	13144	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	12	Sul 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	62171	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	13	Sul epidemiology.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tx, sh, ct, tc, id, tm]	1567712	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	14	Sul 12 and 13	3366	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	15	Sul remove duplicates from 14	3068	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	16	Sul disease burden.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tx, sh, ct, tc, id, tm]	28681	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	17	Sul 15 and 16	11	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	18	Sul cost effectiveness.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tx, sh, ct, tc, id, tm]	211747	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	19	Sul 15 and 18	31	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	20	Sul remove duplicates from 19	31	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	21	Sul treatment.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tx, sh, ct, tc, id, tm]	11236065	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	22	Sul 14 and 21	1665	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	23	Sul remove duplicates from 22	1523	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	24	Sul remove duplicates from 22	1522	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	25	Sul recovery.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tx, sh, ct, tc, id, tm]	1051856	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	26	Sul 12 and 25	1984	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	27	Sul remove duplicates from 26	1382	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	28	Sul 26 or 27	1984	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	29	Sul 24 or 26	3474	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	30	Sul dropout.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy, tx, sh, ct, tc, id, tm]	26301	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	31	Sul 12 and 30	422	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	32	Sul 29 and 31	49	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	33	Sul 12 and 29	3474	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	34	Sul remove duplicates from 32	46	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	35	Sul remove duplicates from 29	2668	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	36	Sul 34 and 35	46	Advanced	Display Results More	<input type="checkbox"/>
<input type="checkbox"/>	37	Sul retention (Including Limited Related Terms)	46093	Basic	Display Results More	<input type="checkbox"/>

Appendix B.3. Ethical Approval (Institutional Review Board)



30 April, 2014

Dr. Hisham Al Arabi

Head, Health Education Section

Department of Public Health and Research, NRC

Re: NRC, Research Ethics Committee review

Dear Dr. Hisham,

Thank you for submitting your application and research proposal "National Rehabilitation Center: Suboxone Treatment and Recovery Trial" to the committee.

Your proposal was reviewed on April 22nd, 2014 by the full REC and was provisionally approved with recommended changes. The submitted amended protocol was recirculated to the REC members and I am pleased to inform you that your proposal is now fully approved.

Please make sure that your co-investigators who did not already take the NIH course "Protecting Human Research Participants" available online at <http://phrp.nihtraining.com/users> need to do so and submit their certificate of completion to me prior to starting the study.

In the course of conducting your research should you change or amend the proposal, or discover new findings that may affect subject's safety or confidentiality you should notify the REC of such changes or findings.

You should submit annual reports and end of study report to the committee as well as any copies of abstracts or publications.

I wish to take this opportunity to wish you success with this important study.

With kind regards,

Ahmed ElKashef, M.D.

Chair, NRC Research Ethics Committee

Appendix B.4. Approval for Ph.D. upgrade

**Institute of
Psychiatry**

at The Maudsley

Education Support Team
Box 090
De Crespigny Park
London
SE5 8AF

Postgraduate Research
(MPhil/PhD)
Tel +44 (0)20 7848 0170
Postgraduate Taught Courses
(MSc/PgDip)
Tel +44 (0)20 7848 0335
Fax +44 (0)20 7848 0620
iop.educationsupport@kcl.ac.uk

KING'S
College
LONDON

Ref: H/RPCA/0846925

22/Oct/2014

Dr Hesham Elarabi
178
Overhill Road
Flat 6
London
SE22 OPS

Dear Dr Elarabi

PhD Upgrade title- Optimizing opioid therapy outcomes for opioid use disorder using personalized dosing and therapeutic drug monitoring: a randomized controlled trial

I am pleased to tell you that following your response to the reviewers' comments, your proposal for a PhD upgrade has been considered by the ADDICTION BIostatISTICS CHILD & DEVELOPMENTAL PSY MPhil/PhD Sub-committee and it has been approved.

Your progress will continue to be monitored by the ADDICTION BIostatISTICS CHILD & DEVELOPMENTAL PSY MPhil/PhD Sub-committee. As a full time student you must submit your thesis within three calendar years from your date of registration 01/Jul/2013. Please note this does not include any approved interruptions that you might have during your course of study.

If you find yourself in a situation where an extension needs to be sought, please do so at your earliest opportunity by contacting the Education Support Team to complete the relevant paperwork.

Yours sincerely,



Mr Benjamin Harrison
Postgraduate Research Officer
Education Support Team

cc JOHN MARSDEN
Adem, Prof A

Appendix. B.5 End of study audit report

ADDICTIONS DEPARTMENT



H.E. Mohamed Al Hameli
Director General
Scholarship Office
Ministry of Presidential Affairs
United Arab Emirates

23rd January 2017

Excellency,

DATA QUALITY ASSURANCE AUDIT FOR SUBOXONE TREATMENT AND RECOVERY TRIAL (START TRIAL)

During 16-20 January 2017, a 100% (26 hour) case audit of the clinical data compiled for the completed START Trial was conducted at the new National Rehabilitation Centre and the existing clinical facilities in Abu Dhabi.

The objective of the audit was to calculate (and verify) the final collected outcome measure data for the study. The **complete clinical research** record for the trial was evaluated for standards of data management and accuracy. The primary outcome measure for the START trial is as follows:

“The percentage of laboratory confirmed negative urine drug tests for opioids during the 16-week active treatment phase”

This percentage was computed as the proportion of negative urine tests recorded, with imputation as a positive test result for all scheduled tests that the patient did not attend. The approach of 'imputing missed tests as positive' strategy ensures that the effect size for a trial is conservative for this NRC study.

RESULTS

All patient cases randomised for the START Trial were reviewed (n= 141). For each case, the primary (source) clinical file for the trial (clinical assessments, pupilometry, TDM parameters, and adverse event records), was accessed with cross-referencing to the associated file on the MedEZ database.

Data entry (electronic from case file) and individual toxicology reports (from the NRC laboratory) for the following variables were recorded and verified against the trial data file:

- *Randomisation to group allocation;*
- *Number of scheduled clinical appointments (at which a urine drug screen was expected);*
- *Number of scheduled appointments attended by the patient;*
- *Number of laboratory (GCMS confirmed) drug screens for opioids;*
- *Status at completion of trial treatment phase (completed treatment or dropped out);*
- *Time (in weeks) to exit from treatment for each patient who dropped out.*

Each of the 141 cases in the study was checked, separately coded, and then re-checked (i.e. all cases were checked twice to ensure accuracy).

At completion of the audit:

- All cases had been correctly recorded as randomised to their assigned group (Therapeutic Drug Monitoring [experimental condition; n=70] or Treatment as Usual [control condition; n=71]);
- All cases had been correctly recorded as either treatment 'completer' or 'drop out' (i.e. left treatment prior to completion and without agreement);
- The time to exit for all drop outs was also correctly recorded.

PRIMARY OUTCOME RESULT

The audit confirmed rates for the primary outcome measure is as follows:

TDM (experimental): % negative opioid tests = 76.71 (standard deviation = 25.00)

TAU (control): % negative opioid tests = 63.46 (standard deviation = 34.68)

This gives a **13.25 percentage point difference** for the two trial conditions. This accords well to the statistical power calculation for sample size that was done during study planning (i.e. a difference of 15-percentage points anticipated).

There is a statistically significant, 0.44 effect size (Cohen's d; 95 CI 0.10 to 0.77) *

* i.e. $\text{experimental \%} - \text{control \%} / \text{pooled SD}$) in favour of the TDM intervention where the pooled SD is $\sqrt{[\sigma_1^2 + \sigma_2^2 / 2]} = 30.26$.

SUMMARY

The headline finding from the START trial is that therapeutic drug monitoring of patients receiving suboxone maintenance treatment is clinically effective. More patients receiving TDM were able to have their suboxone treatment calibrated to their response, supporting take-home medication benefits and helping them to stay away from illicit opioids that those receiving standard suboxone treatment. This result highlights that TDM is acceptable to patients and delivers improved treatment performance.

Excellency, I trust you will be very satisfied to have this positive outcome confirmed by audit.

I believe these results are very impressive and reflect the good use of resources allocated to this research and the commitment and hard work devoted to the project by Hesham Al Erabi. The clinical results will now inform the analysis of cost-effectiveness which I anticipate will also show very positive results.

Taken together, I believe the findings from the trial will secure a wide international audience and will lead to several strong publications from Hesham's PhD thesis in academic journals. This work will showcase the results of this landmark study conducted by the clinical team at the NRC. There is wealth of data collected for the trial (both clinical and health economic) which I trust will be of assistance to the NRC for future service delivery and other applications.

Yours sincerely,



Professor John Marsden
King's College London

Appendix. B 6. Nursing training



Health Authority - Abu Dhabi CME/CPD Section

Nursing Training on management of opioid addiction with focus on Assisted Treatment with Buprenorphine/ Naloxone

3/11/2015

HAAD Credit Designation

This activity has been planned and implemented in accordance with the HAAD's Accreditation Standards & Policies and the Essential Areas and their Elements.

The Health Authority of Abu Dhabi (HAAD) is an independent CME/CPD accrediting body for institutions and organizations that sponsor CME/CPD for physicians and health care professionals.

HAAD serves as the accrediting body for all CME/CPD activities provided by medical education institutions and societies in the region. HAAD aims at development and promotion of standards for quality CME/CPD utilized by physicians and other healthcare professionals in their maintenance of competence and incorporation of new knowledge, in order to improve quality health services provided for patients and their communities

The Health Authority of Abu Dhabi (HAAD) presents this activity for educational purposes only. Participants are expected to utilize their own expertise and judgment while engaged in their practice.

The content of the presentations is provided solely by presenters who have been selected because of their recognized expertise.

HAAD Accreditation Statement

HAAD Accreditation Review Committee designates this education activity for a maximum of 13 hours in the Category 1 credit of HAAD Designation. Each health professional must claim only those credits that he/she actually spent in the activity.

Commercial Support of CME/CPD Activities

HAAD is committed to keep all Continuing Education activities free of commercial interest. To avoid any commercial bias, the CME/CPD section at HAAD maintains absolute control over all CME/CPD programs and makes sure HAAD Guidelines and Standards for Commercial Support of CME/CPD are adhered to prior to any activity being awarded Category 1 Credit.

Conflict of Interest Disclosure

It is the policy of Health Authority of Abu Dhabi (HAAD) to ensure balance, independence, objectivity, and scientific rigor in all its accredited educational programs.

All faculty participating in CME/CPD activities accredited by HAAD are required to disclose to the program audience any real or apparent conflict of interest related to the content of their presentations. All faculty are also required to disclose any discussions of unapproved uses of drugs or devices.

Monitoring & Auditing

HAAD randomly *monitor* some CME/CPD events - large or small to ensure that all criteria of accreditation are fulfilled

Emirate of Abu Dhabi
Health Authority - Abu Dhabi

TRANSCRIPT DATE:
February 17, 2015

Designated CME/CPD Accreditation Approval

Name of Activity : Nursing Training on management of opioid addiction with focus on Assisted Treatment
Individual/Department/Organization : ~~Qatari~~ **Baptism** morphine/ Naloxone
CME/CPD Contact Person : Ayesha Ateeq Al Dhaheri

Accreditation Unique ID #:
NRC/S/4379/2015

Activity Type	Location	Date	Start Time	End Time	No. of Recurrent Sessions	Total Granted Hours
Training	KRC	03/11/2015	08:00	16:00	0	13
Activity Date March 11, 2015		Activity Title			Lecturer	CME Hours
Start Time	End Time					
Session	2					
08:30	09:00	Opioid Epidemiology			Dr Tarek Gawad	00:30
Session	3					
09:00	10:30	Pharmacology and Pathophysiology of Opioid Addiction			Dr.Ahmed Elkashef, Dr. Hesham Elarabi	01:30
Session	4					
11:00	12:30	Ethical and management framework			Dr Tarek Gawad	01:30
Session	5					
13:00	15:30	Clinical Evaluation (Clinical Picture, patient assessment and placement)			Dr. Ahmed Yousif	02:30
Session	6					
15:30	16:00	Role of Nurses and clinical support services in Opioid Addiction Management			dr nael	00:30
Session	7					
08:00	08:30	Review of day one learning			panel	00:30
Session	8					
08:30	10:30	Induction, Stabilization and maintenance using Buprenorphine and Naloxone			Dr. Mansour Shawky, Dr. Nael Hasan, Dr.Doaa Radwan	02:00
Session	9					
11:00	12:00	Suboxone Treatment and Recovery Guidelines and			Dr.Nael Hasan, Dr. Hesham Elarabi	01:00
Session	11					
14:00	15:30	Clinical case Discussion: Maintenance			panel	01:30
Session	12					
15:30	16:00	Summary and assessment of training			panel	00:30

Appendix.B.9.Consent Form



المشاركة في دراسة علمية

المراقب / الباحث الرئيس للدراسة : هشام فاروق العربي
المراقبين / الباحثين المشاركين ، د. نائل حسن ود. دعاء رضوان

عنوان الدراسة :

دراسة المركز الوطني للتأهيل باستخدام السبكترون/البكسون للعلاج والتأهيل "ستارت"

محل الدراسة :

العلاج الداخلي (المقيم) والعيادة الخارجية في مرافق المركز الوطني للتأهيل في أبوظبي.

أنت مدعو للمشاركة في دراسة علمية تقام في المركز الوطني للتأهيل في أبوظبي. لذا، تأكد من قراءة وفهم المعلومات التالية بعناية قبل الموافقة على المشاركة في الدراسة. وعليه، نرجو أن لا تتردد في الاستفسار عن وطلب أي معلومات إضافية تفيدك في اتخاذ قرارك بشأن المشاركة في هذه الدراسة.

طبيعة الدراسة :

الغرض من الدراسة هو مقارنة فعالية استخدام علاج السبكترون التعويضي حسب الاجراءات المألوفة والاعتيادية بعلاج السبكترون ضمن منهج ادارة وتحفيز الالتزام بالعلاج المتكامل. على أن يتم تحديد معدلات الجرعات العلاجية سواء كانت جرعة يومية، أو أربعة مرات أسبوعياً أو ثلاث مرات أسبوعياً حسب الاحتياج الشخصي، وتتضمن الدراسة التي تستمر لمدة 6 اشهر اجراء تقييمات نفسية واجتماعية، وجمع 8 عينات دم (5 مل لكل عينة) وعينة لعاب من كل مشارك.

الإطلاع على المعلومات والسجل الطبي :

لحفاظ على سرية المعلومات، يحق فقد للباحثين والمعالجين العاملين في المركز الوطني للتأهيل الاطلاع على بياناتك وسجلك الطبي لأغراض البحث فقط.

التعرف على العينات والبيانات الخاصة بك :

كافة العينات والتقييمات توثق بـ "شفرة سرية" تحافظ على سرية هوية وبيانات المشارك الشخصية ولا يتم افضاء هوية المشارك تحت أي ظرف. فقط مراقبي البحث هم المتاح لهم الاطلاع على المعلومات المرتبطة بعلاج المريض.

الحفاظ على سرية المشاركين :

يتم تأمين المحافظة على سرية معلومات المريض من خلال السياسات النافذة والخاصة بسرية المعلومات ، والتي لا تسمح بتسريب بيانات المريض. يتم استخدام الشفرة السرية الخاصة بكل مريض في توثيق العينات والمقاييس النفسية والاجتماعية.

مدة حفظ المعلومات :

يتم حفظ المعلومات الخاصة بالدراسة طوال مدة الدراسة (ثلاث سنوات) على أنه بإمكانك ترك الدراسة في أي وقت وعليه سوف يتم بالتخلص من المعلومات والبيانات الخاصة بك المرتبطة بالدراسة.

الفوائد من المشاركة :

مشاركتك سوف تسهم في تطوير مناهج علاج الادمان وقد تتحسن فرص تعافيك، إلا أنه لا يمكن ضمان مدى استفادتك من المشاركة في هذه الدراسة. وسوف تتيح الدراسة معلومات دورية عن مقدار تعافيك وحالتك بشكل دوري وشامل. في حال حدوث أي إصابة -لا قدر الله- سوف يتم اتخاذ الاجراءات القياسية المتبعة في المؤسسات الطبية وبدون أي تعويض مالي.

سرية النتائج :

عند موافقتك على المشاركة في هذه الدراسة، قد يتم نشر نتائج الدراسة في دوريات علمية دولية ومحكمة أو عرض نتائج الدراسة في المحافل العلمية والطبية بدون المساس بخصوصية وسرية معلومات الشخصية.

يحق لك الاطلاع على نتائج الدراسة بناءاً على طلبك وبدون المساس بسرية المعلومات الشخصية للمشاركين.

حرية المشاركة :

لك مطلق الحرية للمشاركة في هذه الدراسة وبإمكانك مناقشة الأمر مع أحد المراقبين منك قبل اتخاذ قرار المشاركة. تذكر أنه بإمكانك الانسحاب من الدراسة في أي وقت تريده.

تأكد بأن قرارك بعدم المشاركة لن ينتج عنه حرمانك أي من الحقوق أو المميزات التي تحصل عليها ولن تتعرض لأي شكل من أشكال المحاسبة في حال انسحابك من الدراسة. وفور انسحابك من هذه الدراسة، سوف يتم التخلص نهائياً من المعلومات التي تم جمعها في اطار هذه الدراسة

أقرار المراقب

أقر بأنني قمت بشرح طبيعة الدراسة ومتطلباتها للمريض / المشارك _____ وأجبت على كافة استفساراته وأسئلته. وسوف يتم اخطار المشارك حال حدوث أي تطورات أو مضاعفات تطرأ خلال الدراسة.

التاريخ

المراقب

الإمضاء

أقرار المشارك/ المريض

أقر أنا _____ بأنني قمت بقراءة وفهم كافة المعلومات المعطاة لي وقد تم الاجابة على كافة اسئلتي بوضوح تام. وادرك تماماً أنني قادر على الانسحاب من هذه الدراسة بدون أي قيد أو شرط و بدون أن تتأثر حقوقي كمريض.

وأنا على علم أن المراقب الرئيس د. هشام العربي مستعد للاجابة على اسئلتي واستفساراتي وانه يمكنني التواصل معه على الرقم 050.4460781 ادر ك أن كافة المعلومات التي أقوم باعطائها تخضع لاجراءات السرية المشددة ولن يتم تسريبها من قبل مراقبي الدراسة. تم شرح لي نوعية المعلومات التي يتم جمعها وكافة الاجراءات والهدف منها وكيفية استخدام والاستفادة من هذه المعلومات عند اتمام الدراسة والانتهاء من تحليل بيانات الدراسة.

أوافق أن يتم نشر البيانات العلمية والمعلومات المرتبطة بالدراسة على أن يتم المحافظة على سرية هويتي ومعلوماتي الشخصية.

التاريخ

المشارك

الإمضاء

Consent to participate in a clinical study

Principal Investigator: Hesham Elarabi

Investigators: Dr. Nael Hasan & Dr. Doa Radwan

Study name: Suboxone Treatment and Recovery (START)

Study setting: Inpatient units and outpatient clinics at the National Rehabilitation Center (NRC)

You are invited to participate in a clinical/scientific study/research to be conducted at the NRC –Abu Dhabi. Hence, please ensure that you carefully read and understand the following information before you agree to participate in the study. Please do not hesitate to inquire or request additional information and clarification that may assist you in deciding to participate in the study.

Nature of the study:

The aim of this study is to contrast the outcomes/effectiveness of using suboxone assisted treatment under the usual conditions, and suboxone assisted treatment under medication and motivational frame work. Under this experimental frame work, dosing is allocated to daily, alternate day and thrice weekly according to individual needs. This study extends to 5 months and includes administration of psychological assessments, and collection of up to 8 blood samples each 5 mL volume.

Access to information and medical records:

In order to protect your confidentiality, only the investigators and individuals involved in the study will have access to your medical records for strictly study related purposes.

Information and sample identification:

All samples, assessment results and patient information are ‘coded’ and stored accordingly to protect confidentiality of all information related to you. Other than the investigators and study team, information related to you cannot be identified.

Confidentiality:

Confidentiality and privacy of information is protected under currently effective acts, policies and procedures governing privacy and confidentiality. The patient codes are used to exchange and information.

Duration of storing data:

Data related to the study will be stored for ‘three calendar years’. You can exist/withdraw from the study at any time with which your information/data related to the study will be immediately destroyed.

Benefits from participating in the study:

Your participation in this study will contribute to the development of treatment and care protocols of substance use disorders. Your chances for better recovery might be enhanced yet it is not possible to anticipate extend of your acquired benefit from participating in the study. Participating in this study will facilitate structured regular monitor of your recovery status.

In the even of adverse events or emergencies, standard of care optimal procedures will be implemented without financial indemnity.

Confidentiality of results and publication:

Further to your consent to participate in this study, results generated from this study may be published in peer reviewed scientific journal or presented in scientific conferences without violating the confidentiality of participant personal information.

You are entitled to be informed of the study results notwithstanding the confidentiality requirements.

Freedom of participation:

Your participation in this study is entirely voluntary and you are free to discuss the matter with your next-of-kin or a close person/relative before you decide. Remember that you can withdraw from the study at any point in time at your discretion.

Please be assured that your decision not to participate in the study will not be associated with any ramifications or consequences and would not deprive you from any of your rights or privileges, and you are not accountable for your decision to withdraw from the study. All information gathered in the context of the study will be destroyed.

Declaration of the investigator:

I declare that I have explained the nature of the study and its associated procedures/requirements to and I have responded to all queries and questions. I declare that the participant will be informed with any updates or unanticipated adverse events during the course of the study.

Date

Investigator

Signature

Declaration of the participant:

I.....declare that I have read and understood all the information provided to me and that all my questions were clearly answered. I am aware that I am free and able to withdraw from the study at any point with no restrictions or conditions that my affect my rights as a patient.

I am also aware the principle investigator Dr. Hesham Elarabi is read to answer my questions and queries and I can reach him over the telephone number 050-4460781. I am aware that all the information provided by me is governed by strict confidentiality standards and will be respected and protected by the study investigators.

I declare that the nature of the information to be gathered for the purpose of the study was explained including all related procedures and the underlying objective and how the data will be used at the end of the study and after completing the data analysis.

I consent to publish the data related to the study provided that the confidentiality of my identity and personal information are protected.

Date

Participant

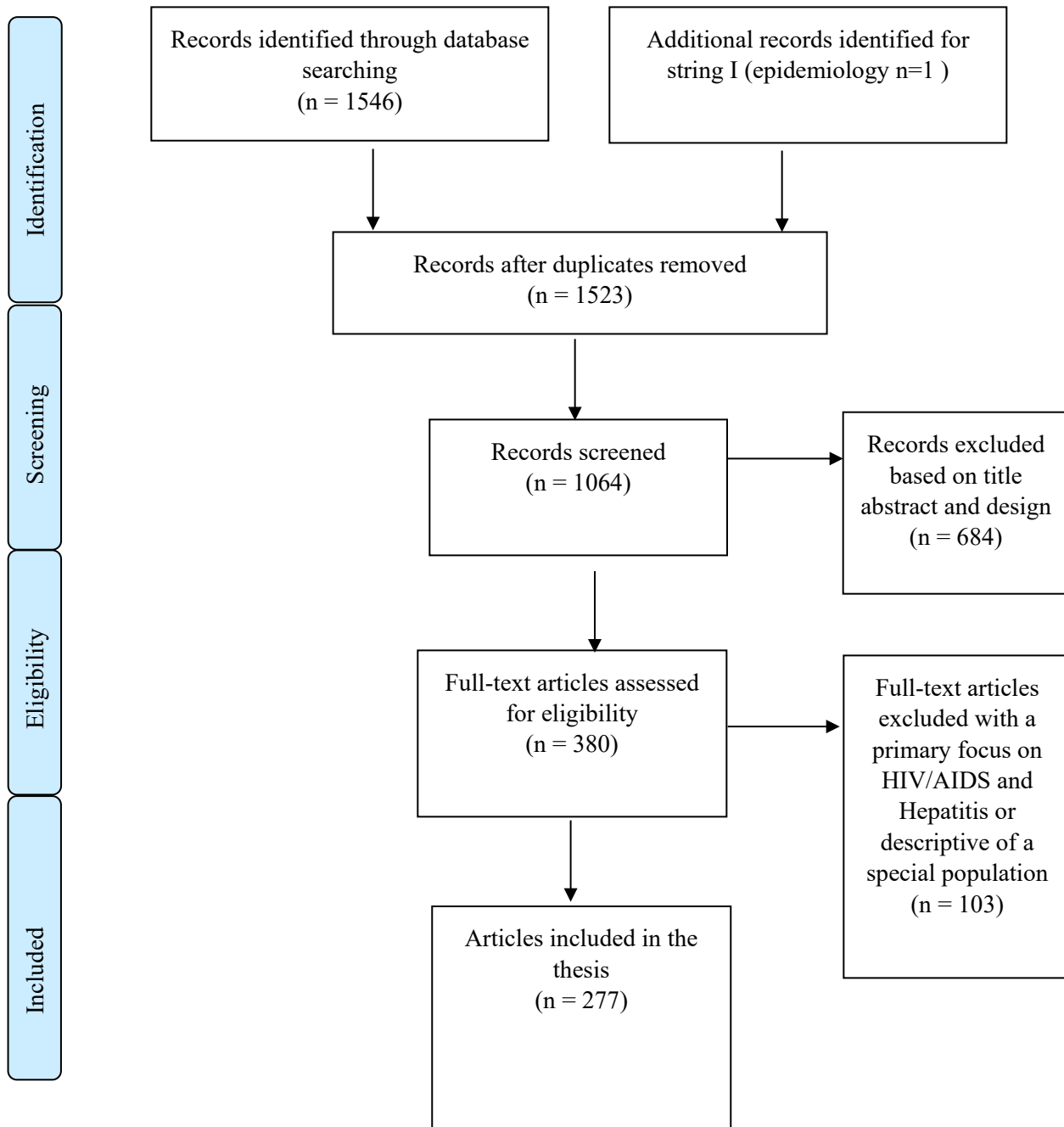
Signature

Appendix A7. Staff contribution

Staff	Title/Position	Contribution	Address
Tarek Gawad	Psychiatrist-Medical Director	Provided input on integration of the protocol in clinical management, eligibility criteria	Tarek.Gawad@nrc.ae; P.O.Box 55001, ABU DHABI, SHAKHBOOT CITY, AD, UAE
Abulegasim Al Rasheed	Clinical Scientist	Developed the detailed method of BUP quantitation. Performed all laboratory assays assisted by the student	Abuelgasim.Elrasheed@nrc.ae ; P.O.Box 55001, ABU DHABI, SHAKHBOOT CITY, UAE
Ahmed Yousif	Chief Psychiatrist	Provided input on the research tool selection, the management of adverse events and comorbidity, study design and supervised clinical management	<u>Ahmed.ali@nrc.ae</u> ; P.O.Box 55001, ABU DHABI, SHAKHBOOT CITY, UAE
Doaa Nader	Psychiatrist (Detoxification)	Gathered consent and recruited participants. Performed clinical management at the detoxification.	<u>Doa.nader@nrc.ae</u> ;P.O.Box 55001, ABU DHABI, SHAKHBOU CITY, UAE
Nael Hasan	Psychiatrist (Inpatient care)	Provided input in clinical management of the detoxification/induction phase for poly substance users, stabilization and early recovery phase of the study. NH has performed step one the internal audit. Contributed to the pilot phase	<u>nael.hasan@nrc.ae</u> ; P.O.Box 55001, ABU DHABI, SHAKHBOOT CITY, UAE
Mansour Shawky	Psychiatrist (outpatient)	Provided input on study design. Screened participants at intake for study eligibility. Performed clinical management	<u>mansour.shawky@nrc.ae</u> ; P.O.Box 55001, ABU DHABI, SHAKHBOOT CITY, UAE

		at the outpatient service.	
Mohamed Al Junaibi	Psychiatrist (outpatient)	Performed clinical management at the outpatient service	
Helal Al Kathiri	Social Worker (outpatient)	Contacted participants for end of study assessments both in treatment and dropouts. Participated in administering end of study assessment	
Ahmed Al Alawi	Social Workers (outpatient)	Contacted participants for end of study assessments both in treatment and dropouts	
Ahmed Kashmar	Registered Nurse (inpatient)	Performed dose stabilization and coordinated drawing BUP peak and trough concentrations	
Ameera bin Amro	Medical Records officer	Performed step two of the internal audit	
Rinso Paul	Medical Records officer	Performed step two of the internal audit	
Alison Gonzalez	Medical Secretary	Performed step two of the internal audit	
Abdu Adem	Professor of therapeutics-Second Supervisor	Provided input on the design of the study and supervised its delivery	P.O.Box 15551, Alain, AD, UAE
John Marsden	Professor of Addictions Psychology-First Supervisor	Participated in developing the study concept, supervised the implementation and performed external audit	John.marsden@kcl.ac.uk

Figure 2.1 Literature Search Flow



Appendix. C. Patient Management and education materials

- Appendix C.1.** Adapted Medication Therapy Management foundation form
- Appendix C.2.** Medication Therapy Management Session follow up form
- Appendix C.3** Medication adherence form
- Appendix C.4** Patient Education Handout
- Appendix C.5** Emergency card
- Appendix C.6** Patient Recovery Passport (Patient diary)
- Appendix C.7** Patient Counselling Check list
- Appendix C.8** Buprenorphine/naloxone counseling
- Appendix C.9** Adverse Event Form
- Appendix C.10** Adverse Events Management
- Appendix C.11** Pharmacotherapy consultation form and progress report

Appendix C1. Adapted Medication Therapy Management foundation session form

Participant ID: _____ Date: _____

Therapist / Researcher:

MEDICATION MANAGEMENT FORM (FOUNDATION SESSION)

Session start time:

	<u>Y</u>	<u>N</u>
Perform UDS		
Take Waist, Hip measurements (Ratio > or < 90) and Body Weight		
Provide feedback on patient status		
Invite Reflection from the patient		

Session Introduction:

Explain diagnosis and how it applies to the patient		
Assess motivation Level		
Ask the patient to provide two main goals for treatment		
1.		
2.		

Craving

Educate patient on Craving and recovery Process		
Ask the patient to identify two main cues for craving		
1.		
2.		
Ask the patient to identify two relapse preventions skills		

Suboxone

Counsel the patient on Suboxone (Refer to Counseling Checklist)		
Provide printed material		
Provide Emergency Card		
Provide medication diary		

Session end time: _____ (hr:min a.m./p.m.)

*Tick 'Yes' or 'No' to indicate whether the line item has been completed.

Appendix C2. Medication Therapy Management Session follow up form

Participant ID: _____ Date: _____

Therapist / Researcher:

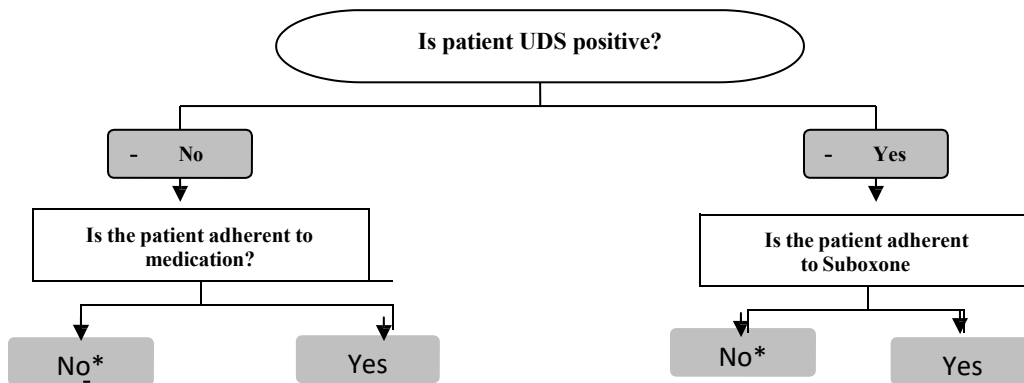
MEDICATION MANAGEMENT FORM (Follow up form)

Session start time:	Completed	
1. <u>Opening statement</u> -- ‘how have you been?’	Yes	No
2. Perform all assessments as indicated	Yes	No
3. Evaluate Patient Status		
4. Review medication diary and adherence	Yes	No
5. Review TDM results	Yes	No
6. Is there discrepancy between patient reporting and TDM	Yes	No
7. Determine patient’s status (circle only one):	Yes	No
Abstinent/Adherent Non-Abstinent/Adherent		
Abstinent/Non-Adherent Non-Abstinent/Non-Adherent		
6. Provide necessary counseling	Yes	No
7. Patient change since in treatment? (circle only one) Improved	Yes	No
Minimal Change Worse		
8. Did the patient experience new problems?	Yes	No
If Yes what _____		
9. Remind patient how medication works & promote continued use	Yes	No
10. Encourage/praise patient’s efforts	Yes	No
11. Schedule/verify next session	Yes	No

Session end time: _____ (hr:min a.m./p.m.)

MTM Follow-up Session Dialogue Flowchart

(Adapted from 'Helping Patients Who Drink Too Much: A Clinician's Guide', National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, (updated 2005), p. 22; www.niaaa.nih.gov/guide)



Congratulate patient for being abstinent
Review benefits of abstinence
Review benefits

Reinforce patient's ability to follow advice and stick to the plan
Ask what the patient did to achieve this outcome

Review goals of treatment
Review benefits of abstinence
Review benefits of abstinence

Praise any small steps toward abstinence
Review benefits of abstinence
Review benefits

Ask why BUP/NX is not taken Regularly

Encourage patient to stick with the plan- 'keep up the good work!'

Review reasons for nonadherence
Create new adherence plan
Ask patient to 'give treatment a chance'
Set the next appointment

Remind patient that medication takes time to work
Set the next appointment

Explore remedies to correct nonadherence

Review benefits of abstinence

Set the next appointment

Set the next appointment

Other recommendations (e.g. side effects management, new adherence plan): _____	

Follow-up:	-Continue the current treatment plan
	-Change the treatment plan as follows: _____

	-Refer for medical evaluation
Next appointment date:	_____

*Examined and predicted BUP concentrations are outside the 20% range

Appendix. C3. Medication adherence form

Participant ID: _____ Date: _____

Therapist / Researcher:

Review common reasons for non-adherence

Ask patient, 'Might any of the following common situations be problems for you when taking medication?' (Circle number next to any that apply)

- | | |
|---|---|
| 1. Forgets to take or loses medications | 5. Desires to use drugs or 'get high' |
| 2. Worries about side effects | 6. Tired of taking pills every day |
| 3. Believes he/she is taking placebo | 7. Disagrees about having an opioid dependence disorder |
| 4. Has misinformation about medications (e.g., expects instant changes in | 8. Feels like he/she no longer needs medication |
| | 9. Has never liked taking pills – even aspirin |

Tell patient, 'If any of these situations occur, please talk to me about it.'

Notes:

A. Discuss Successful Suboxone taking Strategies

List agreed effective Strategies to enhance adherence:

- 1.
- 2.
- 3.



أعاني من النسيان فكيف أتذكر تناول الدواء

في موعده المحدد

- حاول التزم أحد أفراد الأسرة المريضين على علاجك ومن يراعي الدقة والمتابعة معهم لتذكرك بالجرعات والتأكد من التزامك بها.

- استخدم أي آلية تساعد على تذكرك بموعد الجرعة، مثلا، قم بضغط جهاز التنبيه في هاتفك المحمول أو ساعتك أو قم دائما بتدوين موعد الجرعة.

- في حال نسيان أحد الجرعة في الوقت المحدد، قم بأخذها فور التذكر حتى ساعتين قبل الجرعة التالية ولكن إذا قل الوقت عن ساعتين انتظر موعد الجرعة التالية واستمر في جدول الجرعات المعتاد ولا تأخذ الجرعتين سوياً.
- قم بتدوين الموعد الفعلي للجرعة وأسباب عدم تناولها في الموعد المحدد إن حدث ذلك.



أحس بالأعراض الجانبية من الدواء فلا أستطيع تناوله

باستمرار، ماذا أفعل؟

غالباً لا تحدث الأعراض الجانبية لكل المرض وإذا حدثت فهي مؤقتة وتقلت في الصدمة وتتخطى بمرور الوقت. والأعراض الجانبية للسبكونز يمكن التعامل معها حسب الإرشادات التي تتلقاها من طبيبك، ومن هذه الأعراض الشعور بالصداع، الإسهال والغثاس، اضطراب في الرؤية، والأرق (صعوبة في النوم) وهي غالباً قليلة الحدوث الصدمة.

راقب هذه الأعراض وأبلغ طبيبك عنها.

كيف أتناول الدواء؟

هذا الدواء يتوفر في شكل رقائق يتم وضعها تحت

اللسان حتى تذوب كاملة ولا

يتم ارتذائها، قبل فتح الغلاف

المحيط بالكابول لإخراج

تأكد من أنه قد حُصلت

يديك ولشفتها جيداً.

• إذا كانت جرعتك عدة رقائق، قم بوضع كل

واحدة على حدة، متصلة تحت اللسان بحيث لا تلتصق الرقائق ببعض وتخرج هذا

الاجزاء (راجع الصور التوضيحية)

• لا تقوم بلع أو قطع أو مضغ الرقائق فهذا قد يؤثر على فعالية الدواء.

ما هي الجرعة التي يجب أن أأخذها؟

يتم وصف الجرعات حسب احتياج كل شخص على حدة، وقد تكون جرعتك لأوحد مرة

في اليوم أو مرة كل يومين أو كل ثلاث أيام في الأسبوع.

تذكر أن المحافظة والالتزام بالجرعات ومواعيدها للوصول لتساعدك على سرعة الشفاء.

لا تقم بتغيير الجرعات من تلقاء نفسك إلا بعد الرجوع الى طبيبك للعلاج.

إني حين يجب أن تناول هذا الدواء؟

هذا الدواء ليس كالأدوية التي يتم تناولها عند الحاجة ولكنه مشابه لأدوية

الأمراض المزمنة كضغط الدم والسكري والتي يجب تناولها باستمرار، لذلك، حتى تصقن

أفضل نتيجة وتحافظ على التصاق يجب المحافظة على العلاج وتناول الدواء حسب ما هو

موصوف لمدة لا تقل عن 6 أشهر.

تذكر أن مواظبتك على العلاج تسهم في تحقيق واستدامة الشفاء.

لا تتوقف عن استخدام الدواء من تلقاء نفسك واستشر طبيبك حيال رغبتك بالتوقف

عن الدواء. إن التوقف المفاجيء قد يسبب أعراض مشابهة للأعراض الإسجابية.

تذكر أن المواظبة في تناول الدواء تساعدك على الشفاء بشكل كامل

قد تم وصف عقار السبكونز من قبل طبيبك وذلك ضمن علاجك من مرض

الإدمان على الأفيونات (الزمامادول، المورفين، الهيروين).

قد لا تكون مسؤولاً عن حدوث المرض، ولكن العلاج مسؤوليك ومدك، وحتى تصقن

القائدة المبرومة من هذا العقار، فإنت مدعو إلى فهم ومراعاة محتوى هذا المنشور

التوعوي:

ما هو السبكونز؟

السبكونز هو الإسم التجاري لعقار يحتوي على مادة تسمى البيبوتريدين "ومشابه لعقار

معروف باسم السبيونكس". لهذا العقار كفاءة عالية مسندة بالبحوث العلمية في التعالي

من الإدمان على الأفيونات كالهيروين وأشياء الأفيونات كعقار الزمامادول.

لماذا لم وصف هذا العقار لي؟ وما الذي يجب أن أتوقعه من هذا العقار؟

يوصف عقار السبكونز للأشخاص الذي تم تشخيصهم بمرض الإدمان على الأفيونات

حيث أنه يساعد على خفض الأعراض الإسجابية نتيجة التوقف عن استخدام المادة

المخدرة، ويساعد في خفض الشعور بالشرق والحمين للمخدرات، بالإضافة إلى خفض

مستوى التشنج من استخدام المادة المخدرة وبذلك يسهم في تحقيق والمحافظة على

التصاق.

"تذكر أن هذه العبارة يتم الحصول عليها فقط عند الالتزام بتناول الدواء حسب

التعليمات والجرعات الموصوفة، قد تأخذ بعض الوقت للحصول على الفائدة القصوى

للدواء، فلا تستعمل النتائج، سوف يقوم للعلاج وطبيبك بتحديد فعالية الدواء واتجاه

التدخلات اللازمة".

تذكر أن العلاج يشمل أدوات مختلفة بجانب الدواء، ولذلك يجب المحافظة والالتزام بكل

مكونات العلاج الأخرى كالعلاج النفسي والأرباط الأخرى و تكوين شبكة دعم اجتماعي

بالإضافة إلى الأنشطة الدينية والروحانية كالمحافظة على الصلاة و قراءة القرآن. كإضافة هذه


الأدوات تعيدك على استمرار التصاق و عدم عودتك للتعاظم مرة أخرى.

Appendix C.5 Buprenorphine/Naloxone Emergency Card

**البيرينورفين / نالوكزون**
بطاقة الطوارئ

هذه البطاقة لتعريف مقدمي الخدمات الصحية أن
السيد/السيدة..... يتناول
عقار السبكسون (البيرينونورفين / نالوكزون) بجرعة قدرها..... في
اليوم / ثلاث مرات في الاسبوع / أربع مرات في الاسبوع. تم وصف عقار السبكسون في
المركز الوطني للتأهيل بأبوظبي (www.nrc.ae) لهذا المريض بدءاً
من ____ / ____ / ٢٠١١ والمتوقع أن يستمر في تلقي العلاج الى تاريخ ____ / ____ / ٢٠١١

الطبيب الرئيس:
رقم التواصل: +٩٧١ -٢- ٥٥٧ ٤٠٤١

**Buprenorphine/Naloxone**
Emergency Card

This card informs health care providers that
Mr/Mrs..... is on Suboxone®
(Buprenorphine / Naloxone) dose ofmg / O.D, Q1W,
TIW. Suboxone has been prescribed at the National Rehabilitation
Center – Abu Dhabi (www.nrc.ae) on for this patient
on ____ / ____ / 2011 and is expected to continue until ____ / ____ / 2011

Primary psychiatrist:
Contact number: 00971-2-557 4041

Appendix. C.6. Patient Passport to Recovery (Patient diary)



رقم الجواز.....

اسم صاحب الجواز.....

الوجه.....

.....

.....

.....

تاريخ الإصدار..... تاريخ الإنتهاء.....

إرشادات عامة

١. هذا الجواز ملك للمركز الوطني للتأهيل، لذا في حال فقدان هذا الجواز والعثور عليه يرجى الإتصال على رقم . ٠٤١ ٥٥٧٤ ٢+
٢. استكمال بيانات الجواز بشكل دوري مسؤولية صاحب الجواز
٣. الحصول علي التأشيرات الخاصة بمراحل التعافي مسؤولية صاحب الجواز

توقيع صاحب الجواز

Week 1 Assessments

	Score				
Date					
PHQ - 9					
GAD - 7					
Personality Disorder Screener					
Barrett's Impulsivity Scale					

Substance Use Assessment

	Score				
Date					
ADAPT					
ASI-LITE					
Pupillometer					
Craving Scale					
Sleep Quality					
* PSQI0					

Discharge Medications

	Name	Dose	Frequency
1			
2			
3			
4			
5			
6			
7			

VISA
التأشيرة

CONGRATULATIONS

تهنئتنا

YOU HAVE SUCCESSFULLY COMPLETED ALL THE VISA
REQUIREMENT FOR THIS PHASE OF RECOVERY.

قد أكملت بنجاح كافة متطلبات تأشيرة التعافي
في هذه المرحلة



Week diary

المشرف على الجرعة	سبب عدم الالتزام أو النسيان	موعد الجرعة الفعلي	الوقت	التاريخ	اليوم
					الأحد
					الاثنين
					الثلاثاء
					الأربعاء
					الخميس
					الجمعة
					السبت

Appendix C.7. Patient counselling checklist

Buprenorphine/Naloxone Counseling Checklist

Patient ID: _____ Session # _____ Date: _____

#	Area	Yes	No
	Provide Suboxone nomenclature and class		
	Explain reason for prescribing Suboxone and set patient expectations from the medication		
	Educate the patient on how to take the medication and not to cut, chew, swallow		
	Educate the patient how to record the doses and what to do in case of missed dose		
	Educate the patient on importance of compliance		
	List the most important strategies to optimize adherence		
	Suggest to invite a family member to this medication session		
	Counsel the patients on special precautions while being on Suboxone and its ability to impair common activities like driving		
	Educate the patients on the incidence of side effects and what to do in case it occurs		
	Educate the patient how to self-monitor his progress		
	Provide the patients with Emergency Cards		
	Provide the patients with medication diary		
	Inform the patient on follow up and take home doses		
	Inform the patient of how to store the medication		
	Counsel the patient on what to do emergency situations		
	During the session, adjust the instruction to appropriately accommodate the patient's responses		
	Assess patient understanding and verify skills and information learned		
	Address any concerns		
	Close with a positive statement and commitment to adherence		

Appendix C.8. Buprenorphine/naloxone counseling

Before induction on BUP/NX the PI/investigator reviews all medications used by the patient, whether prescribed at the NRC or by other physician, or are 'over the counter'. The PI reviews the doses completed in the medication diary section of the 'Patient Passport'. The diary lists all medications the patient is using; their doses and time of use. The diary comprises of fields to check that the BUP/NX-F has been taken. If a dose is missed, the reason for missing the dose will hence be recorded in the 'Patient Passport' address questions, concerns, and reach a conclusion.

The PI/Investigator verifies the patient's knowledge and understanding of the medications prescribed and addresses any incomplete or misunderstandings observed. Briefly, the PI/Investigator summarised the concept of OAT and its purpose to achieve recovery. The PI/Investigator may repeat some of the information covered earlier, while explaining the treatment and diagnosis as this is critical to encouraging patient adherence.

The PI/Investigator ensures the patient's understanding that Suboxone[®] is prescribed to further to the diagnosis of opioid use disorders. The PI/Investigator clearly indicates that Suboxone[®] increases tolerance to opioids or decreases the patient's sensitivity to opioids. Furthermore, highlights that Suboxone[®] decreases craving and decreases/eliminates withdrawal syndrome. Adding to that, the PI/Investigator reinforces the importance of taking the medication, as prescribed, to achieve the better control of craving hence decreases the chances of relapse over time while highlighting that response to treatment differs from one person to another.

Finally, the PI/Investigator reinforces that treatment is holistic and the value of the medication prescribed is best realised within such comprehensive approach. At large the aim of the PI/Investigator is to ensure he has informed the patient of the trade and generic names of BUP/NX-F and its therapeutic class, and explained why Suboxone[®] is being prescribed to this patient and help set expectations.

After transferring the patient to the recovery unit at which the patient is stabilised on BUP/NX received under supervision by a medical professional, the PI/Investigator details the steps of applying the BUP/NX films with the aim the medication information leaflet and the illustrations developed for this purpose. PI/investigator informs the patient that hands need to be washed and dried well before applying the film. The PI/investigator demonstrates to the patient, how to tear the strip cover, remove the film, and finally place it under the tongue until the film completely dissolves. The PI/Investigator stresses on the

fact that the patient should not attempt to remove the BUP/NX-F after applying it. In case more than one film is to be applied, e.g. the patient dose is 16 mg (i.e. two films of 8 mg), the PI/Investigator counsels the patient to place the films apart as much as possible under the tongue to avoid any overlap. The PI/Investigator explains that the patient should not swallow cut or chew the film, as it will affect its release and effectiveness.

The PI/investigator explains the **dosing structure and actions recommended in-case of missed doses**. The dose schedule and timing are explained. The PI/Investigator discusses best timings for the patient to take their doses and the importance of not changing these timings. Furthermore, strategies to ensure that the patient remembers to take the medication on time, for example, ask a family member to support and monitor dose administration is further discussed with the patient. In case of missed doses, the PI/Investigator informs the patient to take the medication as soon as he remembers and that such incidences should be, documented on the medication diary recording the actual time of taking the medication.

The PI **encourages medication adherence** by summarising the value of adherence in controlling craving and supporting the patient's efforts to achieve abstinence and optimal treatment outcomes. For example, the PI states *'in order for you to benefit from Suboxone[®] prescribed to support your treatment goal of abstinence, you must take the medication consistently and as prescribed. It can take some time for the medication to have its full effect on helping you to change your disease approach.'* This medication is not like Panadol, which is taken only when you feel you need it. This medication can help you maintain abstinence, only if you take it consistently every day, as you would take insulin or a hypertension medicine.'

Next, the PI counsels the patient on special precautions using the BUP/NX -F as it can affect the patient ability to drive or operate hazardous machinery, highlighting that this is particularly common in early stages of treatment and during dose adjustments. The PI further notifies the patient not to perform such tasks until they are comfortable doing so and the medication is not adversely affecting their ability to perform such tasks. The PI further informs the patient to let his doctor/dentist be aware of their use of Suboxone[®]. The patient is then handed over the 'Emergency Card' to be kept in the patient's wallet at all times, for any emergent situation. The card states the dose of Suboxone[®], STAR-T date and expected end date, name of the primary medical provider and treatment centre their emergency contact numbers.

The PI further counsels on the medication safety highlighting: i) the danger to take drugs like benzodiazepine along with alcohol while on BUP/NX; ii) the need to discuss all new medications that affect mood or sleep , iii) to keep Suboxone[®] off the reach of children and steps to be taken in case of accidental use happen, iv) not to share Suboxone[®] with family members or friends as well as that selling medication is illegal.

The PI then explains the **potential common and severe adverse effects that may occur, and actions to prevent or minimise their occurrence, and actions to take if such events occur.** The PI informs the patient that adverse events neither occur in all participants nor do all listed adverse events occur. The PI further highlights that if these events should occur, they are usually temporary and ultimately manageable and participants should not expect that adverse events are permanently occurring. Next, the PI outlines common adverse events like headache, constipation, vomiting, disturbance in vision and insomnia and explains how these events are managed. The PI also highlights the response procedure in case other serious non-expected adverse events occur.

The PI ensures informs the patient on how to store the medication away from heat and/or humidity. Additionally, the PI provides the patient with clear steps, phone numbers and actions to be taken in case of any emergency. This includes if the patient decides to travel abroad, and the need to review regulations of controlled medications at destination country.

Appendix C.9. Adverse Event Form : Record diagnoses (if known) or signs/symptoms the participant/subject experienced during the study that qualify as adverse events. Has the participant/subject had any adverse events during the study? Yes No

Adverse Event	Start Date and Time	End Date and Time	Severity	Relatedness	Action Taken with Study Intervention	Other Action Taken	Outcome	Serious Adverse Event?
	Date: ___/___/20___ (mm/dd/yyyy) Time: ___:___ (hh:mm) <input type="checkbox"/> AM <input type="checkbox"/> PM <input type="checkbox"/> 24-hr clock	Date: ___/___/20___ (mm/dd/yyyy) Time: ___:___ (hh:mm) <input type="checkbox"/> AM <input type="checkbox"/> PM <input type="checkbox"/> 24-hr clock	<input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe <input type="checkbox"/> Life-threatening/ <input type="checkbox"/> Disabling <input type="checkbox"/> Death	<input type="checkbox"/> Unrelated <input type="checkbox"/> Unlikely <input type="checkbox"/> Probable <input type="checkbox"/> Possible <input type="checkbox"/> Definite	<input type="checkbox"/> None <input type="checkbox"/> Study Intervention Interrupted <input type="checkbox"/> Study Intervention Discontinued <input type="checkbox"/> Study Intervention Modified	<input type="checkbox"/> None <input type="checkbox"/> Non-Study Treatment Required	<input type="checkbox"/> Not Recovered/Not Resolved <input type="checkbox"/> Recovered/Resolved <input type="checkbox"/> Recovered/Resolved With Sequelae <input type="checkbox"/> Recovering/Resolving <input type="checkbox"/> Fatal <input type="checkbox"/> Unknown	<input type="checkbox"/> No <input type="checkbox"/> Yes *
	Date: ___/___/20___ (mm/dd/yyyy) Time: ___:___ (hh:mm) <input type="checkbox"/> AM <input type="checkbox"/> PM <input type="checkbox"/> 24-hr clock	Date: ___/___/20___ (mm/dd/yyyy) Time: ___:___ (hh:mm) <input type="checkbox"/> AM <input type="checkbox"/> PM <input type="checkbox"/> 24-hr clock	<input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe <input type="checkbox"/> Life-threatening/ <input type="checkbox"/> Disabling <input type="checkbox"/> Death	<input type="checkbox"/> Unrelated <input type="checkbox"/> Unlikely <input type="checkbox"/> Probable <input type="checkbox"/> Possible <input type="checkbox"/> Definite	<input type="checkbox"/> None <input type="checkbox"/> Study Intervention Interrupted <input type="checkbox"/> Study Intervention Discontinued <input type="checkbox"/> Study Intervention Modified	<input type="checkbox"/> None <input type="checkbox"/> Non-Study Treatment Required	<input type="checkbox"/> Not Recovered/Not Resolved <input type="checkbox"/> Recovered/Resolved <input type="checkbox"/> Recovered/Resolved With Sequelae <input type="checkbox"/> Recovering/Resolving <input type="checkbox"/> Fatal <input type="checkbox"/> Unknown	<input type="checkbox"/> No <input type="checkbox"/> Yes *
	Date: ___/___/20___ (mm/dd/yyyy) Time: ___:___ (hh:mm) <input type="checkbox"/> AM <input type="checkbox"/> PM <input type="checkbox"/> 24-hr clock	Date: ___/___/20___ (mm/dd/yyyy) Time: ___:___ (hh:mm) <input type="checkbox"/> AM <input type="checkbox"/> PM <input type="checkbox"/> 24-hr clock	<input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe <input type="checkbox"/> Life-threatening/ <input type="checkbox"/> Disabling <input type="checkbox"/> Death	<input type="checkbox"/> Unrelated <input type="checkbox"/> Unlikely <input type="checkbox"/> Probable <input type="checkbox"/> Possible <input type="checkbox"/> Definite	<input type="checkbox"/> None <input type="checkbox"/> Study Intervention Interrupted <input type="checkbox"/> Study Intervention Discontinued <input type="checkbox"/> Study Intervention Modified	<input type="checkbox"/> None <input type="checkbox"/> Non-Study Treatment Required	<input type="checkbox"/> Not Recovered/Not Resolved <input type="checkbox"/> Recovered/Resolved <input type="checkbox"/> Recovered/Resolved With Sequelae <input type="checkbox"/> Recovering/Resolving <input type="checkbox"/> Fatal <input type="checkbox"/> Unknown	<input type="checkbox"/> No <input type="checkbox"/> Yes *

Appendix. C.10. Adverse event management

Event	Management
Headache	Paracetamol 1g qid (prn)
Pain	Paracetamol 1g qid (prn)
Asthenia	Evaluate Sleep and general life style. Counsel the patient on health promotion
Constipation	Bisacodyl 5mg prn
Insomnia	Evaluate the cause of insomnia. Check if new drugs were added or dose adjustment to current concurrent medications Evaluate sleep wake cycle. Check for withdrawal syndrome if present increase the dose by 4 mg. If absent add Zopiclone 7.5 mg or Hydroxyzine 10 mg.
Orthostatic Hypotension	Discuss possible reasons with his primary physician. Advise the patient not to abruptly stand from supine or sitting positions
Dizziness	Discuss possible reasons and interventions with primary physician.
Abdominal Pain	Hyoscine HBr TID
Nausea	Assess severity. Advice on food intake.
Vomiting	Domperidone 30 mg (Peripheral Dopamine Blocker)
Dyspepsia	Esmoperazole 20 mg per required need

Appendix C.11 Pharmacotherapy consultation form and progress report

Example 1

Date of Visit:

Chief Complaint (CC): Hypotension, increased craving

Cognitive impairment assessed by MMSE (Score 23) on the 18-July has subsided (MMSE score 9). Patient described unanticipated severe anxiety with hyper-arousal, fear and intense crying doesn't get resolved until the patient cuts himself and would only relax after he sees the blood then sleeps

Subjective: Patient description	Objective: Nursing confirming patient's request for a knife to harm himself
Assessment: Assess for panic disorder/ PTSD	Plan: Close observation Increase BUP/NX dose to 10 mg

Pharmacotherapy Recommendations:

1. Rx Sertraline 50 mg/OD

Non-Pharmacotherapy Intervention:

1. Psychology evaluation of PTSD, Depression, BPD
2. Social work evaluation of patient family approaches

Example 2

Date of Visit:

Chief Complaint (CC): Agitation and sleep disturbance

Patient presents with mix state mood disorder including and impulsiveness. He is currently on Haloperidol 5 mg BiD, Atomoxetine 60 mg OD, Depakine 1500 mg BID, and Quetiapine 200 mg h/s and Clomipramine 150 mg h/s. The patient reports fatigue and avolition possibly due to poor sleep quality.

Subjective: Agitation and fatigue	Objective: BIS 82.
Assessment: Re-consider the use of Atomoxetine.	Plan: Minimise poly-therapy and control agitation

Pharmacotherapy Recommendations:

1. D/c Haldol, Depakine, Triptizol, Quetiapine
2. R/x Zyprexa 10 mg H/s for both mood and sleep
3. R/x Lamotrigine IR 25 mg OD for two weeks, then increase by 50 mg every two weeks with close monitor for SJS
4. R/x Buspirone 5 mg TiD

Non-Pharmacotherapy Intervention:

1. Sleep hygiene
2. Behavioral Activation

Example 3.

Date of Visit:

Chief Complaint: Mixed mood disorders

Patient referred for pharmacotherapy consult for increased fatigue and lack of response to treatment.

<p>Subjective: Patient reporting severe fatigue and avolition</p>	<p>Objective: Poor quality of sleep (PSQI = 10)</p> <p>Current medication: (i) haloperidol 5 mg twice daily, (ii) atomoxetine 60 mg once daily, (iii) valproic acid 1500 mg twice daily, (iii) quetiapine 200 mg at bedtime, and (iv) clomipramine 150 mg at bedtime.</p>
<p>Assessment: Problematic polypharmacy</p>	<p>Plan: Reduce fatigue symptoms and adjust pharmacotherapy as follows:</p> <ul style="list-style-type: none">i) Discontinue haloperidol, clomipramine, valproic acid, and quetiapineii) Initiate olanzapine 10 mg at bedtime, based on evidence of efficacy in addressing both mood and sleep issuesiii) Initiate lamotrigine Immediate Release 25 mg once daily for two weeks, to be increased by 50 mg every two weeks with close monitoring

Appendix D. Buprenorphine laboratory detection and quantitation

Appendix D.1.1	Method for extraction of buprenorphine and norbuprenorphine
Appendix D.1.2	Preparation of reagents
Appendix D.2.1	Calibration Curve for Buprenorphine
Appendix D.2.2	Calibration Curve for norbuprenorphine
Appendix D.3.1	Chromatogram for blank sample
Appendix D.3.2	Signal-to-Noise ratio
Appendix D.4	Norbuprenorphine peak and trough concentrations

Appendix D.1.1 Method for extraction of buprenorphine and norbuprenorphine

Extraction was performed using SPE procedures developed and published by United Chem (n.d.). 1 mL of plasma provided was mixed with 1 mL of acetate buffer (PH 5.0 100 mM), 20 uL of ISTD (5 PPM), 50 uL, and 5,000 units/mL β -Glucuronidase, and was left to hydrolyse at 65 °C overnight before adding 3 mL of phosphate buffer (100 mM, pH 6). Following a centrifuge, the sample was checked and pH was adjusted to 6.0 ± 0.5 using 100 mM monobasic or dibasic sodium phosphate. Centrifuge was performed again for 10 minutes at 2,000 rpm and the pellet was discarded. The sample was next rinsed with 3 mL of methanol, before adding 3 mL of distilled water and lastly 3 mL of phosphate buffer (100 mM, pH 6.0). Each solvent was applied immediately after the previous one. Aspiration was then performed at soft pressure to avoid complete dryness, before passing 1 mL of the sample through the SPE column at a rate of 1 mL/min. The column was washed with 3 mL of distilled water, 3 mL of acetic acid (100 mmol or 1 Molar), and 3 mL of methanol to remove the excess sample matrix, after which it was left to dry for 10 minutes (at 50 psi). Analytes were eluted from the SPE column by rinsing with 3 mL DCM: IPA: NH₄OH (dichloromethane: isopropyl alcohol: ammonium hydroxide, 78:20:2) before applying soft pressure to elute residual solvents from the column. The elution solvent was prepared daily and was evaporated to dryness at <40 °C (at 5–15 psi). The sample was reconstituted in 200 μ L of 20 MPB (mobile phase B: 0.1% formic acid aqueous) 80 MPA (mobile phase A: 0.1% formic acid in methanol). Finally, the concentrated extract was transferred to a micro-volume autosampler vial.

Extraction Column: CLEAN SCREEN DAU 200 mg, 6 mL Tube.CSDAU206 – UCT

External Standards (Cerilliant, TX-USA): Buprenorphine, 100 ng/mL;
Norbuprenorphine, 100 ng/mL

Internal Standards (Cerilliant, TX-USA): Buprenorphine-D4, 100 ng/mL;
Norbuprenorphine-D3, 100 ng/mL

Calibrators:

Stock I: Standards of each drug were prepared by dilution with methanol.

Standard	Concentration	Volume of standard in 100 mL
Buprenorphine	500 ng/mL	0.5 mL
Norbuprenorphine	500 ng/mL	0.5 mL
Buprenorphine-D4	500 ng/mL	0.5 mL
Norbuprenorphine-D3	500 ng/mL	0.5 mL

Stock II: Prepare by combining the following standards and make up the volume with phosphate buffer (100mM, pH 6.0).

50mL Calibrator 100mL ISTD	BUP	B-BUP	BUP-D4	N-BUP D3
Calibrator (100 ng/mL)	10 mL	10 mL	-	-
ISTD (100 ng/mL)	-	-	20 mL	20 mL

Working Standards: dilute stock II in phosphate buffer (100mM, pH 6.0)

	Amount of mix in 50mL	Amount of ISTD in 50mL
STD I (0.2 ng/mL)	0.1 mL	15 mL
STD II (1 ng/mL)	0.5 mL	15 mL
STD III (5 ng/mL)	2.5 mL	15 mL
STD IV (10 ng/mL)	5.0 mL	15 mL
STD V (20 ng/mL)	10.0 mL	15 mL
ISTD (30 ng/mL)	-	15 mL

ISTD: International Standard

Appendix D.1.2 Preparation of reagents

Solvents

- Methanol HPLC Grade
- Dichloromethane HPLC Grade
- IPA HPLC Grade
- Ammonium Hydroxide NH_4OH 14.8 M, 28%
- Glacial acetic acid CH_3COOH 17.4 M, 100%
- Deionised water (DI H_2O)
- Sodium Phosphate Dibasic Na_2HPO_4 MW 141.96
- Sodium Phosphate Monobasic Monohydrate $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ MW 137.99
- Formic Acid 98-99%

100 mM Sodium Phosphate Dibasic (MW 141.96) : Dissolve 3.549 g Na_2HPO_4 in 150 mL de-ionised water. Dilute to 250 mL using DI water. Mix. *Store at 5°C in glass and inspect daily for contamination for one month.*

100 mM Sodium Phosphate, Monobasic (MW 137.99): Dissolve 3.44975 g $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ in 150 mL DI water. Dilute to 250 mL with DI water and mix. *Store at 5°C in glass and inspect daily for contamination for one month.*

Phosphate buffer, 100 mM pH 6 : 1.721 g Na_2HPO_4 + 12.125 g NaH_2PO_4 dilute to 1000 mL with deionized water. Adjust to pH 6 with 100 mM Na_2HPO_4 (raises pH) or 100 mM NaH_2PO_4 (lowers pH). *Store at 5°C in glass and inspect daily for contamination for one month.*

Acetic Acid (1 Molar): In 50 mL flask add DI water, then add 2.86 mL acetic acid and make up the volume by deionized water. *Store at 25 °C in glass or plastic for 180 days.*

Methylene Chloride/Isopropanol/Ammonium Hydroxide (78:20:2) extraction solvent: To 20 mL IPA, add 2 mL concentrated NH_4OH . Mix. Add 78 mL CH_2Cl_2 and mix. *Store at 25 °C in glass or fluoropolymer plastic for one day*

0.1% Formic Acid (FA) in Water: To 500 mL DI water add 1 mL formic acid, make up the volume to 1 L. *Store at room temperature for 180 days.*

0.1% FA in Methanol: To 500 mL Methanol add 1 mL FA make up the volume to 1 L. *Store at room temperature for 180 days.*

ACN: IPA: MeOH: H2O 25:25:25:25 with 0.2% FA : Add 125 from each solvent to get 500 mL from ACN: IPA: MeOH: H2O. Mix To 200 mL of mixture add 1 mL formic acid and make up the volume to 500 mL

MeOH:ACN:IPA 50:25:25 With 0.4% FA: To 250 mL methanol add 125 mL acetonitrile then add 125 mL isopropanol, substitute 2 mL from the mixture with formic acid.

Mix at 0.3 mL/min Mobile Phase A: 0.1% FA aq; Mobile Phase B: 0.1% FA in MeOH

Washing solvent: Mix A and B for 120 minutes at 0.25 mL/min

- A: ACN:IPA:MeOH:H2O with 0.2% FA (80)
- B: MeOH:H2O (20)

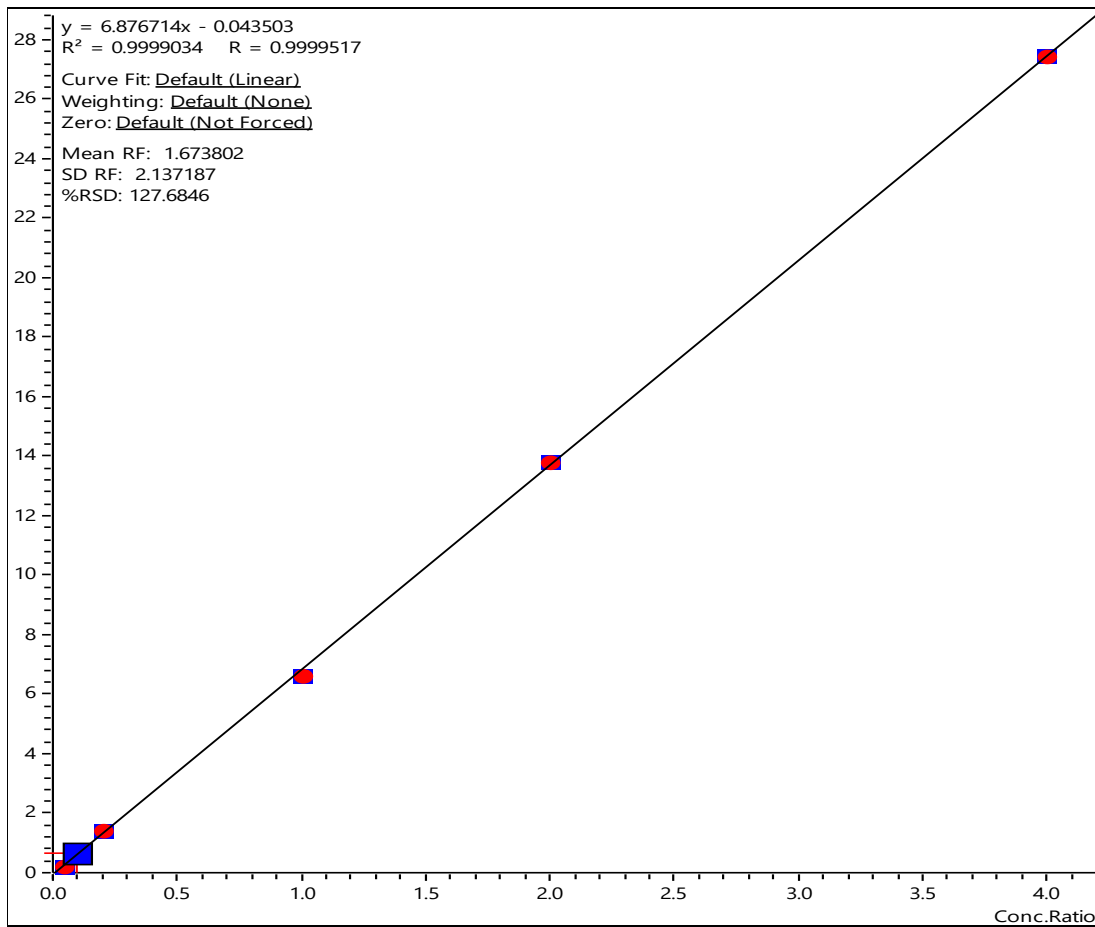
Auto-sampler:

- Hard wash: 50:25:25 MeOH:ACN:IPA with 0.4% FA
- Soft wash: initial state of mobile phase.

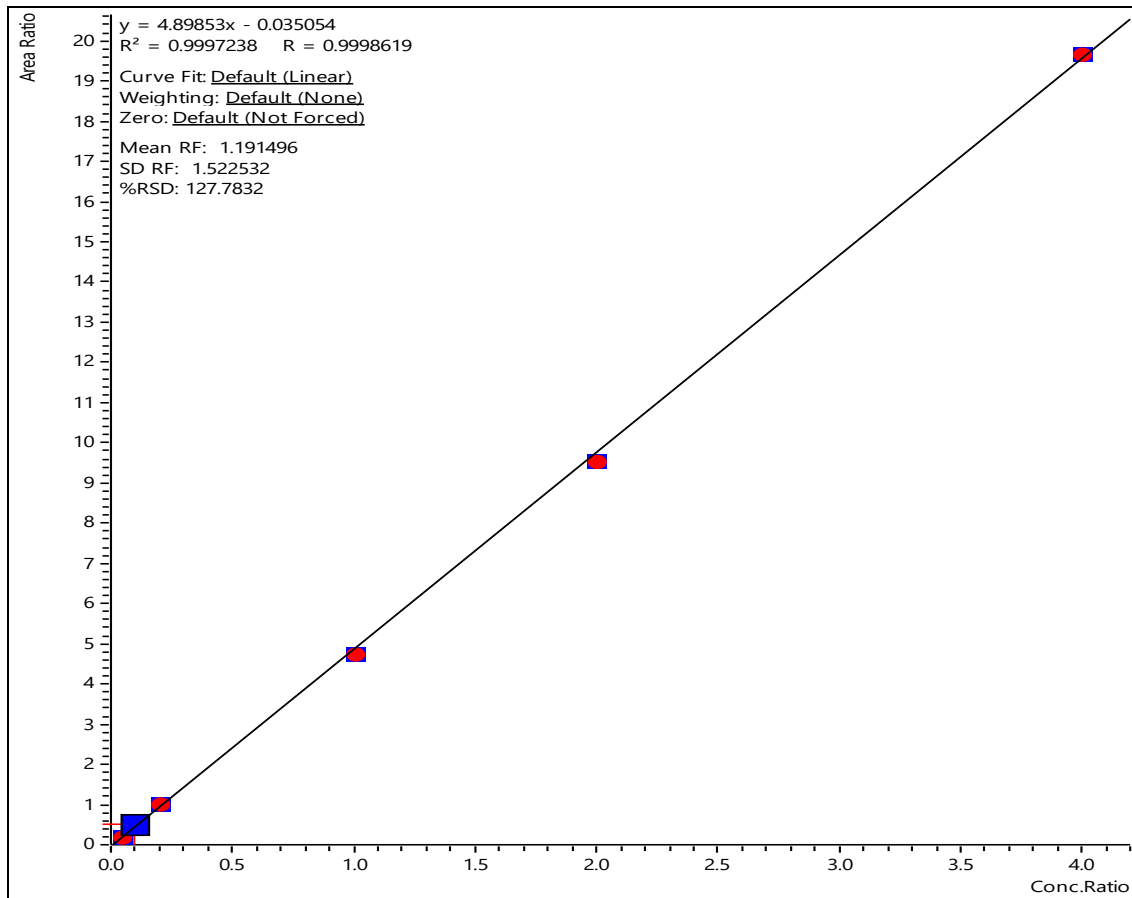
Analyser conditions:

Flow:	0.2 mL/min
Injection Volume:	20 µL
Interface:	Electron Spray Ionisation (ESI)
Nebulizing Gas Flow:	2.50 L/min
Drying Gas Flow:	10.00 L/min
Analytical Column:	Raptor C18 (Restek 9304A12)

Appendix D.2.1 Calibration Curve for Buprenorphine



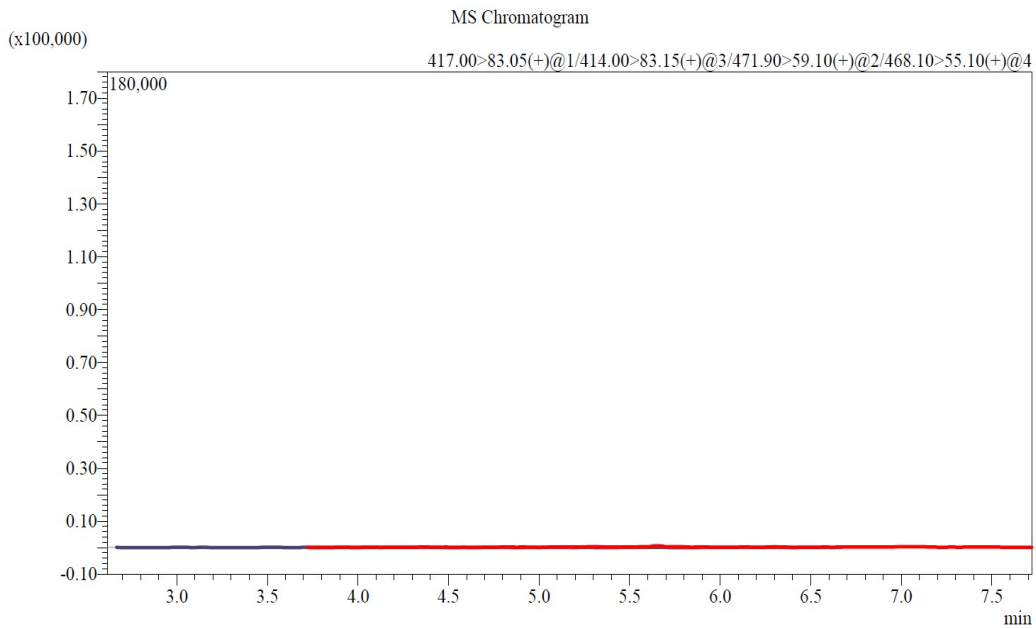
Appendix D.2.2 Calibration Curve for Buprenorphine



Appendix D.3.1. Chromatogram for blank sample

```

Patient Name      : BLANK_002
NRC Number       : BLANK_002
Tray#            : 1
Vial#            : 7
Injection Volume  : 20
Data File        : BLANK_002.lcd
Method File      : BUP_NORBUP_03.02.2015.lcm
Original Method   : BUP_NORBUP_03.02.2015.lcm
Report Format     : REPORT.lsr
Tuning File      : Tuning_23.10.2014.lct
Location         :
    
```



MS Quantitative Table

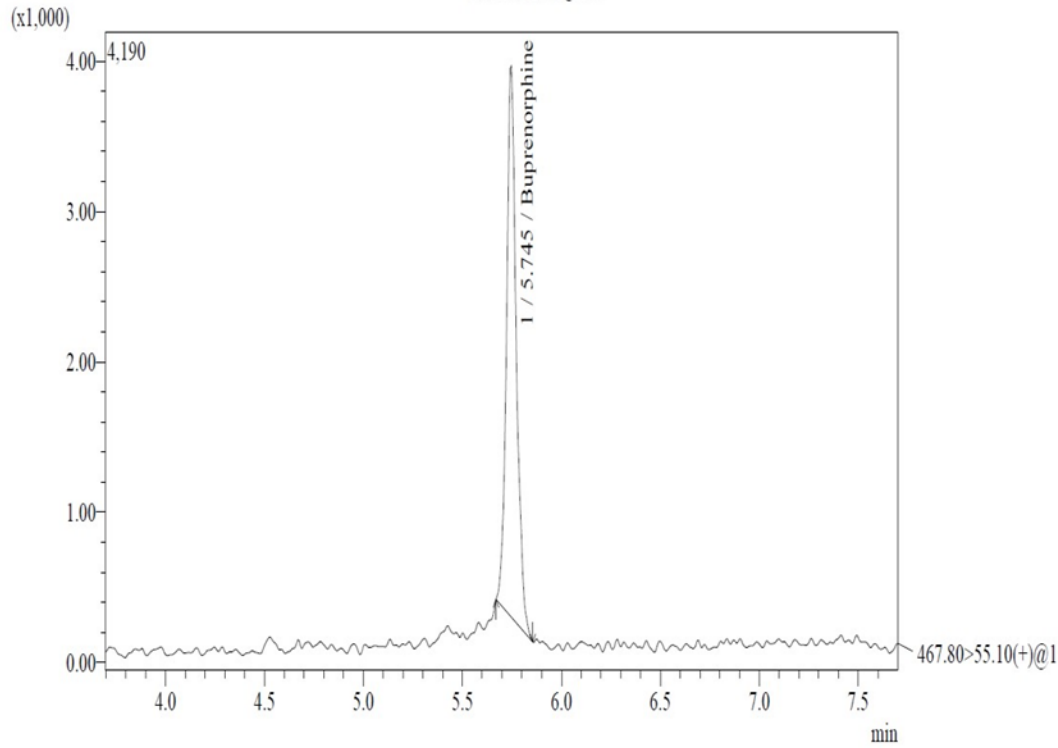
ID#	Name	Ret. Time	m/z	Conc.	Area	Unit
1	N-D3	--	417.00>83.05	N.D.(W/B)	--	
2	N	--	414.00>83.15	N.D.(W/B)	--	
3	B-D4	--	471.90>59.10	N.D.(W/B)	--	
4	B	--	468.10>55.10	N.D.(W/B)	--	

Appendix D.3.2. Signal to noise ratio

Sample Information

Acquired by : System Administrator
 Date Acquired : 1/20/2015 5:47:28 PM
 Sample Type : Unknown
 Level# : 0
 Sample Name : Blank TA
 Sample ID : Blank TA
 ISTD Amount : (Level Conc.)
 Sample Amount : 1
 Dilution Factor : 1
 Tray# : 1
 Vial# : 1
 Injection Volume : 20
 Data File : Blank TA.lcd
 Method File : 19.01.2015_BUP_TA.lcm
 Original Method File : 19.01.2015_BUP.lcm
 Report Format File : Bup_Report.lsr
 Tuning File : Tuning_23.10.2014.let
 Processed by : System Administrator
 Date Processed : 5/26/2015 11:13:37 AM

MS Chromatogram



MS Quantitative Table

ID#	Name	Ret. Time	m/z	Conc.	Area	Height	Unit
1	Buprenorphine	5.745	467.80>55.10	0.071	12686	3668	µg/L
Total					12686	3668	

Appendix D.4. Norbuprenorphine plasma concentrations (peak, trough, observed)

Participant	C _{max} N-BUP ng/mL	C _{min} (1) N-BUP ng/mL	C _{min} (2) N-BUP ng/mL	BUP/ N-BUP ratio	Time for random sample (hrs. post dose)	Obs. Conc. of random sample ng/mL
1	8.25	3.76	5.3	0.54	(20)	5.96
2	1.61	0.84	0.99	0.54	(10)	0.1
3	1.76	0.78	0.86	0.66	(7)	1.28
4	0.55	0.52	0.53	0.93	(20)	0.53
5	6.99	4.14	5.27	0.52	(5)	6.11
6	19.74	6.22	0.64	0.16	(7)	11.36
7	28.3	29.3	29.28	0.4	(20)	35.92
8	14.19	1.90	6.01	0.31	(8)	18.17
9	6.31	1.01	1.02	1.32	(12)	8.81
10	3.56	1.01	2.21	0.65	(11)	1.59
11	20.42	4.67	3.77	0.26	(11)	12.69
12	1.37	1.04	0.98	1.20	(20)	0.98
13	13.83	7.40	6.37	0.61	(18)	3.37
14	1.76	1.28	1.53	0.88	(14)	1.29
15	0.83	0.52	0.48	0.89	(8)	*****

Obs: Observed C_{max}: Peak concentration; C_{min}: Trough concentration; ***** Missing data

In summary, the findings provided sufficient evidence in support of the clinical feasibility of applying TDM and accuracy of predicting and monitoring BUP concentration in all 15 participants. Thus, the study progressed from the internal pilot phase.

Appendix. E. 1. Prospective dose assignment and dose adjustment

Prospective dose assignment criteria which recommends that patients with injecting street heroin/morphine receive daily BUP/NX-F doses, while non-injecting users are, assigned to alternate daily doses, and prescription opioid users receive thrice-weekly doses. In addition, participants with either severe psychiatric co-morbidity, or multiple substance use, or with a BMI of more or equal to 30 are placed on the next more frequent dosing schedule, i.e. TIW to alternate-day to daily. For instance if the participant is a non-injecting morphine/heroin user he/she is a candidate of alternate day dosing, and in the presence of psychiatric comorbidity and/or BMI of 30 or more, he/she is placed on daily dose schedule which is the maximum frequency. Similarly, participants with prescription opioid use are placed on TIW, and in the presence of co-occurring disorders are placed on alternate day, and with added BMI is over 30, they are assigned to daily dose schedule.

Alternate-day regimen, is administered four-times-a-week i.e. dosing every other day. This regime is implemented as '3' similar 48-hour doses (Sunday, Tuesday, Thursday), and one 24-hour dose (Saturday). The 48 hours that is double the 24 hour dose able to bring COWS score below 5. Patients who observe withdrawal between doses –quantified by COWS and pupil reflexes- receive fine dose adjustments to the 48 hour dose with a maximum of 32 mg, then adjustment to the 24 hour dose at a maximum of 32 mg. If the patient cannot be stabilised on alternate day dosing, due to the onset of withdrawal, cravings, side effects or features of intoxication, the patient is, transferred to daily dose schedule (24 hour dose).

The TIW dose is implemented as: one 72-hour dose, i.e. triple the 24-hour dose, e.g. Sunday and, two 48-hour dose on Wednesday and Friday. Fine dose adjustment is first made to the largest dose (72-hours) at a maximum of 32 mg. If the 24-hour dose is less than 12mg, then the 72-hour dose is initially two times the 24-hour dose and if withdrawal is observed, dose is increased to three times the 24-hour dose with a maximum dose set at 32mg. Finally, if subjects do not tolerate the TIW dosing schedule, patients are stepped down to alternate day dose and like-wise to daily dose frequency. Cravings and withdrawal symptoms will indicate the need to increase the dose to a maximum of 32mg. On the other hand, if concerns over intoxication emerge -normally four hours post dose- the 72-hour dose is reduced.

APPENDIX E. DETAILED BASELINE DATA, COMPLETION RATE AND SECONDARY OUTCOME ACCORDING TO CITY OF RESIDENCE

PARTICIPANT CHARACTERISTICS

This section reports on baseline sociodemographic characteristics, type and pattern of opioid use, and type of non-opioid substances used.

Sociodemographic characteristics

Gender: With only two females recruited, males constituted the majority of the study sample (n=169, 98.8%). One of the females recruited was, discharged against medical advice before reaching the randomisation stage, while the second female was randomised to the experimental group and completed the 16-week study period.

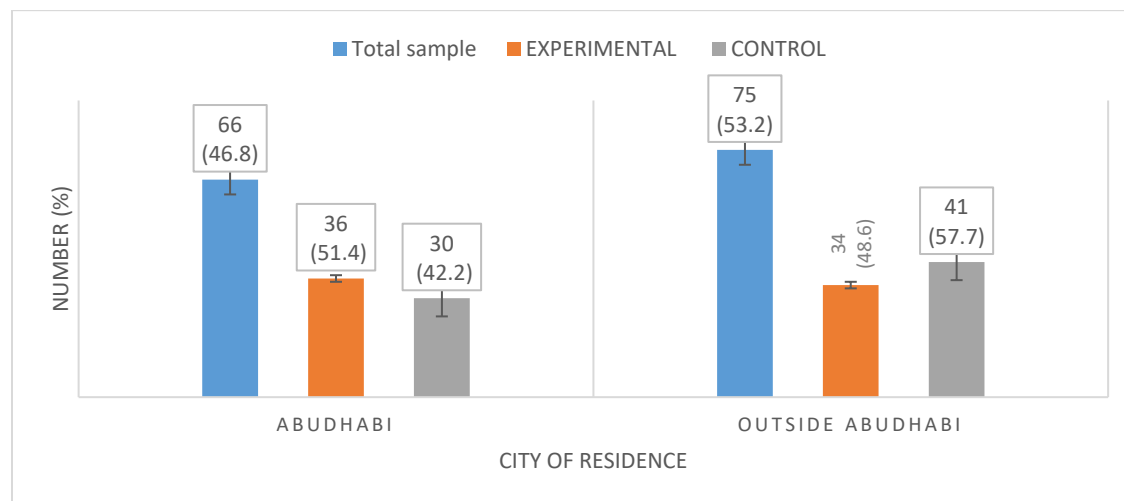
Age at presentation to treatment: Overall, the mean age at presentation to treatment in the total sample randomised was 29.0 years (Standard deviation: *SD* 8.03). Participants in the experimental group were significantly older compared to participants in the control group [30.40 years (*SD* 8.50) versus control group 27.70 years (*SD* 7.40) ($t = 1.99$; $df = 139$, $p = 0.04$)].

Age at first opioid use: The mean age at first use of any opioids in the total sample randomised was 17.5 years (*SD* 4.0). The mean age of first use in the experimental group was 18.3 years (*SD* 4.90), and in the control was 17.2 years (*SD* 3.40). The difference was not significant ($t = 1.56$, $df = 136$, $p = 0.12$).

Duration of illness: This variable was calculated by subtracting the ‘age at first opioid use’ from the ‘age at presentation to treatment’ minus one year¹. Overall, the median duration of illness in the total sample randomised was 9.03 years (Interquartile range: *IQR* 5.58–15.88). The median duration of illness in the experimental group was 9.94 years (*IQR* 5.67–17.28) and in the control group was 8.87 years (*IQR* 5.43–14.71). The difference was not significant ($Z=2.59$, $p=0.86$).

City of residence: Just over half the total sample randomised (n = 75; 52.20%) resided outside the city of Abu Dhabi. For most participants, this required a minimum of 90-minute drive to reach the NRC. The remaining participants (n = 66; 46.80%) resided in Abu Dhabi city with less than a 30-minute drive to the clinic. The proportion of participants in the experimental group residing in Abu Dhabi (n = 36; 51.40%) was not significantly higher than in the control group (n = 30; 41.40%) (Pearson $\chi^2 = 1.19$, p = 0.25). **Figure E.1** illustrates the distribution of participants according to the city of residence.

Figure E.1 Participant city of residence for the total sample and by group



Marital Status: More than half of the participants in the total sample randomised were single (n = 81; 57.4%) and approximately 30% of the participant were married (n = 41; 29.0%). In the experimental group, the proportion of participants who were married (35.7%, n = 25) was higher than in the control group (22.5%, n = 16). No significant difference in the marital status between both groups was found (p=0.08)

Family history of substance use: The prevalence of family history for any substance use among first- and second-degree relatives in the total sample randomised was 18.5% (n = 21). This prevalence was not significantly different between the experimental group (n=10; 18.1%) and control group (n=11; 18.9%) (p=0.78).

History of imprisonment: The majority of the participants reported at least one imprisonment episode (n = 93; 65.90%). In the experimental and the control groups, 48 (68.5%) participants and

46 (64.70%) participants, respectively, were imprisoned at least once. The median imprisonment events in the total sample was 1.0 (*IQR* 0.0–2.0) and 1.0 in the experimental group (*IQR* 0.0–2.0) and 1.0 in the control group (*IQR* 0.0–3.0). The difference was not statistically significant ($p=0.27$).

History of overdose or seizure: The median number of participants who reported at least one incident of overdose or seizures in the total sample randomised was 0.0 (*IQR* 0.0–1.00). The majority of the participants in the experimental group ($n = 53$; 75.70%) and the control group ($n = 50$; 70.40%) reported no history of seizures or overdose with no significant difference (Pearson $\chi^2 = 0.50$, $p = 0.48$). In the experimental group the median number of reported overdoses or seizures was 0.0 (*IQR* 0.0–0.0) compared to 0.0 (*IQR* 0.00–1.0) in the control group. The difference was not statistically significant ($p=0.65$).

Employment status: The majority of the randomised participants ($n = 92$; 65.6%) were unemployed. In this unemployed group, 42 participants (32.0%) were never employed and 44 participants (33.5%) were terminated from their jobs due to substance use, 6 participants (4.2%) were students or recruits of national reserve. In contrast, majority of the employed participants ($n=49$) were government employees ($n=39$) while 10 participants were self-employed. No significant difference in the employment rate was established between the experimental and control groups ($p=0.77$).

Body Mass Index (BMI): All randomised participants were considered to be slightly overweight with a mean BMI of 26.1 (*SD* 6.20). In the experimental group, a mean BMI of 26.35 (*SD* 6.24) compared to 25.90 (*SD* 6.24) in the control group was calculated with no significant difference between the groups ($t = 0.43$, $df = 135$, $p = 0.93$).

Pattern of substance use: At baseline, more than two-thirds of the participants were polysubstance users, i.e. reported the use of two or more substances in addition to the primary opioid with no significant difference between the group (experimental $n = 54$, 77.1% versus control $n = 50$, 70.4%; Pearson $\chi^2 = 0.82$, $p = 0.36$). **Tables E.1** displays the type and pattern of opioid use. Overall, morphine/heroin was the primary opioid reported by the majority of the randomised participants ($n = 111$, 78.10%) with no significant difference between groups (experimental $n=55$, 78.5% versus control $n=55$, 77.5%; $p=0.95$). Within the group reporting heroin/morphine as their primary opioid, the number of participants reporting injecting morphine/heroin was higher in the

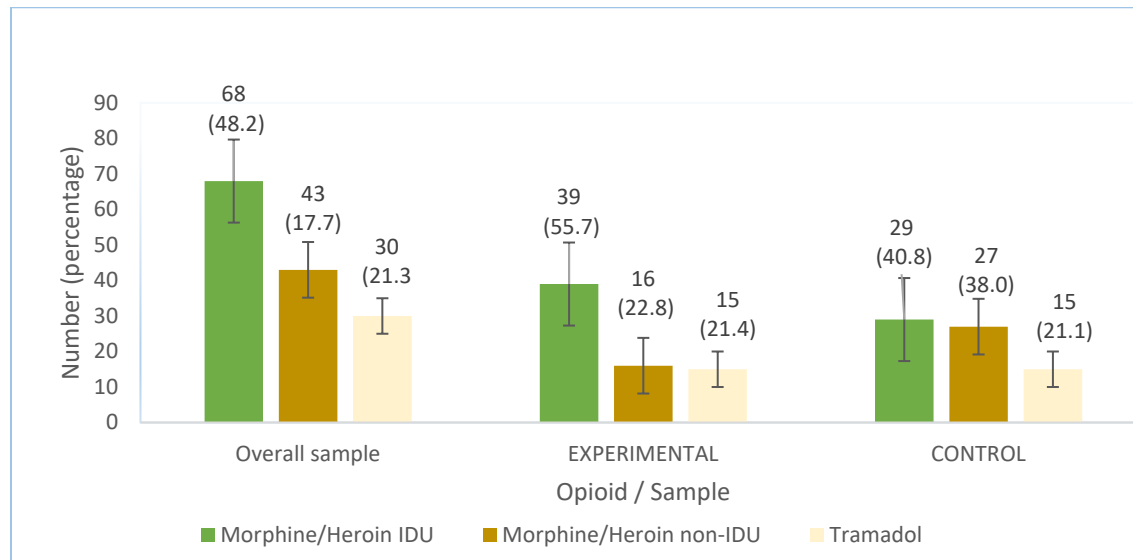
experimental group (n=39, 55.7%) compared to the number in the control group (n=28, 39.4%). In contrast in the total randomised group while 30 (21.30%) participants reported Tramadol, a prescription opioid, as their primary opioid with no significant difference between groups (experimental n=15, 21.4% versus control n=15, 21.1%; $p=0.96$). The difference was not statistically significant ($p=0.05$). **Figure E.3** illustrates the opioid use by type and pattern in the experimental and control groups.

Table E.1 Baseline pattern of opioid use for the total sample and by group

Opioid	Total (%)	Experimental n (%)	Control n (%)	p-value
Morphine/Heroin IDU*	67 (47.50)	39 (55.70)	28 (39.40)	0.05
Morphine/Heroin non-IDU	43 (30.50)	16 (22.90)	27 (38.0)	0.05
Tramadol	30 (21.30)	15 (21.40)	15 (21.10)	0.96

*IDU, Injecting Drug Use

Figure E.2 Type of opioid and pattern of use at baseline for total sample and by group



For non-opioid substance use in the total randomised sample, pregabalin was the non-opioid frequently reported (n = 76; 53.90%), followed by benzodiazepines (n = 44; 31.20%), cannabis (n

= 37; 26.20%) and trihexyphenidyl and procyclidine (n = 23; 16.30%). The prevalence of secondary substance of use was similar with no significant difference in both groups (**Table E.3**).

Table E.3 Baseline non-opioid drugs of abuse for total sample and by group

Non-opioid substances	Total n(%)	Experimental n(%)	Control n(%)	p-value
Pregabalin	70 (49.60)	38 (54.30)	38 (53.50)	0.92
Benzodiazepine	76 (54.0)	25 (35.70)	19 (26.80)	0.25
Cannabis/Hashish	44 (31.20)	19 (27.10)	18 (25.40)	0.81
Carisprodol	30 (21.30)	13 (18.60)	17 (23.90)	0.43
Trihexphenidyl/ Procyclidine	23 (16.30)	12 (17.10)	11 (15.50)	0.79

BASELINE MEASURES

This section summarises the completion rate of the study measures by the participants, the mean and median values for, the baseline scores of the study measures and pupil reflexes (maximum and minimum pupil diameters). We also report the estimated BUP EL.R and measure BUP trough plasma concentrations.

Completion rate

In the total sample randomised, the rate of completing the study measures by participants ranged from 67.3% to 100%. The measure associated with the lowest completion rate (or the highest percentage of missing values) was the WSAS, while the ASI-Lite version was the measure with the highest completion rate (or the lowest percentage of missing values). **Table E.4** displays the completion rate for the total sample and by group for each of the study measures.

Table E.4 Completion rate of study measures

Measures	Total	Experimental	Control
		<i>n (%)</i>	
PHQ-9	127 (90.0)	65 (92.80)	62 (87.30)
GAD-7	131 (92.90)	66 (94.20)	65 (91.20)
BIS-11	104 (73.70)	55 (78.50)	49 (69.0)
PSQI	111 (78.70)	56 (80.0)	55 (77.40)
ASI-Lite	141 (100)	70 (100)	71 (100)
PDS	105 (74.40)	53 (75.70)	52 (73.20)
WSAS	95 (67.30)	51 (72.80)	45 (63.30)

PHQ-9: Patient Health Questionnaire – 9 items; GAD-7: Generalised Anxiety Disorder – 7 items; BIS-11: Barratt Impulsiveness Scale 11th version; PSQI: Pittsburgh Sleep Scale Index; ASI-Lite: Addiction Severity Index-Lite; PDS: Personality Disorder Screener; WSAS: Work and Social Adjustment Scale;

Measures of psychosocial functioning and pupil reflexes

The valid mean (*SD*) or median scores (*IQR*) for the measures of depression, anxiety, quality of sleep, personality disorders, impulsiveness, work and social adjustment are displayed in **Table E.5**. For the pupil reflexes, only the mean (*SD*) maximum and minimum pupil diameters are reported.

Table E.5 Baseline measures of psychosocial functioning for the total sample and by group

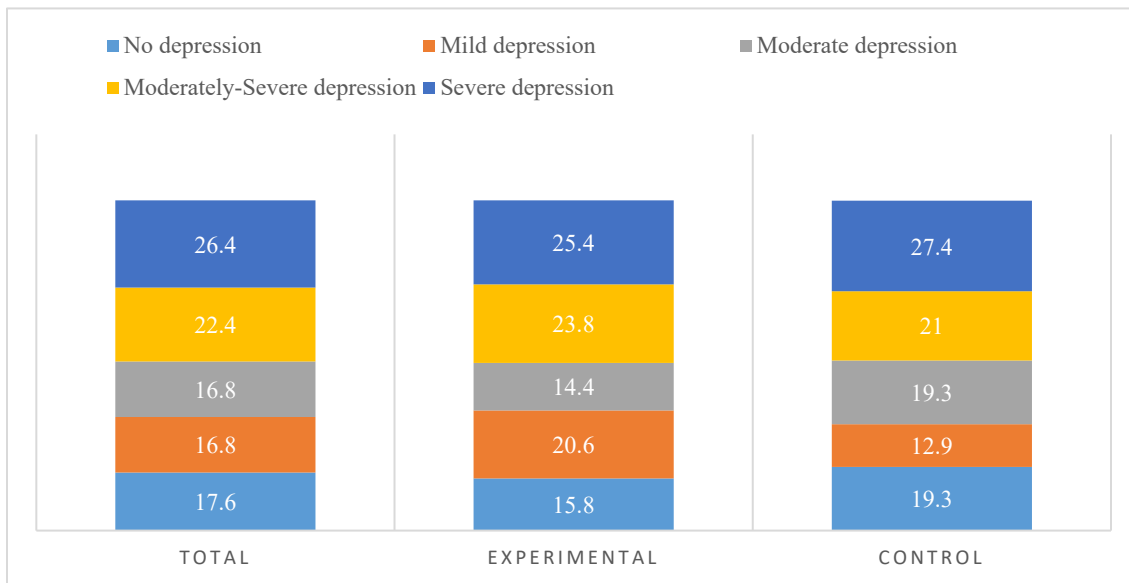
Measures	Total	Experimental	Control	p-value
PHQ-9	13.22 (6.72)	12.85 (6.60)	13.61 (6.85)	0.55
GAD-7	10.0 (5.0–17.0)	10.0 (4.0–15.0)	10.0 (5.0–15.0)	0.83
PSQI	11.0 (7.0–13.0)	11.0 (7.0–14.0)	10.0 (5.0–15.0)	0.40
BIS-11	71.70 (14.60)	72.30 (14.6)	71.70 (14.20)	0.67
WSAS	23.10 (9.71)	22.10 (9.80)	24.20 (9.20)	0.28
Personality Disorders				
BPD	86 (82.0%)	45 (84.90%)	41 (78.80%)	0.24
OCPD	29 (27.61%)	14 (27.50%)	15 (30.0%)	0.78
DPD	57 (54.28%)	26 (55.30%)	31 (35.40%)	0.86
PPD	43 (30.5%)	23 (46.90%)	20 (40.0%)	0.34
APD	83 (79.04%)	42 (80.80%)	41 (80.40%)	0.59
Anxious PD	64 (60.95%)	31 (59.60%)	33 (64.70%)	0.99
MCOS percentage intensity	86.35 (28.0)	88.60 (23.7)	83.90 (31.5)	0.02
Number of urges				
MCOS duration of urges (minutes)	8.0 (3.0–20)	15.0 (3.0–20)	8.0 (3.0–15.0)	0.67
	50.0 (15.0–90.0)	50.0 (15.0–90.0)	25.0 (15.0–90.0)	0.06
Pupil Maximum Diameter (mm)	4.58 (1.18)		4.58 (1.14)	
Pupil Minimum Diameter (mm)	3.22 (0.67)	4.54 (1.25)	3.24 (0.63)	0.99
		3.24 (0.73)		0.85

Data are presented as n (valid percentage); Mean (*SD*), Median (Interquartile Range); PHQ-9: Patient Health Questionnaire 9 items, GAD-7: Generalized Anxiety Disorder 7 items; BIS-11: Barratt Impulsiveness Scale 11th version; WSAS: Work and Social Adjustability Scale; ASI: Addiction Severity Index; BPD: Borderline Personality Disorder; OCPD: Obsessive Compulsive Personality Disorder; DPD: Dependent Personality Disorder; PPD: Paranoid Personality Disorder; APD: Antisocial Personality Disorder; MCOS (Minnesota Craving Opioid Scale)

Depression: Quantified by the PHQ-9 scores, the mean score in the total sample randomised was 13.22 (*SD* 6.72) suggesting moderate depression. In the experimental group, the mean PHQ-9 score was 12.85 (*SD* 6.60) and in the control group was 13.61 (*SD* 6.85). The difference was not significant ($t=-0.64$, $df=125$, $p = 0.55$).

Clinically, 26.4% (valid percentage) of the total sample were, screened for severe depression, while 22.4% were, screened for ‘moderately-severe’ depression and 16.8% were screened for ‘moderate’ depression, and 16.8% for ‘mild’ depression. In the total sample randomized, the number of participants with ‘no depression’ or a PHQ-9 score < 5 were 22 (17.6%). The depression profile was comparable between both groups and is illustrated in **Figure E.4**.

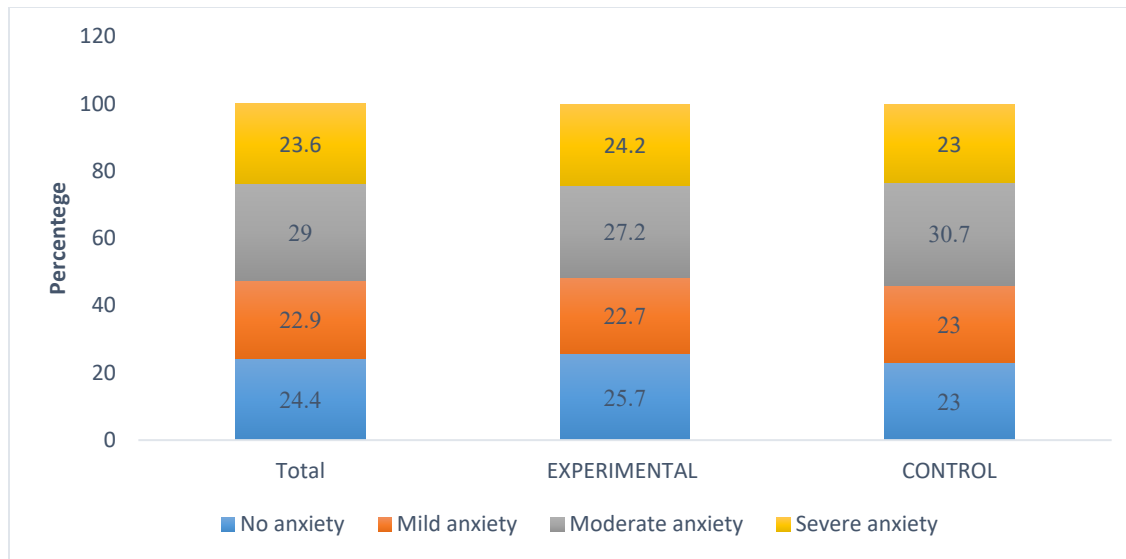
Figure E.4 Distribution of severity of depression according to Patient Health Questionnaire-9 scores for total sample and by group



Anxiety: Quantified by the GAD-7 scores, the median score for the total sample randomised was 10.0 (IQR 5.0–17.0) suggesting moderate anxiety. In the experimental group, the median GAD-7 score was 10.0 (IQR 4.0–15.0) and in the control was 10.0 (IQR 5.0–15.0). There was no significant difference in the GAD-7 median score between both study groups ($Z=-0.24$, $p = 0.81$).

Clinically, 22.90% and 29.0% of the total randomized sample were screened with ‘mild’ anxiety and ‘moderate’ anxiety respectively. While, 23.60% of the participants were screened with ‘severe’ anxiety and approximately quarter (24.40%) of the randomised participants presented with ‘no’ anxiety. The anxiety profile was comparable between both study groups as illustrated in **Figure E.5**.

Figure E.5 Distribution of severity of anxiety according to Generalised Anxiety Disorder-7 scores for total sample and by group



Quality of sleep: Quantified by the PSQI, the median PSQI score for all randomised participants was 11.0 (*IQR* 7.0–13.0), reflecting poor quality of sleep. In the experimental group, the median score was 11.0 (*IQR* 7.0–14.0) and in the control group was 11.0 (*IQR* 7.0–13.0) with no significant difference ($Z=-0.83$, $p = 0.40$).

Work and Social Adjustment Scale: In the total sample randomised, the mean WSAS score was 23.10 (*SD* 9.71) suggesting ‘severe’ work and social impairment. Both groups presented with severe work impairment with no significant difference [experimental 22.1 (*SD* 9.80) compared to control 24.10 (*SD* 9.20); ($t=-1.13$, $df=94$, $p = 0.08$)]

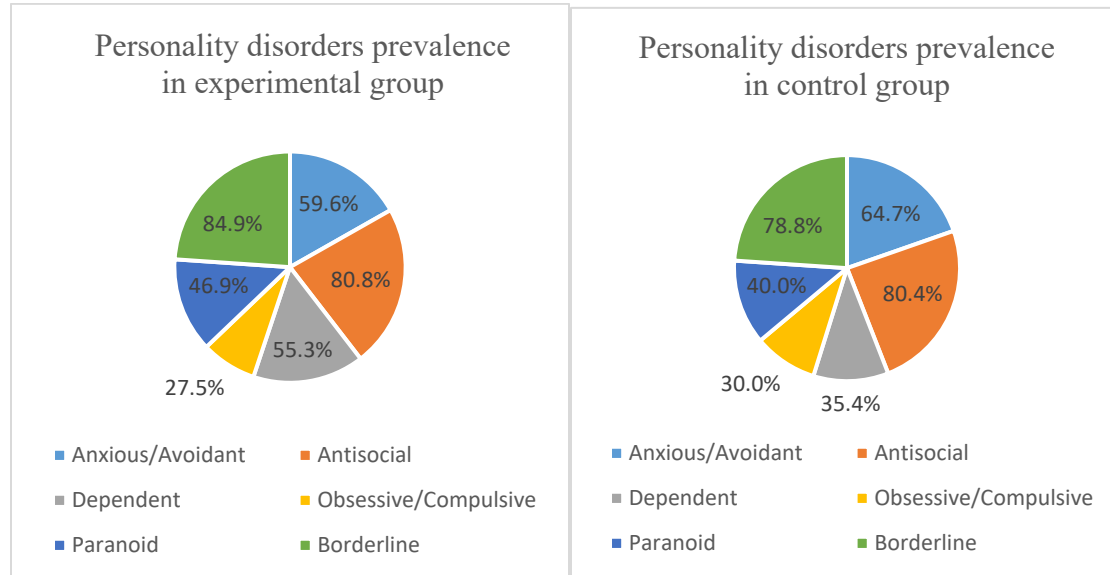
Impulsiveness: Quantified by the BIS-11, the mean score for the total sample randomised was 71.60 (*SD* 14.56). In the experimental group, the mean BIS-11 score was 72.30 (*SD* 14.60) and in the control group was 71.70 (*SD* 14.20) with no significant difference ($t=0.19$, $df=102$, $p = 0.84$)

Personality disorders: In the total sample randomised, the most prevalent personality disorder according to the valid percentages was the ‘borderline’ personality disorder (experimental 84.90%; control 78.80%) while the least was obsessive-compulsive personality disorder (experimental group 27.50%; control group 24.20%).

There were no significant differences in the prevalence of these disorders between the experimental and control groups (borderline personality: $p = 0.24$; antisocial personality: $p = 0.59$; anxious-avoidant personality: $p = 0.99$; paranoid personality: $p = 0.34$; and obsessive-compulsive

disorder: $p = 0.78$; dependent personality disorder, $p=0.86$). **Figure E.6** illustrates the findings obtained for the valid percentage of screened personality disorders.

Figure E.6 Prevalence of personality disorders by group



Minnesota Cocaine-Craving Scale (adapted for Heroin/Opioids): The mean intensity of craving reported by the participants and expressed as percentage was significantly higher in the experimental compared to the control group [experimental = 88.6% (SD 23.7); control = 83.9% (SD 31.5), ($t=1.06$, $df=139$, $p=0.02$)]. The median number of urges per day in the experimental group was 15.0 (IQR 3.0–20.0) and in the control group was 8.0 (IQR 3.0–15.0). The difference was not significant ($Z=-0.46$, $p=0.64$). The median duration of craving urges in the experimental group was higher than in the control group (50 minutes (IQR 15.0–90.0) and 25.0 (IQR 15.0–90.0). This difference was not significant ($Z= -1.86$, $p=0.06$).

Addiction Severity Index: Table E.6 displays the median ASI scores and interquartile ranges by group. No significant difference on any of the ASI subdomains was found between the study groups (Medical: $Z=-1.22$, $p = 0.22$; Social $Z=-0.95$: $p = 0.34$; Legal: $Z=-1.46$, $p = 0.15$; Family: $Z=-0.75$, $p = 0.45$; Mental health: $Z=-0.46$, $p = 0.439$; Alcohol use: $Z= -0.55$, $p = 0.47$; Drug use $Z=-0.01$, $p = 0.64$).

Table E.6 Baseline Addiction Severity Index scores for the total sample and by group

ASI domains	Total	Experimental	Control	p-value
Medical	0.000 (0.000–0.355)	0.000 (0.000–0.347)	0.000 (0.000–0.416)	0.22
Social	0.500 (0.254–0.754)	0.500 (0.254–0.625)	0.500 (0.312–0.750)	0.34
Alcohol	0.000 (0.000–0.104)	0.000 (0.000–0.117)	0.000 (0.000–0.032)	0.47
Drug use	0.219 (0.103–0.366)	0.216 (0.091–0.380)	0.223 (0.105–0.364)	0.99
Legal	0.000 (0.000–0.200)	0.000 (0.000–0.186)	0.025 (0.000–0.200)	0.15
Family	0.200 (0.042–0.485)	0.200 (0.045–0.405)	0.200 (0.035–0.533)	0.45
Mental health	0.472 (0.124–0.702)	0.454 (0.124–0.472)	0.515 (0.113–0.704)	0.64

Data are Median (IQR: Inter Quartile Range); ASI: Addiction Severity Index

Pupil reflexes: There was no significant difference in the maximum and minimum pupil diameter captured at baseline and prior to emergence of withdrawal signs. In the experimental group the maximum pupil diameter was 4.54 mm (*SD* 1.25) compared to 4.58mm (*SD* 1.14) ($t = -0.13$, $p = 0.99$). Similarly, the minimum pupil diameter in the experimental group was 3.24mm (*SD* 0.73) compared to 3.24mm (*SD* 0.63) in the control ($t = -0.18$, $p = 0.85$).

SECONDARY OUTCOME MEASURE

In **Table E.9**, of the 73 participants who completed 16-week study period, a higher number resided outside of Abu Dhabi city ($n = 40$; 54.8%) compared to those residing in Abu Dhabi city [$n = 33$; 45.2%) with an OR of 1.08 (95% CI 0.56–2.09)]. In the experimental group, a higher number of study completers resided in Abu Dhabi ($n = 22$; 55%) with an OR of 1.22 (95% CI 0.57–2.62) compared to non-residents of Abu Dhabi city. In contrast, majority of the study completers in the

control group were non-residents of Abu Dhabi city ($n = 22$; 66.7%) with an OR of 2.55 (95% CI 0.94–6.35) compared to residents of Abu Dhabi city.

In summary, there was no significant difference in the number of participants completing the study period whether by group or by city of residence.

Table E.9 Study completion by city of residence

City of Residence	Total		Experimental		Control	
	Completers n (% of total)	Non-completers n (% of total)	Completers n (% of total allocation)	Non-completers n (% of total allocation)	Completers n (% of total allocation)	Non-completers n (% of total allocation)
Abu Dhabi	33 (23.40)	32 (22.60)	22 (31.40)	14 (20.0)	11 (15.50)	18 (25.30)
Outside Abu Dhabi	39 (27.60)	37 (26.20)	18 (25.70)	16 (22.90)	21 (29.60)	21 (29.60)