Suicide prevention in clinical populations with substance use problems

Prianka Padmanathan

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Abstract

People with substance use problems are at substantially greater risk of suicide than the general population. Yet within clinical services, the provision of care to prevent suicide and reduce self-harm in this population can be challenging. This thesis aims to broaden the evidence base for such care.

First, I describe a cohort study that used national primary care data (n=8,070 patients) to investigate the risk of suicide and self-harm during and after opioid agonist treatment (OAT) for opioid dependence. OAT was associated with a reduced risk of self-harm (adjusted risk ratio in periods off treatment: 1.50; 95% confidence intervals: 1.21, 1.88). Risk of self-harm (aRR: 2.60; 95% CI: 1.83, 3.70) and suicide (aRR: 4.68; 95% CI: 1.63, 13.42) were both elevated in the first four weeks after stopping OAT compared with stable periods on treatment. The findings indicate that OAT has an important role in suicide prevention.

Next, I report a systematic review that aimed to evaluate the effectiveness of suicide prevention interventions among people with substance use problems. Six randomised controlled trials (n=468 participants) were identified, which were all likely to have been underpowered to detect differences between groups. Several feasibility trials of interventions involving cognitive behavioural therapy, dialectical behavioural therapy, and dynamic deconstructive psychotherapy showed promise. However, adequately powered trials investigating effectiveness are required.

Finally, I describe a Delphi method study that included people with lived and occupational experience in the development of a brief psychosocial intervention for people attending hospital with self-harm and substance use problems. The developed intervention consists of weekly follow-up phone calls for up to one month, delivered by Liaison Psychiatry practitioners, in which both self-harm and substance use problems are explored, and patients are supported in accessing community services. A case series testing the acceptability and feasibility of this intervention is currently underway.

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Author's declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

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List of abbreviations

OAT	Opioid agonist treatment
aRR	Adjusted risk ratio
ASSIP	Attempted Suicide Short Intervention Program
BSSI	Beck Scale for Suicide Ideation
CBT	Cognitive behavioural therapy
CBT-RP	Cognitive behavioural therapy-relapse prevention
CCI	Charlson Comorbidity Index
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
CTI	Critical Time Intervention
DBT	Dialectical behavioural therapy
DDP	Dynamic deconstructive psychotherapy
DSM	Diagnostic and Statistical Manual of Mental Disorders
ED	Emergency department
FRAMES	Feedback about the adverse effects of excessive alcohol consumption, an emphasis on Responsibility for change lying with the individual, provision of Advice about reducing alcohol consumption, a Menu of options for further intervention if this is required, an Empathic stance towards the patient, and the enhancement of Self-efficacy
GP	General practitioner
HES	Hospital Episode Statistics
HES APC	Hospital Episode Statistics Admitted Patient Care
ICD	International Classification of Diseases
IMD	Index of Multiple Deprivation
IQR	Interquartile range
MDMA	3,4-methylenedioxymethamphetamine
mg	milligrams
ml	millilitres

NHS	National Health Service
ONS	Office for National Statistics
OR	Odds ratio
PPI	Patient and Public Involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PWLE	People with lived experience
PWOE	People with occupational experience
REDCap	Research Electronic Data Capture
RCT	Randomised controlled trial
ROB	Risk of Bias
RR	Risk ratio
SIQ-S	Suicidal Ideation Questionnaire-Senior Version
SMART	Self-Management and Recovery Training
SMR	standardised mortality ratio
UK	United Kingdom
USA	United States of America
VAMP	Value Added Medical Products
WHO	World Health Organization

Publications associated with this thesis

1. Padmanathan P., Forbes H., Redaniel M.T., Gunnell D., Lewer D., Moran P., Watson B., Degenhardt L., and M. Hickman. Self-harm and suicide during and after opioid agonist treatment among primary care patients in England: a cohort study. Lancet Psychiatry. 2021;9(2): 152-159.

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2. Padmanathan P., Hall K., Moran P., Jones H.E., Gunnell D., Carlisle V., Lingford-Hughes A., and M. Hickman. Prevention of suicide and reduction of self-harm among people with substance use disorder: A systematic review and meta-analysis of randomised controlled trials. Comprehensive Psychiatry. 2020;96: 152135.

Author contribution statement: P.P. conceived the idea for the review. P.P. drafted the proposal, all co-authors of the proposal provided feedback. The search strategy was first performed including all publications until September 2017. It was then re-run to include all publications between August 2017 and January 2019. In the first round, K.H. and P.P. independently screened titles and abstracts, reviewed full texts of all potentially relevant studies, extracted data using a standardised extraction form and assessed included studies for bias using the Cochrane Risk of Bias 2 Assessment Tool. V.C. and P.P. performed the same tasks for results obtained when the search strategy was re-run. P.P. performed the meta-analysis with advice from H.E.J. P.P. drafted the paper with feedback from all co-authors.

3. Padmanathan P., Cohen R., Biddle L., Griffith E., Breheny K., Gunnell D., Hickman M., Munien N., Patel A., Crocker E., and P. Moran. Development of a suicide prevention intervention for Emergency Department attendees presenting with co-occurring self-harm and harmful substance use: a Delphi study. (in submission).

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Other publications during PhD

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Chapter 1. Introduction

1.1 Preface

Whilst working in Liaison Psychiatry, I observed that the provision of safe and effective care for people who presented to the Emergency Department (ED) with self-harm and co-occurring substance use problems was particularly challenging. Despite this patient group being at increased risk of suicide compared with the general population, they regularly appeared to fall through a gap in services. Substance use was frequently cited as an exclusion criterion for accessing mental health services, while drug and alcohol services were not commissioned to offer immediate, acute care. Furthermore, for many patients experiencing a suicidal crisis, substance use treatment was not their priority. Consequently, discharging patients from hospital with only signposting to drug and alcohol services seemed unsatisfactory. This clinical observation, which I soon realised has been a longstanding issue within health services in England, became the starting point for my PhD.

1.2 Introduction

Globally, people with substance use problems are considered to be at a greatly increased risk of suicide compared with the general population [1]. Estimates of the extent to which their suicide risk is increased vary between studies and types of substances. However, a Global Burden of Disease study estimated the increased risk of suicide to range from almost five times for amphetamine use problems and seventeen times for cocaine use problems [1]. Furthermore, of all diagnoses relating to mental health and substance use, alcohol use problems are estimated to be the second-largest contributor to suicide-related disability-adjusted life-years worldwide after depression [1]. In England, over half of patients known to mental health services who die by suicide have a history of substance use problems [2]. Although such problems are modifiable risk factors for suicide, this population are often highly stigmatised [3]. They also remain marginalised within clinical services despite many years of policy and guidance advocating for change [4]. Suicide prevention research focused on people with substance use problems is therefore, urgently required.

1.3 Chapter summary

In this chapter, I begin by defining suicide, self-harm, and substance use problems as these terms are used throughout this thesis. I outline epidemiological aspects of each behaviour, consider the mechanisms underpinning the associations between the behaviours, highlight relevant national policies and guidelines, describe the evidence base for prevention, and outline the aims and objectives of this PhD.

1.4 Definitions

1.4.1 Suicide and self-harm

Throughout this thesis I use the word "suicide" to refer to "the act of deliberately killing oneself" [5], and "self-harm" to refer to any intentional "act of

self-poisoning or self-injury carried out by a person, irrespective of their motivation" [6].

Although the definition of suicide is relatively consistent in clinical and epidemiological research, in practice there is considerable variation in the classification of deaths as suicides. In England and Wales, suicides are determined by coroners, who usually have a background in law, based on information from a variety of sources including the police, witnesses, families, and medical staff [7]. The threshold for a suicide conclusion has recently shifted from "beyond reasonable doubt" to "on the balance of probabilities" [8]. Where there is insufficient evidence of suicidal intent to meet the threshold for a suicide conclusion, suicides may receive alternate conclusions such as "open" or more detailed "narrative" conclusions. Most deaths due to injury or poisoning that receive open conclusions are thought to be suicides on review by clinicians [9, 10].

Definitions of self-harm vary more widely within clinical and epidemiological research. In recent years, there has been growing recognition of a distinction between two types of self-harm based on suicidal intent: suicide attempts and non-suicidal self-injury [11, 12]. Suicidal intent is, however, often ambiguous and can fluctuate, and both behaviours are important risk factors for suicide. It has, therefore, been argued that differentiating these behaviours based on suicidal intent may not be clinically useful [13]. National clinical guidance on self-harm in England currently includes all intentional self-injury (including self-poisoning), irrespective of suicidal intent, within their definition [6, 14]. In this thesis, I use this broad definition of self-harm (i.e., an intentional act of self-poisoning or self-injury, irrespective of suicidal intent) partly due to data availability and partly to minimise the exclusion of important information.

Increasingly, there is an awareness of how the use of stigmatising terminology in mental healthcare can influence the uptake and quality of treatment, thereby impacting health outcomes [15]. Although culturally appropriate language changes over time and there is often debate around preferred terms, some terms are considered to be more broadly acceptable than others [16]. When describing

suicide in this thesis, I therefore intentionally use phrases such as, "died by suicide" and "ended their life", rather than the phrase "commit suicide", for which opinions are polarised due to its criminal connotations dating back to pre-1961 when suicide was illegal in England [16].

1.4.2 Substance use problems

Defining substance use problems is complicated by the range of substances included within the definition, the changing nature of use both within a single day and over longer periods of time, developments in our understanding of the psychological and physiological effects of use, the need to avoid stigmatising language, as well as socio-economic, cultural, and political influences [17, 18].

With regards to alcohol use, national guidelines typically categorise the risk of harm to health based on the units consumed each week [19]. Less than 14 units consumed evenly throughout a week is considered "lower risk" for both women and men, whilst "higher risk" has been defined as regular consumption of over 35 units in women and 50 units in men [20].

Substance use problems can also be defined according to criteria set out in two widely used diagnostic classification systems for mental disorders: Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD) (Figure 1.1) [11, 21]. The conceptualisation of cases within these classification systems has changed over time. DSM-IV, ICD-10, and ICD-11 describe two distinct diagnoses, "abuse"/"harmful pattern of use" and "dependence", which each have a different specific set of criteria [21-23]. In contrast, the current version, DSM-V integrates these two diagnoses into mild, moderate or severe "substance use disorders" (Table 1.1) [24]. ICD-11 includes two additional diagnoses of an "episode of harmful substance use" and "hazardous substance use", equivalents of these are not included in DSM-V [25]. "Hazardous substance use" refers to a pattern of use that increases the risk of harm to oneself or others but has not yet caused harm.

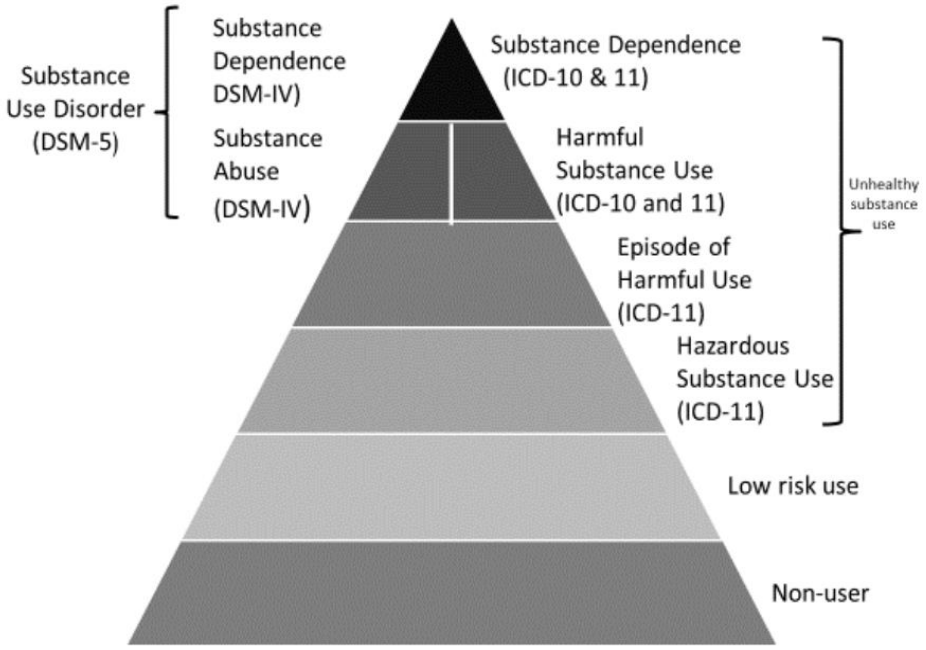


Figure 1.1: Comparison of substance use-related diagnostic classifications [25]

A household survey of 12,182 "regular alcohol users" and 1,788 "regular cannabis users" in ten countries, which compared the diagnostic classification systems, found variable agreement between ICD-11 and DSM-V. Concordance was low between "harmful use" in ICD-11 and mild "substance use disorders" in DSM-V [26].

Within healthcare settings, cases identified by clinicians do not necessarily correspond with those identified based on diagnostic classification definitions [27]. Simpler, alternative definitions have, therefore, been proposed to identify people who would benefit from healthcare. One option, "heavy substance use over time" is based on the observation that this consumption pattern is most often responsible for physiological features of dependence and the substance-attributable burden of morbidity and mortality [17]. Another option is to define cases simply based on substance-related harms to oneself and others [28], although this too may lack consistency, especially between substances.

Table 1.1: Summary of diagnostic criteria for substances use problems [25, 29]

ICD-11		DSM-V	
Definition	*Criteria*	*Definition*	*Criteria*
Substance use dependence:	≥2 of the following criteria for ≥ 12 months (or if continuous use for ≥3 months): 1)Impaired control over use 2)Use increasingly prioritised over other aspects of life 3) Physiological features indicating neuroadaptation to substance	**Substance use disorder (2-3=mild, 4-5=moderate, ≥6=severe)**	≥2 of the following criteria within a 12-month period: 1) Using larger quantities, or for longer, than intended 2) Inability to stop/control use despite a desire to do so 3) Cravings 4) Substantial amount of time spent on activities related to using 5) Neglected important life roles due to use 6) Given up activities due to use 7) Social harms related to use 8) Harms to health related to use 9) Hazardous use 10) Tolerance 11) Withdrawal
Harmful pattern of substance use:	Episodic use for ≥12 months/continuous use ≥3 months: Pattern of use that has caused "clinically significant" harm to the physical or mental health of oneself or others, that is not better explained by another medical condition or mental disorder.		

In this thesis, except where otherwise specified, I use the broad term "substance use problems" flexibly to refer to people whose heavy substance use over time causes problems to themselves or others. I intentionally avoid other broad terms such as "misuse" or "abuse", due to concerns that they make judgements about the appropriateness of substance use [30]. For clarity, where I refer to data from other sources, the terms used within these sources are specified in quotation marks.

When referring to "substances", I include alcohol and other illegal psychoactive substances as these are the substances for which people in England most commonly access drug treatment services [31]. In particular, most treatment access relates to alcohol and opioids, therefore the evidence that I cite predominantly relates to their use. Nonetheless, many of the principles also apply to other substance use problems treated within clinical services, such as problematic use of crack cocaine, cocaine, and cannabis [31].

1.5 Epidemiology

As people who self-harm, die by suicide, and/or use substances are often stigmatised and marginalised, they are frequently under-represented within observational data. Although in some cases methods have been developed to try to account for this, these too may have their own biases. As such, the estimates presented in this section require cautious interpretation.

1.5.1 Suicide and self-harm

An estimated 700,000 people die by suicide globally each year [32]. For every suicide, there are estimated to be 20 suicide attempts, although this figure is likely to vary by demographics and region [5]. Additionally, over 100 other people may be affected by each suicide death [33]. Based on World Health Organization (WHO) estimates (which do not include deaths of undetermined intent) the United Kingdom (UK) age-standardised suicide rate in 2019 was

lower than the global age-standardised suicide rate (6.9 per 100,000 in the UK compared with 9.0 per 100,000).

In the UK, for over a decade, suicide has been the leading cause of death in both males and females between 20 to 34 years of age [34]. Based on 2020 national data, which includes deaths of undetermined intent, the overall suicide rate in England and Wales is 10.0 per 100,000 [34].

Middle age, male sex, and socioeconomic deprivation are important risk factors for suicide. The national suicide rate is three times higher in males compared with females, and highest amongst people aged between 40 to 49 [35]. Suicide rate is twice as high in the most deprived areas in England compared to the least deprived [36].

Previous self-harm is considered to be the most important risk factor for suicide. Within a year of presenting to hospital with self-harm, approximately one in five people repeat self-harm, whilst within five years of presentation one in 25 people end their life [37]. In England, amongst children and adolescents with a primary care record indicating self-harm, the risk of death by suicide may be almost 18 times higher compared to those without such a record [38].

A vast array of other risk factors for suicide have also been identified. These have been conceptualised within a range of different theoretical models, many of which place emphasis on a particular set of risk factors. For example, the Interpersonal Theory, the Integrated Motivational-Volitional Model, and the Three-Step Theory all pay close attention to the transition from suicidal ideation to suicidal behaviour (known as the ideation-to-action framework) [39]. As such, these models tend to emphasise individual-level experiences, such as perceived burdensomeness, lack of social connectedness, emotional pain, and acquired capability. Alternatively, the socioecological model takes a multi-level perspective and categorises risk factors as occurring at an individual (e.g., mental health diagnoses, chronic physical illnesses),

interpersonal (e.g., domestic violence or bereavements), community (e.g., community violence or barriers to accessing healthcare), and societal (e.g., access to lethal means or poverty) level [40].

National suicide rates have fluctuated over time (Figure 1.2) [41]. In 2016, NHS England set a target to reduce suicide rates (including undetermined deaths) by 10% by 2020/21 [42]. Paradoxically, following the setting of this target, a downward trend in suicide rates in England reversed, and in 2019 rates reached their highest level in men and women since 2000 and 2004, respectively [35]. The rise did not appear to be driven by the legal change in the standard of proof required to classify a death as a suicide, but contributory factors have yet to be determined [43]. More recent data indicate that since the start of the COVID-19 pandemic in the UK (March 2020) there has been a decline in overall suicide rates driven by a decrease in suicides among males, which has partially been attributed to death registration delays [35]. Other important age- and sex-specific trends in suicide rates in England include decade-long increases amongst young women aged 10-24 years and middle-aged men aged 45-65 years [43].

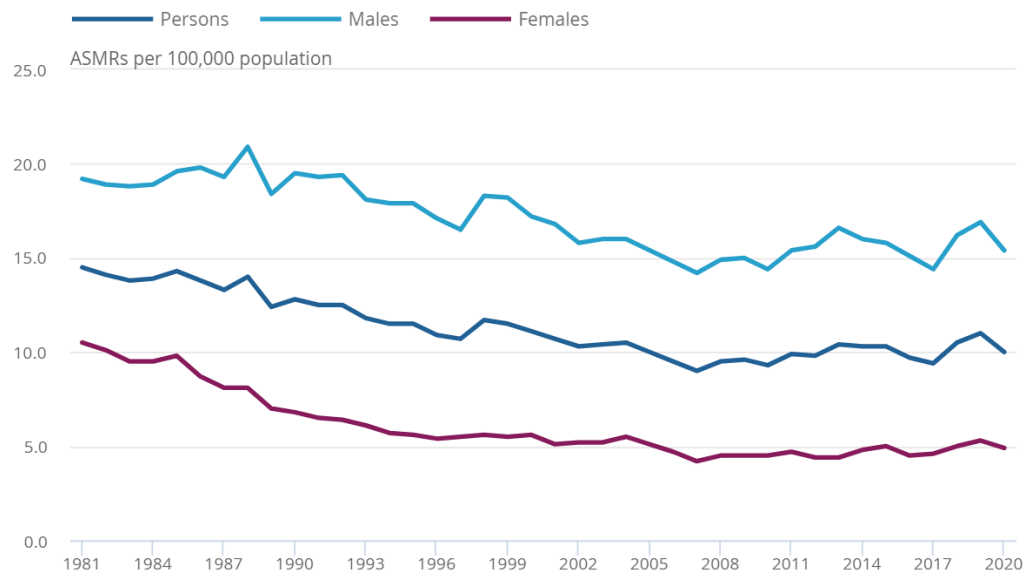


Figure 1.2: Time trends in suicide rates in England and Wales, age-standardised by sex (1981-2020) [35]

Self-harm rate estimates vary substantially depending on the setting studied and the method of data collection. Estimates are highest in community self-reported surveys and lowest in hospital admission statistics [44-46]. In 2014, the lifetime prevalence of non-suicidal self-harm in England was estimated to be 6.4% in a community sample of 16–74-year-olds, an increase of 4% compared to 2000 [46].

Routinely collected national data on emergency department presentations and hospital admissions for self-harm are available via Hospital Episode Statistics (HES) [47]. HES emergency department data are only available from 2007 onwards and underestimate self-harm presentations [48]. HES admission data are more robust but only about 50% of people presenting to emergency departments with self-harm are admitted to hospital, and admission rates vary between hospitals [49]. Instead, bespoke data collection from a Multicentre Study of Self-harm is considered to provide more reliable estimates of national rates of hospital-presenting self-harm in England [48]. Based on this data, annual national rates between 2010-2012 were estimated to be 424 and 577 per 100,000 for men and women, respectively [48]. Recent trends in hospital-presenting self-harm rates, based on data from the Multicentre Study, are consistent with national trends in suicide rates [50].

1.5.2 Substance use problems

1.5.2.1 Alcohol

Alcohol is thought to be the most widely used psychoactive substance globally, although the majority of the world's population abstains from its use [51]. "Harmful use of alcohol" is estimated to have caused three million deaths worldwide in 2016 [52]. Based on WHO estimates, the prevalence of "alcohol use disorder" is higher in the UK compared with globally (8.7% vs. 5.1%) [52].

The annual Health Survey for England, commissioned by NHS Digital, provides the main source of national data on alcohol use [20, 53]. In the most recent

survey carried out in 2019, 30% of men and 15% of women reported consuming more than the nationally recommended limit of 14 units per week [20]. Overall, between 2011 and 2019 there was a downward trend in the proportion of both men and women reporting alcohol consumption above this recommended limit [20]. Since the start of the COVID-19 pandemic, several other surveys have measured self-reported alcohol use [54]. Together, these surveys have found that although for most people alcohol consumption has remained level, for a smaller proportion of people who likely consumed higher levels of alcohol pre-pandemic, consumption has increased further. There was also a sudden rise in the proportion of people with "increasing risk" and "higher-risk" alcohol use around the start of the pandemic, which was maintained throughout the year [54]. Overall, between March 2020 and March 2021 the proportion of people with "increasing risk" and "higher-risk" alcohol use increased by almost 60%.

The Adult Psychiatric Morbidity Survey in England, last undertaken in 2014, provides data on "harmful alcohol use" and "alcohol dependence" [55]. The last survey indicated that approximately 3.1% of the population were drinking alcohol at "harmful or probably dependent" levels; the prevalence of "drinking at harmful or probably dependent levels" was more common in men than women, highest in young adults, and gradually decreased with age. Other factors associated with "harmful or probably dependent" levels of drinking included White British ethnicity, receipt of social welfare payments, health service use, and treatment for mental or emotional problems. The survey also found that most people with "probable dependence" did not recall receiving an alcohol dependence diagnosis, and few were prescribed medication for dependence. The report concluded that in England "alcohol dependence remains under-diagnosed and under-treated".

A review of the public health burden of alcohol by Public Health England published in 2016 reported that "among those aged 15 to 49 in England, alcohol is now the leading risk factor for ill-health, early mortality, and disability" [56]. A systematic review and meta-analysis estimated that one in

five hospital inpatients in the UK meet the ICD-10 criteria for "harmful use of alcohol", whilst one in ten inpatients are estimated to meet the criteria for "alcohol dependence" [57].

In 2017, the Office of National Statistics moved to report alcohol-specific deaths (i.e., deaths wholly attributable to alcohol), having previously reported alcohol-related deaths [58]. Two conditions, "chronic hepatitis, not elsewhere classified" and "fibrosis and cirrhosis of the liver", were excluded from this new definition [59], while several other conditions were added, such as "excess alcohol levels" and "alcoholic myopathy". On direct comparison, however, average annual death counts were approximately 20% lower using the new definition [59].

In 2020, 607,922 deaths were registered in England and Wales [60], of which 7,433 (1.2%) were considered alcohol-specific deaths [61]. In the same year, the UK alcohol-specific death rate was 14.0 per 100,000. The rate was more than twice as high in males compared with females, and most common in middle age [58]. Alcoholic liver disease accounted for over two-thirds of alcohol-specific deaths, whilst about one in eight deaths were a result of "mental and behavioural disorders due to the use of alcohol", and about one in sixteen deaths were attributed to an "external cause of deaths, including accidental poisoning by and exposure to alcohol" [58].

Between 2019 and 2020 the largest year-on-year increase in the alcohol-specific death rate was observed since records began in 2001 (Figure 1.3). Prior to this, the death rate had been stable for several years. The rise was observed in both men and women, and in deaths due to alcohol poisoning, mental and behavioural disorders, and most notably, alcoholic liver disease [54]. Acute-on-chronic liver failure, which is responsible for most alcoholic liver disease deaths, is linked to heavy alcohol use [54]. Therefore, although the underlying causes of the increase in the alcohol-specific death rate were likely to be multifactorial, it appears to reflect the observed increase in alcohol consumption amongst some individuals since the COVID-19 pandemic.

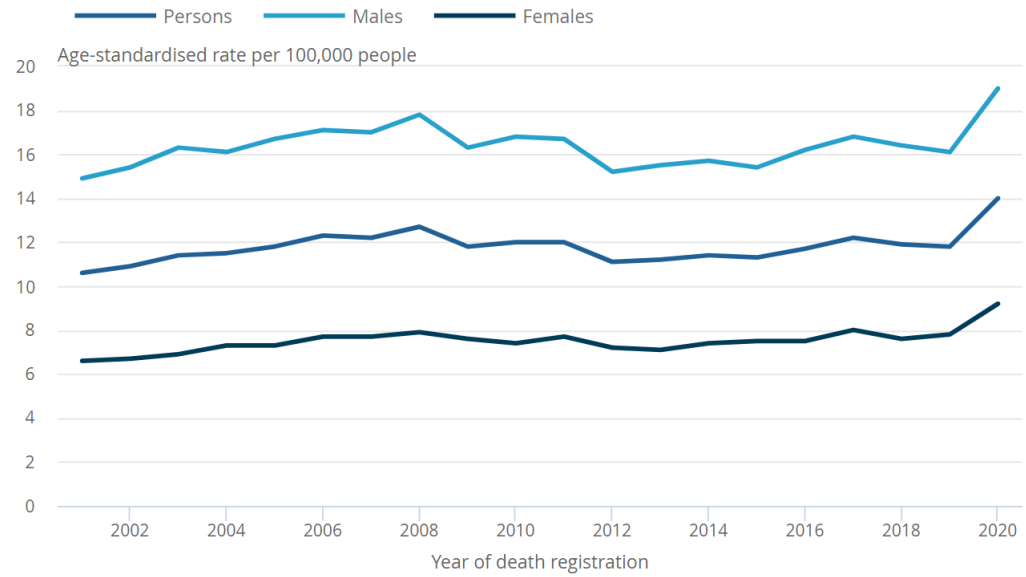


Figure 1.3: Time trends in alcohol-specific death rates in the UK, age-standardised, by sex (2001-2020) [58]

1.5.2.2 Other illegal psychoactive substances

Worldwide, in 2019 about 5.5% of people aged between 15-65 years were estimated to have used illegal drugs at least once in the previous year, and the global prevalence of "drug use disorders" was estimated to be approximately 0.7% [62]. Whilst cannabis was most widely used, "opioid use disorders" were thought to account for the largest proportion of disability-adjusted life years (DALYs) and deaths caused by "drug use disorders" [62].

In England and Wales, the most recent Crime Survey found that 9.4% of 16-59-year-olds had used one or more illegal drugs in the previous year [63]. Men were almost twice as likely to have used any drug in the last year compared with women, a finding that was consistent across each of the drug categories. Younger age groups were more likely to have used any drug in the last year compared with older age groups. Last-year cannabis use was most prevalent (7.8%), followed by the use of powder cocaine (2.6%), MDMA (1.4%), ketamine (0.8%), and amphetamines (0.3%). The observed prevalence of last-year heroin and methadone use was less than <0.1%. These figures are likely

to have been substantial under-estimates as data collection involved face-to-face interviews of people living in private households.

National data on "illicit drug dependence" was collected in the 2014 Adult Psychiatric Morbidity Survey [55]. "Signs of drug dependence" in the previous year were observed in 3.1% of participants, of which 2.3% showed "signs of dependence" on cannabis only. As with illegal drug use, "signs of dependence" were more common in men and younger age groups. People who used heroin or methadone were noted to be under-represented in the sample.

As the prevalence of opioid dependence is particularly difficult to estimate, indirect prevalence estimates produced by mathematical modelling are often used, but these too are subject to biases. In one study, approximately 280,000 (0.8%) 15-64 year olds in England were estimated to have illicit "opioid dependence" between 2008-2009 [64]. By comparison, in that same year, about 170,000 people received treatment relating to opiates within drug and alcohol services in England [65]. This figure has since fallen to about 140,000 between 2020-2021, but adults receiving treatment for opiates comprise over half of those in drug and alcohol services [65]. Although there are growing concerns about prescription opioid dependence, its contribution to the morbidity and mortality due to opioid dependence in the UK is currently unclear [66, 67].

Like suicide, a wide range of risk factors have been identified for "opioid dependence" that can also be categorised based on a socioecological model as occurring at an individual (e.g., male sex, genetics, adverse childhood experiences, mental health conditions), household/ community (e.g., parental conflict, peer substance use, social disadvantage) or societal/global (e.g., access to drugs, social norms) level [68].

The Office for National Statistics classifies deaths as being due to "drug misuse" where the underlying cause is "drug abuse" or "drug dependence", or where the deaths involved any substances controlled by the Misuse of Drugs Act 1971

[69]. In England in 2020, 5.2 deaths per 100,000 met this criterion; the rate was over twice as high amongst men compared to women, and overall rates were highest in the middle-age group [69]. Most of these deaths are due to heroin and morphine [70]. An upward trend in overall deaths due to "drug misuse" has been observed since 2012 (Figure 1.4). Possible explanations include the introduction of austerity measures within drug and alcohol services, increases in drug purity, availability and polydrug use, and an ageing population of people with drug use problems [70-72]. However, recent research into mortality amongst "people who used illicit opioids" in England between 2001 and 2018 found that population ageing did not explain the rise in death rates in this population [73].

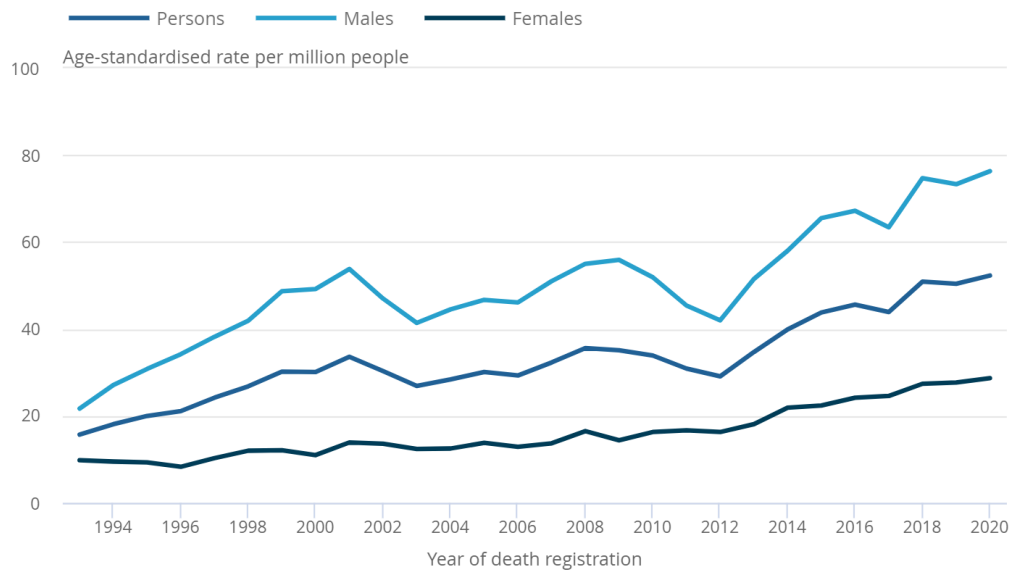


Figure 1.4: Time trends in "drug misuse" death rates in England and Wales, age-standardised by sex (1993-2020) [69]

1.5.3 Substance use and suicidal behaviour

Substance use problems and suicidal behaviour are deeply intertwined. In this section I outline three ways in which they are linked based on epidemiological evidence: 1) deaths related to drug and alcohol use problems and suicide have been grouped together using the term "deaths of despair"; 2) substance use problems greatly increase suicide risk, and are common, amongst people who

self-harm and die by suicide; 3) suicide is an important cause of death among people who use substances.

A rise in drug overdoses, alcohol-related liver disease, and suicides ("deaths of despair") amongst middle-aged people of White ethnicity was first identified in the USA, when investigating the cause of a reverse in previously increasing life expectancy amongst this group [74]. The rise was predominantly observed in people without a college degree and has been partly explained by a long-term decline in economic and social prospects for this group [74]. The increases in mortality have been exacerbated further by an epidemic of opioid use [75]. In England, a similar, but smaller-scale, rise in "deaths of despair" has been reported amongst middle-aged people [76]. However, between 2001 and 2016, trends in overall and age-standardised mortality rates for each of the three causes did not closely co-vary [77]. Instead, over the last three decades, higher rates of "drug misuse" deaths and suicide have been observed in "Generation X", the generation born in the 1960s and 1970s, than in other generations [78]. Although the reasons for this are likely to be complex, the difference in risk between the generations is most notable in the most deprived communities [78].

The extent to which substance use problems increase suicide risk varies by substance. The relationship between alcohol and suicidal behaviour has been most comprehensively studied. Most recent estimates indicate that "alcohol use disorders" are associated with roughly two to three times increased risk of suicidal thoughts, suicide attempts, and suicide deaths [79, 80]. Alcohol use more broadly has also been found to be associated with an elevated, but slightly lower, risk of suicide than alcohol use problems [81]. Furthermore, increased quantity and frequency of alcohol use appear to be associated with a greater risk of suicide [81]. Findings regarding gender differences in the relationship between alcohol use and suicide have been mixed, with no difference being identified in some studies [79, 82]. Where differences have been identified, the risk of suicide has been greater amongst women than men [81, 83]. However, in a large-scale longitudinal study of 4.8 million people

receiving Veterans Health Administration care in the USA, these differences were markedly attenuated after adjustment for other factors, particularly psychiatric diagnoses [84].

Although a consistent link has been found between other substance use problems and suicide, estimates are based on limited substance-specific data and effect sizes vary widely. Nonetheless, in a recent meta-analysis, "substance use disorders" in general were associated with between 50-150% increased risk of suicidal ideation, suicide attempts, and suicide deaths [85]. Global Burden of Disease substance-specific relative risk estimates are considerably higher (Table 1.2) [1].

Table 1.2: Pooled relative risk of suicide by substance use problem [1]

Substance use problem	Number of studies	Pooled relative risk (95% CI)
Opioid dependence	21	6.9 (4.5, 10.5)
Cocaine dependence	3	16.9(6.01, 47.2)
Amphetamine dependence	1	4.5(1.1, 9.03)

Substance use problems are common among people who self-harm or die by suicide. Within mental health services, over half of the people who died by suicide in England between 2008 and 2018 had a history of alcohol and/or drug "misuse", of which only 21% were under the care of drug and alcohol services [2]. In over half of National Health Service suicide-related compensation claims the deceased had a history of "substance misuse" [86]. Furthermore, "alcohol misuse" has been identified in over a third of patients presenting to hospital with self-harm in England [87], and "drug misuse" is estimated to be a factor contributing to almost a third of hospital admissions for suicide or self-harm [88].

Little recent data are available regarding the incidence of suicide among people with substance use problems nationally. However, in a large cohort study of causes of death among people with a "history of illicit opioid use" in England, where drug poisonings were analysed separately to suicides by other

causes, the latter accounted for about 5% of deaths and were the fourth most common cause of mortality. Drug poisonings (including drug poisoning suicides) were the most common cause of mortality [73]. Additionally, a 2016 investigation into the upward trend in "drug-related" deaths beginning around 2013, identified an increase in the number of suicides resulting from drug poisoning among "drug users" as a contributory factor [70]. This trend runs counter to the overall trend in suicides in the general population over the same period (Figure 1.2).

1.6 Mechanisms of association

Several theoretical models have been proposed to conceptualise the relationship of different types of alcohol use with suicidal behaviour; these models have categorised risk factors as pre-disposing vs. precipitating [89, 90] or proximal vs. distal [91-93]. In this section, I consider chronic substance use as a pre-disposing (or equivalent) risk factor for suicidal behaviour and acute episodes of intoxication as a precipitating (or equivalent) risk factor. Although acute episodes of intoxication are not the focus of this PhD, given that they are likely to occur in relation to episodes of suicidal behaviour amongst people with substance use problems, their mechanisms of association with suicidal behaviour are also described.

Proposed mechanisms by which acute alcohol use precipitates suicidal behaviour include intensifying psychological distress, aggression, and impulsivity; removing barriers such as fear of pain; and impairing cognitive ability to identify and use alternative coping strategies [91]. Disinhibition, impulsivity, and reduced decision-making capabilities have also been described as mechanisms contributing to suicide risk during opioid intoxication [94]. The availability of high strength or large quantities of substances can also provide or enhance access to lethal means [95]. Although difficult to definitively demonstrate a direct contribution of acute substance use to increased suicide risk, the possibility of such a contribution is supported by a range of findings. For example, in a community sample of suicide deaths

due to self-injury in England, post-mortem findings indicated alcohol intoxication in over a quarter of cases [96]. Cocaine was detected in 8.4% of descendants, far exceeding national estimates of cocaine use. Furthermore, higher levels of acute alcohol use have been found to be associated with a greater risk of suicide attempts compared with low levels of acute alcohol use [81, 97].

Disentangling the numerous biopsychosocial mechanisms that contribute to the association between substance use problems and suicide-related behaviours is challenging; they share many of the same risk factors and the occurrence of these risk factors in relation to substance use can be bi-directional. Examples of shared risk factors include genetics, adverse life events, impulsivity, chronic physical health conditions including pain, psychological distress, psychiatric conditions, unemployment, social isolation, and marginalisation (including within health services) [90, 91, 94, 98-102]. Additionally, chronic substance use can negatively impact cognitive function and impair judgement, which in turn may increase suicide risk [100, 103, 104].

Several neurobiological characteristics appear to be shared between suicide and substance use problems, such as serotonergic dysfunction and hypothalamic-pituitary-adrenal axis dysfunction [100, 105]. These impairments are also associated with depression. However, increases in suicide risk associated with alcohol and opioid "use disorders" have only been partially explained by co-morbid psychiatric diagnoses in longitudinal studies [84, 106, 107].

Conner et al. (2016) have proposed a concise, testable conceptual model of suicidal behaviour among people with "substance use disorders" (SUDs) including alcohol, based on current research findings (Figure 1.5) [108]. The authors acknowledge that this is an emerging area of research, therefore the model is mainly based on research relating to "alcohol use disorders" and may require expansion as evidence emerges regarding other risk factors and substance use problems. In this model, severe "SUDs" are described as distal

risk factors, whilst active "SUDs" are described as proximal risk factors. Additionally, the model includes aggression/impulsive personality traits and negative affectivity as distal risk factors, and depression and interpersonal stress as proximal risk factors. The proximal risk factors are considered partial mediators of the relationship between the distal risk factors and suicidal behaviour, whilst distal factors can have a moderating effect in combination with other variables. Furthermore, factors within the proximal/distal categories can influence each other.

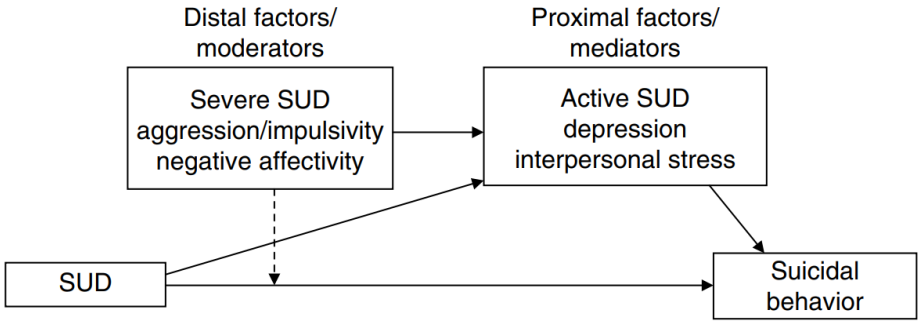


Figure 1.5: Conceptual model of suicidal behaviour and "substance use disorders"[108]

Qualitative research involving people with experience of "alcohol use" and self-harm illustrates the complexities of the relationship between the two at an individual level [109]. In one qualitative study of eleven participants in England and Wales with lived experience of self-harm and alcohol use, all participants reported that the two behaviours were linked. However, the nature of the relationship varied between participants and, for some, it also changed over time. For example, all participants reported that drinking magnified their feelings, but this was not always perceived as being problematic. Although, for some people, drinking contributed to negative feelings becoming uncontrollable, for others it had a positive effect of enabling them to express their feelings. Similarly, although many participants linked their drinking to worse self-harm injuries, some indicated that their drinking was a coping method, which helped them to avoid self-harm.

1.7 National policies and guidance

1.7.1 Suicide prevention strategy

England's most recent National Suicide Prevention Strategy was published in 2012 [110]. The cross-government strategy identified "people who misuse drugs and alcohol" as a population who require "*a tailored approach to their mental health…if their suicide risk is to be reduced*". The strategy advocated measures to address "alcohol and drug dependence", referring to existing drug and alcohol strategies, and highlighting the importance of developing links between health, social, and criminal justice services to offer more holistic support for recovery. Progress reports are published at regular intervals, with the fifth progress report published in 2021 [43].

1.7.2 Drug strategy

The UK Government published a 10-year drug strategy in 2021, which focused on reducing the supply of illegal drugs through law enforcement, reducing demand through major investment in treatment services, and promoting activities to deter recreational drug use [111]. Suicide is not specifically mentioned, and self-harm is listed only within an example of the complex needs of young people who have "drug problems". Nonetheless, the strategy acknowledged that, *"People with drug addiction often have physical and mental health needs which must be met to enable a successful outcome from treatment. Mental health problems and trauma are often central to an individual's dependency on drugs and alcohol, and all too often people fall through the gap between services."*. In response to this, the strategy proposed to, *"explore opportunities for better commissioning to make sure that there is locally joined-up service provision between specialist mental health services and substance misuse services for people with co-occurring issues".*

1.7.3 Co-occurring mental health conditions and substance use

Alongside policies and guidelines addressing suicide and substance use individually (which often include only brief references to their frequent co-existence), a range of policies and guidance specifically addressing co-occurring mental health conditions and substance use have also been published that are of relevance to suicide prevention amongst people with substance use problems.

A Good Practice Guide was initially published by the Department of Health in 2002, which advised that integrated care for people with "severe mental health problems and problematic substance misuse" should be delivered within mental health services [112]. Over a decade later, in 2017, Public Health England published a guide for service providers and commissioners, which reported that people with "co-occurring mental health and alcohol/drug use conditions" continued to be excluded from services [113]. The guide highlighted that this co-morbidity is the norm rather than an exception, and it outlined two key principles to guide the provision of clinical services: "*no wrong door*" and "*everyone's job".* These principles have since been reiterated by clinical quality standards on co-occurring severe mental illness and "substance misuse", which recommend that, "*people aged 14 and over are not excluded from mental health services because of coexisting substance misuse or from substance misuse services because of coexisting severe mental illness*" [4].

The lack of change since the publication of the Good Practice Guide is illustrated by the findings from a 2018 survey of staff working in drug and alcohol services and mental health services in the UK [114]. When asked about how current practice within local services compared to the principles set out in Public Health England's 2017 guidance, more than two-thirds responded negatively. Additionally, the majority reported that "alcohol use disorder" continued to be a barrier to accessing mental health care. For example, one respondent stated:

"I don't believe anything has changed in all the years of my working in drug and alcohol services. We still see mental health services refusing to treat people until their substance misuse is addressed…"

Most respondents identified a lack of funding, fragmented services, and stigma as key barriers. Alongside addressing these issues directly, increasing awareness and training amongst staff was a popular solution.

The importance of policy implementation has been further emphasised by a study investigating the impact of a range of mental health service changes within National Health Service (NHS) Trusts in England [115]. Although limitations of the study meant it was not possible to determine the effect of each service change independent of other changes, a 25% reduction in suicide rates was observed after the implementation of a policy on care for patients with "dual diagnosis" (defined as "drug or alcohol misuse" and co-morbid major mental illness).

1.8 Suicide prevention amongst people with substance use problems

Current evidence regarding suicide prevention interventions for people with substance use problems appears to be limited. Reductions in substance use-related suicidal behaviour have, however, been reported in several observational studies following policy changes and drug treatment. Table 1.3 summarises potential interventions based on these observations.

Ecological studies have generally observed a decline in suicidal behaviour, predominantly amongst males, following restrictions in access to alcohol [116]. Types of restrictions have included increasing alcohol pricing and raising the minimum alcohol purchasing age. At an individual level, treatment for substance use problems [117, 118], and more specifically opioid agonist treatment for opioid dependence [119-121], have also been found to be associated with reduced suicidal behaviour.

Table 1.3: Evidence for suicide prevention interventions for people with substance use problems

Level of implementation	Interventions supported by existing evidence
Population	Restricting access to alcohol (e.g., increasing prices) [116]
Clinical services	Implementing clinical policies on the management of people with "dual diagnosis" [115]
Individual	Treatment of substance use problems [117-120]

1.9 Aims and objectives

1.9.1 Aims

This PhD aims to first, investigate the possibility of critical periods of elevated suicide risk in people with substance use problems in clinical services in England, and then, develop a brief intervention to better support this population.

1.9.2 Objectives

The objectives are to:

1) Determine whether there are critical periods of elevated suicide and self-harm risk during and after opioid agonist treatment for opioid dependence.
2) Systematically review the literature to identify and evaluate the effectiveness of suicide prevention interventions among people with substance use problems.
3) Develop a brief psychosocial intervention for people with substance use problems who present to hospital with self-harm.

Chapter 2. Risk of suicidal behaviour and timing of opioid agonist treatment

2.1 Overview

In this chapter, I focus on opioid agonist treatment (OAT) for opioid dependence. I describe a study that investigated whether there are critical time periods during and after OAT, in which people are at increased risk of suicide and non-fatal self-harm. The identification of critical time periods can improve the targeting of suicide prevention interventions. Findings from this chapter were published in The Lancet Psychiatry in 2022 [122].

2.2 Introduction

Opioids, such as heroin, are the main substances for which people access drug treatment in England [31]. They are involved in almost half of drug-related deaths in England and Wales (n=2,263 deaths in 2020) [69], and the UK has one of the highest rates of drug-related deaths in Europe [123]. Although suicidal intent can be difficult to determine in many opioid-related deaths [124], there is evidence that opioid dependence is associated with a markedly increased risk of suicide [1].

OAT is the most extensively evaluated treatment for heroin dependence [125]. It involves the prescription of long-acting opioids, such as methadone and buprenorphine, alongside the provision of other psychosocial interventions. Methadone and buprenorphine reduce withdrawal symptoms and cravings for short-acting opioids without producing extreme highs. This provides stability that enables individuals to focus on broader aspects of their recovery. Consequently, OAT has wide-ranging individual, population, and societal benefits; it is associated with improved mental and physical health as well as a reduced risk of blood-borne virus infections, mortality, and criminal activity [68]. The recommended duration of OAT is generally not specified, although

there is evidence that increased retention of people in treatment is associated with better treatment outcomes [68, 126].

Despite the benefits of OAT, in recent years, strong evidence has emerged of a substantial increase in mortality risk around the time of starting and stopping treatment [120]. This research has predominantly focused on all-cause mortality and drug-related deaths. The first four weeks of treatment initiation with methadone are associated with a doubling of the risk of all-cause mortality compared with stable time on treatment (RR: 2.01; 95% CI: 1.55, 5.09) [120]. This increase in risk has not been observed with buprenorphine (RR: 0.58; 95% CI: 0.18, 1.85) [120]. Additionally, OAT in general is associated with a six times greater risk of all-cause mortality in the first four weeks after stopping treatment (RR: 6.01; 95% CI: 4.32, 8.36) [120]. Specific causes of death contributing to the elevated risk of mortality have not yet been extensively investigated.

To date, research investigating suicidal behaviour in relation to OAT has mainly been limited to comparing time on and off treatment. A meta-analysis found that the risk of suicide is lower during treatment compared with after treatment (pooled RR: 0.48; 95% CI: 0.37, 0.61) [120]. Yet, people often experience substantial psychological, social, and behavioural changes during the transitional periods into and out of treatment, which may be associated with an additional increase in the risk of suicidal behaviour. One Australian study, which investigated suicide during treatment initiation and cessation, observed a higher risk during these periods compared with overall time on and off treatment but this was not formally tested [127].

The aims of the study described in this chapter were to: a) investigate the overall risk of suicide among people prescribed OAT for opioid dependence in England compared with the general population; b) determine whether rates of self-harm and suicide among people with opioid dependence in England differ during treatment initiation, cessation, and the remainder of time on and off OAT. The study hypothesis was that self-harm and suicide would be higher in

the first four weeks after both OAT initiation and cessation, compared with stable periods of OAT.

2.3 Methods

2.3.1 Data sources

I conducted a cohort study using: 1) primary care data from Clinical Practice Research Datalink (CPRD) Gold to identify people prescribed OAT and their sociodemographic and health-related characteristics; 2) hospital admission data from Hospital Episode Statistics (HES) to identify hospital admissions with self-harm; and 3) mortality data from the Office for National Statistics (ONS) to identify suicides.

2.3.2 Primary care data (CPRD)

2.3.2.1 Overview

CPRD maintains two large databases of anonymised patient primary care records called CPRD Gold and CPRD Aurum. The division of records between the two databases is determined by the clinical management software used by a general practice. Data recorded in Vision® are included in CPRD Gold, whilst data recorded in EMIS Web® are included in CPRD Aurum [128].

CPRD Gold is the original CPRD database, which first began under the name Value Added Medical Products (VAMP) in 1987. It expanded over time to include practices throughout the UK and became known as CPRD in 2012. CPRD Aurum became accessible to researchers in 2018 and mainly includes data from practices in England and Northern Ireland. Due to differences in the data structure and coding between the two software systems that inform the databases, at the time of this study, the data could not be combined. CPRD Aurum has been found to include approximately three times the number of people who use illicit opioids compared with CPRD Gold [129]. However, CPRD

Gold was used in this study due to a licensing arrangement at the University of Bristol.

2.3.2.2 Data quality

In England, patients seeking non-urgent healthcare are required to initially visit a general practitioner (GP) to access secondary, tertiary, and diagnostic health services. GP visits are free of charge. Consequently, GP registration is high [130], and primary care clinical records include an abundance of health and lifestyle data.

The CPRD databases are updated each month. For this analysis, the February 2020 update of CPRD Gold was used. This update included data from 18.5 million patients, of whom 2.9 million (4.5% of the UK population) were currently contributing through registration at a CPRD GP practice (rather than having died or transferred to a non-CPRD practice) [131]. Out of 9,124 GP practices in the UK at the time of the dataset being released, 371 (4.1%) were currently contributing to CPRD, and 896 had contributed at some point. The overall CPRD Gold sample is considered to be approximately representative of the UK population in terms of age, sex, and ethnicity [132].

General practitioners in the UK directly record and code diagnostic and therapeutic information, including referrals and prescriptions, in electronic health records [133]. For practices that have opted into contributing to CPRD, patient records are transferred from the software in which they were recorded to a single database held by CPRD.

CPRD staff perform quality checks on the data provided. Patient records are deemed to be of "acceptable" quality if their records include continuous follow-up and meet a series of conditions. For example, a patient's practice registration date and the dates of their health care episodes should not occur before their year of birth, and a patient's age at the end of follow-up should not be over 115 [132]. Practice records are deemed to be "up-to-standard" once

practice mortality rates fall within an expected range, and there are no periods of time during which gaps in recording are observed. In the primary analysis, to maximise statistical power, "acceptable" individual patient data, recorded whilst overall practice data were not considered "up-to-standard", were included. This affected about 15% of patients, and a sensitivity analysis was conducted excluding this data.

The completeness and validity of data within each health record vary over time and are particularly influenced by financial incentives [134, 135]. For example, the Quality Outcomes Framework is a national pay-for-performance scheme that was introduced in 2004. The framework aimed to improve patient care by offering payments to GP practices that achieved pre-specified clinical indicators. The introduction of some indicators, such as "The percentage of patients aged 15 or over whose notes record smoking status in the preceding 27 months", has been associated with predictable increases in the recording of the related measure [136]. However, unintended effects have also been observed. For example, after the introduction of several depression-related indicators such as, "In those patients with a new diagnosis of depression, the percentage of patients who have had an assessment of severity at the outset of treatment using an assessment tool validated for use in primary care", there was a decrease in the documentation of diagnoses (e.g., "depression") in favour of symptoms (e.g., "low mood") [137]. To date, there have not been any indicators that refer specifically to the recording of opioid dependence or opioid agonist treatment.

In England, a substantial proportion of people with opioid dependence receive treatment from specialist drug services [138]. The extent to which details of this care are shared with primary care, and therefore prescriptions are recorded in primary care records, is unknown. Some OAT prescriptions may, therefore, be missing from this dataset. This is discussed further in the limitations section of this chapter.

2.3.2.3 Data format

Data provided by CPRD are divided into several file types based on their content. The file types can be linked using a shared patient or practice identifier. The file types and examples of content relevant to this study are described in Table 2.1.

In CPRD Gold, GPs record clinical observations using the Read code classification system, whilst prescribing information is recorded as Multilex codes. CPRD has produced dictionaries, in which these codes have been converted into "medical" and "product" codes, respectively.

Table 2.1: Description of CPRD Gold file types used in this study

File types	Relevant content
Patient	*Patient-level non-clinical data:* age, sex, year of birth, date of current registration at the practice, date of transfer out of the practice.
Practice	*Practice-level data:* date of last collection of patient records from the practice, date when practice data was judged to be of research quality
Clinical	*Patient-level clinical data:* diagnosis, symptom, date of event
Therapy	*Patient-level prescribing data:* drug, quantity, frequency, date of prescription
Additional clinical	Additional detail relating to clinical record, such as smoking status

2.3.3 Hospital admission data (Hospital Episode Statistics)

2.3.3.1 Overview

HES is a clinical dataset that includes demographic, clinical, and administrative information on all NHS hospital admissions, outpatient appointments, and accident and emergency attendances in England [47]. Collection of HES admission data began nationally in 1989, but the linkage of individual patients' hospital admission records using a pseudonymised patient identifier only began in 1997 [47]. HES Emergency Department data became available in 2007, but as explained in Chapter 1, it has been found to substantially under-estimate the number of hospital presentations with self-harm when compared with a bespoke self-harm data collection from five general hospitals in England [48]. As such, in keeping with standard practice for research in this field [139], only HES Admitted Patient Care (APC) data were used in this study.

2.3.3.2 Data quality

Almost all inpatient hospital care in England is funded by the NHS, and treatment for self-harm in private hospitals is rare, therefore the coverage of HES admission data is considered to be universal [47]. Clinical codes are generated by trained coders in each hospital based on the information provided in clinician-completed patient discharge summaries. Until 2004, the primary purpose of the data was to inform service provision. Since then, the data has also been used to pay hospitals for the care that they have provided, whilst also being made available for research. Consequently, the completeness of demographic and clinical characteristics is generally considered to be high [47].

NHS Digital, a national provider of health and social care data in England, extracts, validates, and cleans the data each month using pre-specified rules [140]. Errors have been identified generally in the coding of the data [141]. Furthermore, longitudinal linkage of each patient's hospital records is heavily

dependent on the accurate recording of their NHS numbers. In a study of paediatric intensive care HES records, readmission rates were found to be under-estimated by almost 4% when the HES patient identification algorithm was compared to a reference standard [142]. Nonetheless, research comparing HES admission self-harm data with data from the Multicentre Study of Self-harm has provided support for its overall accuracy [48].

Approximately half of the people who present to the hospital with self-harm are admitted [49]. It is commonly assumed that admission is determined by the severity of self-harm and consequently suicidal intent, but this has been challenged by variation in admission rates between hospitals, which were not explained by indicators of severity such as duration of admission [139]. Additionally, hospital admission rates may vary over time. For example, in 2004 a target was introduced for Emergency Department attendees to be admitted, transferred, or discharged within four hours of presentation, which coincided with an increase in brief paediatric emergency admissions [143].

2.3.3.3 Data format

Diagnostic data are made available in two formats, organised by either "hospitalisation" or "episode". A "hospitalisation" refers to the total duration of the inpatient admission, whilst an "episode" refers to the duration of continuous care provided by a single consultant. There can be multiple "episodes" within a "hospitalisation". For example, a patient may be admitted with self-harm but develop appendicitis when in hospital, requiring a referral for surgery. This study used the diagnostic information organised by "hospitalisation". This provided unique ICD codes across a hospital admission, as well as the start and end date of each admission. Diagnostic coding in HES is based on the tenth revision of the World Health Organization's International Classification of Disease [23, 47].

2.3.4 Mortality data (Office for National Statistics)

2.3.4.1 Overview

ONS collates and codes all deaths, including suicides [35]. The data have a wide range of uses and users, for example, informing government policy decisions as well as private sector financial risk estimation models [144].

2.3.4.2 Data quality

In England, it has been a legal requirement to certify and register all deaths since 1837, and checks are regularly made to ensure that registration has taken place. Coverage of deaths in England is, therefore, almost complete [145].

Deaths should be registered within five days of their occurrence. However, there can be a delay, particularly where a coroner's inquest is required because deaths cannot be registered until an inquest is complete. Any death that may have been a suicide requires a coroner's inquest, and in 2020, the median registration delay for suicides was 165 days from death to registration [35, 144].

Death certification involves physician/coroner completion of the following fields relating to the cause of death: "1a) Disease or condition directly leading to death", "1b) Other disease or condition, if any, leading to 1a)", "1c) Other disease or condition, if any, leading to 1b)", "Other significant conditions contributing to the death but not related to the disease or condition causing it" [144].

The cause of death is determined by a medical practitioner or a coroner. To create consistent and comparable mortality statistics, for most deaths, ONS use specialist computer programs to automatically code the text from the death certificates. A series of internationally agreed rules are then applied to assign an underlying cause of death, and further checks are performed [144].

Causes of death certified after a coroner's inquest are, however, coded manually by trained coders due to the free text format of the data [145].

2.3.4.3 Data format

This study utilised the date of death and causes of death information included within the ONS mortality dataset. The linked ONS dataset listed an underlying cause of death as well as up to fifteen additional causes of death for each patient (cause, cause one, cause two etc.). It did not differentiate between conditions leading to the underlying cause of death and those contributing to, but not related to, the cause of death. Diagnostic coding in ONS is based on the tenth revision of the World Health Organization's International Classification of Disease [23, 47].

2.3.5 Linkage of CPRD to HES admissions and ONS mortality data

Linkage between CPRD data and other datasets is available for GP practices in England that have consented to participate in the linkage scheme [146]. At the time of this study, of the 12.7 million patients with CPRD records in England, 8.9 million were eligible for linkage (approximately 70%) [131]. Although the use of linked data resulted in a reduction in sample size, a validation study found that this was outweighed by the increased sensitivity in identifying suicides [147].

The linkage process involves the transfer of patients' personal identifiers from GP practice software to NHS Digital, alongside the patient and practice codes used in CPRD. NHS Digital carry out the linkage by comparing the personal identifiers (e.g., NHS number, sex, and date of birth) of each dataset iteratively against a set of criteria of decreasing restrictiveness, which each require some identifiers to match exactly. Approximately 96% of CPRD patient records matched HES records on at least NHS number, sex, and date of birth [146]. Previous research has demonstrated that suicide rates in ONS-linked practices are generally comparable to suicide rates nationally [147].

2.3.6 Participants

The study population consisted of people who were prescribed methadone or buprenorphine as OAT at least once in primary care in England between 2nd January 1998 and 30th November 2018.

To avoid inclusion of people prescribed these drugs for other indications, such as analgesia or a cough in palliative care: 1) age was restricted to at least 18 years at cohort entry, and 65 years or younger at the time of their first OAT prescription; 2) patients were excluded if they were prescribed methadone or buprenorphine, did not have a Read code indicating illicit opioid use, and they met the following criteria: a) any prescriptions for an injectable or transdermal formulation, because these are most commonly used for pain (14); b) any prescriptions with dosage text stating "for pain"; c) maximum daily dose across all the patient's prescriptions of <4mg buprenorphine and <40mg methadone. These doses were selected to balance sensitivity and specificity, since they are at or above the maximum recommended doses for pain, and at the lower end of prescribed doses for OAT (Table 2.2) [148]. These criteria were a refinement of those used in previous CPRD studies of people prescribed OAT [149, 150].

2.3.7 Follow-up

In keeping with standard approaches for CPRD studies [151, 152], patients entered the cohort at the latest date out of the first recorded OAT prescription, the date the patient registered at their general practice, and 2nd January 1998 (the earliest date for when linked data were available) (Figure 2.1). Patients with a first record of OAT before their practice registration date were included in the primary analysis to maximise statistical power. This may have introduced bias if the risk of suicide decreases with time after treatment, as only patients who did not die during the initial period after treatment were able to join a CPRD practice and be included in the analysis. A sensitivity analysis was, therefore, performed excluding these patients.

Table 2.2: Indications for methadone and buprenorphine prescribing in adults [148]

Drug	Indication	Route	Dose	Likely max dose based on dose information
Methadone	Adjunct in treatment of opioid dependence	Oral solution	Initially, 10-40mg daily depending on tolerance, increase by 5-10mg daily, max weekly increase 30mg; usual dose 60-120mg.	120mg
	Severe pain	By mouth or injection	5-10mg every 6-8 hours	40mg
	Palliative cough	By mouth using linctus	1-2mg every 4-6 hours	12mg
Buprenorphine	Adjunct in the treatment of opioid dependence	Sublingual using sublingual tablets	Initially, 0.8–4 mg daily, adjusted by 2–4 mg daily; usual dose 12–24 mg; maximum 32 mg.	32mg
		By mouth using oral lyophilisate	Initially, 2 mg daily, adjusted by 2–6 mg daily; maximum 18 mg per day.	18mg
	Moderate to severe pain	Sublingual	200–400 micrograms every 6–8 hours	1.6mg
		Injection	300–600 micrograms every 6–8 hours	2.4mg
	Pre-medication	Sublingual	400 micrograms	400 micrograms
		Injection	300 micrograms	300 micrograms
	Intra-operative analgesia	Injection	300-450 micrograms	450 micrograms

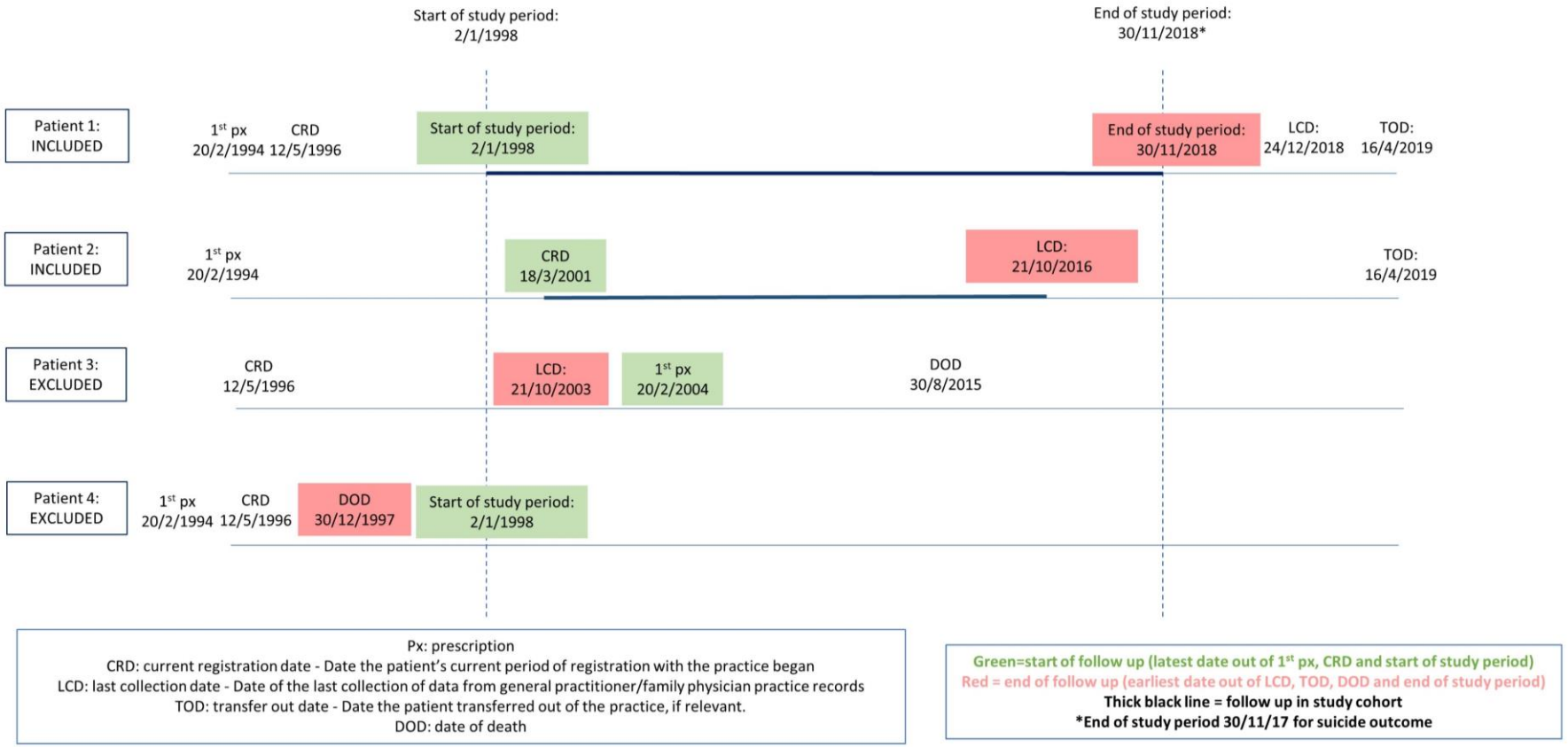


Figure 2.1: Study cohort inclusion criteria illustrated by example scenarios

Patients were followed up until the earliest date out of 30th November 2018 (the last date when linked data were available), the last date of data collection from the practice, transfer away from the practice, or death (Figure 2.1). For analyses of suicide data, follow-up ended on 30th November 2017, one year before the most recent date for which linked data were available. This accounted for the potential time delays in suicides being included in ONS death registration due to the investigation process required for unnatural deaths [153].

2.3.8 Exposure

The exposure categories were selected to reflect the time periods investigated within the OAT literature [120], and to facilitate future comparisons. Time on and after OAT was divided into: (1) the first four weeks on treatment, (2) the remainder of time on treatment, (3) the first four weeks after treatment, and (4) the remaining time after treatment (Figure 2.2).

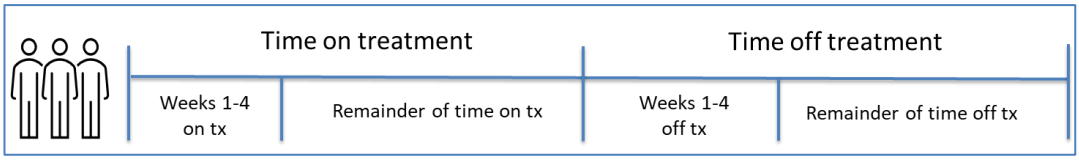


Figure 2.2: Illustration of exposure time periods (tx=treatment)

In keeping with previous studies [149, 150], treatment episodes (i.e. time "on treatment") were defined as periods of one or more prescriptions of methadone or buprenorphine as OAT, where there were 28 days or less between the expiry date of one prescription and the start of the next. A gap of greater than 28 days was considered a new treatment episode. The practice of considering up to a 28-day gap to be time "on treatment" when working with UK primary care OAT prescribing data is based on the rationale that this is more likely to occur due to incomplete prescribing information, rather than a patient genuinely stopping and re-starting treatment. In other countries, where prescribing data is more complete, a smaller gap such as seven days has been used [154]. Time "off treatment" was defined as beginning from the

expiry date of the last prescription in a treatment episode and ending on the first day of a new treatment episode (if it occurred).

2.3.9 Outcomes

The outcomes were hospital admissions for non-fatal self-harm (identified using HES admissions data) and death by suicide (identified using ONS mortality data) (See Table 2.3 for ICD codes). Data on these outcomes are also available in CPRD but are under-recorded [147]. Hospital admissions for self-harm were selected as an outcome, instead of GP presentations, due to their likelihood of increased severity and suicidal intent. This assumption is based on variation in methods within different settings. For example, hospital presentations with self-harm are more commonly due to self-poisoning, while self-cutting is more commonly identified in the community and used in non-suicidal self-injury [45, 155].

As suicidal intent can fluctuate and be difficult to determine, and any self-harm including non-suicidal self-injury is an important risk factor for suicide, self-harm of undetermined suicidal intent was included in the case definition [13]. This is in keeping with current national guidance in England for the treatment of self-harm [6]. Deaths of undetermined intent were also included as suicides since most of these deaths are probable suicides [9]. To maximise sensitivity, events were classified as suicide or self-harm regardless of the position of relevant codes in the diagnostic lists.

2.3.10 Generation of code lists

Within each dataset, multiple codes may relate to a single observation of interest, such as a diagnosis or medication. To efficiently identify all patient records that contain an observation of interest, code lists need to be created and merged with the dataset.

An ICD code list to identify suicide and self-harm within HES and ONS is already well-established (Table 2.3) [147].

Table 2.3: ICD codes for suicide and self-harm

ICD 10	ICD9
X60–X84 (intentional self-harm)	E950–E959 (suicides and self-inflicted injury)
Y10–Y34 (undetermined intent), excluding Y33.9 (verdict pending)	E980–E989 (injury undetermined), excluding E988.8

To define the population in this study, code lists were created of CPRD product codes for methadone and buprenorphine and CPRD medical codes for illicit opioid use.

Product codes that *might* indicate the prescription of OAT were identified by, first, searching for the terms "methadone" and "buprenorphine" in the 'Drug substance name' field of a data dictionary provided by CPRD. To ensure codes with a missing 'Drug substance name' were also included, the 'Product name' field of the dictionary was also searched for brand names of each medication, which were identified using the British National Formulary [148]. An independent search of the dictionary for product codes was carried out by my colleague (D.L.). Search terms and code lists identified in each search were compared, and disagreements were resolved through discussion. The combined code list was also compared with a code list from a published study [150], and no additional codes were identified. Section 2.3.6 includes details of the steps subsequently taken to ensure that people who were prescribed methadone or buprenorphine for indications other than OAT were excluded.

Medical codes that *probably* indicate a history of illicit opioid use were identified by searching for relevant terms within the 'Read terms' field in the CPRD data dictionary. Again, an independent search of the dictionary for medical codes was carried out by D.L. Search terms and code lists identified in each search were compared, and disagreements were resolved through

discussion. The combined search terms are listed in Table 2.4, and the agreed code lists are included in Appendix A.

Table 2.4: Search terms to identify medical codes indicating a history of illicit opioid use [129]

Population	Dictionary	Search category	Search term (anywhere in string)
People prescribed methadone	Product	Drug substance name	methadone
		Product name	amidone, dolophine, eptadone, heptadon, metado, methadone, methadose, methex, methodex, physeptone, pinadone, symoron
People prescribed buprenorphine	Product	Drug substance name	buprenorphine
		Product name	bunavail, buplast, bupramyl, buprenorphine, busiete, butec, butrans, cizdol, espranor, gabup, hapoctasin, natzon, panitaz, prefibin, prenotrix, probuphine, reletrans, relevtec, sevodyne, sublocade, suboxone, subutex, temgesic, trephine, transtec, turgeon, zubsolv
People who use illicit opioids	Medical	Read Term	abus, addict, buprenorphine, dependen, drug user, heroin, inject, methadone, misus, opiate, opiate substitution, opioid, overdose

In this study, the medical codes were used in conjunction with the product codes for methadone and buprenorphine to validate illicit opioid use. For example, the presence of a medical code such as "H/O heroin use" within the records of a patient who had a product code indicating a buprenorphine prescription, increased the likelihood that the buprenorphine was prescribed for OAT rather than for another indication. As such, medical codes for prescriptions, tests, or adverse effects of buprenorphine and methadone were excluded where the drug indication was unclear. Codes indicating the injection of illicit drugs without specifically mentioning opiates were included because in the UK almost everyone who injects drugs uses heroin [156].

2.3.11 Confounders and other variables of interest

The following potential confounders were specified a priori due to the possibility of each variable being independently associated with both the OAT time periods and suicide or self-harm: age, sex, socioeconomic status (using postcode-linked Index of Multiple Deprivation score quintiles [157]), number of previous OAT treatment episodes, previous self-harm, previous mental illness and major chronic illness score (using the Charlson Index [158]). Ethnicity was not included as a co-variate due to concerns regarding the completeness and accuracy of the data [135]. However, the available data on patient ethnicity have been presented as baseline characteristics.

The methods for defining each confounder, and other variables for which baseline data are presented, are provided below. The code lists used to define co-variates have been uploaded to a GitHub repository for this study: https://github.com/ppadmanathan/OAT-suicide-CPRD-cohortstudy.

2.3.11.1 Age

In CPRD, the year of birth is available for all "acceptable" patients to ensure anonymity. The day and month of birth were not provided for any patients within the cohort to ensure anonymity. To calculate the age of each patient, with consistency, at different times throughout each year, a date of birth was generated with each patient assigned the 1st of January as their day and month of birth.

2.3.11.2 Sex

CPRD data includes a variable labelled 'gender', but the options within this variable were described in a file labelled 'sex'. The options were "male", "female" and "indeterminate", therefore, the variable is referred to as 'sex' in this study. There were no patient records of indeterminate sex within the study cohort.

2.3.11.3 Ethnicity

Within primary care records, ethnicity can be ascertained from over 100 different codes. A code list, defined in a previous publication [159], was used to identify ethnicity codes within each patient's CPRD record. Where more than one ethnicity code was identified within a patient's record, the most frequently recorded ethnicity was used. Where there was no mode or no record of ethnicity in CPRD, the ethnicity recorded within HES admission data was used instead [135]. HES admission data included the following categories: Bangladeshi, Black African, Black Caribbean, Black Other, Chinese, Indian, Mixed, Other Asian, Other, Pakistani, Unknown, White. To facilitate comparisons between the data from these two sources, CPRD and HES ethnicity codes were categorised into five broad ethnicity groups used by ONS: Asian, Black, Mixed, Other, White [160].

2.3.11.4 Socioeconomic status

Patient- and practice-level linked Index of Multiple Deprivation (IMD) data are available with CPRD Gold. IMD is a composite deprivation score derived from a range of socioeconomic indicators. The score was first produced in 2000 and was updated in 2004, 2007, 2010, 2015, and 2019. The 2015 version was the most recent linked data available for use in this study. In this version, 37 indicators were used to derive scores for seven different 'domains' of deprivation: income, employment, education, health, crime, barriers to housing and services, and living environment (Table 2.5) [161]. The overall IMD score was calculated as a weighted sum of the seven 'domain' scores. For each patient in CPRD, a quintile IMD score was provided based on their home postcode; quintile one represents the greatest deprivation, whilst quintile five represents the least [162]. Where patient-level IMD scores were missing, practice postcode-linked IMD scores were used instead.

Table 2.5: Components of Index of Multiple Deprivation [161]

Domain	IMD score weighting (%)	Example indicator
Income deprivation	22.5	Adults and children in Income Support families
Employment deprivation	22.5	Claimants of Jobseeker's Allowance
Health deprivation & disability	13.5	Years of potential life lost
Education, skills & training	13.5	Secondary school absence
Crime	9.3	Recorded crime rates for violence, burglary, theft, criminal damage
Barriers to housing & services	9.3	Housing affordability
Living environment deprivation	9.3	Houses without central heating

2.3.11.5 Previous self-harm

HES admission data were searched for the ICD codes described in Section 2.3.10, which indicated a hospital admission for self-harm. Only codes recorded before the start of each period of follow-up were included.

2.3.11.6 Previous mental illness

CPRD records were searched for medical codes, using pre-existing code lists, which indicated one of the following diagnoses: depression, anxiety, personality disorder, schizophrenia, bipolar disorder [163]. Only codes recorded before the start of each period of follow-up were included.

2.3.11.7 Previous major chronic illness score

The Charlson Comorbidity Index (CCI) is a validated measure of co-morbidity that is widely used in research [158, 164]. The score is determined by identifying and weighting a range of co-morbidities, such as cerebrovascular disease and congestive heart disease, according to their associated one-year mortality. It, therefore, accounts for both the quantity and severity of a patient's co-morbidities. A pre-existing code list [165] was used to search each

patient's CPRD records for medical codes recorded before each period of follow-up, which indicated the presence of one of the diagnoses that contribute to the CCI. These were then weighted, and the scores were totalled to determine an overall major chronic illness score for each patient.

2.3.11.8 Alcohol dependence

A pre-existing code list [166] was used to search CPRD records for medical codes indicating alcohol dependence that were recorded before the start of each patient's follow-up.

2.3.11.9 Smoking

Smoking status was recorded for >90% of patients within the Additional Clinical Details CPRD file. Smoking history was defined as a status of "yes" or "ex" before the start of each patient's follow-up. Smoking status was recorded before the start of follow-up for >75% of patients.

2.3.12 Cleaning prescribing data

2.3.12.1 Understanding the data

In CPRD, prescribing information is divided among a number of variables that are included within several different source files. CPRD provides definitions of each variable. To gain a better understanding of these prescribing-related variables and how they related to methadone and buprenorphine prescriptions, I explored and summarised the characteristics of the data. Table 2.6 describes the summary characteristics and completeness of the regular prescriptions for oral methadone or buprenorphine recorded in CPRD, which did not have text specifying their use for pain.

Table 2.6: Methadone and buprenorphine prescribing data recorded in CPRD (Definitions provided by CPRD)

Variable	Definition	Source File	Methadone (n=486, 903)					Buprenorphine (n=222,241)				
			No. missing	% missing	IQR	Median	Mode	No. missing	% missing	IQR	Median	Mode
daily_dose	"Numerical daily dose extracted from dosage text"	Common Dosage	359,362	73.8	20-55	40	50	132,628	59.7	2-4.5	3	2
dose_duration	"If specified, the number of days the prescription is for"	Common Dosage	486,623	99.9	1-1	1	1	221,653	99.7	1-7	7	7
dose_frequency	"How often a dose is taken in a day"	Common Dosage	358,837	73.7	1-1	1	1	128,458	57.8	1-3	1	1
dose_interval	"Time span in days that the dose is over, e.g., 1 every 2 weeks = 14, 4 a day = 0.250"	Common Dosage	365,350	75.0	1-1	1	1	132,543	59.6	1-1	1	1
dose_number	"Amount in each dose"	Common Dosage	359,467	73.8	20-55	40	50	133,886	60.2	1-2	1.5	1
dose_unit*	"Unit of each dose"	Common Dosage	377,157	77.5	N/a	N/a	"ML"	0	0	N/a	N/a	"TAB"
numdays	"Number of treatment days prescribed for a specific therapy event"	Therapy	429,997	88.3	7-14	14	14	207,701	93.5	14-28	14	14
numpacks	"Number of individual product packs prescribed for a specific therapy event"	Therapy	429,997	97.9	30-100	50	30	218,199	98.2	7-50	50	50
qty	"Total quantity entered by the GP for the prescribed product"	Therapy	0	0	234-700	420	700	0	0	14-56	28	14
packtype_desc*	"Pack size or type of the prescribed product e.g., tablet/bag/gram/mls"	Product Pack Type	33,607	6.9	N/a	N/a	"MLS"	28,742	12.9	N/a	N/a	"TABLET(S)"
strength*	"Strength of the product e.g., 200microgram or 0.3mg/ml"	Product dictionary	0	0	N/a	N/a	1mg/1ml	0	0	N/a	N/a	200 micrograms

*These variables did not contain numeric data; therefore, it was not possible to calculate medians and interquartile ranges.
For all variables with numeric data, results that were recorded as 0, were replaced as missing.

To gain a better understanding of how the variables related to one another, I:

- inspected all the variables within a random selection of individual records.
- combined the Stata commands *'tabulate, sort frequency'* or '*summarize'* with '*if*' to inspect descriptive statistics for specific combinations of variables of interest. For example, the command '*tabulate dosage_text, sort frequency if daily_dose!=.'* listed the most common dosage texts where the daily dose variable was missing.

This approach was used throughout the data cleaning and analysis process, to check that coded commands had been executed as intended.

2.3.12.2 Estimating prescription end dates

Within the CPRD data, start dates were provided for each prescription, but not end dates. Instead, there was a variable that specified the duration of the prescription ('dose_duration' in Table 2.6), but this information was almost always missing. As all prescriptions within the dataset specified the total quantity prescribed, it was instead possible to use the daily dose to calculate the duration and end date of each prescription:

$$prescription\ duration = \frac{total\ 'quantity'\ prescribed}{'daily\ dose'}$$

2.3.12.3 Extracting dose information

In CPRD, the daily dose information is recorded as free text by the GP. CPRD has an algorithm to convert the most used instructions into numeric values [167]. However, where the instructions are uncommon, the daily dose information is not completed.

I inspected the dosage text for prescriptions with missing daily dose information. For both buprenorphine and methadone, the most common

dosage texts were either unspecified or "as directed". The dose data were more commonly missing for methadone. This may reflect the use of bespoke instructions for administration because methadone is usually prescribed as an oral solution of varying concentrations, rather than a tablet. For buprenorphine, there were no dosage texts that provided daily doses where these were missing, however for methadone I was able to manually extract daily doses for an additional 6,285 prescriptions from the dosage texts. Examples of these dosage texts were "60", "50" and "70mls". These were later combined with the recorded concentrations to calculate the dosages in milligrams (see Section 2.3.12.5).

2.3.12.4 Estimating missing daily doses

Of the regular prescriptions for oral methadone or buprenorphine recorded in CPRD that did not have text specifying their use for pain, almost three-quarters of methadone prescriptions and over half of all buprenorphine prescriptions had a missing 'daily_dose' (Table 2.6).

There are a range of approaches to dealing with missing daily dose data in CPRD. These include:

- excluding patients
- using the median daily dose within the dataset
- using a guideline-recommended dose
- "hot-decking" (using data from a similar entity, e.g. the median dose of prescriptions for the same patient, and then the median dose of prescriptions from patients with similar baseline characteristics) [168]

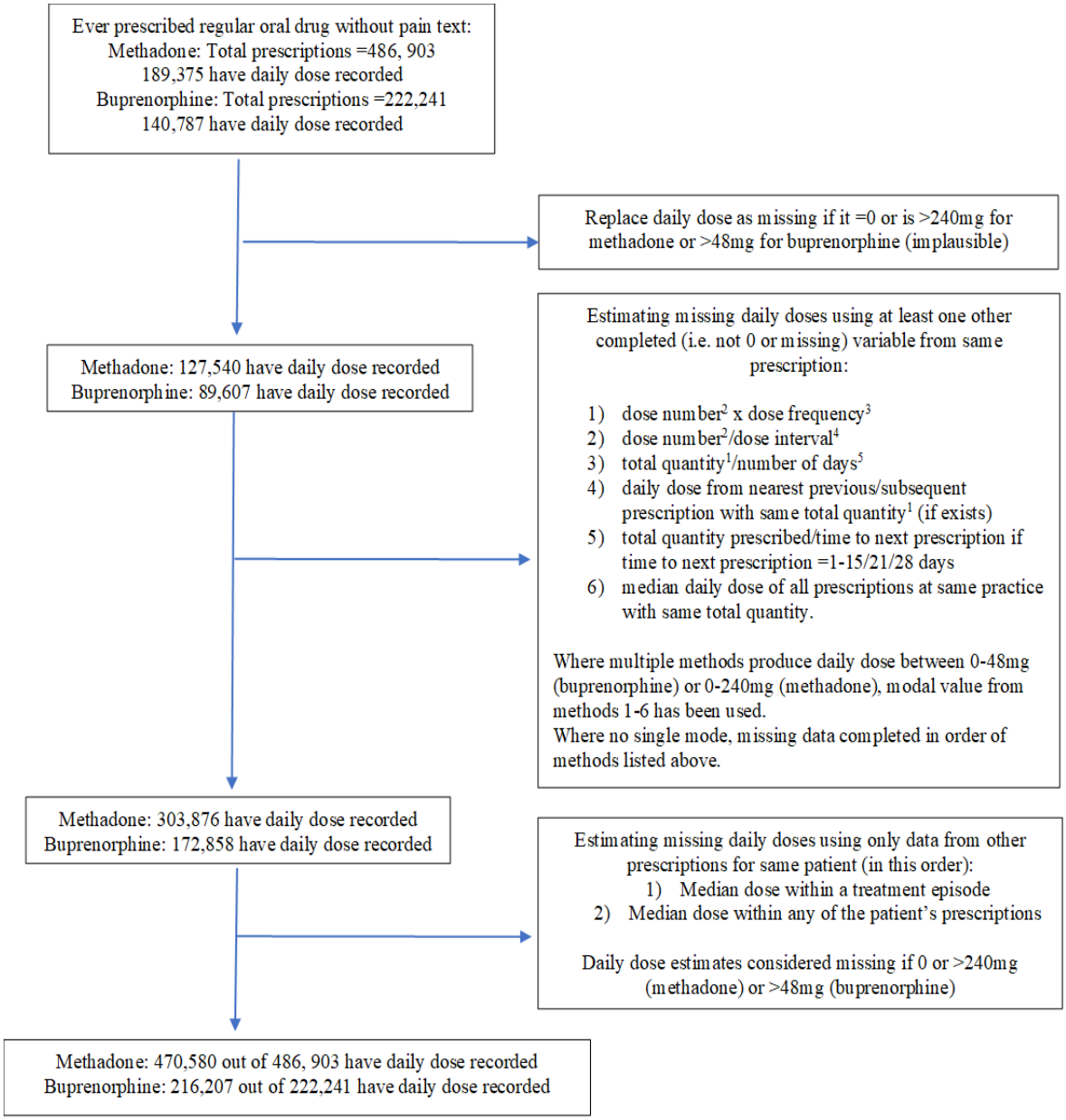
Due to the high volume of missing data, the exclusion of patients was unfeasible. As the daily dose was used to define the exposure in this study, it was important to try to maximise its accuracy. The replacement of all missing data with the median daily dose within the dataset or a recommended dose would likely result in substantial misclassification bias. Many patients often receive lower than recommended doses (Table 2.6) [169]. Based on the

calculation to determine the duration of prescriptions described earlier, frequent overestimation of prescription doses would reduce the length of prescription durations and result in the misclassification of treatment time as time off treatment.

The lack of data for key factors that affect prescribing decisions, such as the quantity of heroin used, prevented the estimation of daily doses based on the doses of patients with similar characteristics. I, therefore, inspected the data closely to develop an alternative, systematic process for estimating the missing dose, in which the estimates were derived using patients' own prescription data. The first stage involved using at least one other completed variable within the same prescription to estimate the missing dose (Figure 2.3).

Further details about this stage, including the validation checks performed, can be found in Appendix B. This stage of the process provided daily dose estimates for 176,336 (36%) of methadone prescriptions and 83,251 (37%) buprenorphine prescriptions. The remaining missing daily doses were estimated using data from other prescriptions for the same patient (Figure 2.3). This provided estimates of the daily dose for 166, 704 (34%) methadone prescriptions and 43,349 (20%) buprenorphine prescriptions. By the end of this process, daily doses were available for 470,580/486,903 (96%) methadone prescriptions and 216,207/222,241 (97%) buprenorphine prescriptions.

However, after estimating missing daily doses, 3,288 patients did not have a daily dose recorded in any of their prescriptions. They were excluded because it was not possible to determine periods on and off treatment. This is described further in the Results section of this chapter. Furthermore, approximately 2% of recorded prescription durations appeared to be implausible (<1 day or >70 days), likely due to inaccuracies in prescription data entry. These durations were replaced with the average prescription duration (14 days) and excluded in a post-hoc sensitivity analysis described in Appendix B.



[1] Total quantity: total quantity entered by the GP for the prescribed product (units specified by variable "dose unit")
[2] Dose number: amount in each dose (units specified by variable "dose unit")
[3] Dose frequency: how often a dose is taken in a day
[4] Dose interval: timespan in days that the dose is over, e.g. 4 a day = 0.25
[5] Number of days: number of treatment days prescribed for a specific therapy event

Figure 2.3: Estimating missing daily doses

2.3.12.5 Standardising dose variables

The 'daily dose' was used as a criterion to exclude patients who may have been prescribed methadone or buprenorphine for other indications. This criterion specified the daily dose in mg, but for the minority of prescriptions where the

'daily dose' was recorded, it was not consistently recorded in mg. The units for the 'daily dose' variable were recorded within a separate variable labelled 'dose unit', and varied between millilitres (ml), milligrams (mg), and tablets. To convert all daily doses to mg, I created a new variable as follows (Table 2.7):

- Where a prescription's 'dose unit' was specified as "mg", the 'daily dose' remained unchanged.
- Where a prescription's 'dose unit' was specified as "ml" or "tablet", the 'daily dose' was multiplied by the 'strength'.

Table 2.7: Example of variables used to calculate the daily dose in mg

Prescription no.	Daily dose	Dose unit	Strength	Daily dose in mg
1	8	mg	8mg	8
2	1	tablet	8mg	8
3	1	ml	5mg/ml	5

Where there were sufficient data to make comparisons, the units of the 'total quantity' prescribed variable corresponded with those of the 'daily dose'. The same process was therefore also used to convert all values within the 'total quantity' variable to mg. This process of standardising the 'daily dose' and 'total quantity' relied on the availability of 'dose unit' data. However, 'dose unit' data were missing for over three-quarters of prescriptions. The methods used to estimate missing 'dose units' are described in Appendix B.

2.3.12.6 Data check

After cleaning the data, to sense-check the exposure group classification, I compared the suicide or self-harm dates for ten patients who had died by suicide and ten patients who had been admitted to hospital with self-harm against their raw prescription data. I selected patients to ensure inspection of both methadone and buprenorphine prescriptions and each of the four exposure groups.

An example of this check is as follows (Table 2.8) Patient X presented twice to the hospital with self-harm during the study follow-up. The first presentation occurred on 30th June 2007 and was classified as occurring during time on treatment, and more specifically during the first four weeks of treatment. The second presentation occurred on 31st March 2011 and was classified as occurring during time on treatment, and more specifically during the remainder of time on treatment (i.e., after the initial 4 weeks). Although the patient's raw prescribing data are incomplete, an inspection of the patient's prescriptions (ordered by prescription date) immediately before and after each hospital presentation supports their study exposure classification. Both presentations appear to have occurred during a treatment episode of consecutive buprenorphine prescriptions, the first presentation within 28 days of starting a treatment episode (on 17th July 2007), whilst the second presentation appears over 28 days after starting a treatment episode (on 2nd February 2011).

Table 2.8: Example of raw prescribing data used to check the exposure classification of a patient's self-harm episodes (unfilled cells represent missing data)

Self-harm date	Prescription date	Product name	Dosage text	Quantity prescribed	Dose unit
	07-Oct-04	Subutex 0.4mg sublingual tablets	4 DAILY	56	
	22-Oct-04	Subutex 0.4mg sublingual tablets	2 DAILY	28	
	05-Nov-04	Subutex 0.4mg sublingual tablets	1 DAILY	14	
30-Jul-07	17-Jul-07	Subutex 8mg sublingual tablets		14	
	23-Jul-07	Subutex 8mg sublingual tablets		14	
	30-Jul-07	Subutex 8mg sublingual tablets		28	
	23-Jun-10	Buprenorphine 8mg sublingual tablets		28	
	13-Oct-10	Buprenorphine 8mg sublingual tablets		28	
	27-Oct-10	Buprenorphine 8mg sublingual tablets		28	
31-Mar-11	02-Feb-11	Buprenorphine 8mg sublingual tablets		28	
	16-Feb-11	Buprenorphine 8mg sublingual tablets		28	
	02-Mar-11	Buprenorphine 8mg sublingual tablets		14	
	02-Mar-11	Buprenorphine 2mg sublingual tablets		42	
	16-Mar-11	Buprenorphine 8mg sublingual tablets		14	
	16-Mar-11	Buprenorphine 2mg sublingual tablets		42	
	30-Mar-11	Buprenorphine 2mg sublingual tablets		42	
	30-Mar-11	Buprenorphine 8mg sublingual tablets		14	

2.3.13 Analyses

2.3.13.1 Standardised mortality ratio

An age- and sex-standardised mortality ratio (SMR) was calculated to compare the study suicide rates to those seen in the general population. Indirect standardisation was used rather than direct standardisation because suicide

rates could not be calculated for every age/sex category as several categories contained no suicides. The following steps were taken to calculate the SMR:

1) For each five-year age/sex category, the expected number of suicides in the CPRD cohort was obtained by, multiplying the follow-up (in person-years) of patients in that category within the CPRD cohort, with the category-specific suicide rate in the general population.
2) The total number of observed suicides in CPRD across all age/sex categories were divided by the total number of expected suicides in CPRD.

General population suicide rates were available in five-year age/sex categories for each year during the study period (1998-2017) [170]. Rather than selecting data from a single year to use as the reference population suicide rates, to account for changes in rates over time, the following steps were taken to calculate an aggregate suicide rate for each age/sex category:

1) For each year, the follow-up time for each five-year age/sex category was obtained by dividing the number of deaths by the suicide rate.
2) The total number of suicides between 1998-2017 was divided by the total follow-up time between 1998-2017.

A 95% confidence interval was estimated, assuming a Poisson distribution in the number of observed deaths.

2.3.13.2 Primary analysis

To calculate the crude rates of self-harm and suicide by exposure group, the time axis was partitioned and for each time period, the total number of occurrences of the outcome was divided by the total person-years follow-up in that period.

The time periods were then used as fixed effects in a Poisson regression model for suicide and a multi-level negative binomial model (with random effects) for self-harm. Multi-level models were used to analyse self-harm data due to the possibility of clustering of self-harm episodes within individuals. Adjusted risk ratios were estimated for each period (with remaining time on OAT as the reference group).

A Poisson regression model was chosen to analyse the suicide outcome due to the use of count outcome data, which occurred over fixed periods of time. However, Poisson regression models assume that the mean and variance are equal (i.e., equidispersion). This assumption may be violated when considering self-harm if: 1) there are individual-level differences in self-harm that are not accounted for by the predictors included in the model; 2) the counts are not independent of each other within an individual [171]. Where this occurs, standard errors will be too small, confidence intervals will be too narrow, and the null hypothesis could be mistakenly rejected (i.e., Type 1 error). Consequently, a negative binomial model was used to analyse self-harm data due to the possibility of over-dispersion of the data. The negative binomial model allowed each patient's data to be modelled by a Poisson model with different mean parameters [171].

As with over-dispersion, unaccounted clustering results in an under-estimation of standard errors and increased risk of Type 1 error. An important consideration when working with clustered data is the "residuals". Residuals are the difference between an observed value and a value predicted by a model. Multi-level models enable the separation of residuals into levels, dependent on the hierarchical structure of the data being analysed. This is demonstrated by the following formula:

$$y_{ij} = \beta 0 + u_j + e_{ij}$$

y_{ij}=Self-harm risk for time period i in patient j
$\beta 0$ = The overall intercept
u_j=The level 2 residual (or random effect): the unobserved patient level factors that influence self-harm risk
e_{ij}=The level 1 residual (or random effect): the unobserved time period level factors that influence self-harm risk

In this study, the different time periods (level 1) were clustered for each patient (level 2). By separating residuals, variability can be accounted for at each level e.g., some patients, on average, have a higher self-harm risk than others. Level 1 co-variates were measured at the start of each treatment period and comprised of age, number of previous OAT treatment episodes, previous self-harm, previous mental illness, and previous chronic illness score. Level 2 co-variates were sex and socioeconomic status (Table 2.9).

Table 2.9: Example of multi-level data structure

Patient ID	Start of follow-up date	End of follow-up date	Start date of exposure period	End date of exposure period	Exposure groups*	No. episodes of self-harm	Previous self-harm (Level 1 co-variate)	Sex (Level 2 co-variate)
1	1/1/10	5/6/16	1/1/10	28/1/10	1	2	0	1
1	1/1/10	5/6/16	29/1/10	31/3/10	2	1	1	1
1	1/1/10	5/6/16	1/4/10	28/4/10	3	0	1	1
1	1/1/10	5/6/16	29/4/10	31/5/16	4	1	1	1
1	1/1/10	5/6/16	1/6/16	5/6/16	1	0	1	1

*1:First four weeks on treatment; 2:Remaining time on treatment; 3:First four weeks off treatment; 4:Remaining time off treatment

There are a range of approaches to account for clustering, which can produce different results. These include the calculation of cluster-robust standard errors, random effects models (i.e., multi-level models), between effects models, and within effects models (i.e., fixed effects models). A key benefit of multi-level models is that they include all available data. Other benefits are that they allow quantification of: the proportion of variability arising from between-patient differences; the correlation of responses within patients; and the influence of both level 1 and level 2 co-variates on study outcomes. However, multi-level modelling requires a sufficient number of higher-level

units, often at least 50 units are recommended, that are randomly sampled. In this study, there were a large number of higher-level units (i.e., patients). Although patients were not strictly randomly sampled, they were selected independently of the outcomes of interest. The main drawback of multi-level modelling is that variation between the higher-level units may be due to residual confounding, unlike in within/fixed effects models, where higher-level units act as their own controls. A within/fixed effects model was not used for this analysis because in this type of model only higher-level units that change exposure status during follow-up contribute directly to the effect estimate, which would limit statistical power.

2.3.13.3 Secondary analyses

A sex-specific analysis was performed post-hoc as requested during the publication process of the research paper. As an exploratory analysis, an interaction term was fitted to investigate whether the rate of each outcome differed statistically between methadone and buprenorphine. Treatment episodes during which both buprenorphine and methadone were prescribed were excluded from this analysis, as were the time off treatment periods that directly followed these episodes. These time off periods varied in duration as they extended until the earliest date out of the patient's next treatment episode or the end of their follow-up.

2.3.13.4 Sensitivity analyses

A series of pre-specified sensitivity analyses were conducted to check the validity of the findings:

1) Including "accidental" poisoning deaths as many of these may be misclassified suicides [9]. These were specified by the following ICD codes: X40-X49 (Accidental poisoning by and exposure to noxious substances); E850-E858 (Accidental Poisoning By Drugs, Medicinal

Substances, And Biologicals); E860-E869 (Accidental Poisoning By Other Solid And Liquid Substances, Gases, And Vapors).

2) Excluding undetermined intent deaths and hospital admissions as these may not all be suicides and the threshold for suicide verdicts by coroners in England has changed over time [9]. These were specified by the following ICD codes: Y10–Y34 (event of undetermined intent); E980–E989 (injury undetermined, whether accidentally or purposely inflicted).
3) Restricting to people with a Read code for illicit opioid use to maximise specificity. The accuracy of daily dose estimations of some buprenorphine prescriptions may have been reduced to missing dose units (see Appendix B for further details). As a result, some patients may have been included in the primary analysis, who were prescribed buprenorphine for indications other than OAT. This sensitivity analysis investigated the influence that this may have had on the results.
4) Restricting to only incident rather than prevalent cases (i.e., where a patient's first OAT prescription occurs after the date of their registration at the GP practice) due to the possibility of bias if the risk of suicide decreases with time after treatment. Prevalent cases were, however, included in the primary analysis to maximise statistical power.
5) Restricting follow-up of patients to one year after the expiry date of the last prescription in a treatment episode, as the risk of suicide and self-harm may vary with time after stopping OAT.
6) Restricting the analysis to patients' first OAT episode to minimise survivor bias. Although the first treatment episode recorded in CPRD may not be the first that a patient has ever received, of the available data it is least conditional on surviving to enter subsequent treatment episodes.
7) Restricting the analysis to patients from "up to standard" practices only (this was not done in the primary analysis to maximise statistical power).

Two post-hoc sensitivity analyses were also conducted:

1) Excluding 1% of prescriptions with implausible durations (i.e., <1 day or >70 days).
2) Restricting the treatment initiation and cessation windows to two weeks (this was recommended by a peer-reviewer of the published paper).

The study was approved by the Independent Scientific Advisory Committee (protocol 19_005). Patient consent was not required as all data were de-identified. Patients can opt out of their information being shared for research. The protocol, which pre-specified the analyses, is available at: https://osf.io/7esb5. Analyses were conducted using Stata version 15.1.

2.4 Results

The study cohort included 8,070 adults in England who, combined, received 17,004 episodes of opioid agonist treatment between 2nd January 1998 and 30th November 2018. Figure 2.4 outlines the steps taken to define the cohort, as described in the Methods section of this chapter, as well as the number of patients and prescriptions excluded at each stage. The largest number of patients were excluded for having received at least one prescription for injectable or topical buprenorphine in the absence of a Read code indicative of opioid dependence (n=59,742). These patients were likely to have been prescribed buprenorphine for pain rather than as OAT. After estimating daily doses, 2,274 patients prescribed buprenorphine and 1,310 patients prescribed methadone were excluded due to missing daily dose information, which prevented calculation of prescription end dates. A further 8,638 patients prescribed buprenorphine and 1,011 patients prescribed methadone were excluded because they had never been prescribed a daily dose clearly indicative of OAT, and their records did not include a Read code suggestive of opioid dependence.

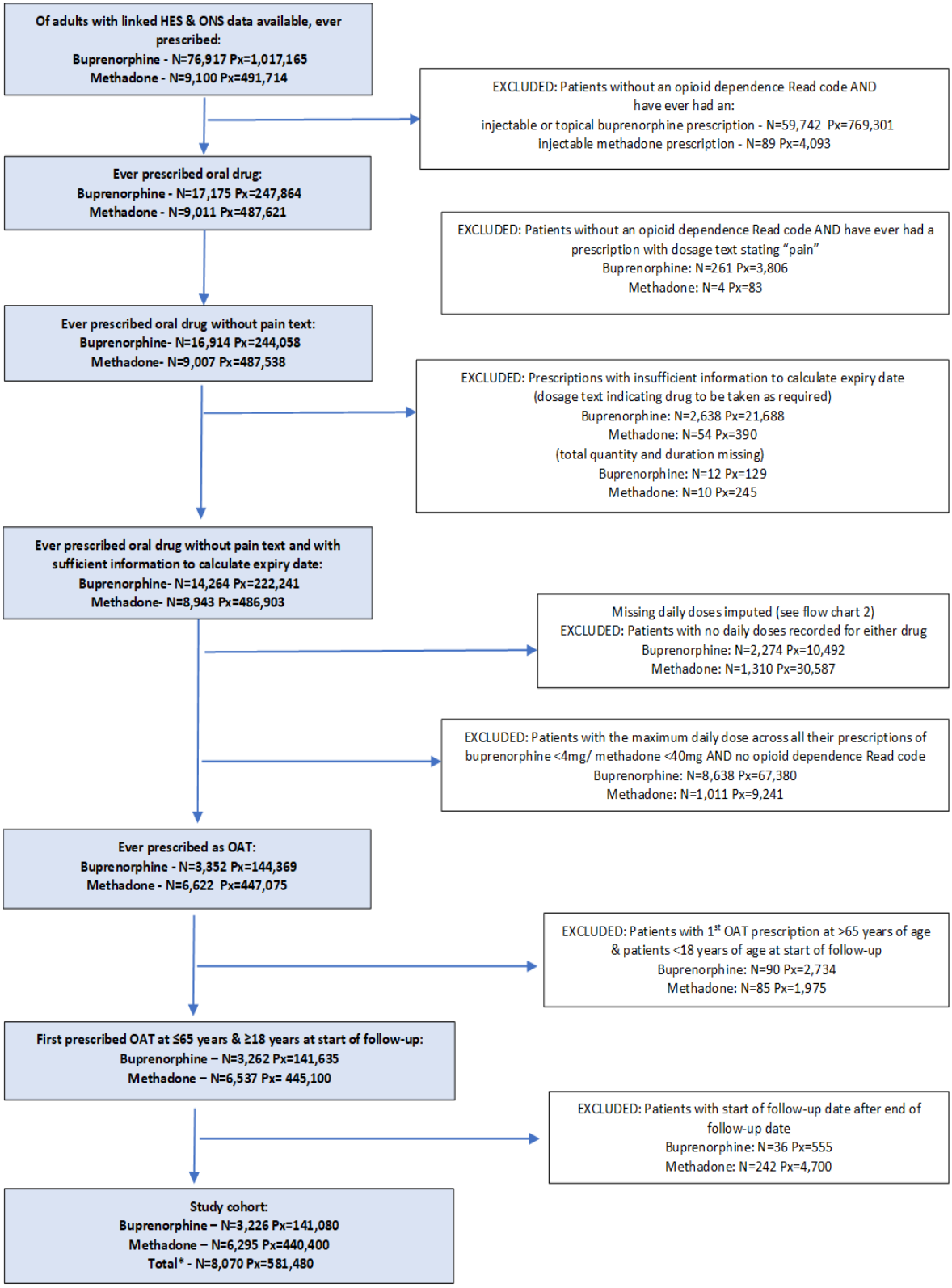


Figure 2.4: Patient selection flowchart(N=patients, Px=prescriptions)
Total figures are not equal to the sum of buprenorphine and methadone figures as some patients are prescribed both medications.

Table 2.10 shows the baseline characteristics of the sample at the start of follow-up. The median age at baseline was 33.3 years (IQR: 27.6-39.9 years). Most patients were male (n=5,594; 69.3%), lived in the most deprived quintile of neighbourhoods (n=3,437; 42.6%), and were of White ethnicity (n=7,006; 86.8%), although ethnicity data were missing for 8.4% (n=677) of patients. Almost a third of the sample were documented to have received OAT before the start of follow-up (n=2,331; 28.9%). Previous self-harm, mental illness, and alcohol dependence were documented in the records of 11.4% (n=922), 44.5% (n=3,590), and 10.2% (n=820) respectively.

Table 2.10: Baseline patient characteristics at the start of follow-up (as recorded in primary care records)

Characteristics	Category	No. (%)
Patients (n= 8,070)		
Sex	Female	2476 (30.7)
	Male	5594 (69.3)
Age in years	18-29	2857 (35.4)
	30-39	3212 (39.8)
	40-49	1479 (18.3)
	50+	522 (6.5)
Ethnicity	Asian	141 (1.8)
	Black	89 (1.1)
	Mixed	67 (0.8)
	Other	90 (1.1)
	White	7006 (86.8)
	Missing	677 (8.4)
Previous OAT	Yes	2331 (28.9)
Previous self-harm	Yes	922 (11.4)
Previous mental illness	Yes	3590 (44.5)
Previous alcohol dependence	Yes	820 (10.2)
Physical health co-morbidity (Charlson score)	0	5543 (68.7)
	1	1983 (24.6)
	2+	544 (6.7)
Smoking history	Yes	5746 (71.2)
Index of Multiple Deprivation score	1 (least)	533 (6.6)
	2	844 (10.5)
	3	1352 (16.8)
	4	1904 (23.6)
	5 (most)	3437 (42.6)

In the analysis of hospital admissions for self-harm, patients were followed up for a total of 40,599 person-years, during which 17,004 OAT treatment episodes occurred (Table 2.11). Median follow-up was 3.4 years (IQR: 1.2-7.4

years). During follow-up, 3,186 (39.5%) patients received more than one treatment episode. The most frequently prescribed OAT drug was methadone (n=6,295; 78.0% of patients received this drug). The median duration of treatment episodes was 84 days (IQR: 20-318 days).

Table 2.11: Treatment characteristics

Characteristics	Category	No. (%) unless otherwise specified
Patients (n= 8,070)		
Follow-up time	Total	40,599.2 person-years
	Median (IQR)	3.4 (1.2-7.4) years
Treatment received	Methadone	4844 (60.0)
	Buprenorphine	1775 (22.0)
	Both	1451 (18.0)
No. of treatment episodes during follow-up	0	1242 (15.4)
	1	3642 (45.1)
	2	1379 (17.1)
	3	699 (8.7)
	4+	1108 (13.7)
Treatment episodes during follow-up (n= 17,004)		
Treatment episode duration	Range	1 day-24.7 years
	Median (IQR)	84 (20-318) days
	Mean (SD)	327 (626) days
Treatment received in each episode	Methadone	11487 (67.6)
	Buprenorphine	4591 (27.0)
	Both	926 (5.4)

2.4.1 Self-harm

During the follow-up period, there were 807 hospital admissions for self-harm among 493 people: 351 patients had one hospital admission with self-harm, 89 had two, 27 had three, and 26 had four or more.

The risk of self-harm was increased in periods out of OAT treatment compared with during OAT treatment (adjusted risk ratio: 1.50; 95% CI: 1.21, 1.88) (Table 2.12). The risk of self-harm was increased in the first four weeks after stopping treatment (aRR: 2.60; 95% CI: 1.83, 3.70), and during the remaining time off treatment (aRR: 1.47; 95% CI: 1.16, 1.86) compared with the remaining time on treatment. There was insufficient evidence of an increased risk of self-harm in the first four weeks on treatment, but this does not exclude

an important association as the confidence intervals were wide (aRR: 1.43; 95% CI: 0.91, 2.23). The same pattern of results was observed for both males and females (Table 2.13).

2.4.2 Suicide

In the analysis of death by suicide, a total of 8,042 people who received OAT were followed up for 40,098 person-years between 2nd January 1998 and 30th November 2017. Within the cohort, there were 516 deaths, of which 46 were suicides. The suicide mortality rate among study patients was 114.7 per 100,000 compared with 11.2 per 100,000 in the general population in England over this period (25). The age- and sex- standardised mortality ratio was 7.5 (95% CI: 5.5, 10.0) (Table 2.14). The age-standardised mortality ratio was 14.1 (95% CI: 6.5, 26.8) for females and 6.7 (95% CI: 4.7, 9.3) for males.

Of the 46 suicides, 24 occurred by hanging, strangulation, or suffocation; 19 by self-poisoning; and three by other methods. Methadone +/- other drugs were involved in eight of the self-poisoning deaths, an additional two deaths involved unspecified opioids, and drugs involved in the remaining nine deaths were unspecified.

There was insufficient evidence of a difference in the risk of suicide when comparing periods after treatment with periods on treatment (aRR: 1.21; 95% CI: 0.64, 2.28) (Table 2.15). However, the risk of suicide was markedly increased in the first four weeks off treatment (aRR: 4.68; 95% CI: 1.63-13.42) compared to stable time on OAT. This pattern of results was observed for both males and females during and post-treatment, and males during the first four weeks off treatment. The low number of suicides amongst females did not permit an analysis by the four treatment periods (Table 2.16).

Table 2.12: Crude rates, and unadjusted and adjusted risk ratios for self-harm by exposure to OAT

	Variable	No. of self-harm admissions	Person-years follow-up	Self-harm/100 person-years (95% CI)	Crude risk ratio (95% CI)	Adjusted risk ratio1 (95% CI)
Treatment status	*Overall on treatment*	225	14447.6	1.56 (1.37-1.77)	1.00	1.00
	Overall off treatment	582	26151.6	2.23 (2.05-2.41)	1.55 (1.24-1.94)	1.50 (1.21-1.88)
Treatment period	*Weeks 1-4 on treatment*	27	1035.7	2.61 (1.79-3.80)	1.45 (0.93-2.26)	1.43 (0.91-2.23)
	Remainder of time on treatment	198	13411.9	1.48 (1.28-1.70)	1.00	1.00
	Weeks 1-4 off treatment	54	1156.8	4.67 (3.58-6.09)	2.66 (1.87-3.77)	2.60 (1.83-3.70)
	Remainder of time off treatment	528	24994.8	2.11 (1.94-2.30)	1.54 (1.21-1.95)	1.47 (1.16-1.86)

Table 2.13: Self-harm analysis stratified by sex

	Variable	No. of self-harm admissions		Person-years follow-up		Self-harm/100 person-years (95% CI)		Adjusted risk ratio1 (95% CI)	
		Male	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
Treatment status	*Overall on treatment*	162	63	10139.1	4308.6	1.60 (1.37-1.86)	1.46 (1.14-1.87)	1.00	1.00
	Overall off treatment	385	197	18407.2	7744.3	2.09 (1.89-2.31)	2.54 (2.21-2.93)	1.35 (1.03-1.78)	1.84 (1.27-2.66)
Treatment period	*Weeks 1-4 on treatment*	21	6	720.6	315.2	2.91 (1.90-4.47)	1.90 (0.86-4.24)	1.55 (0.92-2.62)	1.11 (0.46-2.68)
	Remainder of time on treatment	141	57	9418.5	3993.4	1.50 (1.27-1.77)	1.43 (1.10-1.85)	1.00	1.00
	Weeks 1-4 off treatment	33	21	802.5	354.2	4.11 (2.92-5.78)	5.93 (3.86-9.09)	2.29 (1.46-3.59)	3.37 (1.92-5.92)
	Remainder of time off treatment	352	176	17604.8	7390.0	2.00 (1.80-2.22)	2.38 (2.05-2.76)	1.36 (1.01-1.83)	1.68 (1.14-2.50)

[1] Adjusted for: age, sex, socioeconomic status, number of previous OAT treatment episodes, previous self-harm, previous mental illness, and major chronic illness score

Table 2.14: Indirect standardisation calculation

		CPRD		ONS	
Sex	**Age groups**	**Observed no. suicides**	**Follow-up (person-years)**	**Age-specific suicide rates per 100,000 (1998-2017)**	**Expected no. CPRD suicides**
Male	18-19	1	44.64	6.21	0.00
	20-24	2	1332.93	14.31	0.19
	25-29	4	3929.62	16.92	0.67
	30-34	4	5678.80	19.33	1.10
	35-39	9	5963.08	20.74	1.24
	40-44	12	4714.73	21.81	1.03
	45-49	1	3135.74	21.12	0.66
	50-54	3	1839.81	19.53	0.36
	55-59	1	885.75	17.25	0.15
	60-64	0	669.42	13.57	0.09
Female	18-19	0	42.72	2.28	0.00
	20-24	0	737.73	3.70	0.03
	25-29	0	1849.29	4.47	0.08
	30-34	2	2238.57	4.87	0.11
	35-39	4	2257.09	5.60	0.13
	40-44	2	1795.36	5.84	0.10
	45-49	0	1165.13	6.58	0.08
	50-54	0	755.74	6.83	0.05
	55-59	1	460.89	6.06	0.03
	60-64	0	601.42	5.02	0.03
All		46	40098.49		6.12
SMR= (Observed/ expected no. suicides)		7.51			
Standard error= (√(observed /expected no. suicides))		1.11			
95% confidence intervals		5.50-10.02			

Table 2.15: Crude rates, and unadjusted and adjusted risk ratios for suicide by exposure to OAT

	Variable	No. of suicides	Person-years follow-up	Suicides/100 Person-years (95% CI)	Crude risk ratio (95% CI)	Adjusted risk ratio[2] (95% CI)
Treatment status	*Overall on treatment*	14	14384.6	0.10 (0.06-0.16)	1.00	1.00
	Overall off treatment	32	25714.0	0.12 (0.09-0.18)	1.24 (0.66-2.34)	1.21 (0.64-2.28)
Treatment period	*Weeks 1-4 on treatment*	2	1032.2	0.19 (0.05-0.77)	2.14 (0.48-9.56)	2.12 (0.47-9.51)
	Remainder of time on treatment	12	13352.3	0.09 (0.05-0.16)	1.00	1.00
	Weeks 1-4 off treatment	5	1151.9	0.43 (0.18-1.04)	4.81 (1.69-13.65)	4.68 (1.63-13.42)
	Remainder of time off treatment	27	24562.0	0.11 (0.08-0.16)	1.18 (0.59-2.34)	1.14 (0.57-2.26)

Table 2.16: Suicide analysis stratified by sex

	Variable	No. of suicides		Person-years follow-up		Suicides/100 person-years (95% CI)		Adjusted risk ratio[2] (95% CI)	
		Male	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
Treatment status	*Overall on treatment*	12	2	10092.7	4291.9	0.12 (0.07-0.21)	0.05 (0.01-0.19)	1.00	1.00
	Overall off treatment	25	7	18101.9	7612.1	0.14 (0.09-0.20)	0.09 (0.04-0.19)	1.11 (0.55-2.22)	2.01 (0.42-9.70)
Treatment period	*Weeks 1-4 on treatment*	2	0	718.5	313.8	0.28 (0.07-1.11)	-	2.57 (0.56-11.74)	-
	Remainder of time on treatment	10	2	9374.2	3978.1	0.11 (0.06-0.20)	-	1.00	-
	Weeks 1-4 off treatment	5	0	799.6	352.3	0.63 (0.26-1.50)	-	5.80 (1.98-16.97)	-
	Remainder of time off treatment	20	7	17302.2	7259.8	0.12 (0.07-0.18)	-	1.02 (0.47-2.19)	-

[2] Adjusted for: age, sex, socioeconomic status, number of previous OAT treatment episodes, previous self-harm, previous mental illness, and major chronic illness score

2.4.3 Analyses by drug

Table 2.17 details the baseline characteristics of patients at the start of follow-up by drug. The distribution of age, sex, ethnicities, and socioeconomic background were similar for both drugs. The proportions of people with previous mental illness, previous self-harm, alcohol dependence, or a smoking history were higher amongst those prescribed buprenorphine compared to those prescribed methadone.

Table 2.17: Baseline patient characteristics at start of follow-up of patients by drug

		Buprenorphine	**Methadone**
Characteristics	*Category*	*No. (%) unless otherwise specified*	
Patients*		2555	5814
Sex	Female	755 (29.5)	1781 (30.6)
	Male	1800 (70.5)	4033 (69.4)
Age (years)	18-29	851 (33.3)	2190 (37.7)
	30-39	958 (37.5)	2348 (40.4)
	40-49	504 (19.7)	993 (17.1)
	50-64	242 (9.5)	283 (4.9)
Ethnicity	Asian	66 (2.6)	92 (1.6)
	Black	43 (1.7)	54 (0.9)
	Mixed	14 (0.6)	50 (0.9)
	Other	32 (1.3)	57 (1.0)
	White	2,232 (87.4)	5,036 (86.6)
	Missing	168 (6.6)	525 (9.0)
Previous treatment with the same OAT drug	Yes	543 (21.3)	1897 (32.6)
Previous self-harm	Yes	317 (12.4)	613 (10.5)
Previous mental illness	Yes	1301 (50.9)	2392 (41.1)
Alcohol dependence history	Yes	279 (10.9)	552 (9.5)
Physical health co-morbidity (Charlson score)	0	1736 (67.9)	4016 (69.1)
	1	620 (24.3)	1440 (24.8)
	2+	199 (7.8)	358 (6.2)
Smoking history	Yes	1920 (75.1)	4004 (68.9)
Deprivation (IMD score)	1 (least)	214 (8.4)	345 (5.9)
	2	299 (11.7)	569 (9.8)
	3	434 (17.0)	970 (16.7)
	4	588 (23.0)	1374 (23.6)
	5 (most)	1020 (39.9)	2556 (44.0)

* Where patients received buprenorphine and methadone in separate treatment episodes, they have been included in the counts for both drugs. Patients who received only treatment episodes that included both methadone and buprenorphine within each episode have been excluded.

Table 2.18: Self-harm results by treatment period by drug (excluding treatment episodes with both drugs)

Drug	Variable	No. of self-harm episodes	Person-years	Crude rate/100 person-years (95% CI)	Adjusted RR (95% CI)
Methadone	*Overall time on treatment*	117	9956.1	1.18 (0.98-1.41)	1.00
	Overall time off treatment	402	17773.2	2.26 (2.05-2.49)	1.70 (1.28-2.24)
Buprenorphine	*Overall time on treatment*	71	2904.8	2.44 (1.94-3.08)	1.48 (0.97-2.27)
	Overall time off treatment	151	7180.1	2.10 (1.79-2.47)	1.60 (1.14-2.27)
Methadone	*Weeks 1-4 on treatment*	15	984.3	1.52 (0.92-2.53)	1.50 (0.84-2.67)
	Remainder of time on treatment	102	8971.9	1.14 (0.94-1.38)	1.00
	Weeks 1-4 off treatment	30	782.6	3.83 (2.68-5.48)	2.56 (1.62-4.05)
	Remainder of time off treatment	372	16990.7	2.19 (1.98-2.42)	1.70 (1.26-2.29)
Buprenorphine	*Weeks 1-4 on treatment*	12	453.7	2.64 (1.50-4.66)	2.09 (1.04-4.16)
	Remainder of time on treatment	59	2451.0	2.41 (1.87-3.11)	1.42 (0.89-2.27)
	Weeks 1-4 off treatment	20	318.1	6.29 (4.06-9.75)	3.33 (1.89-5.89)
	Remainder of time off treatment	131	6862.0	1.91 (1.61-2.27)	1.50 (1.04-2.17)

Interaction tests: for on/off treatment $\chi 2=3.49$, df=1, P=0.17; for 4 periods treatment: $\chi 2=4.05$, df=3, P=0.40

Table 2.19: Suicide results by treatment period by drug (excluding treatment episodes with both drugs)

Drug	Variable	No. of suicides	Person-years	Crude rate/100 person-years (95% CI)	Adjusted RR (95% CI)
Methadone	*Overall time on treatment*	11	9926.2	0.11 (0.06-0.20)	1.00
	Overall time off treatment	23	17516.7	0.13 (0.09-0.20)	1.04 (0.50-2.16)
Buprenorphine	*Overall time on treatment*	2	2877.4	0.07 (0.02-0.28)	0.69 (0.15-3.14)
	Overall time off treatment	6	7024	0.09 (0.04-0.19)	0.76 (0.28-2.07)
Methadone	*Weeks 1-4 on treatment*	2	983.8	0.20 (0.05-0.81)	-
	Remainder of time on treatment	9	8942.4	0.10 (0.05-0.19)	-
	Weeks 1-4 off treatment	4	780.3	0.51 (0.19-1.37)	-
	Remainder of time off treatment	19	16736.3	0.11 (0.07-0.18)	-
Buprenorphine	*Weeks 1-4 on treatment*	0	451.7	-	-
	Remainder of time on treatment	2	2425.7	0.08 (0.02-0.33)	-
	Weeks 1-4 off treatment	1	315.5	0.32 (0.04-2.25)	-
	Remainder of time off treatment	5	6708.5	0.07 (0.03-0.18)	-

Interaction tests: for treatment classified as on/off $\chi^2=0.65$, df=1, P=0.72

There was no evidence of any difference in the adjusted rates of suicide between buprenorphine and methadone when time on and off treatment were compared (χ^2=0.65, df=1, P=0.72) (Table 2.19). Crude rates of self-harm were slightly higher in patients on buprenorphine compared to methadone during OAT and in the period immediately after OAT (Table 2.18), but there was no evidence for differential effects (interaction comparing on/off methadone and buprenorphine for self-harm: χ^2=3.49, df=1, P=0.17; and between the four time periods: χ^2=4.05, df=3, P=0.40). The four time periods, including treatment initiation and cessation, were not compared in relation to suicide due to insufficient statistical power.

2.4.4 Sensitivity analyses

The first sensitivity analysis broadened the definition of self-harm and suicide to include accidental poisonings (Table 2.20 and Table 2.21). Evidence emerged of a risk of self-harm in the first four weeks on treatment (aRR: 1.84; 95% CI: 1.27, 2.67) compared with stable time on treatment. This was finding was not replicated for suicide. The aRR for suicide during the first four weeks on treatment increased slightly from 1.67 (0.59, 4.73) in the primary analysis to 2.12 (0.47, 9.51), but the confidence intervals remained overlapping. The aRRs for the first four weeks off treatment for self-harm and suicide were consistent with those in the primary analysis.

The second sensitivity analysis restricted the definition of self-harm and suicide to exclude hospital admissions and deaths of undetermined intent, respectively (Table 2.22 and Table 2.23). No suicides were identified during the first four weeks on treatment, indicating that all suicides included in this period in the primary analysis were of undetermined intent. There was also no longer statistical evidence of an increased risk of suicide in the first four weeks after stopping treatment (aRR: 3.23; 95% CI: 0.88, 11.94). This analysis had less power to detect a difference compared to the primary analysis; an important increase could not be excluded due to the broad confidence intervals. Evidence remained of an increased risk of self-harm in the first four

weeks after stopping treatment (aRR: 2.57; 95% CI: 1.80, 3.66). The absolute number of self-harm episodes and related aRRs were similar to those in the primary analysis.

The third sensitivity analysis restricted people to those with a Read code for illicit opioid use to maximise specificity in the definition of the population (Table 2.24 and Table 2.25). Adjusted risk ratios of self-harm and suicide were consistent with the primary analysis.

The fourth sensitivity analysis restricted the cohort to only patients without a treatment episode before their current GP registration, due to the possibility of bias if the risk of suicide decreases with time after commencing treatment (Table 2.26 and Table 2.27). There was a change in direction of the aRR point estimate for self-harm for the first four weeks on treatment (aRR: 0.94; 95% CI: 0.42, 2.13) compared with the primary analysis (aRR: 1.43; 95% CI: 0.91, 2.23) but the confidence intervals overlapped. The aRR point estimate for suicide during the first four weeks off treatment was much higher (aRR: 10.81; 95% CI: 2.15, 54.32), but the confidence intervals were extremely wide due to the small number of suicides (n=3) and overlapped with those in the primary analysis (aRR: 4.68; 95% CI: 1.63, 13.42).

The fifth sensitivity analysis restricted follow-up of patients to one year following the end date of the final prescription in the treatment episode, as risk of suicide/self-harm may vary with time after stopping OAT (Table 2.28 and Table 2.29). The results were similar to the primary analysis for both self-harm and suicide except the point estimate aRR for suicide changed in direction during the remaining time off treatment. The point estimate aRR reduced from 1.14 (95% CI: 0.57, 2.26) in the primary analysis to 0.81 (95% CI: 0.33, 2.01), but the confidence intervals were relatively similar and overlapped.

The sixth sensitivity analysis restricted the data to each patient's first OAT treatment episode to minimise survivor bias, whereby patients need to survive to enter subsequent treatment episodes (Table 2.30 and Table 2.31). As with

the previous sensitivity analysis, the results were consistent with the primary analysis for both self-harm and suicide, despite the point estimate aRR for suicide again changing in direction during the remaining time off treatment from 1.14 (95% CI: 0.57, 2.26) in the primary analysis to 0.97 (95% CI: 0.39, 2.44).

Another important sensitivity analysis restricted the initiation and cessation time periods to two weeks (Table 2.32 and Table 2.33). The aRRs were higher in the first two weeks on treatment for both suicide (aRR: 3.94; 95% CI: 0.88, 17.71) and self-harm (aRR: 1.63; 95% CI: 0.96, 2.77) compared with the respective aRRs for the same exposure group in the primary analysis (suicide aRR: 2.12; 95% CI 0.47, 9.51, self-harm aRR: 1.43; 95% CI: 0.91, 2.23), but the confidence intervals were wider, overlapped, and continued to cross the null value. The aRRs for the first two weeks off treatment were consistent with those in the primary analysis for both suicide and self-harm, also with wider confidence intervals.

The results of two other sensitivity analyses, which checked the effect of: 1) the inclusion of data from practices during periods where they were not considered "up to standard"; 2) the exclusion of prescriptions with implausible durations, are provided in Appendix C.

In all but one of the sensitivity analyses described above, the sample size was reduced compared with the corresponding primary analysis, thereby limiting statistical power to detect differences between the exposure groups. Nonetheless, in all sensitivity analyses, time off treatment was consistently associated with an increased risk of self-harm. Furthermore, when comparing the four time periods, the highest point estimate for the risk of self-harm and suicide occurred during the first four weeks after stopping treatment.

The adjusted relative risk ratios for the primary analyses, the sex-stratified analyses, and the key sensitivity analyses described above are summarised in Table 2.34 and Table 2.35.

Table 2.20: Self-harm sensitivity analysis (including accidental poisonings)

Variable	No. of self-harm episodes	Person-years	Self-harm/100 person-years (95% CI)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Treatment status					
Overall time on treatment	276	14447.6	1.91 (1.70-2.15)	1.00	1.00
Overall time off treatment	743	26151.6	2.84 (2.64-3.05)	1.55 (1.27-1.89)	1.50 (1.24-1.83)
Treatment period					
Weeks 1-4 on treatment	41	1035.7	3.96 (2.91-5.38)	1.82 (1.26-2.64)	1.84 (1.27-2.67)
Remainder on treatment	235	13411.9	1.75 (1.54-1.99)	1.00	1.00
Weeks 1-4 off treatment	60	1156.8	5.19 (4.03-6.68)	2.40 (1.74-3.33)	2.36 (1.71-3.28)
Remainder off treatment	683	24994.8	2.73 (2.54-2.95)	1.65 (1.33-2.04)	1.59 (1.29-1.97)

Table 2.21: Suicide sensitivity analysis (including accidental poisonings)

Variable	No. of suicides	Person-years	Suicides/100 person-years (95% CI)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Treatment status					
Overall time on treatment	36	14384.5	0.25 (0.18-0.35)	1.00	1.00
Overall time off treatment	92	25713.9	0.36 (0.29-0.44)	1.43 (0.97-2.11)	1.40 (0.95-2.06)
Treatment period					
Weeks 1-4 on treatment	4	1032.2	0.39 (0.15-1.03)	1.62 (0.57-4.57)	1.67 (0.59-4.73)
Remainder on treatment	32	13352.3	0.24 (0.17-0.34)	1.00	1.00
Weeks 1-4 off treatment	11	1151.9	0.95 (0.53-1.72)	3.98 (2.01-7.90)	4.12 (2.07-8.21)
Remainder off treatment	81	24562.0	0.33 (0.27-0.41)	1.37 (0.91-2.07)	1.33 (0.88-2.02)

Table 2.22: Self-harm sensitivity analysis (excluding hospital admissions of undetermined intent)

Variable	No. of self-harm episodes	Person-years	Self-harm/100 person-years (95% CI)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Treatment status					
Overall time on treatment	222	14447.6	1.54 (1.35-1.75)	1.00	1.00
Overall time off treatment	564	26151.6	2.16 (1.99-2.34)	1.54 (1.23-1.92)	1.47 (1.18-1.84)
Treatment period					
Weeks 1-4 on treatment	26	1035.7	2.51 (1.71-3.69)	1.40 (0.90-2.20)	1.38 (0.88-2.17)
Remainder on treatment	196	13411.9	1.46 (1.27-1.68)	1.00	1.00
Weeks 1-4 off treatment	53	1156.8	4.58 (3.50-6.00)	2.63 (1.84-3.74)	2.57 (1.80-3.66)
Remainder off treatment	511	24994.8	2.04 (1.87-2.23)	1.51 (1.19-1.92)	1.44 (1.14-1.83)

Table 2.23: Suicide sensitivity analysis (excluding deaths of undetermined intent)

Variable	No. of suicides	Person-years	Suicides/100 person-years (95% CI)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Treatment status					
Overall time on treatment	10	14384.5	0.07 (0.04-0.13)	1.00	1.00
Overall time off treatment	21	25713.9	0.08 (0.05-0.13)	1.22 (0.57-2.60)	1.19 (0.56-2.54)
Treatment period					
Weeks 1-4 on treatment	0	1032.2	-	-	-
Remainder on treatment	10	13352.3	0.07 (0.04-0.14)	1.00	1.00
Weeks 1-4 off treatment	3	1151.9	0.26 (0.08-0.81)	3.48 (0.96-12.63)	3.23 (0.88-11.94)
Remainder off treatment	18	24562.0	0.07 (0.05-0.12)	1.02 (0.47-2.21)	0.98 (0.45-2.15)

Table 2.24: Self-harm sensitivity analysis (restricted to people with illicit opioid use Read code)

Variable	No. of self-harm episodes	Person-years	Self-harm/100 person-years (95% CI)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Treatment status					
Overall time on treatment	198	12654.7	1.56 (1.36-1.80)	1.00	1.00
Overall time off treatment	503	22251.1	2.26 (2.07-2.47)	1.58 (1.25-2.01)	1.53 (1.21-1.94)
Treatment period					
Weeks 1-4 on treatment	23	878.3	2.62 (1.74-3.94)	1.49 (0.93-2.40)	1.47 (0.91-2.37)
Remainder on treatment	175	11776.4	1.49 (1.28-1.72)	1.00	1.00
Weeks 1-4 off treatment	49	982.5	4.99 (3.77-6.60)	2.93 (2.02-4.23)	2.89 (2.00-4.19)
Remainder off treatment	454	21268.6	2.13 (1.95-2.34)	1.54 (1.19-1.99)	1.48 (1.15-1.90)

Table 2.25: Suicide sensitivity analysis (restricted to people with illicit opioid use Read code)

Variable	No. of suicides	Person-years	Suicides/100 person-years (95% CI)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Treatment status					
Overall time on treatment	12	12607.2	0.10 (0.05-0.17)	1.00	1.00
Overall time off treatment	30	21860.6	0.14 (0.10-0.20)	1.41 (0.72-2.77)	1.37 (0.70-2.70)
Treatment period					
Weeks 1-4 on treatment	2	875.5	0.23 (0.06-0.91)	2.66 (0.58-12.16)	2.63 (0.57-12.05)
Remainder on treatment	10	11731.7	0.09 (0.05-0.16)	1.00	1.00
Weeks 1-4 off treatment	5	978.6	0.51 (0.21-1.23)	5.98 (2.04-17.50)	5.76 (1.95-17.07)
Remainder off treatment	25	20882.0	0.12 (0.08-0.18)	1.36 (0.65-2.85)	1.31 (0.63-2.76)

Table 2.26: Self-harm sensitivity analysis (restricted to incident cases)

Variable	No. of self-harm episodes	Person-years	Self-harm/100 person-years (95% CI)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Treatment status					
Overall time on treatment	100	7087.6	1.41 (1.16-1.72)	1.00	1.00
Overall time off treatment	222	13318.7	1.67 (1.46-1.90)	1.65 (1.17-2.32)	1.61 (1.14-2.25)
Treatment period					
Weeks 1-4 on treatment	7	519.1	1.35 (0.64-2.83)	0.90 (0.40-2.03)	0.94 (0.42-2.13)
Remainder on treatment	93	6568.5	1.42 (1.16-1.73)	1.00	1.00
Weeks 1-4 off treatment	20	581.2	3.44 (2.22-5.33)	2.44 (1.41-4.21)	2.59 (1.50-4.48)
Remainder off treatment	202	12737.5	1.59 (1.38-1.82)	1.51 (1.05-2.16)	1.46 (1.03-2.08)

Table 2.27: Suicide sensitivity analysis (restricted to incident cases)

Variable	No. of suicides	Person-years	Suicides/100 person-years (95% CI)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Treatment status					
Overall time on treatment	4	7051.5	0.06 (0.02-0.15)	1.00	1.00
Overall time off treatment	16	13130.1	0.12 (0.07-0.20)	2.11 (0.70-6.39)	2.08 (0.69-6.30)
Treatment period					
Weeks 1-4 on treatment	1	516.8	0.19 (0.03-1.37)	4.20 (0.44-40.39)	4.08 (0.42-39.49)
Remainder on treatment	3	6534.8	0.05 (0.01-0.14)	1.00	1.00
Weeks 1-4 off treatment	3	577.8	0.52 (0.17-1.61)	11.29 (2.28-55.95)	10.81 (2.15-54.32)
Remainder off treatment	13	12552.3	0.10 (0.06-0.18)	2.18 (0.62-7.75)	2.13 (0.60-7.57)

Table 2.28: Self-harm sensitivity analysis (restricted to 1-year follow-up after each treatment episode)

Variable	No. of self-harm episodes	Person-years	Self-harm/100 person-years (95% CI)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Treatment status					
Overall time on treatment	225	14447.6	1.56 (1.37-1.77)	1.00	1.00
Overall time off treatment	271	10566.9	2.56 (2.28-2.89)	1.59 (1.26-2.02)	1.54 (1.22-1.96)
Treatment period					
Weeks 1-4 on treatment	27	1035.7	2.61 (1.79-3.80)	1.45 (0.93-2.26)	1.43 (0.92-2.24)
Remainder on treatment	198	13411.9	1.48 (1.28-1.70)	1.00	1.00
Weeks 1-4 off treatment	54	1156.8	4.67 (3.58-6.09)	2.68 (1.89-3.80)	2.63 (1.84-3.73)
Remainder off treatment	217	9410.1	2.31 (2.02-2.63)	1.50 (1.15-1.95)	1.43 (1.10-1.86)

Table 2.29: Suicide sensitivity analysis (restricted to 1-year follow-up after each treatment episode)

Variable	No. of suicides	Person-years	Suicides/100 person-years (95% CI)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Treatment status					
Overall time on treatment	14	14384.5	0.10 (0.06-0.16)	1.00	1.00
Overall time off treatment	13	10486.1	0.12 (0.07-0.21)	1.18 (0.55-2.53)	1.10 (0.51-2.36)
Treatment period					
Weeks 1-4 on treatment	2	1032.2	0.19 (0.05-0.77)	2.09 (0.47-9.34)	2.01 (0.45-9.05)
Remainder on treatment	12	13352.3	0.09 (0.05-0.16)	1.00	1.00
Weeks 1-4 off treatment	5	1151.9	0.43 (0.18-1.04)	4.71 (1.66-13.37)	4.42 (1.53-12.73)
Remainder off treatment	8	9334.1	0.09 (0.04-0.17)	0.87 (0.35-2.15)	0.81 (0.33-2.01)

Table 2.30: Self-harm sensitivity analysis (restricted to first treatment episode)

Variable	No. of self-harm episodes	Person-years	Self-harm/100 person-years (95% CI)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Treatment status					
Overall time on treatment	120	7207.1	1.67 (1.39-1.99)	1.00	1.00
Overall time off treatment	253	10212.6	2.48 (2.19-2.80)	1.69 (1.21-2.34)	1.48 (1.08-2.04)
Treatment period					
Weeks 1-4 on treatment	9	403.2	2.23 (1.16-4.29)	1.08 (0.52-2.25)	1.07 (0.51-2.21)
Remainder on treatment	111	6803.9	1.63 (1.35-1.96)	1.00	1.00
Weeks 1-4 off treatment	31	441.7	7.02 (4.94-9.98)	3.42 (2.12-5.49)	3.18 (1.98-5.10)
Remainder off treatment	222	9770.9	2.27 (1.99-2.59)	1.47 (1.05-2.07)	1.31 (0.94-1.82)

Table 2.31: Suicide sensitivity analysis (restricted to first treatment episode)

Variable	No. of suicides	Person-years	Suicides/100 person-years (95% CI)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Treatment status					
Overall time on treatment	9	7182.5	0.13 (0.07-0.24)	1.00	1.00
Overall time off treatment	14	10070.2	0.14 (0.08-0.23)	1.07 (0.46-2.49)	1.12 (0.48-2.62)
Treatment period					
Weeks 1-4 on treatment	1	402.4	0.25 (0.04-1.76)	2.07 (0.26-16.58)	2.10 (0.26-16.81)
Remainder on treatment	8	6780.1	0.12 (0.06-0.24)	1.00	1.00
Weeks 1-4 off treatment	3	440.5	0.68 (0.22-2.11)	5.68 (1.51-21.43)	5.68 (1.50-21.46)
Remainder off treatment	11	9629.7	0.11 (0.06-0.21)	0.93 (0.37-2.32)	0.97 (0.39-2.44)

Table 2.32: Self-harm sensitivity analysis (initiation and cessation restricted to two weeks)

Variable	No. of self-harm episodes	Person-years	Self-harm/100 person-years (95% CI)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Treatment period					
Weeks 1-2 on treatment	17	571.0	2.98 (1.85-4.79)	1.62 (0.96-2.74)	1.63 (0.96-2.77)
Remainder on treatment	208	13876.7	1.50 (1.31-1.72)	-	-
Weeks 1-2 off treatment	29	585.7	4.95 (3.44-7.12)	2.68 (1.74-4.11)	2.62 (1.70-4.03)
Remainder off treatment	553	25565.9	2.16 (1.99-2.35)	1.56 (1.23-1.96)	1.48 (1.18-1.86)

Table 2.33: Suicide sensitivity analysis (restricting initiation and cessation restricted to two weeks)

Variable	No. of suicides	Person-years	Suicides/100 person-years (95% CI)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Treatment period					
Weeks 1-2 on treatment	2	569.1	0.35 (0.09-1.41)	4.02 (0.90-17.95)	3.94 (0.88-17.71)
Remainder on treatment	12	13815.5	0.09 (0.05-1.15)	-	-
Weeks 1-2 off treatment	3	583.3	0.51 (0.17-1.59)	5.91 (1.67-21.00)	5.72 (1.60-20.43)
Remainder off treatment	29	25130.7	0.12 (0.08-1.67)	1.28 (0.65-2.53)	1.25 (0.63-2.46)

Table 2.34: Summary of adjusted relative risk ratios for self-harm analyses[3]

Analyses[3]	1°	Male	Female	S1	S2	S3	S4	S5	S6	S7
Treatment status										
Overall time on treatment	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	N/a
Overall time off treatment	1.50 (1.21-1.88)	1.35 (1.03-1.78)	1.84 (1.27-2.66)	1.50 (1.24-1.83)	1.47 (1.18-1.84)	1.53 (1.21-1.94)	1.61 (1.14-2.25)	1.54 (1.22-1.96)	1.48 (1.08-2.04)	N/a
Treatment period										
Weeks 1-4 on treatment	1.43 (0.91-2.23)	1.55 (0.92-2.62)	1.11 (0.46-2.68)	1.84 (1.27-2.67)	1.38 (0.88-2.17)	1.47 (0.91-2.37)	0.94 (0.42-2.13)	1.43 (0.92-2.24)	1.07 (0.51-2.21)	1.63 (0.96-2.77)
Remainder of time on treatment	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	-
Weeks 1-4 off treatment	2.60 (1.83-3.70)	2.29 (1.46-3.59)	3.37 (1.92-5.92)	2.36 (1.71-3.28)	2.57 (1.80-3.66)	2.89 (2.00-4.19)	2.59 (1.50-4.48)	2.63 (1.84-3.73)	3.18 (1.98-5.10)	2.62 (1.70-4.03)
Remainder of time off treatment	1.47 (1.16-1.86)	1.36 (1.01-1.83)	1.68 (1.14-2.50)	1.59 (1.29-1.97)	1.44 (1.14-1.83)	1.48 (1.15-1.90)	1.46 (1.03-2.08)	1.43 (1.10-1.86)	1.31 (0.94-1.82)	1.48 (1.18-1.86)

[3] 1°: Primary analysis; S: sensitivity analyses; S1: accidental poisonings included; S2: undetermined intent excluded; S3: restricted to people with illicit opioid use Read code; S4: restricted to incident cases; S5: restricted to 1 year follow-up after each treatment episode; S6: restricted to first treatment episode; S7: initiation and cessation periods restricted to two weeks (as opposed to the four weeks specified in the "Treatment period" headings); cells are unfilled where there were too few observations to calculate adjusted relative risk ratios

Table 2.35: Summary of adjusted relative risk ratios for suicide analyses

Analyses[4]	1°	Male	Female	S1	S2	S3	S4	S5	S6	S7
Treatment status										
Overall time on treatment	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	N/a
Overall time off treatment	1.21 (0.64-2.28)	1.11 (0.55-2.22)	2.01 (0.42-9.70)	1.40 (0.95-2.06)	1.19 (0.56-2.54)	1.37 (0.70-2.70)	2.08 (0.69-6.30)	1.10 (0.51-2.36)	1.12 (0.48-2.62)	N/a
Treatment period										
Weeks 1-4 on treatment	2.12 (0.47-9.51)	2.57 (0.56-11.74)	-	1.67 (0.59-4.73)	-	2.63 (0.57-12.05)	4.08 (0.42-39.49)	2.01 (0.45-9.05)	2.10 (0.26-16.81)	3.94 (0.88-17.71)
Remainder of time on treatment	1.00	1.00	-	1.00	1.00	1.00	1.00	1.00	1.00	-
Weeks 1-4 off treatment	4.68 (1.63-13.42)	5.80 (1.98-16.97)	-	4.12 (2.07-8.21)	3.23 (0.88-11.94)	5.76 (1.95-17.07)	10.81 (2.15-54.32)	4.42 (1.53-12.73)	5.68 (1.50-21.46)	5.72 (1.60-20.43)
Remainder of time off treatment	1.14 (0.57-2.26)	1.02 (0.47-2.19)	-	1.33 (0.88-2.02)	0.98 (0.45-2.15)	1.31 (0.63-2.76)	2.13 (0.60-7.57)	0.81 (0.33-2.01)	0.97 (0.39-2.44)	1.25 (0.63-2.46)

[4] 1°: Primary analysis; S: sensitivity analyses; S1: accidental poisonings included; S2: undetermined intent excluded; S3: restricted to people with illicit opioid use Read code; S4: restricted to incident cases; S5: restricted to 1 year follow-up after each treatment episode; S6: restricted to first treatment episode; S7: initiation and cessation periods restricted to two weeks (as opposed to the four weeks specified in the "Treatment period" headings); cells are unfilled where there were too few observations to calculate adjusted relative risk ratios

2.5 Discussion

This study found that the risk of self-harm was lower during time on OAT compared to time off treatment, and lowest during the stable period on treatment. There was no evidence of an association between time on and off OAT and death by suicide, although confidence intervals were wide and an important association could not be excluded. The risk of suicide was, however, almost five times higher in the first four weeks after stopping OAT, while the risk of self-harm was almost three times higher during this period, compared with stable periods on treatment. The age- and sex-standardised risk of suicide in this cohort of people with opioid dependence was 7.5 times greater than in the general population.

To date, research has emphasised the burden of overdose deaths among people with opioid dependence. Although suicide is less common, it is an important and neglected cause of death in this population. People with opioid dependence are at a greatly increased risk of suicide compared with the general population (over seven times greater risk in this study), and self-harm is almost twenty times more common than suicide in this patient group.

The protective effect of stable periods of OAT on suicidal behaviour is striking. Possible explanations include direct protective effects of opiate agonism on suicidal behaviour and indirect protective effects of increased support provided alongside OAT medications. Furthermore, the association may be partially attributed to selection bias whereby patients at lower risk of suicidal behaviour remain on OAT for longer periods of time. Nonetheless, the findings provide evidence for the potential benefits of increasing retention in treatment.

2.5.1 Findings in the context of the wider literature

The baseline characteristics of people in the study are comparable to those in previous CPRD studies of people prescribed OAT and people in treatment in

drug and alcohol services [31, 149, 150]. The standardised mortality ratio for suicide of 7.5 (95% CI: 5.5, 10.0) is similar to the pooled relative risk of 6.9 (95% CI: 4.5, 10.5) for opioid dependence in a Global Burden of Disease study [1].

The finding of an increased risk of suicidal behaviour during the first four weeks of treatment cessation is in keeping with a recent systematic review and meta-analysis of unadjusted mortality rates [120]. The review included suicide data from one published study examining periods of treatment initiation and cessation in Australia, which also identified an increased risk of suicide during cessation as well as initiation [127]. In the study described in this chapter, there was also no evidence of an increased risk of suicide during treatment initiation when, in a sensitivity analysis, the exposure time period was narrowed to two weeks (Table 2.32 and Table 2.33). The findings regarding suicidal behaviour during treatment initiation were, however, sensitive to changes in its definition (Table 2.34). The difference in findings could, therefore, reflect variation between countries in the standard of proof required for a suicide conclusion [8, 172]. For example, some deaths classified as accidental in this cohort may have been classified as suicides within the Australian cohort.

Previous studies of non-fatal outcomes in relation to OAT have mainly focused on infections and non-fatal drug overdoses [68]. Two Australian studies have investigated specific risk periods for non-fatal overdoses during and after OAT [173, 174]. Both studies identified an increased risk during treatment initiation. Similarly, in the study described in this chapter, an increased risk of self-harm emerged during OAT initiation when accidental poisonings were included in a sensitivity analysis (Table 2.20).

One Australian study has assessed suicide attempts and suicidal ideation amongst people on entering treatment for heroin dependence and at 12 months' follow-up [121]. Amongst those commencing methadone or buprenorphine maintenance treatment (n=167) there was statistical evidence

of a reduction in the proportion of the sample experiencing current suicidal ideation (21.0% vs. 4.8%; P<0.001), but not suicide attempts in the 12 months prior to each assessment (10.8% vs. 6.6%). This small study may have been insufficiently powered to detect a difference between the latter. Furthermore, participants' treatment status varied before and during follow-up, thereby limiting interpretation and comparison with the study described in this chapter.

Although the recommended duration of OAT is generally not specified, modelling studies indicate that increasing treatment duration to two years would result in a range of population benefits, including a reduction in overdose and HIV-related deaths [126]. The median treatment duration in this study was 84 days, while the mean was 327 days. This implied a skewed distribution in which many patients stopped treatment early and a smaller proportion remained on treatment for a much longer duration.

Slight differences in self-harm rates in patients on buprenorphine compared to methadone were neither borne out in statistical tests of an interaction between time period and OAT modality nor observed for suicide. By contrast, a randomised controlled trial found protective effects of low-dose buprenorphine in relation to suicidal behaviour [175]. Yet, a Swedish population cohort study that investigated suicidal behaviour (including non-fatal suicide attempts) on and off treatment by OAT medication, found that methadone, but not buprenorphine, was associated with a decrease in the rate of suicidal behaviours [119]. More research is required to examine differences in suicidal behaviour between the two medications.

2.5.2 Strengths and limitations

To my knowledge, this is the first large-scale study in the UK to investigate the risk of suicide in relation to the timing of OAT (including periods of treatment initiation and cessation), and the first globally to investigate the risk of self-harm.

Within the field of Addictions research, studies commonly focus on drug-related poisonings, which include both accidental and intentional (i.e., suicide/self-harm) poisonings. Reasons for this grouping include the difficulty of determining suicidal intent and the belief that both types of poisonings are preventable. Yet, the factors contributing to accidental and intentional poisonings, and the interventions required to prevent them, are likely to differ considerably. Investigation of suicide and self-harm specifically is, therefore, important and a key strength of this study.

The large sample size in this study allowed investigation of suicide (a rare outcome) while adjusting for key confounders. Data linkage enabled the examination of hospital-presenting self-harm, a key risk factor for suicide, which was almost twenty times as common and therefore provided greater statistical power for the assessment of suicidal behaviour. Although power was limited in the analysis of suicide (particularly in relation to tests of interaction), there was consistency between the suicide and self-harm analyses regarding increased risk during treatment cessation. There are also several important limitations to consider.

First, there are limitations regarding classification of the exposure, outcome, and co-variates. Misclassification could have occurred due to inaccurate recording of Read, Product, and ICD-10 codes, missing clinical history information, and the complexity of determining suicidal intent. The baseline characteristics and rate of outcomes were, however, comparable to those in the existing literature [1, 129, 149, 150]. Potential misclassification is likely to have occurred in a similar way at different stages of OAT, and therefore the most likely direction of bias is towards the null. Moreover, the pattern of the main findings remained unchanged in the series of sensitivity analyses that were carried out to explore the effects of misclassification.

Misclassification of the timing of outcomes in relation to OAT is particularly important to consider. First, it is worth emphasising that the time periods

reflect estimated prescription end dates rather than whether a patient was taking the medication. Second, to account for the frequent missing data within prescriptions, which may have affected the estimation of prescription end dates, an extended gap of greater than 28 days between prescriptions was considered a new treatment episode. This gap meant that when estimating prescription durations, patients were more likely to be misclassified as "on treatment" when they were "off treatment" rather than vice versa. Conversely, where patients received prescriptions from other sources and these were not documented within their primary care records, patients may have been misclassified as being "off treatment". These two types of misclassification may have differed by outcome and could have each biased the results in opposite directions.

The findings may have been affected by selection bias if patients at lower risk of suicidal behaviour remained on OAT for longer periods of time, so contributed more follow-up time to the "on treatment" exposure group. Selection bias may have also occurred if loss to follow-up, due to patients transferring out of their GP practice, was differentially associated with both the exposure time periods and the suicide or self-harm outcome. This bias could be explored by comparing the characteristics and rate of outcomes amongst people who transferred out of their GP practice during each exposure period.

Due to the lack of complete prescribing information, it was not possible to differentiate between detoxification and maintenance treatments or compare planned and unplanned cessation. Most transitions between time on and off treatment in the UK are, however, likely to be unplanned; in an analysis of OAT CPRD prescription data, there was no evidence of a reducing dose in the 28 days prior to treatment cessation for over two-thirds of treatment episodes [176].

The findings may be affected by residual confounding. In particular, the reasons for discontinuation of OAT may be associated with suicidal behaviour

(i.e., there may be confounding by indication). Data were unavailable regarding many important factors, such as patients' illicit drug use both during and after follow-up and the quality of treatment (including the provision of concurrent behavioural therapies). Data were available within primary care records for factors such as homelessness and prison history, but these were not included as co-variates as they are particularly likely to have been under-recorded. These data are also commonly missing from other large-scale OAT cohorts [177, 178]. Nonetheless, the results in this study did not change substantially when adjusted for measured confounders, and the effect of unmeasured confounders would have had to have been strong to change the overall findings.

External validity may be affected by several factors. First, patients were excluded if they had insufficient information within their prescriptions to calculate treatment episodes. The reason for this lack of prescribing information is unclear, but it is possible that these patients differed from those with sufficient prescribing information available. Second, treatment cohorts may not represent all people with harmful drug use if the risk of self-harm in people not in treatment differs from the risk in people who have entered OAT. Additionally, OAT delivery varies throughout the UK and some people receive prescriptions directly from drug and alcohol services rather than from primary care. Although differences are generally area-based, people in drug and alcohol services may differ from patients managed solely or in shared care arrangements in primary care. A previous study did not find a difference in the duration of OAT between primary care and drug and alcohol services [150]. Nonetheless, if patients within drug services are more complex with more risk factors for suicide, such as poor mental and physical health, they may be more likely to stop treatment abruptly. This may result in this population being at increased risk of suicide and self-harm during treatment cessation. In contrast, additional psychosocial support may be available within specialist drug services, which could instead reduce the risk of suicide and self-harm. Replication of this study in patients treated within drug and alcohol services would, therefore, be useful.

Linked data were only available for a subset of the CPRD population (i.e., consenting GP practices in England). This was unrelated to future risk of suicide and self-harm so was unlikely to bias findings but did reduce statistical power. The use of CPRD Gold rather than Aurum also limited power.

Despite these limitations, observational studies, such as this study, provide the best available evidence, as randomised controlled trials would need unfeasibly large sample sizes to detect differences in suicide rates in people receiving OAT. This was illustrated by a recent systematic review, which identified randomised controlled trials investigating the relationship between OAT and mortality [120]. Amongst the 15 trials identified involving 3,702 participants, only 45 deaths were reported. In seven of these trials, no deaths occurred.

2.6 Conclusion

In this study, stable periods of OAT were associated with a reduced risk of suicidal behaviour, emphasising the importance of improving retention in treatment. The first month following cessation of OAT was a period of heightened risk and may require additional psychosocial support.

Chapter 3. A systematic review of suicide prevention interventions for people with substance use problems

3.1 Overview

In the previous chapter, I reported a protective effect of opioid agonist therapy on suicidal behaviour and a critical period of elevated suicide risk immediately after treatment cessation. In this chapter, I describe a systematic review designed to answer the following research question: What is the effectiveness of suicide prevention interventions among people with substance use problems?

A modified version of this chapter was published in Comprehensive Psychiatry in 2020 [179]. During the writing up of this chapter I identified errors in the calculation of the standardised mean differences. A correction for this has also been published [180]. This correction did not change the overall findings of the published paper.

3.2 Introduction

The national suicide prevention strategy in England highlights substance use problems as a risk factor for suicide and emphasises the need to tailor approaches to improve the mental health of "people who misuse drugs and alcohol" [110]. Yet research and national guidelines on co-existing severe mental illness and "substance misuse" provide minimal tailored evidence regarding the management of suicide risk or self-harm in this population [181, 182]. Furthermore, substance use problems are often an exclusion criterion in randomised controlled trials (RCTs) of interventions addressing suicide and self-harm. In two Cochrane reviews of interventions for self-harm, over a quarter of studies specified a type of substance use in their exclusion criteria [183, 184]. In light of the lack of evidence in this area, I sought to identify and evaluate the effectiveness of interventions to prevent suicide or reduce self-harm, specifically among people with substance use problems.

3.3 Methods

The reporting of this review conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement), a widely endorsed checklist to improve the quality and transparency of reporting of systematic reviews [185]. The review protocol for this study is accessible on PROSPERO (CRD42017076236).

3.3.1 Search strategy

I searched the following databases for publications, without language restriction, from the inception of the databases to 13th January 2019: Cochrane Central Register of Controlled Trials Register, PsycINFO, Medline, Embase, and Web of Science. Search terms broadly included: (substance [including alcohol]) AND (problematic use) AND (suicide OR self-harm) AND (randomised controlled trial). Within the search terms, I specified the key substances or substance groups encountered within drug treatment services [31]. Due to the lack of consensus about definitions for substance use problems, and the broad range of non-specific terms used within the literature, a large number of records were identified. Based on a librarian's advice, I used pre-established database-specific filters to identify RCTs, and in databases where it was possible to specify the balance of sensitivity and specificity used by the filter (Medline, Embase, and PsycINFO), I selected a filter that balanced sensitivity and specificity. The full search strategies are included in Appendix D. I also screened reference lists of all included studies and key systematic reviews of related interventions [95, 181, 186-191] to identify additional studies.

3.3.2 Eligibility criteria

The eligibility criteria were restricted to individual or cluster randomised controlled trials. Although reviews were excluded, they were used as a secondary source for relevant papers.

Studies were only included if all participants had substance use problems (including alcohol but excluding tobacco). In the protocol, I intentionally did not include a strict definition for this, as I was aware that there would be considerable variation in definitions within the literature; due to the lack of evidence in this area, any data were likely to be of value irrespective of definition. I also did not apply restrictions on participant characteristics such as age, gender, or comorbidities.

I included any trials investigating suicide, suicidal ideation, suicide attempts or non-suicidal self-harm (or a combination of the latter two, commonly referred to as self-harm) as a primary outcome. Studies were excluded if they only included suicide- or self-harm-related outcomes as secondary or supplementary outcomes. This distinction diverged from the pre-specified protocol due to the difficulty in identifying all studies that included relevant secondary outcomes when screening titles and abstracts and, consequently, the risk of publication bias. This distinction also enabled an assessment of whether studies were adequately powered to demonstrate an effect. Details of studies identified during the review process with suicide- or self-harm-related secondary or supplementary outcomes are provided in Appendix E.

3.3.3 Study selection

After deleting duplicates, I screened the titles and abstracts of all identified studies and then reviewed the full texts of all potentially relevant studies. The independent duplication of this process was shared between two colleagues (K.H. and V.C.). We used the online software Covidence to collate our decisions and identify discrepancies [192]. We were able to reach a consensus on all discrepancies through discussion.

3.3.4 Data extraction

I extracted data on study characteristics, population, method, intervention, outcome, and results using a standardised extraction form (Appendix F).

Independent duplicate extraction was shared between my two colleagues (K.H. and V.C.), and a consensus was reached on any differences through discussion.

3.3.5 Risk of bias assessment

I assessed the studies included in this review for bias using the Cochrane Risk of Bias (ROB) 2 Assessment Tool [193]. The Cochrane Risk of Bias tool is the most commonly used tool for assessing the risk of bias in RCTs [194]. The most recent version comprises five domains relating to different stages of a trial. Each domain includes signalling questions, which inform a domain-specific judgement regarding the level of risk of bias (low, some concerns, or high). The tool notes that the risk of bias will vary depending on the analysis of interest and therefore requires this to be specified. This review aimed to assess the effect of introducing an intervention within a health system instead of the specific effect on an individual who was compliant with treatment; therefore, the ROB assessments focussed on intention-to-treat analyses.

For each study, an independent duplicate ROB assessment was carried out by one of my two colleagues (K.H. and V.C.). Again, differences in ratings were resolved through discussion. To enhance the accuracy of the risk of bias assessments, we also aimed to inspect study protocols where available. For studies without a linked online protocol, I contacted study authors to request access (n=5). Three authors responded but were unable to provide pre-specified protocols.

In keeping with guidance for using the ROB 2 tool [193], the overall ROB for each study was classified as:

- "low risk of bias" if all domains were judged to be low risk of bias;
- "some risk of bias" if some concerns regarding bias were identified in one to four domains, but no domains were considered to be at high risk of bias;

- "high risk of bias" if one or more domains were judged to be at high risk of bias or there were some concerns regarding the risk of bias for all five domains.

All studies were included in this review irrespective of their risk of bias.

3.3.6 Data analysis

Randomised controlled trial data retrieved during a systematic review can be presented as a narrative review or a meta-analysis with or without a pooled summary estimate. Whilst narrative reviews offer in-depth analyses of individual studies, meta-analyses: 1) use clear, objective, transparent criteria for analysing data; 2) rely less on reports of statistical significance within each included paper by providing a mechanism to compare effect sizes and inspect heterogeneity of the results across studies; 3) enhance understanding of the findings of each study in the context of the other included studies [195].

In my systematic review protocol, I pre-specified that a meta-analysis would be performed if enough homogenous studies were identified. After finalising the studies to be included in the review, I realised that decisions about the appropriate number of studies and level of homogeneity to warrant a meta-analysis are not clear cut [195].

Diversity amongst studies included in a meta-analysis is common, especially when eligibility criteria are broad. It can be accounted for using random effects models, which assume a distribution of true effects across studies rather than a single true effect (as in a fixed effects model). The pooled summary estimate provided by such models represents the estimated mean of all the true effects. Heterogeneity can also be useful. When enough diverse studies are synthesised within a meta-analysis, variation in findings can be closely examined (e.g., using meta-regression) to improve understanding of the range of effects in different populations and interventions. However, this is not possible for reviews with only a few diverse studies. In such reviews, there is also an increased likelihood of error in pooled summary estimates [195]. Yet, proponents of the use of pooled summary estimates argue that there is

transparency in the way that they are calculated; when they are not provided, readers often formulate their own idiosyncratic summary [195].

One suggestion to help decide whether to take a narrative or meta-analytic approach when synthesising a small number of studies is to base this decision on the research question [195]. In the published paper related to this chapter, I presented a meta-analysis with a pooled summary estimate as I was initially interested in gaining an overall sense of the effect of any interventions within this field. Insufficient data were, however, obtained to formally investigate how different aspects of the diverse population, intervention, comparison groups, and outcomes influenced the range of effects identified. When developing an intervention (detailed in Chapter 4), it became evident that the details and nuance of each study were more informative than a statistical pooled value; therefore, in this chapter, I primarily present a narrative synthesis.

A forest plot without a pooled summary estimate is, however, also presented to facilitate inspection and comparison of the effect of each intervention on suicide-related outcomes. To maximise the comparability of the results in this forest plot, I initially included only follow-up data at six months following randomisation (or as close to six months as possible) as this was the follow-up duration that was most consistent across studies. As a sensitivity analysis, I have included only follow-up data immediately post-intervention (or as close to immediately post-intervention as possible). Further sensitivity analyses were considered unlikely to provide meaningful insights due to the small sample size of included studies.

To present data across outcome types in the forest plot, I first calculated study-specific standardised mean differences (SMDs) for continuous outcomes and odds ratios (ORs) for binary outcomes, each with 95% confidence intervals (CIs). I then approximated SMDs and standard errors of SMDs from ORs using standard formulae [195]. This process converted each effect size to a single, common metric. Analyses were conducted using Stata [196].

The formulae used to calculate SMDs for continuous outcomes were [195]:

$$SMD = \frac{\overline{X_1} - \overline{X_2}}{S_{within}}$$

$$S_{within} = \sqrt{\frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2}}$$

$$Variance\ of\ SMD = \frac{n_1 + n_2}{n_1 n_2} + \frac{SMD^2}{2(n_1 + n_2)}$$

$\overline{X_1}$ and $\overline{X_2}$ = sample means in each group; S_{within} = pooled within-group standard deviation; n_1 and n_2=sample sizes in each group; S_1 and S_2 = standard deviations in each group.

The SMD calculation assumes that the population standard deviations for the intervention and control groups are the same. The standard deviations are pooled for each group within the sample (S_{within}) to increase the accuracy of the estimated population standard deviation.

The formulae used to calculate SMDs for binary outcomes were [195]:

$$SMD = LogOddsRatio \times \frac{\sqrt{3}}{\pi}$$

$$Variance\ of\ SMD = Variance\ of\ LogOddsRatio \times \frac{3}{\pi^2}$$

$$Variance\ of\ LogOddsRatio = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}$$

π = the mathematical constant pi (approximately 3.1415); a = no. cases amongst controls; b = no. unaffected amongst controls; c = no. cases amongst treatment group; d = no. unaffected amongst treatment group

This method for standardisation of odds ratios was first described in 1995 by Hasselblad and Hedges [197]. It assumes that each group has an underlying continuous element with a logistic distribution, but it is recognised that this would be difficult to assess in practice [195].

For one study, it was not possible to obtain the mean score and standard deviation for suicidal ideation from the aggregate data described within the paper. These were instead provided by the study author on request [198]. For another study, where there was more than one intervention group consisting of different doses of medication with no placebo/control group, the largest and smallest doses were compared due to ambiguity regarding the classification of the middle dose as an intervention or control [199]. In one study, data were available for two relevant outcome measures at six months (the presence of suicidal ideation and the Beck Scale for Suicide Ideation); these were averaged to form a composite SMD [195, 200]. The correlation (*r*) between the two outcomes was unknown and was assumed to be 0.5, as all outcomes were expected to be positively correlated. The formulae used to derive this composite SMD were [195]:

$$Pooled\ SMD = \frac{1}{2}(SMD_1 + SMD_2)$$

$$Variance\ of\ SMD = \frac{1}{4}\ (V_{SMD1} + V_{SMD2} + 2r\sqrt{V_{SMD1}}\sqrt{V_{SMD2}}$$

V_{SMD1} and V_{SMD2} = variance of SMD in each sample

To assess publication bias, I produced a funnel plot, which allowed visual inspection of the relationship between sample size and effect size. Smaller studies are more likely to be published if they have a large enough effect size to demonstrate statistical significance leading to publication bias. Publication bias decreases with larger sample sizes because larger studies are more likely to be published irrespective of their findings than smaller studies. Consequently, asymmetric funnel plots are suggestive of publication bias. Formal tests were not employed to assess publication bias and its impact due

to the small number of studies (n=6) and lack of large-scale trials identified in the systematic review. Furthermore, formal tests assume that asymmetry within a funnel plot is due to publication bias and neglect the possibility of small-study effects in which all smaller trials that have been conducted have produced larger effect sizes. These small-study effects can occur for various reasons, such as bias within studies or differences in study characteristics [195].

3.4 Results

3.4.1 Search results

Based on the search strategy described above, 6,862 references were identified, of which 2,214 were duplicates. After screening titles and abstracts, 4,577 articles were excluded. Of 71 full-texts assessed for eligibility, seven were included, which described six RCTs [198-204]. The reasons for study exclusion are summarised in Figure 3.1.

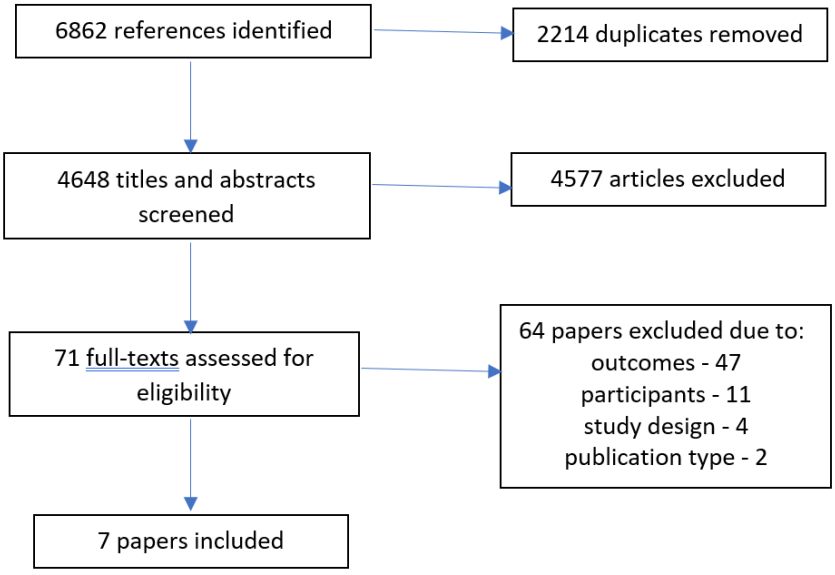


Figure 3.1: PRISMA flow diagram[5]

[5] Studies excluded due to "participants" did not specify substance use problems within their participant inclusion criteria. Studies excluded due to "outcomes" did not investigate suicide-related outcomes as a primary outcome.

3.4.2 Study characteristics

The six randomised controlled trials included in this review represented 468 participants at the point of randomisation. Study characteristics are summarised in Table 3.1. All studies were individually randomised and ranged from 30 to 185 participants. Three of the included RCTs were based in the USA [198, 202-204]. The remaining trials were based in Australia [200], the UK [201] and Iran [199].

With regards to the population included, three trials included people with alcohol use problems [201-204], two included people with alcohol and/or drug use problems [198, 200], and one included only people with opioid use problems [199]. Four trials specifically restricted the population to those who reported suicidal ideation [198, 200, 204], had attempted suicide [198, 200], or had presented to hospital with self-harm [201]. In three trials, co-morbid mental health symptoms or conditions were specified within the inclusion criteria: major depressive disorder [199], borderline personality disorder [202, 203], and high levels of emotional dysregulation [204]. All studies investigated interventions for adults, except one which focused on adolescents aged 13-17 years [198].

Mental health conditions involving psychosis, such as bipolar disorder or schizophrenia, were listed in the exclusion criteria of four trials [198, 200, 202, 204]. Intellectual impairment was a reason for exclusion in three trials [198, 200, 202]. Two trials specified the exclusion of homeless people [200, 201], and two specified the exclusion of people who were unable to communicate in English [201, 204].

The recruitment site varied between inpatient settings [198, 199], emergency departments [201], a range of settings including outpatient services [200, 202], and online [204].

One trial investigated a pharmacological intervention (a one-off dose of buprenorphine) [199]. The other five trials investigated psychosocial interventions:

- brief intervention using FRAMES: "Feedback about the adverse effects of excessive alcohol consumption, an emphasis on Responsibility for change lying with the individual, provision of Advice about reducing alcohol consumption, a Menu of options for further intervention if this is required, an Empathic stance towards the patient, and the enhancement of Self-efficacy" [201]
- online dialectical behavioural therapy (DBT) [204]
- cognitive behavioural therapy (CBT) (two trials) [198, 200]
- dynamic deconstructive psychotherapy (DDP) (single trial, two publications) [202, 203]

The interventions differed greatly in their intensity. The pharmacological intervention and FRAMES brief intervention involved a single dose or contact [199, 201], whilst the trials of online DBT and CBT for adults involved eight sessions each [200, 204]. In contrast, the trial of a 12-month CBT intervention for adolescents required adolescents to participate in at least 24 sessions to be considered to have completed treatment [198], and the trial of DDP consisted of weekly sessions for between 12 to 18 months [202].

There was also substantial variation in the care received by participants in the comparison groups both between and within studies. Comparators included a waiting list for the intervention [204], a leaflet containing information about the impact of excessive alcohol use and relevant helplines [201], treatment as usual [200], optimised or enhanced treatment as usual [198, 202], and a lower dose of buprenorphine [199].

Suicidal ideation was investigated as an outcome in four trials [198-200, 204]; self-reported self-harm [202, 203], and emergency department re-attendance with self-harm [201] were outcomes in the remaining trials. Additionally, two studies planned to investigate suicide attempts as an outcome measure. Due

to their rarity, in one study, this data was not analysed [200], whilst in another study, data collected at multiple follow-up periods were aggregated and analysed over 18 months [198]. No papers described an assessment of suicide deaths within their Methods, although two papers reported on suicide deaths [200, 202]. In the trial of CBT for adults, there were no suicides [200], whilst in the trial of DDP, one suicide occurred in the control group [202]. The maximum follow-up time for measuring outcomes ranged from three days [199] to 18 months [198].

Table 3.1: Summary of included studies[6]

Study	Country	Participants at randomisation	Substance use	Mental health comorbidity	Age/ sex if restricted	Setting of recruitment and intervention	Intervention	Comparison group	Outcomes	Risk of bias
Ahmadi et al. (2018) [199]	Iran	N=51	Severe opioid use disorder	Major depressive disorder	Male	Recruited from and delivered on inpatient psychiatric ward	Single, sublingual dose of buprenorphine (64 mg or 96 mg)	Single, sublingual dose of buprenorphine (32 mg)	Suicidal ideation (Beck Scale for Suicide Ideation score)	Some concerns
Crawford et al. (2010) [201]	UK	N=103	Alcohol misuse	Nil specified	>18 years	Recruited from emergency department Intervention setting not specified	"FRAMES" approach Single 1:1 session & leaflet	Leaflet	Emergency department re-attendance with self-harm	Some concerns
Esposito-Smythers et al. (2011) [198]	USA	N=40	Alcohol/ cannabis use disorder	Nil specified	13-17 years	Recruited from inpatient units Outpatient intervention	CBT Separate 1:1 sessions for adolescents and parents with reducing frequency from twice weekly to monthly over 12 months	Enhanced treatment as usual	Suicidal ideation (Suicidal Ideation Questionnaire-Senior Version score) Suicide attempts (K-SADS-PL depression module)	High

[6] (CBT: Cognitive behavioural therapy; DBT: dialectical behavioural therapy; DDP: dynamic deconstructive psychotherapy; FRAMES: Feedback about the adverse effects of excessive alcohol consumption, an emphasis on Responsibility for change lying with the individual, provision of Advice about reducing alcohol consumption, a Menu of options for further intervention if this is required, an Empathic stance towards the patient, and the enhancement of Self-efficacy)

Study	Country	Participants at randomisation	Substance use	Mental health comorbidity	Age/ sex if restricted	Setting of recruitment and intervention	Intervention	Comparison group	Outcomes	Risk of bias
Gregory et al. (2008), (2009) [202, 203]	USA	N=30	Active alcohol abuse or dependence	Borderline personality disorder	18-45 years	Recruited through range of clinical settings including emergency department and hospital settings Outpatient intervention	DDP Weekly 1:1 sessions +/- group therapy over 12-18 months	Optimised community care	Self-harm (adapted 3-month version of the Lifetime Parasuicide Count)	High
Morley et al. (2014) [200]	Australia	N=185	Alcohol/drug misuse	Nil specified	18-65 years	Recruited from emergency dept. or outpatient drug & alcohol services Outpatient intervention	CBT 8x 1:1 sessions with homework and 1x group workshop 3 months later	Treatment as usual	Suicidal ideation (Presence of, and Beck Scale for Suicide Ideation) Suicide attempts	High
Wilks et al. (2018) [204]	USA	N=60	Heavy episodic drinking (alcohol)	High emotional dysregulation	≥18 years	Recruited through online forums Delivered online	DBT Weekly modules with homework over 8 weeks	Waiting list for intervention	Scale for Suicidal Ideation (Beck)	Some concerns

Table 3.2: Risk of bias summary (green=low, yellow = some concerns, red=high)

	Study					
	Ahmadi et al. (2018)	Crawford et al. (2010)	Esposito-Smythers et al. (2011)	Gregory et al. (2008), (2009)	Morley et al. (2014)	Wilks et al. (2018)
Risk of bias arising from the randomisation process						
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)						
Risk of bias relating to missing outcome data						
Risk of bias in measurement of the outcome						
Risk of bias in selection of the reported result						
Overall risk of bias						

3.4.3 Quality assessment

Although all studies described the effectiveness of the interventions, three described themselves as pilot/feasibility trials [198, 202, 204], the other three studies acknowledged their sample size and/or power to be a limitation [199-201].

Of the six trials included, three were assessed to be at high risk of bias [198, 200, 202, 203], whilst there were some concerns regarding the risk of bias for the remaining studies (Table 3.2). Morley et al. (2014)'s study was judged to be at "high risk of bias arising from the randomisation process" due to limited information about the nature of the allocation sequence and substantial baseline differences in the intervention groups despite a reasonably large sample size (n=185) [200]. Some concerns about the "risk of bias due to deviations from the intended intervention" were recorded where blinding was unfeasible, and there was a lack of evidence indicating that this had little impact on intervention assignment and the study outcomes [198, 200-203]. Some concerns about the "risk of bias in the measurement of the outcome" were recorded for studies that relied on self-reported outcomes by participants who were unblinded [198, 200, 202-204]. Some concerns regarding the "risk of bias in selection of the reported result" were recorded for all but one study [204], as no pre-specified protocol was available [198-203]. Finally, some concerns regarding the "risk of bias due to missing outcome data" were recorded for studies where outcome data were missing for more than 10% of randomised patients, and there was a lack of evidence to suggest that this did not bias the result [198, 202-204].

Participant retention was problematic in several studies, even where the risk of bias due to missing data was classified as low based on the ROB 2 tool. For example, in the FRAMES brief intervention trial, although over a quarter of participants were lost to follow-up, outcome data were collected from hospital records, so data were available for all randomised participants [201]. Meanwhile, in the trial of CBT for adults, over half of the randomised

participants were lost to follow-up, but there were no statistically significant differences in baseline characteristics when compared with those retained in the study [200].

3.4.4 Study findings

The only trial of a pharmacological intervention included in this review involved the randomisation of 51 men with "severe opioid use disorder" and major depressive disorder to receive one of three one-off high doses of buprenorphine (32mg, 64mg, or 96mg) following admission to an inpatient psychiatric ward in Iran [199]. The justification for the trial was preliminary evidence of the effectiveness of low-dose buprenorphine in reducing acute suicidal ideation amongst individuals without substance use problems, possibly through its action as a k-receptor antagonist [175, 199]. In this trial, a placebo group was not included due to the risks of drug withdrawal. The lowest dose used in the trial (32mg) was reported to be the maximum dose used in clinical practice at the time of the study. Suicidal ideation was measured daily from day one to day three. Of the 51 men randomised, 47 received the intervention and provided follow-up data. Statistical evidence of a reduction in suicidal ideation scores was observed in all three groups during this time, but there was no evidence of a difference between groups.

The trial of a brief intervention involved the randomisation of 103 patients who had attended a UK emergency department with self-harm [201]. Patients were included in the trial if they had been "misusing alcohol" based on the Paddington Alcohol Test but were not already under alcohol treatment services and had not specifically requested help for their alcohol use. All randomised patients received a health information leaflet that included contact details for relevant national helplines. Those randomised to the intervention group were also offered a single appointment with an alcohol specialist nurse, usually on the same day as their attendance, which specifically focused on their alcohol use using the FRAMES approach. Of the 51 patients randomised to the intervention, only 24 (47.1%) attended their

appointment. Follow-up data on re-attendance with self-harm were based on hospital records and were available for all participants. There was no evidence of a between-group difference in the proportion of people re-attending the emergency department at six-month follow-up. There was also no evidence of a difference in this outcome between those who did and did not attend their alcohol nurse specialist appointment.

The trial of online DBT involved the randomisation of 60 participants, recruited through online forums and advertisements, who had experienced suicidal ideation, two episodes of "heavy episodic drinking" in the last month, and high levels of emotional dysregulation [204]. Those randomised to the intervention were offered eight sessions of weekly online DBT, whilst those in the comparison group were put on a waiting list for the intervention. Each DBT session was focused on developing skills in relation to mindfulness, reducing harmful drinking, emotional regulation, and tolerating distress. After eight weeks, participants in the control group were offered access to the intervention. Less than half of the participants randomised to the intervention group completed each of the final four sessions. Technology-related problems were commonly cited as a reason for dropping out. Outcomes were measured during paid monthly assessments for four months. The final follow-up assessment was completed by 77% of individuals in the intervention group and 90% of individuals in the comparison group. During the study, no evidence of a between-group difference was observed for suicidal ideation scores. However, a large between-group effect size in favour of the intervention group was reported at two months (d=-0.72), which had increased further by four months (d=-1.06). Confidence intervals and p-values for these effect sizes were not reported.

In the Australian-based trial of CBT for adults, 185 people with "alcohol or other drug misuse" and current suicidal ideation or a suicide attempt within the last three months, were opportunistically recruited from a range of settings and randomised (2:1 to intervention/comparison group) [200]. The intervention consisted of eight one-to-one outpatient sessions over three

months and a group workshop three months later. During the sessions, a wide range of CBT techniques was used, which targeted suicidal thoughts and behaviours as well as substance use problems. The comparison group received treatment as usual. At baseline, there was evidence of differences between the intervention and control group for a range of factors. The control group were, on average, younger, less likely to be employed, more likely to have used a variety of illicit drugs, and more likely to have accessed drug and alcohol services. This group also had a higher average suicidal ideation score. These factors were included as covariates in the main analysis. Of the 122 participants randomised to receive the intervention, only 44 (36%) completed the full study (including attending a 6-month follow-up appointment), and less than half of the participants received at least four out of the eight sessions. Loss to follow-up was also high in the comparison group, with only 30 (48%) participants completing the 6-month follow-up. During the six-month follow-up, there were no suicides. Two suicide attempts were reported but not formally analysed due to their rarity, and the arm in which they occurred was not specified. At six months, the proportion of people experiencing (weekly) suicidal ideation and average suicidal ideation scores were lower in both groups, but there was no evidence of between-group differences in either outcome.

The other trial of CBT included in this review involved the provision of a more intensive intervention for adolescents recruited from an inpatient psychiatric setting in the USA and their families [198]. Forty adolescents with "alcohol and/or cannabis use disorder" and a recent suicide attempt or suicidal ideation were randomised to a 12-month CBT intervention or enhanced treatment as usual. The intervention focused on the use of CBT techniques to address maladaptive cognitions and behaviours relating to both substance use problems and suicidality. Sessions reduced in frequency over 12 months (six-month active treatment, three-month continuation phase, three-month maintenance phase). In addition, a single motivational interviewing session was offered to adolescents and, separately, their parents, and case management calls were made to other services involved in the care of each

adolescent as required. Treatment for the comparison group was determined by external providers but was supplemented with a diagnostic assessment and evaluation report, which was shared with community services, and medication management undertaken by the trial psychiatrist. Treatment completion was defined as an adolescent attending 24 sessions and their parents attending 12 sessions. Based on this definition, 74% of families completed treatment. Outcomes were assessed at 3, 6, 12, and 18 months, and 80% of the sample completed the final follow-up assessments. Over the 18-month follow-up, no evidence of a difference was observed between the groups for suicidal ideation. There was, however, evidence of a difference between groups in the proportion of participants who attempted suicide when these were aggregated over 18 months (treatment group: n=1; control group: n=6; Cohen's h=0.8, p=0.02).

The final trial included in this review investigated the effect of 12-18 months of weekly dynamic deconstructive psychotherapy sessions [202]. Thirty patients who had a diagnosis of borderline personality disorder and "active alcohol abuse or dependence" were recruited from a variety of settings. They were randomised to either the therapy or optimised treatment as usual. The therapy was a newly developed adaptation of psychodynamic psychotherapy for complex cases of borderline personality disorder, which aimed to address a range of neurocognitive impairments. In particular, it included exploration of the context and function of specific episodes of problematic behaviours whilst maintaining a non-directive stance. Individuals in the optimised treatment as usual group were referred to alcohol rehabilitation centres if they weren't already in treatment. They were also provided with contact details for relevant therapists and psychiatric clinics. The trial investigated self-harm, including suicide attempts (described in the paper as "parasuicide"). At baseline, a greater proportion of participants in the intervention group reported self-harm compared to the control group (73% vs. 47%), although the difference was not formally tested. By 12 months, 10 out of the 15 (67%) participants in the intervention group remained engaged in the therapy. The 12-month follow-up was completed by 67% of the intervention group and

60% of the comparison group. The authors' reported evidence of a reduction over time in the proportion of DDP participants reporting self-harm, which was not observed in the control group. However, there was no evidence of a between-group difference for this outcome during the study. One participant (in the control group) died by suicide at approximately nine months.

3.4.5 Standardised results

The results at or closest to six months from the four studies that investigated continuous outcomes (all suicidal ideation) are summarised in Table 3.3 and Figure 3.2. These studies investigated CBT for adolescents and separately for adults, online DBT, and different doses of buprenorphine. The SMD was estimated to be negative, favouring the intervention, in all studies. The SMD effect sizes were small in all studies, except in the study of online DBT, in which the effect size was moderate (SMD=-0.52). An SMD of -0.52 indicates that, on average, there was a difference of 0.52 standard deviations between the outcomes in the intervention and the comparison group. However, all confidence intervals were wide and inconclusive. When data collected immediately post-intervention were included in the sensitivity analysis (Figure 3.3), a moderate effect size was also observed in the study of CBT for adolescents (SMD=-0.62). Nonetheless, all confidence intervals remained wide and inconclusive.

The six-month results from the three studies that investigated discrete outcomes relating to suicidal ideation or self-harm are summarised in Table 3.4 and Figure 3.2. Amongst the intervention groups at six months, there was an estimated 43% reduction (odds ratio: 0.57; 95%CI: 0.17, 1.78) in the odds of re-attendance at the emergency department with self-harm following a brief intervention using the "FRAMES" approach [201], and an estimated 52% (OR: 0.48; 95% CI: 0.06, 3.49) reduction in self-reported self-harm following DDP [202]. The standardised mean difference for the DDP study reduced from -0.41 (95%CI: -1.35, 0.53) to -0.08 (95%CI: -1.15, 0.98) in the sensitivity analysis using post-intervention data. However, confidence intervals around these

results were wide and inconclusive. In Morley's trial of an opportunistic CBT intervention, there was an estimated 42% (OR: 1.42; 95% CI:0.27, 9.51) increase in the proportion of people experiencing an increase in suicidal ideation, but again the confidence intervals were wide and inconclusive. Furthermore, this contrasted with the reduction in the mean difference of suicidal ideation scores noted in Table 3.3 [200].

Table 3.3: Summary of continuous outcome data (SD: standard deviation; SMD: standardised mean difference; CI: confidence intervals; BSSI: Beck Scale for Suicide Ideation; SIQ-S: Suicidal Ideation Questionnaire-Senior Version)

Study	Measure, timepoint	Intervention, no. participants with outcome data available	Intervention, mean (SD)	Control, no. participants with outcome data available	Control, mean (SD)	Mean difference	SMD (95% CI)
Ahmadi et al. (2018)	BSSI, day 3	14	0.00 (0.00)	16	0.63 (2.50)	-0.63	-0.34 (-1.06, 0.38)
Esposito-Smythers et al. (2011)	SIQ-S, 6 months	17	28.65 (22.17)	17	38..24 (35.54)	-9.59	-0.32 (-1.00, 0.35)
Morley et al. (2014)	BSSI, 6 months	44	5.82 (5.58)	30	6.00 (6.61)	-0.18	-0.03 (-0.49, 0.43)
Wilks et al. (2018)	BSSI, 4 months	24	5.45 (6.62)	26	9.59 (8.99)	-4.14	-0.52 (-1.09, 0.04)

Table 3.4: Summary of discrete outcome data (SMD: standardised mean difference; CI: confidence intervals)

Study	Measure, timepoint	Intervention, no. participants (% of participants with outcome data available at 6 months)	Control, no. participants (% of participants with outcome data available at 6 months)	Odds ratio (95% CI)	SMD (95% CI)
Crawford et al. (2010)	Re-attendance at emergency department with self-harm, 6 months	7 (13)	11 (21)	0.57 (0.17, 1.78)	-0.31 (-0.89, 0.26)
Gregory et al. (2008)	Self-reported self-harm, 6 months	5 (45)	7 (64)	0.48 (0.06, 3.49)	-0.41 (-1.35, 0.53)
Morley et al. (2014)	Presence of suicidal ideation (weekly), 6 months	6 (14)	3 (10)	1.42 (0.27, 9.51)	0.19 (-0.62, 1.00)

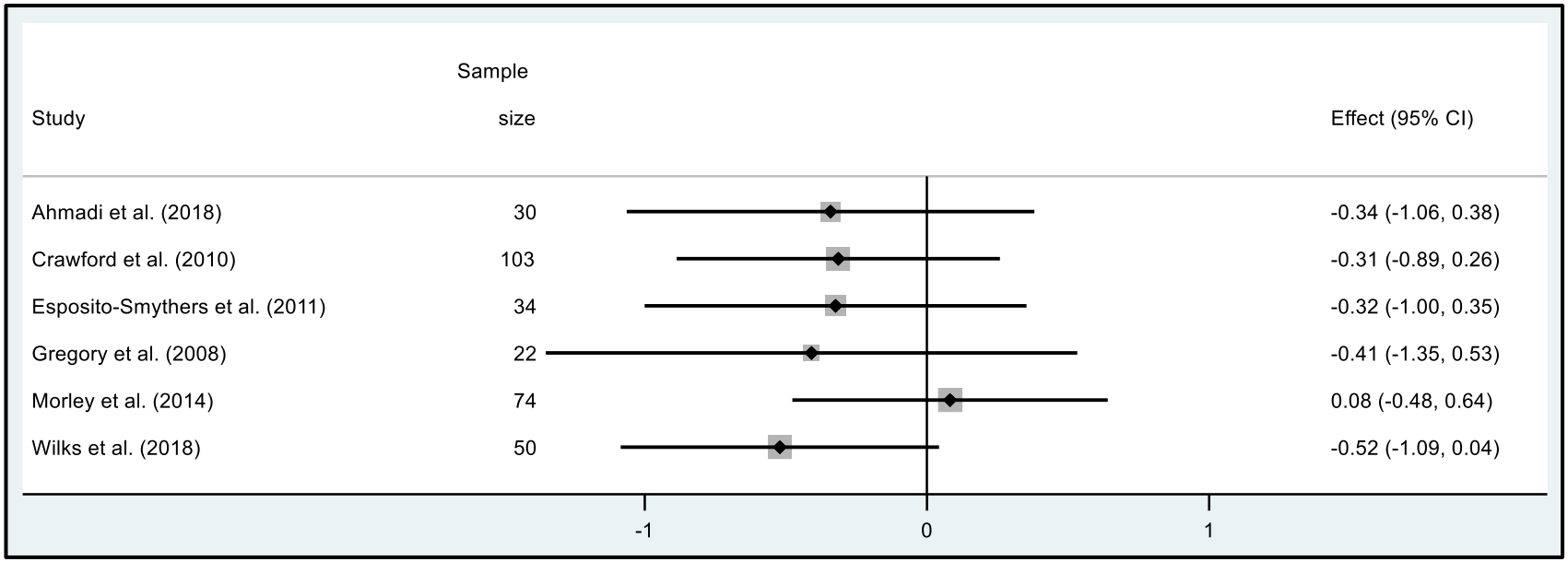


Figure 3.2: Forest plot of standardised mean differences (outcomes measured at, or as close to, 6 months in each included study; below 0 favours intervention; composite outcome of BSSI and presence of suicidal ideation included for Morley et al. (2014) [200])

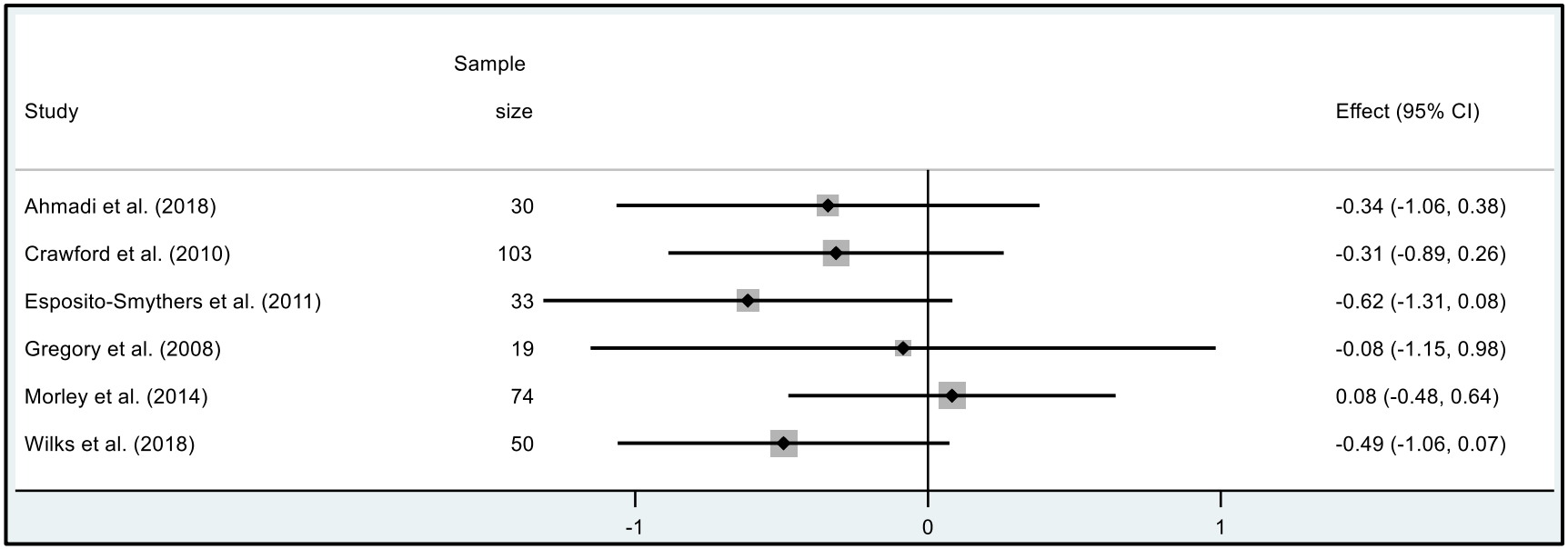


Figure 3.3: Sensitivity analysis forest plot of standardised mean differences (post-intervention outcomes; below 0 favours intervention; composite outcome of BSSI and presence of suicidal ideation included for Morley et al. (2014) [200])

The funnel plot (Figure 3.4) based on six-month outcome data was difficult to interpret due to the small number of studies. It appeared to be asymmetrical, with fewer small studies with weaker effect sizes. This indicated the possibility of publication bias but it may have also been caused by other small-study effects, as described in the Methods section of this chapter.

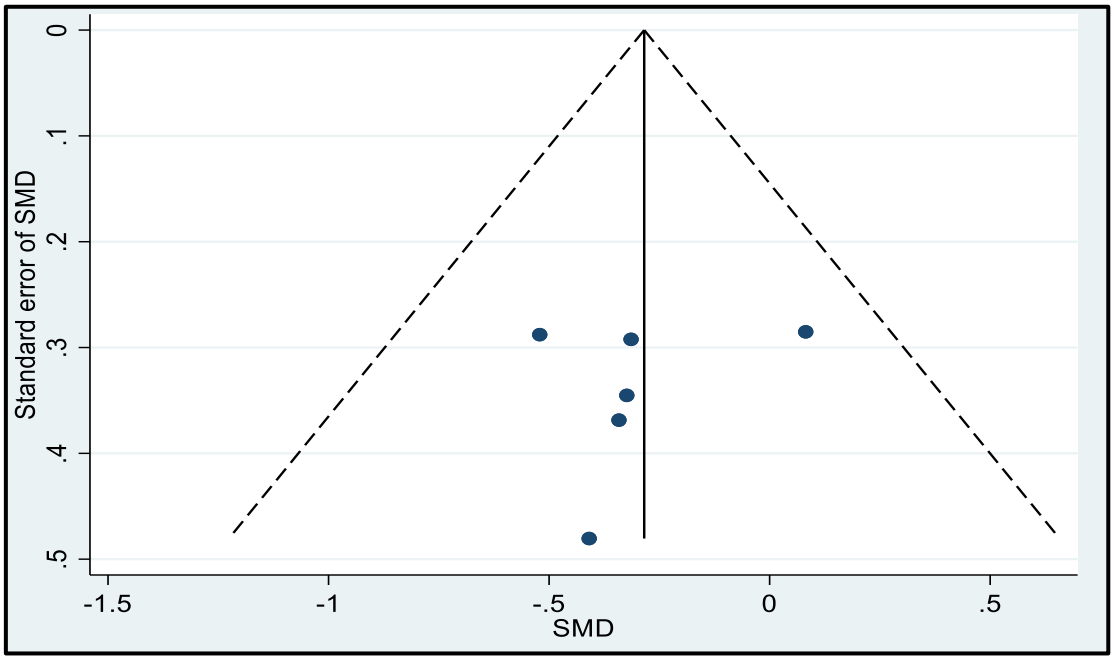


Figure 3.4: Funnel plot

3.4.6 Review update

Since the publication of this systematic review, I have not identified any further relevant studies when updating my searches to December 2021. I have, however, identified two new pilot RCTs [205, 206] that meet the review inclusion criteria through SafetyLit [207]. SafetyLit is a service that identifies and collates new injury prevention research by screening the results of a highly sensitive database search daily and hand-searching journals. Weekly updates summarising relevant research are provided.

The first pilot trial compared 20 weeks of outpatient Cognitive Behavioural Therapy-Relapse Prevention (CBT-RP) in combination with enhanced treatment as usual, to enhanced treatment as usual alone [205]. Thirteen

adolescents with suicidal ideation or a recent suicide attempt, “alcohol or cannabis abuse/dependence disorder”, and a depressive disorder were randomised. The intervention aimed to reduce and prevent recurrences of suicidal thoughts, depression, and substance use problems by focusing on the management of high-risk situations, use of alternative behaviours, increasing self-efficacy, and developing a positive lifestyle balance. The intervention consisted of up to twenty-three scheduled sessions. Additionally, participants had access to optional emergency sessions and telephone contact. For all participants, case managers provided monthly support with determining treatment needs and referrals, and their evaluations were shared with community providers. The groups differed in terms of primary substance use problems, with cannabis the primary substance for all participants in the intervention group but only half of the participants in the comparison group. Compensation was provided for participation in assessments. All but one person in the intervention group remained in the intervention at 20 weeks, and follow-up data were available for all but this one participant. Due to the small sample size, only descriptive outcome data were provided. Participants in the intervention group appeared to have quicker and more consistent reductions in suicidal ideation than those in the control group. One participant in each group attempted suicide during the study, and there were no suicides.

The second pilot trial compared an inpatient intervention, a modified version of the Attempted Suicide Short Intervention Program (ASSIP), with treatment as usual [206]. Thirty-four patients with “substance use problems”, who had been admitted following a suicide attempt, were randomised. The intervention consisted of three inpatient sessions followed by a fourth session after discharge. As such, only patients whose admission was sufficiently long to participate in the three sessions were included. ASSIP is a manualised intervention that involves video-recording a narrative interview about a patient’s suicide attempt, re-playing the recording in a subsequent session, and developing a formulation, alongside the use of cognitive-behavioural techniques. This modified version addressed substance use problems alongside suicide risk. A previous version of this trial was discontinued after

two suicide deaths occurred. Safety measures were added, including, for all participants, up to three telephone check-ins in the month post-discharge. All four therapy sessions were completed by 69% of the participants. Six-month follow-up was completed by approximately three-quarters of the participants in each group. A multi-source method for assessing repeat suicide enabled outcome data to be obtained for several of those lost to follow-up. As the sample size was assumed to be too small to examine efficacy, between-group differences were not examined. At six months, based on multi-source data, 38% of participants had attempted suicide, and one person (in the intervention group) had died by suicide. Descriptive results indicated the possibility of a greater improvement in suicidal ideation in the intervention group at six months.

3.5 Discussion

In this systematic review, I initially identified only six randomised controlled trials of interventions for people with substance use problems with a suicide-related primary outcome. The trials represented a total of 468 participants and varied in terms of populations, interventions, comparators, and outcomes. All but one study investigated psychosocial interventions. The trials were mainly exploratory in nature, and all studies were likely to have been insufficiently powered to examine effectiveness. Furthermore, engagement with the intervention was problematic in several of the trials.

One study [198] identified evidence of a between-group difference. In the pilot feasibility trial of an intensive 12-month CBT intervention for 40 adolescents and their parents, there was evidence that the proportion of people reporting suicide attempts was substantially lower in the intervention group when data were aggregated over the 18-month follow-up. The stability of this finding may be affected by the small sample size and requires cautious interpretation. There was no evidence of a difference between groups in suicidal ideation scores, but it is also noteworthy that engagement with the intervention was relatively high. The other trial of CBT in this review did not observe between-

group differences in suicidal ideation. The 6-month composite SMD for suicidal ideation in Morley et al. (2014) was 0.08 (95% CI: -0.48, 0.64), whilst the SMD for suicidal ideation in Esposito-Smythers et al. (2011) was -0.32 (95% CI: -1.00, 0.35) [200]. However, comparisons between the two studies are limited by major differences in study populations and the nature of the interventions.

Several other interventions also showed promise despite a lack of an observed between-group difference. In the online DBT feasibility study for people who reported heavy episodic drinking, a moderate to large effect size was observed for suicidal ideation. This occurred in the context of variable levels of engagement, commonly due to technology-related issues. However, the use of waitlist controls may lead to an overestimation of treatment effects due to the possibility of a nocebo effect in the control group [208]. In the feasibility trial of DDP for people with a diagnosis of borderline personality disorder, there was evidence of a reduction in self-reported self-harm in the intervention group but not the control group. Retention of participants at 12 months was also relatively high. The two additional studies that were published after conducting this systematic review (CBT-RP and ASSIP) also reported encouraging findings.

In addition to the small number of identified trials measuring suicide- or self-harm-related outcomes as the primary outcome, several trials were found that investigated these as secondary or supplementary outcomes [209-218] (Appendix E). None of these studies required participants to have had previous suicide-related thoughts or behaviour. In keeping with the studies reviewed here, overall, these studies also found little evidence for treatment effects, and they were frequently subject to similar limitations to the studies included in this review.

3.5.1 Strengths and limitations

To my knowledge, at the time of publication of the paper related to this chapter, this was the first systematic review evaluating interventions aimed at reducing self-harm or preventing suicide among people with substance use problems. This thesis chapter provides an alternative, pre-dominantly narrative, approach to the presentation of the data, which provides more in-depth information on each study. I followed standardised procedures for the assessment of bias and followed PRISMA guidelines in reporting my findings.

There are also a number of limitations to consider. The review identified only a small number of trials, all with limited sample sizes. In the brief intervention trial using FRAMES, Crawford et al. (2014) estimated that a sample size of 1,400 would have been required to detect a 30% reduction in self-harm repetition at six months with 80% power and 5% level of statistical significance [201]. The combined total of all participants across all six trials (n=468) in my review was approximately a third of this number required to detect a potentially clinically important effect. However, sample size requirements are affected by how the self-harm outcome is measured. Crawford et al. (2014) investigated the *proportion of people* who re-attended the Emergency Department based on hospital records at six months [201]. Whereas analysis of the *frequency of repeat self-harm*, and identification of these episodes using a multi-source method that includes self-reported episodes [206], may increase the repetition rate and reduce the sample size requirement. For example, although there are other important differences to consider, a power calculation for a trial of DBT for adolescents with recent repeat self-harm and features of borderline personality disorder, indicated that only 80 participants were required in total to demonstrate a difference in the repetition rate of self-harm [219]. Nonetheless, the patient group in the study had an exceptionally high risk of repeat self-harm; the sample size calculation was based on an observed repetition rate of 83% in the control arm, compared to a repetition rate of 14% in the control arm of Crawford et al. (2014) [201].

In addition to concerns about power, there were concerns of bias for all included studies. In particular, I was unable to obtain pre-specified protocols for all but one of the studies.

The trials identified were diverse in terms of population, interventions, comparison groups, and outcomes, which limited the inferences that could be made by comparing them. Furthermore, the review may have been affected by publication bias; some smaller studies with weaker or negative effect sizes may not have been published.

The identification of new relevant papers outside of my database searches highlighted two important limitations of my search strategy. First, a vast range of terms is used to describe substance use problems, many of which I have only become aware of during the course of this PhD. Due to the non-specific nature of many of these terms, the search strategy involved a trade-off between sensitivity and specificity. A greater reliance on subject heading terms may be helpful in minimising this trade-off in future reviews. Second, filters used to identify randomised controlled trials are generally designed to identify high quality scientifically strong clinical studies [220]. As much of the research within this field is in the form of pilot trials, other small but relevant studies may have been missed. Nonetheless, no additional studies meeting the inclusion criteria of this review were identified by two subsequent systematic reviews of interventions for alcohol use problems and suicide-related thoughts or behaviour [221, 222]. The difficulty in ensuring an exhaustive search strategy was also evident in these reviews; both reviews identified relevant studies outside of their database searches.

In the presented forest plot, results relating to suicidal ideation and self-harm were combined. However, there is growing evidence to support the ideation-to-action framework, in which there are distinct explanatory factors for the emergence of suicidal ideation and the transition from ideation to suicidal behaviour [223]. Combining the two outcomes could, therefore, mask important differences between the effects of interventions on each. In

particular, there is preliminary evidence that alcohol may have a role in facilitating the transition from suicidal thoughts to behaviour [224], which may result in interventions having a greater impact on suicidal behaviour than suicidal ideation.

Due to the relative rarity of suicide and the large sample sizes required to demonstrate the effectiveness of suicide prevention interventions, many relevant studies may have avoided including suicide as a primary outcome. For example, an uncontrolled pilot study, which is soon to be followed by an RCT, of a suicide prevention module for patients attending a group-based addiction treatment, measured knowledge and attitudes towards suicide prevention [225, 226]. Studies may also have avoided the investigation of self-harm (e.g., frequency of self-reports or hospital presentations) as a primary outcome as its validity has been challenged by people with lived experience; outcomes that investigate engagement with self-care, social life, and services are considered to be more meaningful [227]. Consequently, restricting this review to studies with suicidal thoughts and behaviour as a primary outcome may have excluded valuable findings from secondary or sub-group analyses of trials of interventions aimed at achieving broader change. Additionally, the restriction on study design might have resulted in the exclusion of useful service evaluations and observational studies describing relevant "real world" interventions. Nonetheless, the inclusion of any type of intervention for people of all ages, irrespective of whether they had a history of self-harm, meant that five out of the six studies included had not been included in the comprehensive Cochrane systematic reviews of interventions for self-harm [183, 184].

3.5.2 Findings in the context of the wider literature

A broad review of suicide prevention interventions reported that evidence is limited for interventions other than means restriction, schools-based awareness programmes, and treatment of psychiatric conditions [188]. Two Cochrane systematic reviews of psychosocial and pharmacological interventions for self-harm (irrespective of intent), which were restricted to

adults, were also limited in their findings [183, 184]. The review of psychosocial interventions found some low-quality evidence indicating a reduction in the repetition of self-harm following CBT-based interventions, in keeping with the CBT trial for adolescents in this review but not the CBT trial for adults [198, 200]. Evidence for a range of other approaches was inconclusive. The review of pharmacological interventions included only seven trials of 574 patients in total, and the quality of the evidence was judged to be low or very low, preventing conclusions from being drawn. Many of the studies included in these reviews excluded people with substance use problems. Systematic reviews on dual diagnosis have not explored suicide- or self-harm related outcomes [181, 189].

Since the publication of my review, two further reviews have been published investigating interventions to reduce suicidal behaviour amongst people with alcohol use problems [221, 222]. These have differed from mine in their inclusion criteria; therefore, our reviews have included some but not all of the same studies. Both reviews included studies in which suicidal behaviour was not the primary outcome, as well as studies in which only some participants had alcohol use problems (based on their definitions). Witt et al. (2021) specifically reviewed psychological interventions aimed at reducing alcohol use and did not restrict their inclusion criteria to RCTs, while Hurzeler et al. (2021) focused their review on psychosocial outpatient interventions.

Witt et al. (2021) identified eleven studies, of which nine included quantitative data. They performed a series of meta-analyses and found, in a post-hoc analysis of pooled data from end of follow-up assessments, some evidence of a reduction in self-harm and suicide attempts (OR: 0.57; 95% CI 0.33, 0.97 based on six studies with 491 participants). However, no evidence of a reduction in self-harm and suicide attempt was found in pre-specified analyses at 3, 6, 12 months follow-up, and post-intervention. There was also no evidence of a reduction in suicidal ideation or suicides, including in the post-hoc analyses of pooled data from end of follow-up assessments.

Hurzeler et al. (2021) identified six studies representing 400 participants. They performed a narrative review and described the potential of several of the interventions highlighted in this review [198, 202, 204]. However, in keeping with this review, Hurzeler et al. (2021) concluded that large high-quality RCTs were lacking, and there was no strong evidence of an effective intervention.

A rapid meta-review with broad inclusion criteria, which asked the question "*What alcohol and other drug interventions have been shown to be effective in reducing suicidal thoughts and behaviours?*", identified evidence regarding a wider range of interventions, including government-led policies and community-based programs alongside my own review of mainly psychosocial interventions [228].

3.6 Conclusion

Evidence is currently lacking regarding effective interventions to prevent suicide and reduce self-harm among people with substance use problems. Given the importance of suicide and self-harm in this population, there remains a pressing need for adequately powered and robustly conducted trials investigating the effectiveness of new and existing interventions. However, this appears to be an emerging research area, and several interventions have shown promise in feasibility trials. Although the small number of highly diverse trials made it difficult to derive overarching lessons, a notable shared feature of the promising interventions was their integration of care for suicide-related behaviours alongside substance use problems. This observation informed the intervention development described in the next chapter.

Chapter 4. Development of a brief intervention for self-harm and concurrent substance use problems

4.1 Overview

So far in this thesis, I have identified that the first four weeks after stopping OAT is a critical period of elevated suicide risk. I have also found a lack of evidence from large-scale randomised controlled trials for suicide prevention interventions for people with substance use problems. In this chapter, I describe a Delphi method study to develop a suicide prevention intervention for people with substance use problems during another period of elevated suicide risk - immediately after a hospital presentation with self-harm. A research paper summarising findings in this chapter is currently in submission for publication.

4.2 Introduction

The presentation of patients to hospital with self-harm represents a key opportunity for suicide prevention. Almost 1-in-5 people presenting to hospital with self-harm go on to repeat self-harm within the following year, 1-in-25 die by suicide within the next five years [37], and the highest incidence of suicide occurs in the first month after presentation [229]. Hospital presentation can also be a "teachable moment", during which individuals may have increased motivation for behavioural change, and low-intensity interventions may be more effective [230].

There is growing evidence to support the use of active contact and follow-up (including brief interventions) to prevent suicide amongst people presenting to hospital with an identified suicide risk [231-238]. The effectiveness of these types of interventions for people with substance use problems is, however, currently unknown. There may also be scope for improving effectiveness with adaptation to meet the additional substance use-related needs of this population.

Currently, in England, people with substance use problems often face barriers in accessing care to meet their needs [109, 113], despite their increased risk of suicide compared with the general population. One major factor contributing to inadequate access is the separate commissioning of NHS mental health services and drug and alcohol services. Until 2012 drug and alcohol services were jointly commissioned by the NHS and local authorities; since 2012 they have become solely commissioned by local authorities [239]. Other factors contributing to inadequate access include: insufficient resources to accommodate complex needs; differing expectations between services about the level of responsibility that service users should be taking for their own safety; disagreements about whether self-harm/mental health or substance use is the primary problem; and a lack of expertise and confidence among staff in working with both self-harm and substance use [113, 240].

More broadly, there appears to be a general perception within the research literature and health services of poor engagement and treatment outcomes amongst this population. Rather than adaptations being made to meet their needs and increase engagement, people with substance use problems are often excluded from research and services. This creates a vicious cycle that limits opportunities to test the effectiveness of new interventions (Figure 4.1). Research focused on improving the evidence base of effective interventions specifically for this population offers a chance to break this cycle.

Over the last forty years, there has been a move towards evaluating behavioural interventions with similar standards of methodological rigour as pharmacotherapies. Similar to the stages of RCTs for pharmacological treatments, a Stage Model of Behavioural Therapies research has been described in which: Stage 1a involves developing a therapy and a manual, and testing these on an open series of patients; Stage 1b involves conducting a pilot trial to test acceptability and feasibility; Stage 2 involves conducting an RCT to assess efficacy, and exploring mechanisms of action; Stage 3 involves assessing the generalisability of interventions with demonstrated efficacy in multiple trials [241]. This chapter describes research undertaken within Stage 1a to

inform the development of a therapy manual. Guidance suggests that Stage 1a work is typically based on clinical judgement [241]. However, the inclusion of people with lived experience in intervention development can optimise the process and help ensure that an intervention meets the needs and preferences of service users [201, 206, 242].

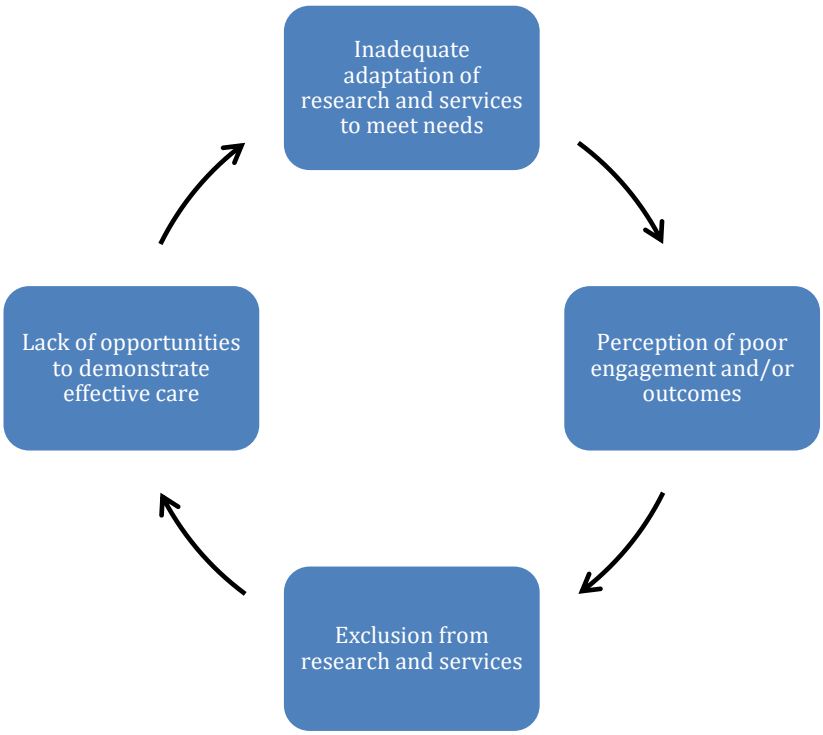


Figure 4.1: Cycle of exclusion

The aim of this study was to combine current research evidence with the expertise of people with occupational or lived experience (PWOE and PWLE) to inform: 1) the core components of a new brief psychosocial intervention for people presenting to hospital with self-harm and substance use problems; 2) the design of a future randomised controlled trial of the new intervention.

4.3 Methods

4.3.1 Consensus methods

Consensus methods are used in health research to synthesise information where statistical methods such as meta-analysis are of limited value due to a

paucity of data, and there are a wider variety of data sources to consider, including expert opinion [243]. Three of the most established methods are the consensus development conference, the Delphi method, and the nominal group technique [243]. The former is resource-intensive and, therefore, was not considered an option.

The nominal group technique involves a face-to-face meeting with a small group of experts (usually up to 12) [243], whilst the Delphi method involves the distribution of surveys, often to a larger number of participants. As a broad range of health services and professionals are often involved in the acute care of people with substance use problems who present to hospital with self-harm, the Delphi method was used in this study to allow as many of these perspectives to be included as possible. The method also allowed greater flexibility in data collection as participants could complete surveys at their convenience. Additionally, it afforded participants a degree of anonymity when expressing their views, which was particularly important given the inclusion of both PWOE and PWLE.

4.3.2 Delphi method

The Delphi method was originally developed and used in the USA in the 1950s by the RAND Corporation to maximise reliability in expert consensus in estimations relating to atomic bombs [244]. It is an iterative multi-round process during which experts individually rate and provide comments on a set of survey items based on their level of agreement [245, 246]. After each round, a summary of ratings and comments is fed back to respondents, who then complete the next round by re-rating the items.

Over time, the method has evolved to include a range of subtypes, which vary in aim, target participants, administration, and the number of rounds [243, 247]. The classical subtype involves an open, qualitative first round followed by postal surveys. The modified subtype can be distributed by other means and begins with pre-selected items that have been informed by a variety of

sources, such as a systematic review or focus groups [247]. In this study, the modified Delphi method was used; the survey was informed by: the systematic review reported in Chapter 3, the broader literature on self-harm risk and interventions in the general population [183, 232-236], telephone discussions with individuals with occupational and lived experience, and clinical judgement (Figure 4.2).

Figure 4.2: Flowchart of modified Delphi method stages in this study

There is an ongoing debate about how best to measure the methodological rigour of studies using the Delphi method [247]. Comparability of studies is hindered by variation in most aspects of the study design, including the participant recruitment method, criteria for consensus, and the methods used to develop surveys and provide feedback. Whilst some view the lack of standardisation of the method as a weakness, others argue that the flexibility that it allows is a strength [247].

There are also differences of opinion about the methodological paradigm (positivist or interpretive) that best fits the Delphi method and, therefore, the quality standards by which studies should be evaluated [247]. Within each of these paradigms, numerous strategies have been suggested to assess and improve methodological rigour, some of which conflict with each other [247]. For example, there are differing opinions about whether increasing the size of a panel leads to an increase or decrease in reliability [247].

In the absence of a clear consensus on quality standards for Delphi studies, I focus on acknowledging the limits of expert opinion as a form of evidence and emphasising the importance of triangulating findings with existing literature and validating them through further research.

4.3.3 Participant (panel) recruitment

Two panels were recruited. The first panel included people with occupational experience (PWOE) who had clinical, research, or service provision experience relating to suicide and/or substance use problems. The second panel included people with any lived experience (PWLE) of substance use problems and suicidal thoughts, attempts, or self-harm.

The same recruitment strategy (described below) was used to recruit to the initial telephone discussions and the survey. All participants who completed a telephone discussion (PWOE: n=10, PWLE: n=7) were also invited to complete the survey. Eight PWOE and six PWLE who had taken part in the telephone discussions also completed the survey. Once sufficient information had been obtained from the telephone discussions to inform the survey, additional participants were invited to take part in the Delphi survey alone.

Decisions about how many individuals to include in a Delphi survey involve balancing the need to achieve a diverse sample, with representation from key stakeholder groups, with the challenges of synthesising a greater quantity of data [245]. Additionally, in small samples, each individual response makes a greater contribution towards an overall percentage agreement threshold, therefore making results less stable between rounds. Where studies have investigated the stability of results, this has been demonstrated with sample sizes of approximately 20 [248]. Although it is unknown whether these findings are generalisable, in this study enough participants were recruited to try to ensure that at least 20 participated in all three rounds (i.e., accounting for likely attrition between rounds).

Non-random sampling techniques such as purposive and snowball sampling techniques are recommended for use in Delphi studies to identify experts with relevant experience [248]. In this study, PWOE were recruited using a purposive sampling strategy; they were either identified by the research team (My colleague (R.C.), my supervisor (P.M.), and I) or by participants who had

already been recruited. Representation was sought from the following services: Liaison Psychiatry (the hospital-based subspecialty for patients with co-morbid mental and physical health needs), drug and alcohol services, Intensive or Crisis teams, and Primary Care. A selected sample of leading academic experts in the fields of suicide or substance use research were also invited to participate. In total, 30 PWOE were invited to take part in the survey: 27 were based in the UK, and three were based internationally (USA: n=2, Australia: n=1). The international participants were invited because they had relevant academic expertise (based on their publication history).

PWLE were recruited using a convenience and snowball sampling strategy. Members of a Patient and Public Involvement (PPI) group, who had previously been recruited to input into this PhD, informed their contacts about the study. Additionally, a post was displayed on UK-based Facebook groups for people with addictions who are in recovery (Appendix G). These posts stated the inclusion criteria: participants had to be aged 18 years or over and have lived experience of substance addictions and suicidal thoughts, suicide attempts or self-harm. Sixteen PWLE expressed an interest in participating during the specified recruitment period. Before recruitment, potential participants were contacted by phone by a member of the research team to clarify the aims of the study and inclusion criteria. Lived experience participants were reimbursed £25 per hour for the telephone discussions that informed the survey, and £25 following completion of the final survey round.

4.3.4 Survey development

As described earlier, the development of the survey was partly informed by telephone discussions with PWLE and PWOE. The telephone discussions were conducted by my colleague (R.C.) and me. They were based on a pre-specified topic guide (Appendix H) that focused on the following key aspects of the intervention: the inclusion criteria, delivery (including frequency, timing, location, and staff), content, suicide risk management, recruitment, engagement, and retention, and the design of a future randomised controlled

trial. The discussions were conducted between May-June 2020 and lasted approximately 30-60 minutes. R.C., P.M., and I identified the key themes from transcriptions of the discussions.

The Round 1 Delphi survey consisted of 34-items relating to ten question stems (Appendix I). The questions were categorised into five broader domains. Four domains related directly to the intervention: timing, content, delivery, and ongoing engagement. One domain focused on outcomes for a potential trial. The Round 1 survey was piloted on an independent researcher and by a member of the PPI group who had relevant lived experience. Their feedback was incorporated into its development.

In Rounds 1 and 2, participants were asked to rate each item using a 5-point Likert scale (*strongly agree, agree, unsure, disagree, strongly disagree)* to indicate their opinion as to whether the item should be included in the intervention. A section inviting additional comments from participants was also included at the end of each survey domain in each round. In Round 3, to optimise engagement with the survey by minimising repetition and the time required for completion, the Likert scale was replaced with simplified "Yes/No" options to indicate participants' views as to whether the remaining items should be included in the intervention. Figure 4.3 shows a screenshot of one survey question.

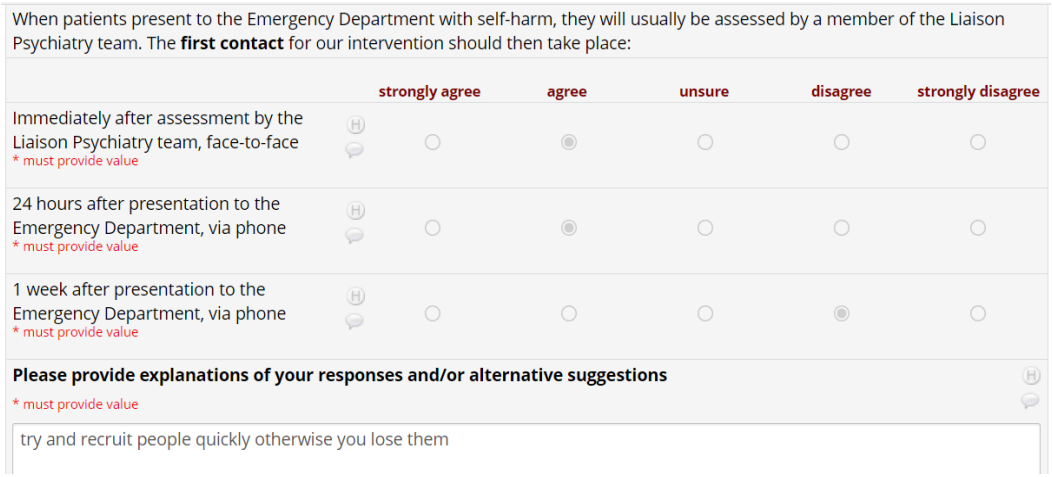


Figure 4.3: Screenshot of example Round 1 survey question

4.3.5 Rationale for pre-determined core components

Several of the core components of the intervention were determined during the information gathering stage of the Delphi method, in advance of the survey. These components were informed by the existing research literature [179, 186, 232-236], stakeholder telephone discussions, and clinical judgement. Where clinical judgement was used, this primarily related to ensuring that the intervention would be feasible to implement within a large-scale randomised controlled trial and within NHS clinical services.

The first pre-determined core component was the eligibility criteria. The proposed intervention would be for adults presenting to the hospital with self-harm and substance use problems; there would not be restrictions on characteristics such as the quantity and frequency of substance use and co-morbid psychiatric diagnoses. Although this would result in considerable heterogeneity within the sample, this is in keeping with standard practice in pragmatic RCTs and enhances generalisability [249].

Other pre-determined core components were the duration and frequency of the intervention and the medium of contact. The intervention would augment standard care and consist of weekly telephone contact during the first four weeks following hospital presentation.

The duration and frequency of the intervention were based on: 1) evidence of an exceptionally high risk of suicide during the first month after hospital presentation [229]; 2) Stanley et al.'s (2018) landmark observational study on a safety planning intervention that included weekly follow-up. In this study, a 45% reduction in suicidal behaviours was observed amongst veterans presenting to hospitals in the USA with a suicide-related concern over six months of follow-up [232]; 3) O'Connor et al.'s pilot of a similar intervention in the UK, which was broadly considered to be both acceptable and feasible (based on personal communication with the authors) [233].

The use of phone calls as the medium of contact in this study was based on: 1) concerns about retention of patients with substance use problems if required to travel regularly to appointments during periods of crisis; 2) shifts to remote working during the COVID-19 pandemic; 3) promising results from several studies of contact-based interventions via telephone for people identified to be at risk of suicide during hospital presentations [232, 233, 236, 238]. Web-based technology was also considered but ruled out due to concerns about digital exclusion, with many of the individuals in the population of interest lacking reliable access to smartphones, a tablet, or a computer. Letters and postcards were ruled out due to limited evidence of their effectiveness in reducing self-harm in Western contexts [183].

4.3.6 Rationale for survey items

The Delphi survey items (Appendix I) were focused on areas of uncertainty regarding the intervention and a future randomised controlled trial.

4.3.6.1 Intervention timing

In studies in the general population, suicide prevention interventions that commence during a patient's presentation to clinical services appear to be more effective than those solely delivered post-discharge [237, 250, 251]. Such an approach may not, however, be acceptable or feasible where people are under the influence of substances when presenting to services. The survey, therefore, asked about preferred timings of the first, second, and subsequent contact.

Previous contact-based interventions have incorporated additional forms of contact, such as postcards and letters [183, 251]. Personalised reminder text messages in between phone calls were considered to be most feasible, but due to the possibility of confidentiality concerns, these were included as survey items for consideration.

4.3.6.2 Intervention content

The proposed options for the content of the intervention included techniques commonly used in clinical services for people with substance use problems and/or self-harm. Some of these techniques are recognised features of existing brief interventions and psychological treatments, such as safety planning [252], motivational interviewing [253], dialectical behavioural therapy [254], cognitive behavioural therapy [255], and Self-Management and Recovery Training (SMART) Recovery [256]. Within the Delphi survey, the use of these techniques was specified in relation to both substance use and self-harm or mental health.

4.3.6.3 Intervention delivery

A choice of delivery of the intervention by Liaison Psychiatry practitioners or a researcher was offered. Although the involvement of peer support workers and the voluntary sector was considered, the survey options were limited by funding and logistic arrangements for the study.

4.3.6.4 Ongoing engagement

Maintaining engagement is frequently challenging among people at risk of suicide and people with substance use problems [250]. In several of the RCTs for people with co-morbid suicide risk and substance use problems described in Chapter 3, lack of engagement was a recognised limitation that affected interpretation of the study findings. Motivational interviewing has previously been suggested as an approach to increase engagement in psychiatric care among people at risk of suicide [250]. Additionally, there is a strong evidence base indicating that rewarding people with substance use problems for meeting therapeutic goals (termed "contingency management") is effective in increasing engagement, based on the principles of operant conditioning [257, 258]. This approach has, however, not previously been used within suicide

prevention interventions. Gift voucher rewards for participating in the intervention were, therefore, proposed in this study.

4.3.6.5 Outcomes for a future trial

Finally, the survey included a range of options for potential outcomes for a future RCT. This was included because qualitative research has challenged the meaningfulness of current outcomes measured in trials of interventions for people who self-harm, and highlighted the importance of ascertaining which outcomes matter to those at whom an intervention is aimed [227].

4.3.7 Data collection

The three rounds of the Delphi survey were conducted online over an 8-week period (July-August 2020). The number of rounds, plan for providing feedback between rounds and criteria for including and excluding items were decided a priori and were informed by the literature [245, 259].

Round 1 of the survey was sent to all 46 participants (PWOE: n=30, PWLE: n=16) described above, whilst subsequent surveys were only sent to participants who had completed the previous round. In Rounds 2 and 3, when asking participants to re-rate items for which consensus had not been reached, participants were provided with the average percentage agreement from the previous round by panel, stratified by group (PWLE/PWOE). Participants were also provided with a concise summary of the relevant free-text answers from the previous round, and they were able to view their original responses to each survey item before re-rating. An example of the feedback to a Round 2 question is provided in Figure 4.4.

The Delphi survey was managed and administered online using REDCap (Research Electronic Data Capture) 9.5.23 tools [260, 261], hosted by the University of Bristol. Anonymous identification numbers were assigned to each participant by the REDCap system.

The second contact will be by phone. This should take place:	Lived experience	Occupational experience	Comments
24 hours after first contact	73% agreed	67% agreed	Some respondents thought that 24 hours may be too soon for second contact Some thought a week may be too long for second contact Some thought that flexibility according to individual needs/circumstances may be useful
72 hours after first contact	60% agreed	81% agreed	
One week after first contact	33% agreed	57% agreed	

Figure 4.4: Example of summary results provided in Round 2

4.3.8 Data analysis

Quantitative survey data were analysed by calculating the pooled percentage of agreement for each item, weighted equally across both groups (PWLE/PWOE). The cut-off used to define agreement was the presence of any agreement; therefore, the responses "agree" and "strongly agree" were combined. Similarly, the cut-off used to define disagreement was the presence of any disagreement; therefore, the responses "disagree" and "strongly disagree" were combined.

A wide range of definitions has been used for consensus in Delphi studies [262]. Most commonly, a consensus is determined by percentage agreement, and the threshold has ranged from 50% to 97% [262]. In this study, an intermediate threshold, which has been used in previous research, was adopted a priori [245]; items with a pooled agreement rate of 80% or more were included, items with a pooled disagreement rate of 80% or more excluded, and the remaining items were carried over into the next survey for re-rating.

Some items provided distinct options relating to the same question; therefore, when one was accepted, the others became redundant and were discarded. An example of this was the options for the timing of the first contact. After inclusion of the item indicating that this should take place at the time of a first

presentation, the items indicating that it should take place 24 hours or one week after a presentation were discarded.

Free-text comments provided by participants were separated into key themes. R.C., P.M., and I discussed the themes at the end of each survey round to decide whether any new survey items needed to be added to subsequent rounds. As a result of this process, an additional item about the need for greater flexibility in the timing of the intervention was added in Round 2.

Where consensus was not obtained on items after Round 3, a decision was made on their inclusion/exclusion by the study advisory group (my colleagues, R.C., P.M., L.B., K.B., N.M., and I). This approach was selected because we were able to consider the opinions of both PWLE and PWOE from the Delphi, previously published literature, and potential constraints arising in the planning of the subsequent feasibility study.

4.3.9 Ethical approval

This study received ethical approval from the NHS South West - Frenchay Research Ethics Committee (Reference 19/SW/0220).

4.3.10 Changes due to the COVID-19 pandemic

The COVID-19 pandemic affected the plans for recruitment and data collection in this study. Ethical approval had already been granted, so amendments were submitted regarding the necessary changes.

PWLE were initially due to be recruited by displaying recruitment posters in places that they were likely to attend, such as drug and alcohol services and venues where mutual aid meetings take place. Due to the national lockdown that commenced in March 2020, this became unviable. Alternative recruitment strategies were discussed with the PPI group, who suggested the use of social media forums.

To inform the survey development, two in-person workshops were planned, one for PWOE and another for PWLE. When face-to-face meetings became unfeasible, online group workshops and 1:1 telephone discussions were both considered as alternative options. As PWOE were extremely busy due to the unprecedented demands on health services due to the pandemic, it was considered more appropriate to gather their opinion through 1:1 discussions organised at their convenience. At the time, teleconferencing was not yet widely used, and there were concerns about maintaining confidentiality during online group workshops, as it would be possible for others in an individual's household to be present or to hear confidential discussions. As such, it was decided that all information would be collected using 1:1 telephone discussions.

4.4 Results

4.4.1 Participants

The Round 1 survey was completed by 21 PWOE and 15 PWLE (Table 4.1). Of those who completed Round 1, 15 (71%) PWOE and 14 (93%) PWLE completed all three surveys. In both groups, respondents were predominantly female (PWOE: n=13; PWLE: n=9). Of the 21 PWOE who completed Round 1, their main area of expertise was mental health/suicide prevention (n=11), addictions (n=9), or both (n=1). Their professional backgrounds included: clinical psychology/psychiatry (n=10), academia (n=9), nursing (n=5), managerial (n=2), general practice (n=1). The item ratings in the Round 1 survey were similar for participants who did and did not complete all three rounds.

Table 4.1: Panel responses by Delphi round

	Round 1 (N)	Round 2 (N)	Round 3 (N)	Completion of all 3 rounds (%)
Occupational experience participants	21	17	15	71%
Lived experience participants	15	14	14	93%

4.4.2 Summary of Rounds

The Round 1 survey included 34 items. After the three rounds, there was a consensus on 22 items (Table 4.2). The number of items included, excluded, added, and discarded after each round are outlined in Figure 4.5. No items reached the threshold level of disagreement to be excluded. A consensus was not obtained for five items relating to two domains ('intervention content' and 'ongoing engagement'). A comprehensive table of all items that were included in the survey and the percentages of agreement can be found in the Appendix J.

Table 4.2: Summary of survey items for which consensus was obtained

Section	Question stem	Item	Survey Round
Intervention timing	*The **first contact** for the intervention should take place:*	Immediately after assessment by the Liaison Psychiatry team, face-to-face	1
	*The **second contact** will be by phone. This should take place:*	24-72 hours after first contact negotiated between the patient and person delivering the intervention	2
	***Subsequent contact** should take place:*	Weekly phone calls for one month plus weekly personalised reminder texts in between phone calls	2
Content of the intervention	*The intervention should involve (Understanding the situation):*	Exploring the patient's views about underlying reasons for substance use & self-harm	1
		Exploring the patient's understanding of the relationship between substance use & mental health	1
		Providing advice on the relationship between substance use & mental health	1
	The intervention should involve (Building motivation for behavioural change):	Asking the patient to discuss the pros and cons of reducing their use of substances and self-harm behaviours	1
		Eliciting the patient's thoughts and feelings about the function of substance use & self-harm in their life	1
	The intervention should involve (Identifying and coping with triggers and urges):	Asking the patient to identify triggers for substance use & self-harm	1
		Encouraging the patient to record and discuss examples of antecedent/triggers, behaviour, consequence in relation to substance use	1
		Encouraging the patient to record and discuss examples of antecedent/triggers, behaviour, consequence in relation to self-harm	1
		Exploring alternative coping strategies and distraction techniques for managing urges to use substance & self-harm	1
	The intervention should involve (Preparing for change):	Jointly developing a safety plan	1
		Monitoring the patient's progress in engaging with other community resources e.g., Alcoholics Anonymous or Samaritans	1
		Jointly developing a plan for change with an explicit focus on both substance use & self-harm	1

Section	Question stem	Item	Survey Round
Intervention delivery	*The intervention should be delivered by the following staff:*	First session and follow-up phone calls by Liaison Psychiatry nurses	3
Outcomes for a trial	*These outcomes should be measured when testing the effectiveness of the intervention:*	Hospital readmissions with self-harm	1
		Self-reported suicidal thoughts, self-harm, and suicide attempts	1
		Self-reported use of substances	3
		Self-reported mental distress	1
		The patient's views regarding whether the intervention was helpful in their recovery	1
		The patient's nominated outcome with regards to goals for substance use +/- self-harm	3

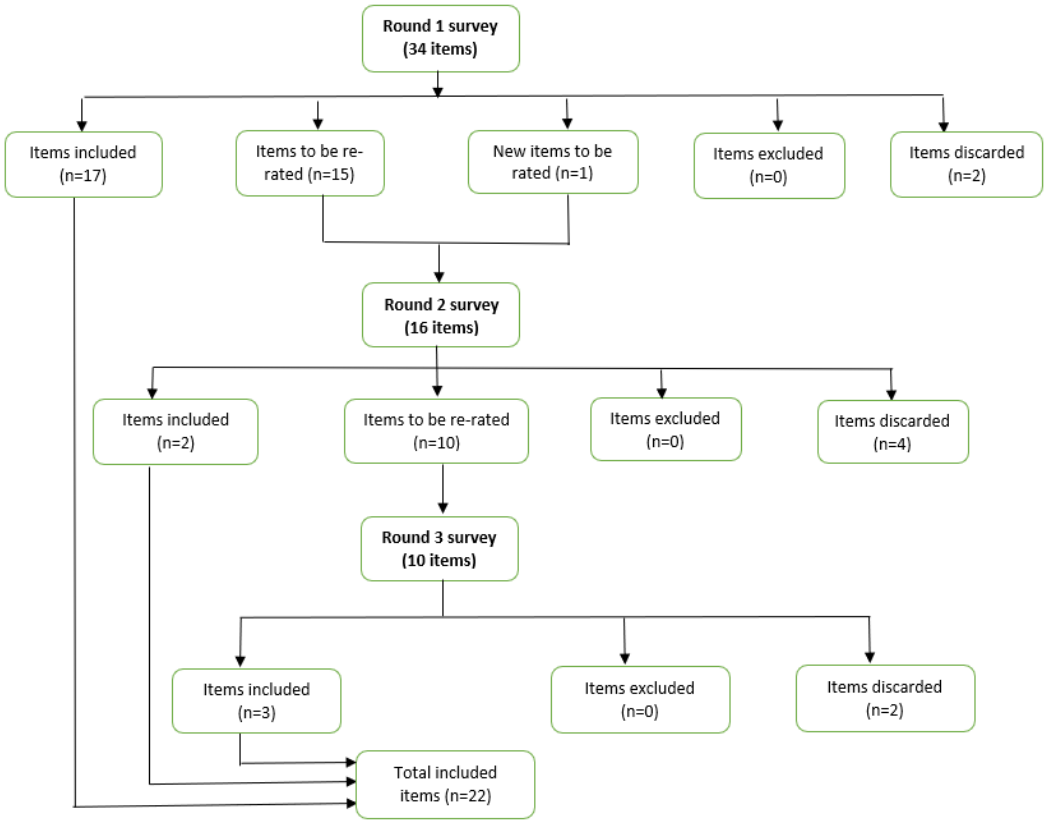


Figure 4.5: Flowchart of survey item outcomes by Delphi round
(Included: ≥80% pooled agreement rate; Excluded: ≥80% pooled disagreement rate; Discarded: item became redundant based on the inclusion of another item [see Methods for further explanation])

4.4.3 Results by domain

4.4.3.1 Intervention timing

Consensus on the timing of the first contact for the intervention was reached in Round 1. Participants agreed that the first contact should take place face-to-face, immediately after a psychosocial assessment has been completed by the Liaison Psychiatry team (PWLE=87%; PWOE=76%; pooled agreement=81%).

A consensus about the timing of the second and subsequent contacts was reached in Round 2. In Round 1, participants provided free-text suggestions that flexibility according to individual needs/circumstances may be useful in relation to the timing of the second contact. An additional item was therefore added, which stated that the second contact would take place "24-72 hours after first contact negotiated between the patient and person delivering the intervention". In Round 2, the percentage pooled agreement for this item was 96% (PWLE=93%; PWOE=100%). It was also agreed that subsequent contact would involve weekly phone calls for one month, as well as weekly personalised reminder texts in between phone calls ((PWLE=79%; PWOE=88%; pooled agreement=83%).

4.4.3.2 Intervention content

A consensus was reached on all but two of the fourteen items relating to the intervention content in Round 1. Items were endorsed in each of the following categories: 1) understanding the situation; 2) building motivation for behavioural change; 3) identifying and coping with triggers and urges; 4) preparing for change. The endorsed items described intervention content that addressed both self-harm and substance use problems. They referred to techniques used within existing NHS mental health and drug and alcohol services, many of which are also features of existing brief intervention and psychological treatments.

The two items for which consensus was not reached related to encouraging patients to record either the quantity of substances used or the number of episodes of self-harm in a diary to increase awareness. In all three rounds, there were higher percentages of agreement for these items amongst PWOE compared with PWLE. In round 3, 80% of PWOE agreed with the items, compared to 64% and 57% of PWLE for items relating to substances and self-harm, respectively. Concerns raised by some PWLE about the use of diaries included their perceived lack of reliability, the possibility that the recordings might exacerbate feelings of guilt and shame and thereby increase the frequency of self-harm or substance use, and the perception of this being a purely data collection exercise. Many PWOE, however, believed that self-monitoring is an important facet of behaviour change and that diaries can serve a useful purpose in informing decisions about future care. In the absence of clear consensus and inclusion of many other items relating to content, the findings were reviewed by the study advisory group, and it was agreed that these items would not be included in the intervention.

4.4.3.3 Intervention delivery

Participants were given the choice of a researcher or Liaison Psychiatry practitioner delivering all, or part, of the intervention. Consensus on items relating to this choice was reached in Round 3. In Round 1, the item with the highest levels of agreement stated that the whole intervention should be delivered by Liaison Psychiatry practitioners (PWLE=80%; PWOE=62%; pooled agreement rate=71%). Participants who agreed with this item cited the expertise of Liaison Psychiatry practitioners, particularly in working with people at risk of suicide. Some PWLE raised concerns about potentially feeling "experimented on" if the intervention were to be delivered by a researcher. In contrast, people who agreed that it should be delivered by a researcher highlighted their ability to maintain consistency in its delivery. By Round 3, 93% of PWLE and 87% of PWOE agreed that the whole intervention should be delivered by Liaison Psychiatry practitioners (Pooled agreement=90%).

4.4.3.4 Ongoing engagement

All three items included in this domain related to the use of gift vouchers to reward patients for taking part in treatment (i.e., a form of contingency management). These items did not achieve consensus over the three rounds. Many participants thought that, if adopted, this might be the only motivation for people to engage in the intervention. However, they differed in opinion about whether patients might gain from the intervention if not fully committed and intrinsically motivated to change. Some PWLE stated that the voucher would make them feel valued, whilst some participants highlighted challenges with the practicalities of providing vouchers following remote contact. The item with the highest support stated that gift vouchers for the same amount should be provided at the end of each session (Round 3: PWLE=71%; PWOE=60% pooled agreement=66%). In comparison, 29% of PWLE and 20% of PWOE agreed that no gift vouchers should be given (pooled agreement=24%). These findings were reviewed by the study advisory group. Although based on operant conditioning principles, rewards would ideally be provided immediately after each phone call, due to cost constraints, it was decided that patients would instead receive a gift voucher upon completion of their final follow-up telephone session.

4.4.3.5 Outcomes for a future trial

A consensus was reached on all proposed outcomes for a future randomised controlled trial. All but two items were agreed upon within Round 1. Self-reported substance use, and the patient's nominated outcome with regards to goals for drinking +/- self-harm, were agreed upon in Round 3.

As with the intervention content item about recording substance use in a diary, PWOE were consistently more in favour of including self-reported substance use as an outcome compared with PWLE. Again, PWLE raised concerns about the reliability of the information and stated a preference for a more objective measure. Nonetheless, by Round 3, the pooled percentage agreement in

relation to including self-reported substance use as an outcome was 82% (PWLE=71%; PWOE=93%).

The patient's nominated outcome was viewed positively for being patient-centred. However, some highlighted that goal-setting takes time, goals can change, and a patient-centred measure may be challenging to analyse. By Round 3, the pooled percentage agreement was 82% (PWLE=71%; PWOE=93%).

4.5 Discussion

This Delphi method study aimed to combine current research evidence with the expertise of people with occupational or lived experience (PWOE and PWLE) to inform: 1) the core components of a new brief psychosocial intervention for people presenting to hospital with self-harm and substance use problems; 2) the design of a future randomised controlled trial of the new intervention. The developed intervention consists of weekly follow-up phone calls for up to a month, delivered by Liaison Psychiatry practitioners, in which both self-harm and substance use are explored, and patients are supported in accessing community services. Further details can be found in Figure 4.6.

Inclusion criteria: adults who present to hospital with self-harm and concurrent substance use problems

First contact: face-to-face in the emergency department immediately after a psychosocial assessment

Second contact: telephone call 24-72 hours later

Subsequent contact: weekly telephone calls for up to one month after hospital presentation

Other features: delivery by a Liaison Psychiatry practitioner, personalised reminder texts between sessions, provision of a gift voucher after completion of the intervention

Intervention content:

Understanding the situation

1) Exploring the patient's views about underlying reasons for substance use & self-harm
2) Exploring the patient's understanding of the relationship between substance use & mental health
3) Providing advice on the relationship between substance use & mental health

Building motivation

4) Asking the patient to describe pros and cons of reducing their use of substances & self-harm
5) Eliciting the patient's thoughts and feelings about the function of substance use & self-harm in their life

Identifying and coping with triggers and urges

6) Asking the patient to identify triggers for substance use & self-harm
7) Encouraging the patient to record and discuss examples of antecedent/trigger, behaviour, consequence (ABC) in relation to substance use & self-harm
8) Exploring alternative coping strategies and distraction techniques for managing urges to use substances & self-harm

Preparing for change

9) Jointly developing a safety plan
10) Jointly developing a plan for change with an explicit focus on both substance use & self-harm
11) Monitoring the patient's progress in engaging with other community resources e.g., Alcoholics Anonymous or Samaritans

Figure 4.6: Intervention summary

4.5.1 Findings in the context of the wider literature

There is currently a lack of evidence regarding brief psychosocial interventions for people with substance use problems during periods of elevated suicide risk [179]. Suicide prevention interventions evaluated in this population have generally focused specifically on substance use problems [201] or provided a longer course of psychological therapy in a specific modality such as cognitive behavioural therapy or dialectical behavioural therapy [198, 200, 202, 204]. There is also a lack of high-quality evidence demonstrating the effectiveness of any particular psychosocial interventions for co-morbid severe mental illness and substance use problems compared with standard care [181]. Nonetheless, within the field of suicide prevention, there has been growing recognition of the value of suicide or self-harm specific interventions [263]. There has also been increasing interest in brief interventions, which are generally considered to be more accessible [263].

The intervention developed in this study most closely aligns with Stanley et al.'s (2018) safety planning intervention with structured telephone follow-up [232]. Their intervention involved the development of a safety plan with patients during their hospital presentation, plus weekly structured telephone follow-up, initially taking place within 72 hours of discharge. The telephone follow-up included: a mood check, suicide risk assessment, review and revision of the safety plan, and problem-solving support around obstacles to treatment [264]. In this Delphi survey, a broader range of items relating to psychoeducational content was endorsed relating to substance use as well as self-harm. This intervention will, therefore, additionally aim to develop a deeper understanding of a patient's situation, build motivation for behavioural change, and prepare for change. Consequently, the intervention may reduce suicide risk both directly as well as indirectly through reductions in substance use and engagement with drug and alcohol services.

The mechanisms by which the intervention may reduce suicide risk amongst people with substance use problems are also likely to be influenced by its

mode of delivery. For example, contact-based interventions can be viewed by patients who have presented to hospital with self-harm as "a gesture of caring" [265]. The effect of such a gesture may be particularly powerful among people with substance use problems, given that they often experience barriers to accessing care. Participants in this study also indicated that the provision of gift vouchers to reward engagement, a novel aspect of this suicide prevention intervention, would make them feel valued.

A consensus was not, however, gained on the use of contingency management within the intervention. Despite strong evidence of the effectiveness of contingency management for the treatment of substance use problems, opinion about its use is often divided. The concerns raised in this survey have also been raised previously. For example, in a survey of drug treatment staff across the USA, objections included concerns that rewards do not address the underlying cause of substance use problems; are coercive; and might stifle internal motivation [266]. Yet, many effective treatments for chronic illnesses are implemented despite not addressing underlying causes. Furthermore, perceptions of contingency management as being coercive can be challenged by re-framing the approach as a skills-based intervention with multiple benefits and no evidence of a negative impact on motivation [258, 267].

A consensus was also not gained on the use of "drink diaries" within the intervention to increase awareness of the quantity of a substance consumed. These are commonly used within drug and alcohol services for a variety of purposes, including self-monitoring and informing treatment decisions [268]. Several NHS versions are available [269]. Although most PWOE agreed that these should be included within the intervention and emphasised their important role in encouraging behaviour change and informing care, opinion was divided amongst PWLE, some of whom did not think that they would be reliable or useful. To date, there does not appear to be evidence specifically investigating the value of such diaries. There are, however, many studies examining self-monitoring in relation to changes in other health behaviours, such as the measurement of blood sugar levels to improve diabetic control. A

systematic review found some evidence that self-monitoring can result in behaviour change, but the quality of studies was variable, and intervention effectiveness was dependent on the specific population and outcomes studied [270].

4.5.2 Strengths and limitations

This study included both PWLE and PWOE. The Delphi survey results from each group were weighted equally to account for different sample sizes. The anonymous nature of the survey enabled participants to respond freely. Of participants who completed Round 1, over 70% of PWOE and over 90% of PWLE completed all three rounds. Where participants did not complete all three rounds, their responses to the rounds that they completed were similar to the responses of those who did not drop out. As such, a consensus in Rounds 2 and 3 was not due to the absence of participants with opposing views. The reasons for the difference in retention rates are unclear but may reflect the reimbursement provided to PWLE for their time and the demands of PWOE's work, which were heightened during the COVID-19 pandemic.

Participants in this study had a broad range of expertise and experience. A consensus was reached quickly, in Round 1, on half of the total number of survey items. This perhaps reflected the value of the review of the research and telephone discussions that informed the survey. Free text comments at the end of each section provided us with further insights regarding participants' ratings and highlighted areas of concern in relation to each domain, which could be fed back to participants.

The public health restrictions to prevent the spread of COVID-19 prevented data collection via face-to-face workshops as had been planned. The opportunity for stakeholders to interact directly with each other may have enabled a broader exploration of ideas for core components of the intervention and enhanced engagement in the process. Nonetheless, one-to-

one discussions allowed detailed information to be collected from individual stakeholders.

Although the core components of the intervention were developed during the Delphi process, some were determined prior to the survey based on the research literature, stakeholder telephone discussions, and clinical judgement. Consequently, the items included in the survey did not offer choices regarding every aspect of the intervention and may not have reflected participants' ideal choices. For example, participants may have preferred an intervention of longer duration and greater intensity. Nonetheless, no items were excluded from the survey, indicating that there was minimal disagreement concerning the proposals.

A consensus was not reached on five items. It is unclear whether this reflects a limitation of the Delphi method, and consensus may have been possible to achieve with face-to-face discussions used in other consensus methods [243]. Furthermore, where consensus was not achieved, decisions on the inclusion of each item were made by my colleagues and me. These items were, however, a minority of those included in the survey, and participants' views were considered in the decision-making process.

A further limitation is that most survey participants were based within the United Kingdom, thereby potentially limiting the generalisability of the findings to other countries. Although Liaison Psychiatry is a growing field globally, there is substantial variation in service models and capacity for assessment and follow-up of self-harm [271-273]. For example, in the USA, psychiatric services are not provided as standard within Emergency Departments [274]. Nonetheless, co-morbid suicidal behaviour and substance use problems are a global concern [1].

Finally, expert opinion is generally considered one of the weakest forms of scientific evidence, but it is valuable in cases such as this, where other forms of evidence are sparse.

4.6 Conclusion

This Delphi method study incorporated existing research and the expertise of PWLE and PWOE into the development of a brief intervention for people presenting to hospital with self-harm and substance use problems. A treatment manual has since been formalised based on these findings, and an open case series testing the feasibility of the intervention is currently underway in two hospitals in Bristol.

Chapter 5. Discussion

In the previous chapters, I described a series of studies relating to suicide and self-harm among people with substance use problems. In this chapter, I summarise the findings of these studies, discuss the overall strengths and limitations of this body of work, and consider the implications and directions for future work.

5.1 Thesis summary

This PhD aimed first to investigate the possibility of critical periods of elevated suicide risk in people with substance use problems within clinical services and then develop an intervention to better support this population.

In Chapter 2, I investigated whether there are critical periods of elevated suicide risk during and after opioid agonist treatment for opioid dependence. In a sample of 8,070 primary care patients in England, followed up for 40,599 person-years between 1998-2018, the overall age- and sex-standardised risk of suicide was over seven times greater than in the general population. There was evidence that the risk of self-harm was around 50% higher after treatment compared with during treatment. Specifically, the risk of self-harm was more than twice as high during the first four weeks following treatment cessation compared to stable periods of time on treatment. Suicide risk was over four times higher during this same period.

In Chapter 3, I carried out a systematic review to identify and evaluate the effectiveness of interventions to prevent suicide or reduce self-harm, specifically for people with substance use problems. I identified only six randomised controlled trials from four countries (Australia, Iran, the USA, and the UK) comprising 468 participants in total. Half of the interventions were for alcohol use problems alone, one was for drug use problems alone, and the remaining two were for both. There was substantial heterogeneity in the populations, interventions, control groups, and outcome measures, and there

were some concerns of bias for all trials. All six trials were likely to have been underpowered to detect differences between groups; three were described as pilot or feasibility trials, whilst the other three acknowledged their sample size or power to be a limitation. I concluded that evidence is currently lacking regarding effective interventions to prevent suicide and reduce self-harm among people with substance use problems. Nonetheless, this is an emerging research area, and several interventions have shown promise in feasibility trials.

In Chapter 4, I conducted a Delphi method study to develop a brief psychosocial intervention for people presenting to hospital with self-harm and substance use problems. Existing research evidence and the expertise of people with occupational and lived experience were incorporated into the intervention development process. The developed intervention consists of weekly follow-up phone calls for up to one month, delivered by Liaison Psychiatry practitioners, in which both self-harm and substance use problems are explored, and patients are supported in accessing community services.

5.2 Strengths and limitations

Specific strengths and limitations of individual studies, including those relating to chance, bias, and confounding, are described within each chapter. In this section, I include a discussion of the over-arching strengths and limitations of this body of work.

This PhD focuses on a neglected yet hugely important area of research. It integrates epidemiological and clinical research to try to improve care for a stigmatised population that is often denied access to care, despite their substantially increased risk of suicide. The epidemiological study (Chapter 2) provided a sufficiently large sample size to test hypotheses relating to relatively rare outcomes, the systematic review (Chapter 3) provided an overview of trials of suicide prevention interventions conducted in this field to date, whilst the Delphi study (Chapter 4) incorporated the views of a wide

range of stakeholders into the development of a brief intervention for suicide prevention in this population. Stakeholder participation in research is important in ensuring that research investigates clinically relevant questions and interventions developed are acceptable to those who will be delivering and receiving them. Furthermore, participation can help bridge the large, well-established gap between the generation of research evidence and its translation into clinical practice [275].

People with lived experience were involved at various stages of the research presented in this thesis. In addition to their inclusion in the Delphi survey, the research was informed by a Patient and Public Involvement (PPI) "group" of four participants with lived experience of both substance use problems and suicidal thoughts and behaviour. Unfortunately, due to public health restrictions to prevent the spread of COVID-19 (from March 2020 onwards), it was not possible to maintain contact via group meetings. Instead, where possible, contact took place via one-to-one telephone calls and email. This limited the amount of discussion possible, and retention was challenging. Nonetheless, participants provided valuable insights. For example, when discussing the use of national primary care data to investigate suicide among people with substance use problems (Chapter 2), participants talked about many people known to them who had died after resuming substance use following a period of abstinence. They speculated that this might be a time of increased suicide risk as people have less support from services once abstinent. Relapse into problematic substance use and reduced clinical support may have contributed to the finding in Chapter 2 of increased suicidal risk during time off treatment. Although not possible to ascertain based on data available in this PhD, these are valuable hypotheses for future investigation.

With regards to the intervention developed in Chapter 4, people with lived experience were particularly helpful in considering how to maximise intervention engagement. For example, participants raised concerns about the likelihood of patients returning to hospital for follow-up after an initial self-

harm presentation, which influenced the decision to deliver the intervention via telephone.

There are also several limitations to consider. Most of the findings in this PhD are specific to clinical practice in the UK. There are many notable differences between countries in the prevalence of, and risk factors for, suicidal behaviours and substance use problems, as well as the types of clinical services freely available. For example, in the USA (another high-income, predominantly English-speaking country), where suicide rates are higher than in the UK [32], there has been a prescription opioid epidemic [276], and both inpatient and community psychiatric provision differ considerably [206, 236].

The identification of critical periods of elevated suicide risk in this population involved the use of routine clinical data, which often lack comprehensive information on key mediators and confounders. For example, data were unavailable regarding the type of OAT interventions provided (e.g., detoxification, maintenance, rehabilitation, and psychosocial interventions), ongoing recreational drug use, and reasons for treatment discontinuation. Furthermore, for variables where data were available, such as previous mental illness, records may be incomplete. One possible solution is to collect more detailed data on a subsample of individuals using a nested case-control study within a cohort. This approach was taken in the VEdeTTE study [277], where people who died of drug-related poisoning in Italy were matched with people living with opioid dependence within the same cohort. This alternative study design strengthened previous findings of an increased risk of overdose mortality out of OAT, particularly during the first four weeks after treatment cessation. Nonetheless, this approach also heavily relies on accurate and comprehensive recording of variables of interest within clinical records.

The intervention development component of this PhD focused on randomised controlled trials. Although RCTs are considered to be the most methodologically rigorous study design for testing clinical interventions, there are several challenges associated with their use [249]. First, in suicide

prevention research, large sample sizes are often required to demonstrate meaningful reductions in the number of recorded suicides. Second, long-term follow-up is often unfeasible due to practical constraints. Third, professionals, patients, research centres, and processes involved in RCTs are commonly unrepresentative of those seen in routine clinical practice. This lack of external validity potentially limits the relevance of findings to policy and practice. Accordingly, two of the largest and most influential studies of brief interventions for people presenting to hospital with identified suicide risk are observational studies [232, 236]. Yet, while observational research is better able to address the challenges associated with RCTs, there is a trade-off with reduced internal validity due to the possibility of selection bias and residual confounding. When findings from these two study designs differ, it can be difficult to determine the extent to which this might be attributed to methodological differences. For example, in a recent meta-analysis of brief interventions for suicide prevention in acute care settings, the two large-scale observational studies described above contributed to three-quarters of the weighting for the suicide-related outcome [232, 236]; these two studies appeared to be responsible for the finding of evidence of an association between these types of interventions and a reduction in subsequent suicide attempts [237]. Nonetheless, this meta-analysis highlighted the value of expanding the inclusion criteria of systematic reviews on suicide prevention interventions to include observational data.

5.3 Implications for policy and practice

In this PhD, I highlighted the elevated risk of suicide and self-harm amongst people with substance use problems. Over the coming years, in response to the long-term effects of the COVID-19 pandemic and the accompanying increased use of alcohol, suicide and self-harm may increase among this population [54, 278]. As such, suicide prevention for people with substance use problems may become even more relevant.

A key finding of this PhD is the elevated risk of suicide and self-harm during the first four weeks of opioid agonist treatment cessation (Chapter 2). Other transitions between health or social care services have also been identified as periods of heightened risk for suicide. In Chapter 4, I described a period of elevated suicide risk immediately after discharge from hospital amongst patients presenting with self-harm, as well as various evidence-based interventions for reducing risk during this time in the general population. Additionally, periods of elevated suicide risk have been identified immediately post-discharge from inpatient psychiatric care [279, 280] and prison [281], and an elevated risk of fatal opioid overdoses among people who use illicit opioids has been identified following discharge from general hospitals [282]. There is some observational evidence that policy initiatives, including recommendations to follow up high-risk patients within a week of discharge from psychiatric inpatient care, are associated with a reduction in the risk of self-harm during this high-risk period [283].

A Critical Time Intervention (CTI) model has been developed, which involves the provision of intensive, time-limited community support for vulnerable people during periods of transition [284]. The model was initially developed in the USA in response to an observation of an elevated risk of becoming homeless amongst people with severe mental illness during the transition from shelter institutions to community housing. Two common features of periods of transition have since been identified: individuals are usually required to "navigate a complex and fragmented system of care", and relationships with their families and friends are often difficult, so their support network may not know how best to help them [284]. Global dissemination of the CTI model is now supported by the Center for the Advancement of Critical Time Intervention [285], and RCTs have demonstrated its effectiveness in improving a range of outcomes in a variety of populations. Recent examples include an RCT in England that showed improvements in engagement with community mental health teams among people released from prison who had a severe mental illness [286], and an RCT in the USA that showed reduced

homelessness amongst people discharged following psychiatric admissions [287].

However, OAT cessation differs compared with the other critical time periods because most discharges are likely to be unplanned [176]. People who have relapsed during an unplanned discharge are no longer in contact with clinical services, which limits the scope for post-discharge engagement. Furthermore, individuals are particularly vulnerable during this time due to reduced physiological tolerance to opioids [288]. The implications that this has for future research are described in the next section.

Although the exact nature of effective interventions to reduce suicide risk associated with OAT cessation requires further investigation, greater joint working between drug and alcohol services and mental health services is likely to be important. It has long been recognised that co-morbid substance use is the norm rather than an exception within mental health services. As such, government policies and strategies have emphasised the need to ensure that adequate care is available to meet the needs of this population within mainstream drug and alcohol and mental health services [111, 113]. It may be argued that the provision of a separate intervention specifically for people with substance use problems who self-harm could undermine this progress. However, given the ongoing lack of improvement in access to care for this population, the barriers to access appear to be deeply entrenched. Improvements in the evidence base for effective treatments specifically for this population may go some way to addressing many of these barriers. For example, evidence-based treatments are more likely to: be prioritised during the allocation of scarce resources, address a lack of confidence and feelings of therapeutic nihilism amongst staff, and ultimately increase willingness to include this population within mainstream mental health services. The new Drug Strategy may offer the opportunity for investment to improve the management of co-morbidity within drug services, alongside the development and evaluation of novel suicide prevention interventions [111].

Finally, in this PhD, I investigated individual-level psychosocial interventions for tertiary prevention. Although these interventions provide vital support, once an episode of self-harm has occurred, psychosocial problems are likely to be more severe and more difficult to change. These interventions are, therefore, often resource intensive. In contrast, population-level primary prevention can intervene at an earlier stage and affect a greater number and range of people, including those who do not present to clinical services before their suicide [289]. Relevant examples include measures to reduce access to alcohol, such as increasing alcohol pricing [116]. More broadly, policies to address underlying socioeconomic factors are also likely to be beneficial and are often overlooked [290-292]. Multi-pronged approaches integrating population-level and individual-level interventions, specified within national policies and strategies, are therefore important [293, 294]. Both types of interventions are also likely to have wider benefits on health and economic measures beyond suicide prevention.

5.4 Directions for future research

Future research is required to improve understanding of how to reduce the elevated risk of self-harm and suicide during OAT cessation. As the absolute risk of these outcomes is relatively low, more information would be useful regarding who, specifically, may need additional support and what support might be acceptable, feasible, and beneficial in the context of unplanned treatment cessation. Although this research could initially be undertaken using large-scale, routine observational data (such as CPRD), as explained above, data on key factors of interest are often poorly recorded. The nested case-control design could enable a more thorough assessment [295]. Qualitative research into the experiences of people who have previously stopped OAT in an unplanned manner may also be of value to enrich current understanding of how treatment cessation is linked to an increased risk of suicidal behaviour.

It would also be useful to assess the extent to which suicide and self-harm risk in relation to OAT may be reduced by improvements in treatment retention and reductions in unplanned treatment cessation. Improving retention in OAT is, however, challenging. Observational studies have found differences in average treatment duration between countries, but factors contributing to these differences have not yet been explored in detail [68]. Among specific behavioural interventions, only contingency management has been found to improve retention [296, 297]. Yet, it has not been widely implemented in clinical practice, despite its promotion in national clinical guidance [298]. In light of this, there has been a recent focus on pragmatically adapting contingency management for implementation within national drug treatment services [299]. Nonetheless, research investigating other strategies for improving retention is also essential, especially since the benefits of OAT retention extend far beyond suicide and self-harm.

Finally, there is a need for more evidence regarding effective suicide prevention interventions for people with substance use problems. Both adequately powered RCTs and observational studies of existing innovative practices would be valuable given the different strengths and weaknesses of each study design. Although there is some evidence to suggest that the treatment of substance use problems is associated with reduced suicide risk [117], most people with substance use problems who die by suicide do not have contact with drug and alcohol services in the year before their death [300]. Furthermore, in a previous randomised controlled trial of a brief alcohol-focused intervention for people presenting to hospital in England with self-harm and alcohol use problems, less than half of patients attended a one-off, usually same-day, appointment with an alcohol nurse specialist [201]. This may reflect the fact that at the time of presentation, many patients consider their substance use to be of lesser importance than their mental distress or self-harm. They may also not be ready to address their substance use. Integrated interventions, in which suicide, self-harm, and substance use content are offered flexibly alongside each other, are likely to appeal more

broadly. They are, therefore, important in maximising engagement during critical periods of elevated suicide risk.

5.5 Conclusion

This PhD aimed to: 1) identify critical periods of elevated suicide risk in people with substance use problems using national primary care data; 2) develop a brief intervention to better support this population by conducting a systematic review of the literature and using a Delphi method study to draw on the experience of key stakeholders. Stable periods of opioid agonist treatment for opioid dependence had a protective effect on suicidal behaviour. However, the month immediately after stopping treatment was identified as a period of substantially elevated risk of suicide and self-harm. The systematic review highlighted a paucity of evidence from adequately powered randomised controlled trials to inform suicide prevention strategies for people with substance use problems. Finally, a brief intervention was developed for people presenting to hospital with self-harm and co-morbid substance use problems, which is currently being piloted in two hospitals in Bristol.

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Appendices

Appendix A : CPRD code lists

Product codes for methadone and buprenorphine

Product code	Product name	Drug
320	Buprenorphine HCl 300micrograms injection	Buprenorphine
396	Buprenorphine 200microgram sublingual tablets sugar free	Buprenorphine
3064	Buprenorphine 400microgram sublingual tablets sugar free	Buprenorphine
3522	Temgesic 200microgram sublingual tablets (Indivior UK Ltd)	Buprenorphine
5936	Transtec 35micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)	Buprenorphine
6040	Transtec 52.5micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)	Buprenorphine
6056	Buprenorphine 8mg sublingual tablets sugar free	Buprenorphine
6181	Transtec 70micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)	Buprenorphine
6210	Subutex 8mg sublingual tablets (Indivior UK Ltd)	Buprenorphine
6547	Buprenorphine 2mg sublingual tablets sugar free	Buprenorphine
6879	Buprenorphine 35micrograms/hour transdermal patches	Buprenorphine
6917	Buprenorphine 52.5micrograms/hour transdermal patches	Buprenorphine
7236	Buprenorphine 10micrograms/hour transdermal patches	Buprenorphine
7238	Buprenorphine 20micrograms/hour transdermal patches	Buprenorphine
7334	Buprenorphine 5micrograms/hour transdermal patches	Buprenorphine
7457	Temgesic 0.3mg/ml Injection (Reckitt Benckiser Healthcare (UK) Ltd)	Buprenorphine
7555	BuTrans 5micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)	Buprenorphine
8017	Temgesic 400microgram sublingual tablets (Indivior UK Ltd)	Buprenorphine
10077	Subutex 2mg sublingual tablets (Indivior UK Ltd)	Buprenorphine
10205	BuTrans 10micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)	Buprenorphine
11584	Buprenorphine 70micrograms/hour transdermal patches	Buprenorphine
13031	Subutex 0.4mg sublingual tablets (Indivior UK Ltd)	Buprenorphine
13300	BuTrans 20micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)	Buprenorphine
35169	Suboxone 8mg/2mg sublingual tablets (Indivior UK Ltd)	Buprenorphine
35170	Suboxone 2mg/500microgram sublingual tablets (Indivior UK Ltd)	Buprenorphine
35269	Temgesic 300micrograms/1ml solution for injection ampoules (Indivior UK Ltd)	Buprenorphine

35681	Buprenorphine 2mg / Naloxone 500microgram sublingual tablets sugar free	Buprenorphine
35682	Buprenorphine 8mg / Naloxone 2mg sublingual tablets sugar free	Buprenorphine
38311	Naloxone hc 2mg + 8mg Tablet	Buprenorphine
40211	Buprenorphine 2mg sublingual tablets sugar free (Teva UK Ltd)	Buprenorphine
40212	Buprenorphine 8mg sublingual tablets sugar free (Teva UK Ltd)	Buprenorphine
40473	Buprenorphine 300micrograms/1ml solution for injection ampoules	Buprenorphine
42074	Naloxone hc 500micrograms + 2mg Tablet	Buprenorphine
50380	Subutex 2mg sublingual tablets (Lexon (UK) Ltd)	Buprenorphine
54806	Transtec 52.5micrograms/hour transdermal patches (DE Pharmaceuticals)	Buprenorphine
56671	BuTrans 5micrograms/hour transdermal patches (Waymade Healthcare Plc)	Buprenorphine
57454	Prefibin 8mg sublingual tablets (Sandoz Ltd)	Buprenorphine
58273	Buprenorphine 2mg sublingual tablets sugar free (A A H Pharmaceuticals Ltd)	Buprenorphine
58766	BuTrans 10micrograms/hour transdermal patches (Waymade Healthcare Plc)	Buprenorphine
59146	BuTrans 20micrograms/hour transdermal patches (Waymade Healthcare Plc)	Buprenorphine
59392	Hapoctasin 70micrograms/hour transdermal patches (Actavis UK Ltd)	Buprenorphine
59473	Hapoctasin 52.5micrograms/hour transdermal patches (Actavis UK Ltd)	Buprenorphine
59618	Transtec 35micrograms/hour transdermal patches (Mawdsley-Brooks & Company Ltd)	Buprenorphine
59970	Buprenorphine 2mg sublingual tablets sugar free (Actavis UK Ltd)	Buprenorphine
60053	Tephine 200microgram sublingual tablets (Sandoz Ltd)	Buprenorphine
60170	Hapoctasin 35micrograms/hour transdermal patches (Actavis UK Ltd)	Buprenorphine
60943	Transtec 35micrograms/hour transdermal patches (Sigma Pharmaceuticals Plc)	Buprenorphine
61100	Tephine 400microgram sublingual tablets (Sandoz Ltd)	Buprenorphine
62675	Buprenorphine 200microgram sublingual tablets sugar free (A A H Pharmaceuticals Ltd)	Buprenorphine
62776	Buprenorphine 4mg sublingual tablets sugar free	Buprenorphine
62874	Buprenorphine 6mg sublingual tablets sugar free	Buprenorphine
62969	Buprenorphine 8mg sublingual tablets sugar free (Zentiva)	Buprenorphine
63640	Subutex 2mg sublingual tablets (DE Pharmaceuticals)	Buprenorphine
63788	Buprenorphine 1mg sublingual tablets sugar free	Buprenorphine
64155	Buprenorphine 400microgram sublingual tablets sugar free (Teva UK Ltd)	Buprenorphine
64847	Gabup 8mg sublingual tablets (Martindale Pharmaceuticals Ltd)	Buprenorphine
65157	Buprenorphine 2mg sublingual tablets sugar free (Sigma Pharmaceuticals Plc)	Buprenorphine
66280	BuTrans 15micrograms/hour transdermal patches (Napp Pharmaceuticals Ltd)	Buprenorphine

66463	Buprenorphine 15micrograms/hour transdermal patches	Buprenorphine
66470	Butec 10micrograms/hour transdermal patches (Qdem Pharmaceuticals Ltd)	Buprenorphine
66689	Butec 5micrograms/hour transdermal patches (Qdem Pharmaceuticals Ltd)	Buprenorphine
66695	Butec 20micrograms/hour transdermal patches (Qdem Pharmaceuticals Ltd)	Buprenorphine
67018	Buprenorphine 35micrograms/hour transdermal patches (A A H Pharmaceuticals Ltd)	Buprenorphine
67356	Transtec 70micrograms/hour transdermal patches (Lexon (UK) Ltd)	Buprenorphine
67901	Transtec 52.5micrograms/hour transdermal patches (Lexon (UK) Ltd)	Buprenorphine
68167	Reletrans 5micrograms/hour transdermal patches (Sandoz Ltd)	Buprenorphine
68172	Reletrans 20micrograms/hour transdermal patches (Sandoz Ltd)	Buprenorphine
68196	Reletrans 15micrograms/hour transdermal patches (Sandoz Ltd)	Buprenorphine
68241	Reletrans 10micrograms/hour transdermal patches (Sandoz Ltd)	Buprenorphine
68402	Panitaz 5micrograms/hour transdermal patches (Dr Reddy's Laboratories (UK) Ltd)	Buprenorphine
68472	Prenotrix 52.5micrograms/hour transdermal patches (Genesis Pharmaceuticals Ltd)	Buprenorphine
68479	Bupeaze 70micrograms/hour transdermal patches (Dr Reddy's Laboratories (UK) Ltd)	Buprenorphine
68559	Panitaz 10micrograms/hour transdermal patches (Dr Reddy's Laboratories (UK) Ltd)	Buprenorphine
68743	Bupeaze 35micrograms/hour transdermal patches (Dr Reddy's Laboratories (UK) Ltd)	Buprenorphine
68848	Buplast 52.5micrograms/hour transdermal patches (Mylan)	Buprenorphine
68888	Sevodyne 20micrograms/hour transdermal patches (Aspire Pharma Ltd)	Buprenorphine
68889	Sevodyne 10micrograms/hour transdermal patches (Aspire Pharma Ltd)	Buprenorphine
68890	Sevodyne 5micrograms/hour transdermal patches (Aspire Pharma Ltd)	Buprenorphine
68910	Suboxone 16mg/4mg sublingual tablets (Indivior UK Ltd)	Buprenorphine
68988	Buprenorphine 8mg oral lyophilisates sugar free	Buprenorphine
68989	Buprenorphine 2mg oral lyophilisates sugar free	Buprenorphine
69243	Bupeaze 52.5micrograms/hour transdermal patches (Dr Reddy's Laboratories (UK) Ltd)	Buprenorphine
69254	Buplast 35micrograms/hour transdermal patches (Mylan)	Buprenorphine
69315	Butec 15micrograms/hour transdermal patches (Qdem Pharmaceuticals Ltd)	Buprenorphine
69795	Prenotrix 35micrograms/hour transdermal patches (Genesis Pharmaceuticals Ltd)	Buprenorphine
69942	Buprenorphine 400microgram sublingual tablets sugar free (Phoenix Healthcare Distribution Ltd)	Buprenorphine
70065	Espranor 2mg oral lyophilisates (Martindale Pharmaceuticals Ltd)	Buprenorphine
70066	Espranor 8mg oral lyophilisates (Martindale Pharmaceuticals Ltd)	Buprenorphine

70117	Panitaz 20micrograms/hour transdermal patches (Dr Reddy's Laboratories (UK) Ltd)	Buprenorphine
70124	Relevtec 70micrograms/hour transdermal patches (Sandoz Ltd)	Buprenorphine
70139	Relevtec 35micrograms/hour transdermal patches (Sandoz Ltd)	Buprenorphine
70283	Buprenorphine 16mg / Naloxone 4mg sublingual tablets sugar free	Buprenorphine
70460	Bupramyl 10micrograms/hour transdermal patches (Mylan)	Buprenorphine
70461	Bupramyl 5micrograms/hour transdermal patches (Mylan)	Buprenorphine
70464	Subutex 2mg sublingual tablets (Waymade Healthcare Plc)	Buprenorphine
70631	Relevtec 52.5micrograms/hour transdermal patches (Sandoz Ltd)	Buprenorphine
71310	Bupramyl 20micrograms/hour transdermal patches (Mylan)	Buprenorphine
71410	Suboxone 8mg/2mg sublingual tablets (Mawdsley-Brooks & Company Ltd)	Buprenorphine
71630	Natzon 0.4mg sublingual tablets (Morningside Healthcare Ltd)	Buprenorphine
71695	Prefibin 0.4mg sublingual tablets (Sandoz Ltd)	Buprenorphine
71711	Busiete 10micrograms/hour transdermal patches (Teva UK Ltd)	Buprenorphine
72098	Turgeon 35micrograms/hour transdermal patches (Teva UK Ltd)	Buprenorphine
72160	Turgeon 52.5micrograms/hour transdermal patches (Teva UK Ltd)	Buprenorphine
2952	Methadone 1mg/ml oral solution	Methadone
5211	Methadone 2mg/5ml linctus	Methadone
5322	Physeptone 5mg tablets (Martindale Pharmaceuticals Ltd)	Methadone
6441	Methadone 5mg tablets	Methadone
9728	Methadone 1mg/ml oral solution sugar free	Methadone
11722	Methadone 10mg/ml oral solution sugar free	Methadone
14086	Methadone 10mg/ml Injection	Methadone
17671	Methadone 50mg/1ml solution for injection ampoules	Methadone
17896	Physeptone 10mg/ml Injection (Martindale Pharmaceuticals Ltd)	Methadone
21562	Physeptone 1mg/ml oral solution sugar free (Martindale Pharmaceuticals Ltd)	Methadone
23158	Methadone 20mg/ml oral solution sugar free	Methadone
24343	Methadose 10mg/ml oral solution concentrate (Rosemont Pharmaceuticals Ltd)	Methadone
24361	Methadose 20mg/ml oral solution concentrate (Rosemont Pharmaceuticals Ltd)	Methadone
24440	Methodex 1mg/ml Mixture (Link Pharmaceuticals Ltd)	Methadone
24584	Methadone 50mg/2ml solution for injection ampoules	Methadone
26277	Physeptone 1mg/ml mixture (Martindale Pharmaceuticals Ltd)	Methadone
28328	Metharose 1mg/ml oral solution sugar free (Rosemont Pharmaceuticals Ltd)	Methadone
29304	Physeptone 10mg/1ml solution for injection ampoules (Martindale Pharmaceuticals Ltd)	Methadone

29769	Methadone 2mg/5ml Oral solution (Martindale Pharmaceuticals Ltd)	Methadone
29911	Methadone 2mg/5ml linctus (Thornton & Ross Ltd)	Methadone
30531	Methadone 1mg/ml oral solution sugar free (Rosemont Pharmaceuticals Ltd)	Methadone
32237	Methex 1mg/ml Mixture (Generics (UK) Ltd)	Methadone
33068	Methadone 10mg/1ml solution for injection ampoules	Methadone
33475	Methadone 35mg/ml Injection	Methadone
33832	Methadone 1mg/ml oral solution (Martindale Pharmaceuticals Ltd)	Methadone
35506	Methadone 20mg/2ml solution for injection ampoules	Methadone
36436	Methadone 50mg/5ml solution for injection ampoules	Methadone
36994	Methadone 5mg/ml oral solution	Methadone
37507	Physeptone 50mg/1ml solution for injection ampoules (Martindale Pharmaceuticals Ltd)	Methadone
37518	Methadone 35mg/3.5ml solution for injection ampoules	Methadone
39437	Eptadone 1mg/ml oral solution (Dee Pharmaceuticals Ltd)	Methadone
41608	Methadone 1mg/ml oral solution (Rosemont Pharmaceuticals Ltd)	Methadone
41720	Methadone 1mg/ml Mixture (Macarthy Medical Ltd)	Methadone
43260	Methadone Oral solution	Methadone
43766	Eptadone 5mg/ml oral solution (Dee Pharmaceuticals Ltd)	Methadone
46578	Physeptone 20mg/2ml solution for injection ampoules (Martindale Pharmaceuticals Ltd)	Methadone
47706	Methadone 1mg/ml oral solution sugar free (Martindale Pharmaceuticals Ltd)	Methadone
55825	Methadone 1mg/ml oral solution sugar free (Thornton & Ross Ltd)	Methadone
59295	Methadone 100mg capsules	Methadone
60944	Methadone 5mg capsules	Methadone
62708	Methadone hydrochloride powder	Methadone
63077	Methadone 1mg/5ml oral suspension	Methadone
64463	Methadone 30mg capsules	Methadone
66921	Methadone 1mg/ml oral solution sugar free (Waymade Healthcare Plc)	Methadone
67342	Methadone 50mg/1ml solution for injection ampoules (Alliance Healthcare (Distribution) Ltd)	Methadone
68959	Methadone 20mg/5ml oral solution	Methadone
69053	Pinadone methadone 1mg/ml Oral solution sugar free (Pinewood Healthcare)	Methadone
70267	Methadone 15mg/5ml oral solution	Methadone

Medical codes for illicit opioid use

Medcode	Description
689	Heroin dependence
4564	[X]Heroin addiction
6111	Drug addictn therap-methadone
10538	[X]Drug addiction - opioids
16243	Opioid type drug dependence
16374	Methadone dependence
20458	Heroin poisoning
20962	Episodic opioid dependence
22059	Morphine dependence
22079	Injecting drug user
24441	Opioid drug dependence NOS
25527	[X]Cold turkey, opiate withdrawal
26061	Combined opioid with other drug dependence
26831	Nondependent opioid abuse
27652	[X]Men & beh dis due opioids: resid & late-onset psychot dis
27960	Opioid dependence in remission
28710	[X]Overdose - heroin
28976	Drug addiction detoxification therapy - methadone
30251	Intravenous drug user
30565	Failed heroin detoxification
30598	Opiate dependence detoxification
30694	Drug addiction maintenance therapy - methadone
30711	[V]Personal history of drug abuse by injection
32709	Previously injecting drug user
32804	Opium dependence
34249	[X]Mental and behav dis due to use opioids: dependence syndr
36241	[X]Mental and behav dis due to use opioids: withdrawal state
37527	Adverse reaction to heroin, diamorphine
37568	[X]Mental and behdav dis due to use of opioids: harmful use
38034	Unspecified opioid dependence
40536	Nondependent opioid abuse, unspecified
42456	[X]Mental & behav dis due to use opioids: acute intoxication
43075	Continuous opioid dependence
43487	Drug addiction maintenance therapy - buprenorphine
47083	Buprenorphine maintenance therapy
47335	[X]Mental and behavioural disorders due to use of opioids
50964	[X]Mental & behav dis due to use opioids: psychotic disorder
51052	Drug addiction detoxification therapy - buprenorphine
51334	[X]Accidental poisoning with heroin

52451	Combined opioid with other drug dependence in remission
52739	[X]Men & behav dis due to use opioids: oth men & behav dis
54560	Accidental poisoning by heroin
56194	Combined opioid with other drug dependence, unspecified
58560	Severity of opiate dependence questionnaire
58731	Nondependent opioid abuse, continuous
60243	SODQ - Severity of opiate dependence questionnaire
60355	Methadone maintenance
64265	Combined opioid with other drug dependence, continuous
64277	Combined opioid with other drug dependence, episodic
64382	Nondependent opioid abuse, episodic
68327	Abstinent from drug misuse on maintenance replacement
69508	Nondependent opioid abuse NOS
73737	Combined opioid with other drug dependence NOS
82479	H/O heroin misuse
85097	H/O methadone misuse
85953	Does not use heroin on top of substitution therapy
86002	H/O daily heroin misuse
86036	H/O opiate misuse
86041	Uses heroin on top of substitution therapy
86771	Previous history of methadone misuse
88372	Previous history of heroin misuse
88760	H/O daily opiate misuse
89145	H/O infrequent heroin misuse
90198	Reinduction to methadone maintenance therapy
91029	H/O infrequent opiate misuse
91256	Previous history of opiate misuse
91801	[X]Ment & behav dis due use opioids: unsp ment & behav dis
92404	H/O daily methadone misuse
93109	H/O weekly methadone misuse
93554	H/O weekly heroin misuse
93980	Opioid agonist substitution therapy
95460	Heroin maintenance
95953	Nondependent opioid abuse in remission
95957	Has never shared drug injection equipment
96081	Reinduction to buprenorphine maintenance therapy
96925	Heroin misuse
97000	Drug injection behaviour
97488	[X]Men & behav dis due opioid: withdrawl state with delirium
97811	Sharing of drug injecting equipment
100632	Methadone therapy
101377	H/O weekly opiate misuse
103842	Clinical opiate withdrawal scale

103991	[X]Mental and behav dis due to use opioids: amnesic syndrome
106342	H/O infrequent methadone misuse
106705	Does not share drug injection equipment
107780	Neck injector
108251	Opioid substitution therapy monitoring
109730	Drug addiction maintenance therapy - naltrexone
109966	Drug addiction maintenance therapy - lofexidine
111551	Groin injector

Appendix B : Additional information about data cleaning

Estimating missing daily doses

Some daily doses could be derived from various combinations of the other prescribing variables, such as $dose\ number \times dose\ frequency$ (Table 2.6). For each prescription, the modal value of the estimates produced by these combinations was compared with daily doses where they were recorded. The percentage agreement between the modal values and available daily doses were 99.8% and 98.9% for methadone and buprenorphine, respectively. Given the high level of agreement, the modal value of daily dose estimates was used where a record of daily dose was missing.

Where there were multiple different estimates of the daily dose without a modal value, an alternative method to select the most accurate estimate was required. Where modal values were available, the percentage match was calculated between, the estimated daily dose produced by each combination of variables, and the modal values (this time including recorded daily doses). A hierarchy of combinations was determined based on these percentage matches (Table). Where a modal value was unavailable, the estimate from the highest ranked combination was selected i.e. an estimate produced by $dose\ number \times dose\ frequency$ was selected in preference of an estimate produced by $dose\ number\ \div dose\ interval$.

Table: Percentage matches between, combinations of variables to produce daily dose estimate, and modal value of all daily dose estimates (where available)

Variables from which daily dose was derived	Methadone prescriptions
daily dose	99.8
dose number × dose frequency	99.6
dose number ÷ dose interval	95.7
total quantity ÷ number of days	94.7
daily dose from nearest previous or subsequent prescription with same total quantity (if exists)	92.4
total quantity prescribed ÷ time to next prescription if time to next prescription =1-15/21/28 days	84.3
median daily dose of all prescriptions at same practice with same total quantity.	83.8

Estimating missing dose units

Prescriptions where 'dose units' were available were inspected to ascertain whether these could be determined by other variables.

I observed that for buprenorphine, all recorded 'dose units' were "tablets", except where the 'strength' was "2mg" or "8mg". For prescriptions with a recorded "strength" of "8mg", the 'dose unit' was:

- recorded as "mg" for prescriptions with 'daily doses' above or equal to "8"
- recorded as "tablets" for prescriptions with 'daily doses' less than "8"

For prescriptions with a recorded 'strength' of "2mg", predictors of 'dose units' recorded as "mg" or "tablets" could not be identified. However, the 'daily doses' recorded in these prescriptions made up less than 10% of all buprenorphine prescriptions. A sensitivity analysis, detailed in Section 2.3.13, was conducted to account for the effect incorrect estimation may have had on defining the cohort.

Based on these observations, missing buprenorphine prescription 'dose units' were estimated as follows:

- Where 'strength'="8mg" and 'daily dose' ≥"8": 'dose unit'=mg
- Where 'strength'="8mg" and 'daily dose' ≥"8": 'dose unit'=tablets
- All other prescriptions: 'dose unit'=tablets

For methadone, the strength for almost all prescriptions with missing 'dose units' was 1mg/ml, therefore the daily dose in mg would be the same regardless of whether mg or ml was imputed as the 'dose unit'.

Appendix C : Additional sensitivity analyses

Restricting to prescriptions from up to standard practices only

Suicide

Variable	No. of suicides	Person-years follow-up	Crude rate/100 person-years (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)
Treatment status					
Overall time on treatment	13	13058.6	0.10 (0.06-0.17)	1.00	1.00
Overall time off treatment	30	23176.3	0.13 (0.09-0.19)	1.26 (0.65-2.42)	1.21 (0.63-2.34)
Treatment period					
Weeks 1-4 on treatment	2	902.9	0.22 (0.06-0.89)	2.44 (0.54-10.99)	2.40 (0.53-10.87)
Remainder of time on treatment	11	12155.7	0.09 (0.05-0.16)	1.00	1.00
Weeks 1-4 off treatment	5	1009.3	0.50 (0.21-1.19)	5.48 (1.90-15.77)	5.26 (1.80-15.32)
Remainder of time off treatment	25	22167.0	0.11 (0.08-0.17)	1.19 (0.58-2.44)	1.15 (0.56-2.35)

Self-harm

Variable	No. of self-harm episodes	Person-years follow-up	Crude rate/100 person-years (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)
Treatment status					
Overall time on treatment	209	13119.3	1.59 (1.39-1.82)	1.00	1.00
Overall time off treatment	551	23584.9	2.34 (2.15-2.54)	1.60 (1.27-2.02)	1.55 (1.23-1.95)
Treatment period					
Weeks 1-4 on treatment	25	906.4	2.76 (1.86-4.08)	1.48 (0.93-2.35)	1.46 (0.91-2.32)
Remainder of time on treatment	184	12212.9	1.51 (1.30-1.74)	1.00	1.00
Weeks 1-4 off treatment	49	1014.2	4.83 (3.65-6.39)	2.67 (1.84-3.86)	2.60 (1.79-3.76)
Remainder of time off treatment	502	22570.8	2.22 (2.04-2.43)	1.60 (1.24-2.06)	1.54 (1.20-1.97)

Excluding prescriptions with an implausible duration (<1 day or >70 days)

Suicide

Variable	No. of suicides	Person-years follow-up	Crude rate/100 person-years (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)
Treatment status					
Overall time on treatment	14	14143.3	0.10 (0.06-0.17)	1.00	1.00
Overall time off treatment	32	25691.4	0.12 (0.09-0.18)	1.22 (0.64-2.30)	1.18 (0.62-2.23)
Treatment period					
Weeks 1-4 on treatment	2	1022.3	0.20 (0.05-0.78)	2.12 (0.48-9.49)	2.07 (0.46-9.29)
Remainder of time on treatment	12	13121	0.09 (0.05-0.16)	1.00	1.00
Weeks 1-4 off treatment	5	1142.5	0.44 (0.18-1.05)	4.77 (1.68-13.54)	4.55 (1.59-13.02)
Remainder of time off treatment	27	24548.9	0.11 (0.08-0.16)	1.15 (0.58-2.29)	1.12 (0.56-2.23)

Self-harm

Variable	No. of self-harm episodes	Person-years follow-up	Crude rate/100 person-years (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)
Treatment status					
Overall time on treatment	223	14205.1	1.57 (1.38-1.79)	1.00	1.00
Overall time off treatment	578	26129.9	2.21 (2.04-2.40)	1.51 (1.21-1.89)	1.48 (1.18-1.84)
Treatment period					
Weeks 1-4 on treatment	27	1056.9	2.55 (1.75-3.73)	1.37 (0.88-2.13)	1.35 (0.87-2.11)
Remainder of time on treatment	196	13148.6	1.49 (1.30-1.71)	1.00	1.00
Weeks 1-4 off treatment	55	1186.6	4.64 (3.56-6.04)	2.53 (1.79-3.59)	2.49 (1.76-3.53)
Remainder of time off treatment	523	24943.3	2.10 (1.92-2.28)	1.48 (1.17-1.88)	1.44 (1.13-1.82)

Appendix D : Search strategy

Free text search

Embase, Psychinfo, Medline

(alcohol*.tw. OR opiate*.tw. OR opioid*.tw. OR cocaine.tw. OR amphetamine*.tw. OR methamphetamine*.tw. OR drug*.tw. OR substance*.tw. OR polydrug*.tw. OR polysubstance*.tw. OR methadone.tw. OR cannabis.tw. OR crack.tw. OR heroin.tw OR marijuana.tw OR psychostimulant*.tw OR hallucinogen*.tw OR buprenorphine.tw) AND (dependen*.tw. OR chronic.tw. OR disorder*.tw. OR abuse*.tw. OR addiction*.tw. OR misuse*.tw.) AND (suicid*.tw. OR parasuicid*.tw. OR self-injurious behavio?r.tw. OR overdose*.tw. OR poison*.tw. OR self-harm*.tw. OR self-destruct*.tw. OR self-poison*.tw. OR self-inflict*.tw.) AND limit to "therapy (best balance of sensitivity and specificity)"

Web of Science

(TS=(alcohol* OR opiate* OR opioid* OR cocaine OR amphetamine* OR methamphetamine* OR drug* OR polydrug* OR substance* OR polysubstance* OR methadone OR cannabis OR crack OR heroin OR marijuana OR psychostimulant* OR hallucinogen* OR buprenorphine)) AND (TS=(abuse* OR addiction* OR dependen* OR chronic OR disorder* OR misuse*)) AND (TS=(suicid* OR self-harm* OR parasuicid* OR self-injurious behavio$r OR overdos* OR self-destruct* OR self-poison* OR poison* OR self-inflict*)) AND (TS=("randomised controlled trial*" OR "randomized controlled trial*"))

CENTRAL

(alcohol or opiate or opioid or cocaine or amphetamine or methamphetamine or drug or polydrug or substance or polysubstance or methadone or cannabis or crack or heroin or marijuana or psychostimulant or hallucinogen or buprenorphine) AND (abuse or addiction or dependence or chronic or disorder or misuse) AND (suicide or self-harm or parasuicide or self-injurious behavior or overdose or self-destruct or self-poison or poison or self-inflict) AND trials filter

Subject headings search

Embase

(exp suicide/pc [Prevention] OR exp automutilation/pc [Prevention]) OR (exp Drug Abuse/ OR exp Alcohol Abuse/) AND limit to "therapy (best balance of sensitivity and specificity)"

Psychinfo

(exp Suicide Prevention/ OR exp self-destructive behavior/) AND exp (Drug Abuse/ OR exp Alcohol Abuse/) AND limit to "therapy (best balance of sensitivity and specificity)"

Medline

(exp Suicide/pc [Prevention & Control] OR exp Self-Injurious Behavior/pc [Prevention & Control]) AND exp Substance-Related Disorders/ AND limit to "therapy (best balance of sensitivity and specificity)" AND limit to "therapy (best balance of sensitivity and specificity)"

CENTRAL

(MeSH descriptor: [Suicide] this term only and with qualifier(s): [Prevention & control - PC] OR MeSH descriptor: [Self-Injurious Behavior] explode all trees and with qualifier(s): [Prevention & control - PC]) AND (MeSH descriptor: [Substance-Related Disorders] this term only OR MeSH descriptor: [Alcoholism] this term only)

Appendix E : Summary of studies with suicide-/self-harm-related secondary, supplementary, or nested outcomes

(MI: motivational interviewing; CBT: cognitive behavioural therapy; DDT: Dynamic deconstructive psychotherapy; DBT: Dialectical behavioural therapy; FIIT: Family Intervention Telephone Tracking; ACT: Acceptance and Commitment Therapy; MBT: Mentalisation-based psychotherapy)

Study	Country	Participants at randomisation	Substance used	Mental health comorbidity	Age /sex if restricted	Setting of recruitment and intervention	Intervention	Comparison group	Outcome	Key findings
Barrowclough et al. (2010) [1]	UK	N=327	Alcohol/illicit drugs	Non-affective psychotic disorder	>16 years	Identified by care coordinators in mental health services Intervention delivered at patient's location of choice, usually their home	MI & CBT (up to 26 sessions over 12 months)	Standard psychiatric care	Self-harm in previous 12 months	At 12 months adjusted odds ratio: 1.38 (95% CI 0.65, 2.96) At 24 months aOR: 1.48 (95% CI 0.56, 3.91)
Gregory et al. (2010) [2]	USA	N=30	Alcohol	Borderline personality disorder	18-45 years	Recruited through range of clinical settings including emergency department and hospital settings Outpatient intervention	DDT (weekly 1:1 sessions +/- group therapy over 12-18 months)	Optimised community care	Self-harm (adapted 6 month version of the Lifetime Parasuicide Count)	Over 30-month follow-up Cohen's d=0.52 (in favour of control), z=3.02, p=0.002 An improvement was observed in both groups, but overall the absolute improvement was greater in the control group due to higher baseline levels of self-harm

Study	Country	Participants at randomisation	Substance used	Mental health comorbidity	Age /sex if restricted	Setting of recruitment and intervention	Intervention	Comparison group	Outcome	Key findings
Handley et al. (2013) [3]	Australia	N=303	Alcohol	Elevated depressive symptoms	>16 years	Referrals & self-referrals. Advertised via media, health, government & non-government services. Outpatient intervention	1x integrated therapy session +/- 9 sessions of one of: 1) depression-focused CBT/MI, 2) alcohol-focused CBT/MI, 3) therapist-delivered integrated CBT/MI, 4) computer-delivered integrated CBT/MI, or 5) person-centred therapy	Multiple intervention groups, comparison group unspecified	Suicidal ideation (item 9 Beck Depression Inventory II)	The following comparisons were made: -Brief (vs. 10 session) CBT - Alcohol (vs. depression) treatment - Integrated (vs. single-focused) treatment - Computer-delivered (vs. therapist-delivered) CBT - PCT (vs. CBT) At 12 months no between-group differences observed after controlling for baseline scores, no. treatments received & client characteristics
Kaminer et al. (2006) [4]	USA	N=144	Alcohol	Nil specified	14-18 years	Receiving CBT in existing RCT Outpatient intervention	Integrated CBT/MI aftercare <u>not</u> focused on suicidal behaviour (4 sessions over 12 weeks): telephone or face-to-face	No aftercare	Suicidal ideation (Suicidal Ideation Questionnaire – JR)	No evidence of between group differences at end of aftercare: p=0.6 (in person vs. no aftercare) p=0.43 (telephone vs. no aftercare)

Study	Country	Participants at randomisation	Substance used	Mental health comorbidity	Age /sex if restricted	Setting of recruitment and intervention	Intervention	Comparison group	Outcome	Key findings
Linehan et al. (1999) [5]	USA	N=28	Drugs: opioids, cocaine, amphetamines, sedatives, hypnotics, anxiolytics	Borderline personality disorder	18-45 years Females only	Referred by area clinicians Outpatient intervention	DBT (Weekly 1:1 &group sessions, phone calls as required for 12 months) Drug maintenance, tapering, then no drug replacement (4 months each)	Treatment as usual	Self-harm (Parasuicide History Interview)	No evidence of a between group difference at 12-month follow-up
Linehan et al. (2002) [6]	USA	N=24	Opioids	Borderline personality disorder	18-45 years Females only	Recruited from mental health clinics, needle exchange programs, drug clinics, methadone maintenance clinics, & non-profit HIV/AIDS prevention organisations	DBT (Weekly 1:1 & group sessions for 12 months) Opiate agonist therapy	Comprehensive validation therapy with 12-step (Weekly 1:1 & group sessions for 12 months) Opiate agonist therapy	Non-suicidal self-injury acts and suicide attempts (Parasuicide History Interview)	No evidence of a between group difference at 12-month follow-up
Nadkarni et al. (2017, 2017a) [7,8]	India	N=378	Alcohol	Nil specified	18-65 years Male only	Recruited from primary health centres Outpatient intervention at health centre/home/telephone as necessary	Counselling for alcohol problems (up to 4 sessions, weekly to fortnightly) & enhanced usual care	Enhanced usual care	Suicidal behaviour: suicide attempts in past 3 months & suicidal thoughts over past 2 weeks (Patient Health Questionnaire-9 item)	At 12 months adjusted prevalence ratio= 1.31 (95% CI: 0.66, 2.61)

Study	Country	Participants at randomisation	Substance used	Mental health comorbidity	Age /sex if restricted	Setting of recruitment and intervention	Intervention	Comparison group	Outcome	Key findings
Philips et al. (2018)[9]	Sweden	N=46	Alcohol/drugs	Borderline personality disorder	18-65 years	Recruited from outpatient addiction treatment services, social service case-finding & newspaper adverts Outpatient intervention	MBT & substance use disorder treatment (1:1 & group over 18 months)	Substance use disorder treatment	Self-harm (Deliberate Self-Harm Inventory-9) Suicide attempts	Over 18-month follow-up Self-harm: Cohen's d= –0.02 (in favour of control) F=0.78; p =0.39 Suicide attempts: Treatment group n=0; control group n=4; p=0.06
Wenze et al. (2015) [10]	USA	N=30	Alcohol/drugs	Bipolar affective disorder	≥18 years	Recruited from private psychiatric inpatients unit & outpatients Outpatient intervention	Adjunctive integrated treatment adherence programme based on FIIT & ACT (Face-to-face & telephone sessions incl with significant other, decreasing frequency over 6 months)	Enhanced assessment & monitoring	Suicidal ideation (Quick Inventory of Depressive Symptoms – Clinicians Rated, item 12)	During 6-month follow-up authors reported "a marginal effect of treatment condition on change over time." (p<0.1)
Zarghami et al. (2013) [11]	Iran	N=201	Heroin→ methadone	Nil specified	18-55 years	Recruited from methadone maintenance therapy clinics Outpatient intervention	Olanzapine (2.5mg-15mg) or sodium valproate (600mg-1000mg) involving twice weekly clinic visits over 12 weeks	Comparison group unspecified	Suicidality (included within Overt Aggression Scale-Modified)	Over 12-week follow-up authors reported: "no significant differences between the two groups" (F=0.10, p-value documented as <0.748)

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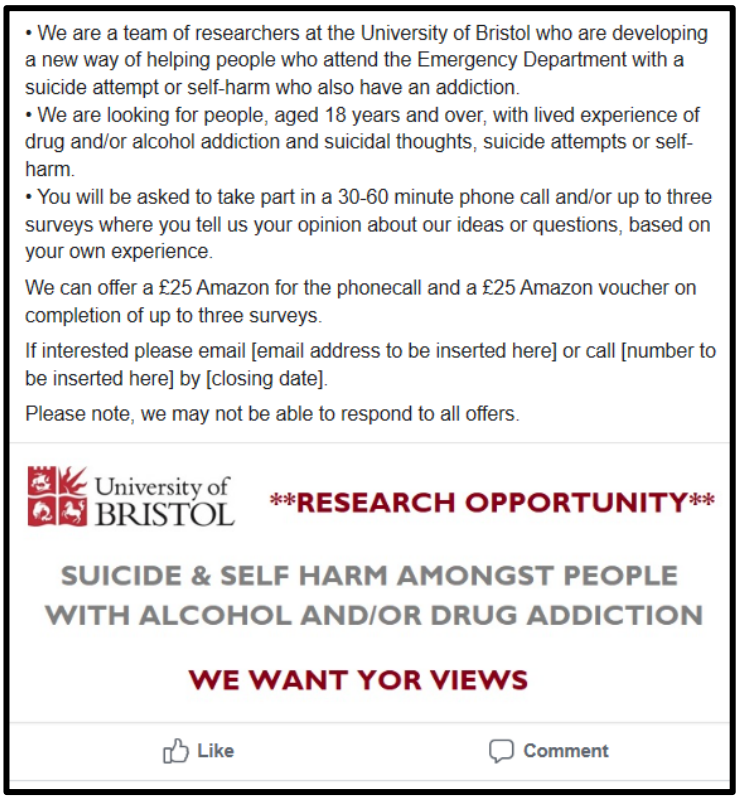
Appendix F : Example data extraction form

General information	
Title	
Lead author	
Year published	
Trial registration number	
Sponsor	
Funding source	
Study information	
Recruitment period	
Country	
Setting	
Population	
Inclusion/exclusion criteria	
Substance misuse diagnosis	
Specified mental health comorbidity	
Method	
Study design	
Analysis of relevant outcome (e.g., intention to treat)	
Intervention	
Type(s)	
Details	
Outcome	
Definition of relevant outcomes, units, criteria	
Time points at which measured	
Results	
No. participants in each group at randomisation	
Baseline demographics: age (mean (SD))	
Baseline demographics: gender (n male (%))	
Baseline measure of relevant	
Cumulative loss to follow-up	
Statistical results for relevant outcomes	

Appendix G : Example Facebook recruitment post



Appendix H : Pre-specified topic guide for telephone discussions

1) Do you think there should be any restrictions regarding the inclusion criteria for the intervention?

2) What do you think about the presented plans with regards to these aspects of intervention delivery:
   - frequency
   - timing
   - location

3) What do you think about the presented ideas for the content of the intervention? Do you have any specific examples of tools or techniques that you have found helpful?

[For staff] How would you advise managing suicide risk that emerges during the intervention?

4) Who do you think would be best to deliver the intervention?

5) [For patients] How can we maximise recruitment and retention of patients?

[For staff] How can we maximise engagement of staff?

6) [For staff] What supervision do you think is appropriate?

7) In a subsequent randomised controlled trial (RCT), what do you think should be the:
   - comparison intervention?
   - primary outcome?
   - secondary outcomes?

Appendix I : Delphi Survey Questions

Please provide explanations of your responses and/or alternative suggestions to each domain in the free text. This will allow circulation of a summary of reasoning for items where there is disagreement.

Please note: To ensure this survey is as broadly representative as possible, the term self-harm refers to both suicidal and non-suicidal self-injury.

Options for answers: strongly agree, agree, unsure/depends, disagree, strongly disagree

Intervention timing

The **first contact** should take place:

1) Immediately after assessment by the Liaison Psychiatry team, face-to-face
2) 24 hours after presentation to the Emergency Department, via phone
3) 1 week after presentation to the Emergency Department, via phone

Please provide explanations of your responses and/or alternative suggestions

The **second contact** will be by phone. This should take place:

1) 24 hours after first contact
2) 72 hours after first contact
3) One week after first contact

Please provide explanations of your responses and/or alternative suggestions

Subsequent contact should take place:

1) Weekly phone calls for one month
2) Weekly phone calls for one month plus weekly personalised texts in between phone calls

Please provide explanations of your responses and/or alternative suggestions

Content of the intervention

The intervention should involve:

Understanding the situation

1) Exploring the patient's views about underlying reasons for substance use & self-harm
2) Exploring the patient's understanding of the relationship between substance use & mental health
3) Providing advice on the relationship between substance use & mental health
4) Encouraging the patient to record the quantity of substances they have used in a diary to increase awareness
5) Encouraging the patient to record the number of episodes self-harm in a diary to increase awareness

Building motivation

6) Asking the patient to describe pros and cons of reducing their use of substances and self-harm behaviours
7) Eliciting the patient's thoughts and feelings about the function of substance use & self-harm in their life

Identifying and coping with triggers and urges

8) Asking the patient to identify triggers for substance use & self-harm
9) Encouraging the patient to record and discuss examples of antecedent/triggers, behaviour, consequence (ABC) in relation to substance use
10) Encouraging the patient to record and discuss examples of antecedent/triggers, behaviour, consequence (ABC) in relation to self-harm
11) Exploring alternative coping strategies and distraction techniques for managing urges to use substance & self-harm

Preparing for change

12) Jointly developing a safety plan
13) Monitoring the patient's progress in engaging with other community resources e.g., Alcoholics Anonymous or Samaritans
14) Jointly developing a plan for change with an explicit focus on both substance use & self-harm

Please provide explanations of your responses and/or alternative suggestions

Intervention delivery

The intervention should be delivered by the following staff:

1) First session and follow-up phone calls by researcher
2) First session and follow-up phone calls by Liaison Psychiatry nurses
3) First session by Liaison Psychiatry nurses, follow-up phone calls by researcher

Please provide explanations of your responses and/or alternative suggestions

Ongoing engagement

There is evidence to suggest that rewarding participants with substance use disorders for taking part in treatment can improve their engagement, mental health and likelihood of abstinence.

Which of these approaches should we use:

1) Gift vouchers for same amount at the end of each session
2) Gift vouchers of increasing amounts at the end of each session
3) No gift vouchers or other reward

Please provide explanations of your responses and/or alternative suggestions

Outcomes for a trial

These outcomes should be measured when testing the effectiveness of the intervention:

1) Hospital readmissions with self-harm
2) Self-reported suicidal thoughts, self-harm and suicide attempts
3) Self-reported use of substances
4) Self-reported mental distress
5) The patient's views regarding whether the intervention was as helpful in their recovery
6) Patient nominated outcome with regards to goals for drinking +/- self-harm

Please provide explanations of your responses and/or alternative suggestions

Appendix J : Delphi survey items with results

Item no.	Statement	Maximum number (%) in agreement (red: agree/strongly agree; green: disagree/strongly disagree; blue: unsure)								Number (%) who responded "yes"			
		Round 1				Round 2				Round 3			
		Lived experience (n=15)	Occupational experience (n=21)	Weighted average %	Item result	Lived experience (n=14)	Occupational experience (n=17)	Weighted average %	Item result	Lived experience (n=14)	Occupational experience (n=15)	Weighted average %	Item result
1	Immediately after assessment by the Liaison Psychiatry team, face-to-face	13 (86.7)	16 (76.2)	81.4	Include	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
2	24 hours after presentation to the Emergency Department, via phone	10 (66.7)	14 (66.7)	66.7	Discard	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
3	1 week after presentation to the Emergency Department, via phone	10 (66.7)	12 (57.1)	61.9	Discard	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
R2 addition	24-72 hours after first contact negotiated between the patient and person delivering the intervention	N/a	N/a	N/a	N/a	13 (92.9)	17 (100)	96.4	Include	N/a	N/a	N/a	N/a
4	24 hours after first contact	11 (73.3)	14 (66.7)	70.0	Re-test	10 (71.4)	12 (70.6)	71.0	Discard	N/a	N/a	N/a	N/a
5	72 hours after first contact	9 (60.0)	17 (81.0)	70.5	Re-test	8 (57.1)	13 (76.5)	66.8	Discard	N/a	N/a	N/a	N/a
6	One week after first contact	8 (53.3)	12 (57.1)	45.2	Re-test	8 (57.1)	12 (70.6)	63.9	Discard	N/a	N/a	N/a	N/a
7	Weekly phone calls for one month	10 (66.7)	12 (57.1)	61.9	Re-test	8 (57.1)	14 (82.4)	69.7	Discard	N/a	N/a	N/a	N/a

Item no.	Statement	Maximum number (%) in agreement (red: agree/strongly agree; green: disagree/strongly disagree; blue: unsure)								Number (%) who responded "yes"			
		Round 1				Round 2				Round 3			
		Lived experience (n=15)	Occupational experience (n=21)	Weighted average %	Item result	Lived experience (n=14)	Occupational experience (n=17)	Weighted average %	Item result	Lived experience (n=14)	Occupational experience (n=15)	Weighted average %	Item result
8	Weekly phone calls for one month plus weekly personalised reminder texts in between phone calls	11 (73.3)	16 (76.2)	74.8	Re-test	11 (78.6)	15 (88.2)	83.4	Include	N/a	N/a	N/a	N/a
9	Exploring the patient's views about underlying reasons for substance use & self-harm	13 (86.7)	20 (95.2)	91.0	Include	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
10	Exploring the patient's understanding of the relationship between substance use & mental health	14 (93.3)	21 (100.0)	96.7	Include	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
11	Providing advice on the relationship between substance use & mental health	13 (86.7)	17 (81.0)	83.8	Include	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
12	Encouraging the patient to record the quantity of substances they have used in a diary, to increase awareness	9 (60.0)	16 (76.2)	68.1	Re-test	8 (57.1)	14 (82.4)	69.7	Re-test	9 (64.3)	12 (80)	72.1	Discuss
13	Encouraging the patient to record the number of episodes of self-harm in a diary to increase awareness	8 (53.3)	14 (66.7)	60.0	Re-test	7 (50.0)	13 (76.5)	63.2	Re-test	8 (57.1)	12 (80)	68.6	Discuss

Item no.	Statement	Maximum number (%) in agreement (red: agree/strongly agree; green: disagree/strongly disagree; blue: unsure)								Number (%) who responded "yes"			
		Round 1				Round 2				Round 3			
		Lived experience (n=15)	Occupational experience (n=21)	Weighted average %	Item result	Lived experience (n=14)	Occupational experience (n=17)	Weighted average %	Item result	Lived experience (n=14)	Occupational experience (n=15)	Weighted average %	Item result
14	Asking the patient to discuss the pros and cons of reducing their use of substances and self-harm behaviours	12 (80.0)	19 (90.5)	85.2	Include	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
15	Eliciting the patient's thoughts and feelings about the function of substance use & self-harm in their life	14 (93.3)	21 (100.0)	96.7	Include	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
16	Asking the patient to identify triggers for substance use & self-harm	13 (86.7)	20 (95.2)	91.0	Include	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
17	Encouraging the patient to record and discuss examples of antecedent/triggers, behaviour, consequence in relation to substance use	12 (80.0)	19 (90.5)	85.2	Include	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
18	Encouraging the patient to record and discuss examples of antecedent/triggers, behaviour, consequence in relation to self-harm	13 (86.7)	19 (90.5)	88.6	Include	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a

Item no.	Statement	Maximum number (%) in agreement (red: agree/strongly agree; green: disagree/strongly disagree; blue: unsure)								Number (%) who responded "yes"			
		Round 1				Round 2				Round 3			
		Lived experience (n=15)	Occupational experience (n=21)	Weighted average %	Item result	Lived experience (n=14)	Occupational experience (n=17)	Weighted average %	Item result	Lived experience (n=14)	Occupational experience (n=15)	Weighted average %	Item result
19	Exploring alternative coping strategies and distraction techniques for managing urges to use substance & self-harm	13 (86.7)	19 (90.5)	88.6	Include	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
20	Jointly developing a safety plan	15 (100.0)	21 (100.0)	100.0	Include	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
21	Monitoring the patient's progress in engaging with other community resources e.g. Alcoholics Anonymous or Samaritans	14 (93.3)	16 (76.2)	84.8	Include	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
22	Jointly developing a plan for change with an explicit focus on both substance use & self-harm	14 (93.3)	19 (90.5)	91.9	Include	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
23	First session and follow-up phone calls by researcher	8 (53.3)	10 (47.6)	40.5	Re-test	9 (64.3)	10 (58.8)	61.6	Re-test	1 (7.1)	0 (0)	3.6	Discard
24	First session and follow-up phone calls by Liaison Psychiatry nurses	12 (80.0)	13 (61.9)	71.0	Re-test	12 (85.7)	12 (70.6)	78.2	Re-test	13 (92.9)	13 (86.7)	89.8	Include
25	First session by Liaison Psychiatry nurses, follow-up phone calls by researcher	8 (53.3)	12 (57.1)	41.9	Re-test	6 (42.9)	7 (41.2)	33.3	Re-test	5 (35.7)	4 (26.7)	31.2	Discard

Item no.	Statement	Maximum number (%) in agreement (red: agree/strongly agree; green: disagree/strongly disagree; blue: unsure)								Number (%) who responded "yes"			
		Round 1				Round 2				Round 3			
		Lived experience (n=15)	Occupational experience (n=21)	Weighted average %	Item result	Lived experience (n=14)	Occupational experience (n=17)	Weighted average %	Item result	Lived experience (n=14)	Occupational experience (n=15)	Weighted average %	Item result
26	Gift vouchers for the same amount at the end of each session	7 (46.7)	14 (66.7)	56.7	Re-test	6 (42.9)	12 (70.6)	56.7	Re-test	10 (71.4)	9 (60.0)	65.7	Discuss
27	Gift vouchers of increasing amounts at the end of each session	8 (53.3)	10 (47.6)	50.5	Re-test	5 (35.7) 5 (35.7)	8 (47.1)	41.4	Re-test	2 (14.3)	4 (26.7)	20.5	Discuss
28	No gift vouchers or other reward	7 (46.7)	8 (38.1) 8 (38.1)	42.4	Re-test	5 (35.7) 5 (35.7)	9 (52.9)	44.3	Re-test	4 (28.6)	3 (20.0)	24.3	Discuss
29	Hospital readmissions with self-harm	12 (80.0)	18 (85.7)	82.9	Include	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
30	Self-reported suicidal thoughts, self-harm and suicide attempts	13 (86.7)	19 (90.5)	88.6	Include	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
31	Self-reported use of substances	11 (73.3)	18 (85.7)	79.5	Re-test	8 (57.1)	14 (82.4)	69.7	Re-test	10 (71.4)	14 (93.3)	82.4	Include
32	Self-reported mental distress	12 (80.0)	18 (85.7)	82.9	Include	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
33	The patient's views regarding whether the intervention was helpful in their recovery	13 (86.7)	19 (90.5)	88.6	Include	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
34	The patient's nominated outcome with regards to goals for drinking +/- self-harm	9 (60.0)	17 (81.0)	70.5	Re-test	7 (50.0)	17 (100.0)	75.0	Re-test	10 (71.4)	14 (93.3)	82.4	Include