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Pilot and Feasibility Studies

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A feasibility study of a co-designed intervention to manage benzodiazepine dependence and high-risk use in those receiving opioid agonist treatment

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Abstract

Background Problematic benzodiazepine use alongside opioids contributes to drug-related deaths among people who use drugs. Clinical management varies considerably. An intervention to address the root causes of benzodiazepine use with opioids has been developed, which included maintenance prescribing of diazepam with anxiety, sleep, and pain management, harm reduction, and safety conversations. This study tested the feasibility of recruiting and retaining people in the intervention to address 'street' benzodiazepine use. Outcome measures and economic evaluation data collection were piloted to determine the feasibility of a future trial.

Methods The study tested the intervention in three sites (Grampian, Lothian and Fife) with a target of 15 patients per site. Inclusion criteria were people who were stable on opioid agonist treatment (OAT) with ongoing street benzodiazepine use. The intervention duration was 4–6 months depending on the site. Validated tools were used to monitor outcomes covering: anxiety (GAD-7), depression (PHQ-9), quality of life (EQ-5D-5L), substance use recovery (SURE), and cognitive function (ACE-III). 'Street' drug use was measured through oral fluid tests and self-report. Resource use data were collected from an NHS perspective using a bespoke questionnaire to inform a future economic evaluation.

Results After revisions to the inclusion criteria, 39 people were recruited (9 women, 30 men), mean age: 42 yrs. Almost all had diagnosed anxiety ($n=38$) and depression ($n=39$,); sleep problems were common ($n=34$), and over half had chronic pain ($n=21$). Retention was 77% at final data collection at 4–6 months ($n=30$). There were indications of improvement in anxiety, depression, self-reported recovery, and quality of life. Cognitive function was stable. Self-reported 'street' benzodiazepine use reduced from 100% ($n=39$) at baseline to 35% at follow-up ($n=10$).

The economic data indicated good completion of the resource use and quality of life questionnaires, but this was dependent on the participants attending clinic appointments.

Conclusion Recruitment was feasible, and there were signs of clinical improvements across anxiety, depression, quality of life, and recovery measures. Findings justify a randomised controlled trial of this intervention vs. standard care of a benzodiazepine tapering dose. However, accurate, objective measurement of current 'street' drug use is required.

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Keywords Benzodiazepines, Diazepam, Opioid dependence, Drug harms, Cost-effectiveness, Intervention, Feasibility, Trial

What uncertainties existed regarding the feasibility?

This feasibility study addressed uncertainty in whether a bespoke intervention that addressed the motivations for use, alongside clinician anxiety around the risks of prescribing, could be delivered in practice in drug treatment settings. In addition, there was uncertainty over the feasibility of recruiting people and whether patients and clinicians would be willing to participate.

What are the key feasibility findings?

Following revisions of the inclusion criteria, recruitment proved feasible. This was enabled by a proactive approach to recruitment at the local site level. Inclusion criteria were adjusted during the study to remove restrictions on time in opioid agonist treatment (OAT) prior to recruitment. There were improvements across clinical measures of anxiety, depression, self-reported substance use, and quality of life.

What are the implications of the feasibility findings for the design of the main study?

- Recruitment was facilitated by positive and proactive research nurses. This needs to be incorporated in a larger trial with a control group.
- Oral fluid testing data was incomplete and therefore inconclusive. The method of self-report was insufficiently granular to identify reductions in quantity of use or frequency of binge use.
- Furthermore, the nature of available 'street' drugs changed during the study so a full trial would need to monitor the emergence of 'new' drugs and patterns in street drug/benzodiazepine use to ensure testing is reliable.
- Fidelity to the prescribing component of the intervention was mixed and clarity regarding the protocol, including further research and good clinical practice training being essential in a large trial.

Background

Drug-related deaths in Scotland are over three times higher than the rest of the UK and the highest in Europe [1]. Polydrug use is one of the defining features of Scottish drug deaths, with more than one drug evident in 79% of deaths in 2022. The most prevalent concurrently used drug groups identified in deaths are opioids with benzodiazepines. Opioids remain the most prevalent drug (evident in 82% of cases in 2022), but 57% of all drug-related deaths had a benzodiazepine implicated [1], a slight reduction from over 60% in 2020 and 2021 [2].

The prevalence of unregulated benzodiazepine use is known to be higher among people with other substance use disorders, especially problematic opioid and/or alcohol dependence. A systematic review identified a high prevalence (typically > 40%) among people on OAT [3]. McAuley et al. examined the phenomenon of benzodiazepine use in people experiencing problem drug use in Scotland. They documented the long-standing relationship of problem drug use with benzodiazepines dating back to the 1980s and the cycles of available benzodiazepines which subsequently emerged in drug death statistics, from prescribable temazepam to diazepam to non-prescribable phenazepam to etizolam, with the content of tablets being extremely variable. These cycles of changes in the benzodiazepine(s) being used (available), policy change, and increased control via classification are ongoing. Authors concluded that a 'safer supply' of benzodiazepines, as a harm reduction measure, was urgently required [4].

Maintenance prescribing of benzodiazepines is not currently recommended in clinical guidance, with deprescribing recommended for people receiving OAT who additionally use benzodiazepines [5]. Public Health England (PHE) recommends deprescribing, whilst noting that limiting prescribed supplies can have adverse effects for people who may be dependent on them [6]. Research evidence has few intervention-based studies. A 2018 Cochrane review concluded, "it is not possible to draw firm conclusions regarding pharmacological interventions to facilitate BZD discontinuation in chronic users" [7].

However, there is an international evidence base on the effect of co-prescribing of opioids with benzodiazepines, which is largely based on epidemiological studies using national datasets. Epidemiological studies of co-prescribing of opioids and benzodiazepines found that all-cause mortality risk was increased in five studies [8–12]. Overdose death risk was noted in a large US study [10] and in England [9]. A Scottish study found

that overdose risk increased with methadone co-prescribed with benzodiazepines but not with buprenorphine [12].

However, co-prescribing of OAT and benzodiazepines improved retention in treatment in some studies [9, 12, 13]. Improved retention in treatment is an important clinical consideration to reduce the risk of relapse and overdose death. Sordo et al.'s meta-analysis of mortality risk during and after OAT provides strong evidence of reduced mortality with both methadone and buprenorphine whilst in treatment [14]. Furthermore, keeping people in treatment may allow time to address underlying causes, e.g. anxiety, trauma, and pain that may contribute to street BZD use [15]. A large epidemiological study analysed the association of benzodiazepine discontinuation (deprescribing) with mortality in prescribed, stable long-term benzodiazepine therapy [16]. Data was stratified by baseline opioid exposure. In the discontinuation group, the mortality risk was 1.6 times that of non-discontinuers, which was the same for those with baseline opioid exposure, raising the potential of unintended consequences of blanket policies of benzodiazepine discontinuation [16].

Confounders such as co-morbidities may exist in these epidemiological studies because comorbidity is increased in people who use benzodiazepines. Brands et al. noted the different clinical profile of people who use benzodiazepines with opioids, highlighting that there are more women and more psychiatric conditions, providing evidence that concurrent users of benzodiazepines with opioids have more co-morbid risk [17].

Even though the risk of harm from 'street' benzodiazepine use is clear from the drug death statistics in Scotland, some prescribers remain reluctant to co-prescribe benzodiazepines with OAT because of the lack of definitive evidence of benefit and concern about adverse effects.

Considering evidence of ongoing high levels of street benzodiazepine use and the lack of good quality evidence, a bespoke, co-designed intervention was developed that considered people's motivations for use alongside what was clinically deliverable. The intervention development process is described in detail in a separate paper [15]. In brief, using a logic model, key inputs (views of stakeholders including those with lived experience, guidance, and research evidence) and outcomes (e.g. clinical benefits such as reduced anxiety, reduced drug use) were mapped then refined through an iterative process into an intervention protocol. This was done through three intervention development workshops and three corresponding meetings with the lived experience group. The resulting intervention was a prescription for diazepam at a maximum of 30mg daily, psychosocial support in the form of management of anxiety, sleep, and chronic pain, psychotrauma support, and harm reduction advice which included 'safety conversations' with a focus on benzodiazepine use. Nurses delivering the intervention received bespoke training to enable them to support patients [15]. This feasibility study tested this intervention in practice.

The aim of the study was to conduct a stand-alone non-randomised single-arm feasibility study of a new intervention, described above, to address 'street' benzodiazepine use in people who also use opioids, in three sites. The study aimed to consider the feasibility of a future randomised controlled trial by considering the following research questions:

1. Is it possible to recruit people who use 'street' benzodiazepines (e.g. etizolam, alprazolam) for a feasibility trial of a benzodiazepine intervention?
2. Will people receiving OAT engage with and be retained in a benzodiazepine intervention?
3. For those that do engage, does the intervention reduce 'street' benzodiazepine use and improve mental health, quality of life, recovery from drug use?
4. What was the level of retention in treatment and satisfaction with the care provider?
5. Is it feasible to collect resource use data to inform a cost-effectiveness study in the future?
6. What were the experiences of those involved in the trial in relation to recruitment, retention, and fidelity?

Methods

Study design

The study used mixed methods. Quantitative data was collected at baseline and monthly intervals. At baseline, data was also collected on demographics, health, drug use history, readiness to change, and cognitive function. Monthly outcome data was collected on anxiety, depression, quality of life, and substance use and resource use. At final data collection (4–6 months), cognitive function and satisfaction with the care provider delivering the intervention were collected. Qualitative interviews with the clinical team provided insight into recruitment and inclusion criteria.

Setting and sites

The intervention was tested in NHS addiction treatment services in three Scottish sites: (i) Aberdeen City, (ii) Edinburgh and (iii) Fife (via sub-clinics in Dunfermline and Kirkcaldy). Sites were chosen to reflect both a geographical variation and a range of current practice and context. In Aberdeen, there has traditionally been little benzodiazepine prescribing. In Fife, there was some tapered dose prescribing and some maintenance. In

Edinburgh, there has been a mixed approach to prescribing, with some GP prescribing of benzodiazepines.

Patient characteristics and recruitment

Inclusion criteria were people in NHS drug treatment services who have achieved a stable dose of OAT (methadone or buprenorphine); who had the capacity to provide informed consent, and who were experiencing ongoing risk of harm from street benzodiazepine use. 'Risk of harm' was defined as: an overdose event in the last 6 months in which a street benzodiazepine was implicated (from toxicology or clinical profile) *and/or* persistent self-report of daily street benzodiazepine use that is confirmed by toxicology screening *and/or* self-report of regular use of high doses/quantities of street benzodiazepines. (Clinical judgment was required as to what constituted high dose given the lack of information on content/reported strength of tablets purchased on the street market).

Exclusion criteria were co-occurring harmful alcohol use, co-occurring harmful stimulant use, pregnancy, participation in any other research study, diagnosed serious mental illness or severe cognitive impairment that clinical staff considered to pose a risk to safety (of patient or staff), non-English speaking, and lack of capacity to provide informed consent. 'Harmful' alcohol or stimulant use was at a level that constituted the dominant problem for that individual as this might require a different approach to the emphasis on benzodiazepine use in the psychosocial component of the intervention (clinical judgement was required).

Potential participants meeting the inclusion criteria were given an information sheet about the study when their clinician considered them sufficiently stable on OAT. At the subsequent appointment, they were asked if they wanted to continue with standard treatment (OAT alone or OAT plus a short benzodiazepine detoxification programme, depending on local practice) or join the feasibility trial. Those interested in joining the trial were referred to the intervention nurse for further discussion. If willing, informed consent was taken, and baseline data were collected with the researcher.

Sample size justification

This feasibility study was required to address key uncertainties ahead of a future pragmatic trial, particularly around identifying and recruiting eligible participants, retaining them in the intervention, and establishing a reliable estimate of the attrition rate [18]. We therefore set a target sample size of 15 participants per site (45 in total), which we judged sufficient to estimate these feasibility parameters with reasonable precision while remaining achievable within the available budget, study timeframe, and site capacity.

Delivery of the intervention at sites

In each site, a specialist nurse employed by the drug treatment service was seconded to the trial 1 day per week. In Fife, two nurses worked a half day each. All research nurses were supported by a senior medical clinician (the local Principal Investigator). Patient participants attended the intervention clinic fortnightly for an appointment lasting up to an hour. Ongoing monitoring of mental health, substance use, and quality of life as part of the intervention was collected monthly by the intervention nurse.

Site training was provided covering the study protocol and intervention delivery. Intervention-specific psychological training (e.g. anxiety management, relapse prevention, sleep management, and advanced psychotrauma education) was provided by an experienced freelance trainer in this field. Training was delivered online [15].

Delays in local approval processes at one site reduced the available time for data collection. Whilst participants were able to receive the intervention for the planned 6 months, final follow-up data collection had to take place at 4 months to allow time to complete the data analysis within the funded study period.

Data collection

Quantitative data collection

Baseline data collection was undertaken by the researcher using a structured questionnaire designed for the study and based on previously used data collection tools. These covered demographics including age, gender, housing, length of drug use, and concurrent diagnosed health issues. In addition, cognitive ability was assessed using the Addenbrooke's Cognitive Evaluation (ACEIII).

Quality of life (EQ-5D-5L), anxiety (e.g. GAD-7), and depression (e.g. PHQ-9), substance use recovery evaluator (SURE), and service use data were collected at baseline and monthly thereafter by the intervention nurse. These were to aid clinical monitoring and provide resource use data.

Final data collection was undertaken at 4–6 months by the researcher. This covered cognitive ability (ACE III), satisfaction with the professionals providing care (Consultation and Relational Empathy (CARE) measure) [19] in addition to quality of life (EQ-5D-5L), anxiety (e.g. GAD-7), depression (e.g. PHQ-9), and the substance use recovery evaluator (SURE).

Substance use was measured using patient self-report and monthly oral fluid drug screening specific to this study, conducted by the intervention nurse.

Economic resource use data

Economic data collected assessed the ease of collecting resource use and quality of life information by piloting the use of data collection instruments. The study perspective was that of the health care provider (the National Health Service), but we also collected participants' out of pocket expenses. The data collected included the use of the primary, pharmacy and secondary care services.

Cost of providing the intervention

The resource use and quality of life data questionnaires were completed at the clinic visit at baseline, and every month over the follow-up period. The cost of the intervention was calculated based on resources used. These included the number of appointments, the grade of staff, time spent on the appointments, the pharmacological treatment, prescribed medication (diazepam), and oral fluid tests. Data on the utilisation of primary (GP doctor and nurse) and secondary healthcare (outpatient and inpatient) utilisation were also collected. These included the number and type of visits to the different health care providers and the use of ambulance services. Data were combined with the unit cost of these resources to estimate the average cost per patient visit of the intervention. Unit cost data came from published sources, namely The Unit Cost of Health and Social Care unit costs, NHS England National Reference of Costs, National Schedule of Unit Costs: Year 2020–2021, and the medication unit cost from the Scottish Drug Tariff [20–23]. See supplementary material.

Quality of life

Quality of life data were collected using the EQ-5D-5L generic instrument [24]. This instrument assessed the quality of life in terms of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Quality-adjusted life years (QALYs) were calculated by applying existing UK general population utility weights (obtained using the Time trade-off method) to the reported EQ-5D-5L health status. Analyses included data completeness and descriptive statistics.

Qualitative data collection

Interviews were conducted with all clinicians and nurses who were part of the intervention delivery in each site ($n=9$). Semi-structured interviews were conducted face to face or online using Microsoft Teams. Interviews covered the fidelity to the intervention as well as the experience of the intervention delivery, views of prescribing and psychosocial components, and the future potential of the intervention. However, only views relating to recruitment, retention, and study fidelity are reported here. Interviews were conducted with a sample of patients at 4–6 months ($n=15$) to explore their experience of the intervention, and full findings will be reported in a separate paper.

Data management and analysis

Quantitative analysis

All quantitative data were entered into SPSS v28 [25] for the generation of descriptive statistics. Before analysis, additional variables were created to group participants according to their follow-up status. A further variable coded the completed participants into those who received four versus 6 months of intervention. A final follow-up variable was created which combined those who completed data collection at 4 months with those who completed at 6 months.

Tables of descriptive statistics were generated to describe participant characteristics (demographics, social background, health problems) at baseline, and to compare study measures at baseline and follow-up.

Categorical and ordinal variables were described using frequency and percentage, and descriptive statistics (mean, standard deviation, minimum, maximum) for continuous variables. As a feasibility study, there was no statistical testing of the effect of the intervention (before and after), and data is presented only to indicate the potential for measuring change in a future trial.

Qualitative analysis

Nurse and clinician interview data was analysed using a combination of deductive and inductive methods. We sought feedback on specific topics (deductive) through a topic guide covering the ability of recruitment, experience of delivery of the intervention, prescribing, and psychosocial components, retention of patients, and fidelity to the protocol. In addition, themes emerging through discussion were highlighted (inductive). A coding framework was developed and applied to the full dataset. Specific codes relating to recruitment, retention, and study fidelity are described here. Within each of these areas, the breadth and range of experience and views are described.

Economic analysis

The primary economic analysis focuses on questionnaire completion rates and item level rates of missing data at each time point for both resource utilisation as well as quality of life data. The study group also explored the feasibility of conducting a cost-effectiveness analysis using the resource use and quality of life data.

Results

Recruitment and retention

Recruitment started in one site in July 2022 but was initially slow, finishing in that site in February 2023. This

was due to a combination of the initial inclusion criteria of people who had been in OAT treatment for no longer than 3 months being too limiting, and initial low nurse confidence in recruitment. Following discussion with local clinical teams and the Study Advisory Group, inclusion criteria were revised to include any length of time in OAT treatment, stable OAT and harmful use of street benzodiazepines. Following these changes, in the second site recruitment took place from 30/09/22 to 09/01/23) and in the third site recruitment took place from 01/02/23 to 28/02/23.

Forty-one participants were referred to the researcher for inclusion in the study. However, during baseline data collection, it became clear that two participants did not meet the inclusion criteria, one due to predominant alcohol dependence and the other due to uncertainty that there was benzodiazepine use. Both patients were subsequently excluded and 39 people were included in the study.

Follow up data was finalised by 30/06/23. Thirty participants were retained in the study, giving a retention rate of 77% at final follow-up. Of the nine people who did not complete the study, one withdrew voluntarily, one moved away, one was remanded in custody, and six were discharged by the clinical team for non-attendance. Figure 1 describes participant retention, withdrawal, and data collection. No unintended harms or effects were recorded.

Quantitative measures

Baseline characteristics

There were 30 men and nine women recruited with a mean age of 42 (SD 7, min 22, max 56) years. Nine people were recruited in Aberdeen, with 15 in both Fife and Edinburgh. Baseline social and health characteristics (self-reported) are presented in Table 1. There is a high level of experience of convictions (89.7%, $n=35$), prison (59%, $n=23$), and thoughts of self-harm (71.8%, $n=28$).

Regarding health status at baseline, diagnosed anxiety and depression were reported in almost all cases ($n=38$ and 39 respectively). Chronic pain and sleep problems were common, with 28 and 34 reporting these respectively. Other health problems included diagnosed epilepsy, hernia, collapsed diaphragm, stomach acid dysregulation, leg ulcers, and underactive thyroid, nerve damage, amenorrhea, severe mood disorder, liver, kidney, and gall bladder problems. Regarding OAT medication, the majority of participants were on methadone ($n=33$), with four participants on depot buprenorphine and two receiving sublingual buprenorphine.

Outcomes: baseline vs. final data collection (4–6 months)

Baseline data is presented for all patients recruited and for those with final data available. Mean score for anxiety and depression reduced between baseline and follow-up, indicating improvement in these symptoms. Cognitive functioning remained stable between baseline

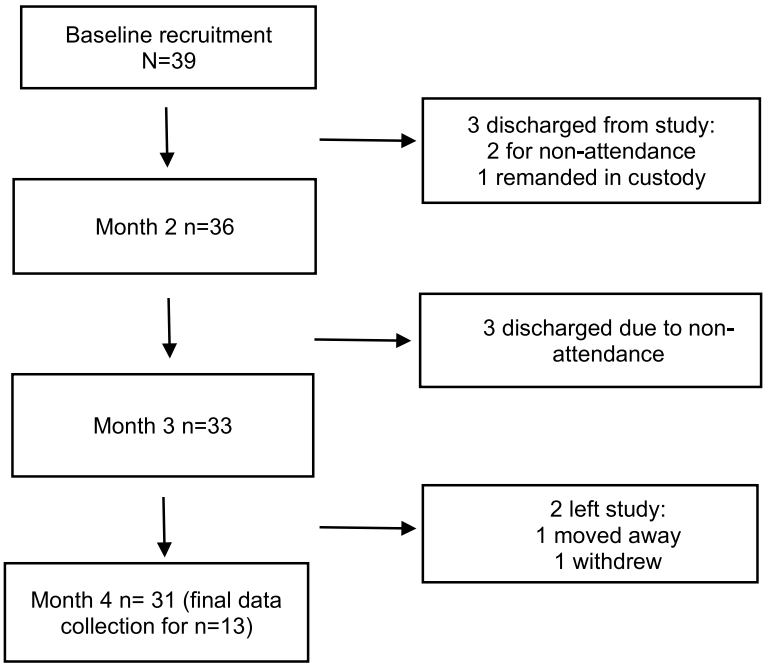

Fig. 1 Participant recruitment and retention flowchart

Table 1 Sites and demographic characteristics of the participants at baseline

Demographics		*N* = 39	(%)
Site	Grampian	9	23
	Lothian	15	38.5
	Fife	15	38.5
Gender	Male	30	77
	Female	9	23
Age (years)	Mean	42	
	Std. Dev	7	
	Min	22	
	Max	56	
Relationship status	Single	30	77
	In relationship	8	20
Health status[a]	Depression	39	100
	Anxiety	38	97.4
	Sleeping problems	34	87.2
	Chronic pain	28	71.8
	Other mental health	23	59.0
	Breathing	16	41.0
	Heart condition	12	30.7
	Blood borne virus	13	33.3
	other	33	84.6
Ethnicity	White Scottish/British	39	100
Education	Secondary (High) School	28	71.8
	Further/Higher Education	11	28.2
Convictions	Yes	35	89.7
Number of convictions *(if Convictions = Yes)*	1–5	8	22.9
	6–15	16	35.7
	Over 15	11	31.4
Ever been to prison	No	16	41
	Yes	23	59
Residential/foster care experienced	No	30	77
	Yes	9	23
Where currently sleeping	Own home	31	79.5
	Temporary accommodation	8	20.5
Ever thought of harming self	No	11	28.2
	Yes	28	71.8

[a] Health status is based on self-report at baseline

and follow-up. Substance use recovery improved between baseline and follow-up (Table 2).

Substance use (self-report)

Self-reported 'street' benzodiazepine, opioid and gabapentinoid (pregabalin and gabapentin) use reduced over time (Table 3). However, there was no change in cocaine or cannabis use. Alcohol use was not included in data collection. At baseline, there were 57 reports of 'street' benzodiazepines used across 39 participants, as some reported more than one benzodiazepine being consumed.

Substance use (oral fluid tests)

Oral fluids tests were conducted monthly from months 2 to 5. Data were incomplete due to some tests going missing in transit to the testing laboratory and some people having difficulty due to dry mouths. Methadone and buprenorphine have some missing positive toxicology. It is not clear whether this was because these drugs were

Table 2 Outcome measurements

	Baseline all recruited			Baseline for those with follow-up			Final data collection point		
	Mean	**SD**	***N***	**Mean**	**SD**	***N***	**Mean**	**SD**	***N***
PHQ-9	18.8	5.1	38	18.7	4.4	29	13.1	6.6	27
GAD-7	17.4	4	38	17.5	3.2	30	13.1	5.7	30
ACE III									
Attention	15.8	2.1	39	15.8	2.2	30	15.6	2.2	27
Memory	18.3	5.4	39	17.9	5.6	30	18.9	5.2	27
Verbal fluency	9.5	2.8	39	9.1	2.8	30	9.9	2.7	27
Language	23.5	2.0	39	23.6	2.0	30	24.0	1.6	25
Visuospatial processing	7.3	1.1	39	7.2	1.2	30	7.4	1.2	25
Total	74.4	9.9	39	73.5	9.7	30	75.9	9.9	25
SURE									
Substance use	10.6	2.6	37	10.7	2.4	29	15.7	2.1	30
Self-care	8.1	2.0	37	8.1	2.0	29	11.0	3.0	29
Relationships	9.7	1.6	37	9.7	1.6	29	10.7	1.5	30
Material resource	7.5	1.4	37	7.4	1.5	29	8.0	1.5	30
Outlook on life	4.5	1.5	37	4.6	1.6	29	6.7	2.2	30
Total	40.6	5.6	37	40.4	5.2	29	52.3	8.0	30

PHQ score 0 to 27 (higher = more depressed)

GAD-7 score 0 to 21 (higher = more anxious)

ACE III 0–100 (higher score better cognitive functioning)

SURE 0–63, (higher score = better self-perceived recovery)

Table 3 Self-reported substance use

	Baseline no of participants reporting use	%	Number reporting use at final data collection	%
Benzodiazepines (any)	39	100	10	35.7
Opioids	12	30.7	6	21.4
Cocaine	13	33.3	13	46.4
Gabapentinoids	9	23.1	4	14.3
Cannabis	18	46.1	18	64.3

not present and may have been diverted or whether this related to the testing procedure (Table 4).

Satisfaction with care provider

The CARE measure, completed at follow up, indicated a high level of satisfaction, with the majority of participants noting excellent responses across all questions. See Fig. 2.

Economic resource use

The intervention

Questionnaires were well completed for all who attended the clinic visits. The participants were seen by a band 6 community psychiatric nurse twice every month. Each appointment was scheduled for 1 hour. The number of completed questionnaires reduced with time. The baseline questionnaire was complete for all the participants, and there were no missing data. Thirty-five questionnaires were completed at month 2, 29 at month 3, 20 at month 4 and 16 at month 5 and 17 at 6 months. Data were missing for some of the participants as they did not reach the 6 months point before the completion of the study, while some participants were missing follow-up data as they did not attend the clinic.

Frequency of health service use

Outpatient visits were the most reported resource use. Most outpatient visits were to clinics and centres that provided addiction support services. There were very

Table 4 Positive toxicology from oral fluid testing ($n = 39$)

	Month 2		Month 3		Month 4		Month 5	
n	**24**		**22**		**13**		**11**	
	Yes *N*	**%**	**Yes *N***	**%**	**Yes *N***	**%**	**Yes *N***	**%**
Opiates	5	20.8	8	36.4	4	30.8	5	45.5
Amphetamines	0	0.0	2	9.1	0	0.0	0	0.0
Cocaine	15	62.5	13	59.1	8	61.5	6	54.5
Methadone	18	75.0	17	77.3	10	76.9	8	72.7
Buprenorphine	3	12.5	1	4.5	0	0.0	2	18.2
Gabapentin	1	4.2	1	4.5	0	0.0	0	0.0
Pregabalin	8[a]	33.3	6	27.3	3	23.1	2	18.2
Diazepam	24[b]	100.0	21	95.5	13	100.0	11	100.0
Alprazolam[c]	2	8.3	2	9.1	0	0.0	0	0.0
Etizolam[b]	1	4.2%	0	0.0%	0	0.0%	1	9.1%

[a] Pregabalin includes 1 prescribed

[b] Diazepam was prescribed but may include street sourced diazepam

[c] Alprazolam and etizolam were known available 'street' benzodiazepines at the start of the study so were specifically tested for

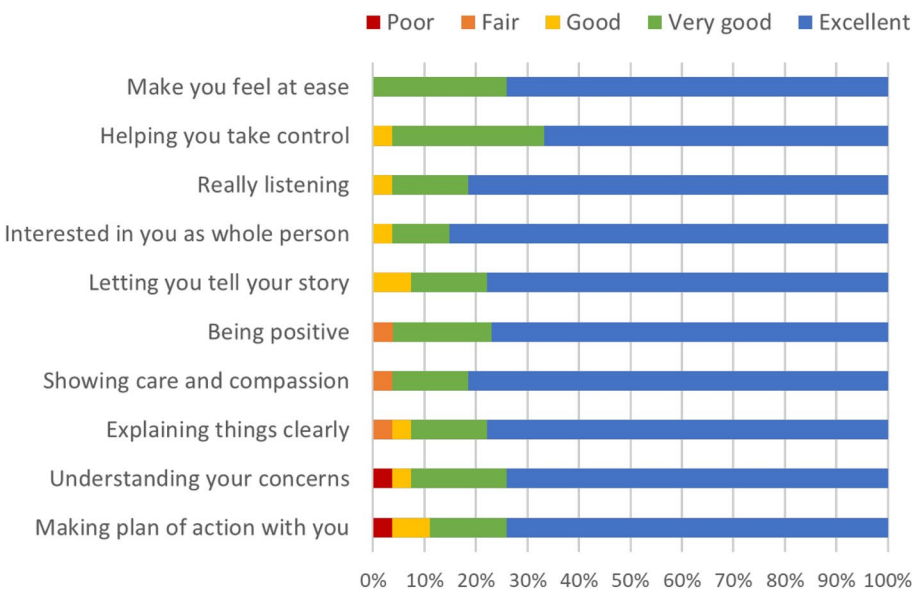

Fig. 2 Consultation and relational empathy measure ($n = 27$)

few visits to the GP and no visits to the emergency department.

Health-related quality of life

All the participants had EQ-5D-5L data at baseline and the numbers that had data in the follow-up period varied, 35 at the 2nd visit, 29 at the 3rd visit, 20 at the 4th, and 20 at the final visit. The frequency and pattern of the responses were assessed. Most of the participants had some level of problems with each of the five domains. The domain with the most reported slight to severe levels of problems was anxiety and depression.

Over time the participants' mean utility scores ranged from 0.349 (baseline) to 0.508 (month 5). Although the score increased over time, it is difficult to draw conclusions about the trend due to the small numbers. Similarly, the self-rated quality of life Visual Analog score (VAS) improved, ranging from 48.26 at baseline to 62.3 at the 6th visit. However, the numbers are too small to draw

Table 5 Quality of life measure: EQ-5D-5L and VAS scores

Time point	Number of participants	EQ-5D-5L utility score Mean (standard deviation)	EQ-5D-5L VAS Mean (standard deviation)
Month 1	38	0.349 (0.246)	48.26 (22.75)
Month 2	35	0.391 (0.264)	53.97 (20.13)
Month 3	29	0.469 (0.245)	58.72 (22.27)
Month 4	26	0.468 (0.248)	56.92 (19.65)
Month 5	19	0.508 (0.224)	66.26 (20.99)
Month 6	17	0.383 (0.314)	62.35 (24.50)

any conclusions about the trend, although the scores appeared to improve over time (Table 5).

Qualitative data on practitioners' views on recruitment, retention and fidelity to the intervention

All five nurses who had been involved in delivering the intervention and all four medical clinicians across sites were interviewed. Participants were specifically asked about recruitment, covering inclusion criteria and patient suitability. Themes arising described the importance of getting local nursing staff in the service involved; the requirement for enthusiasm by the study nurse and clinician. Across themes, the importance of good communication between the nurse and clinician locally was a clear enabler to recruitment.

Getting local nursing staff involved

Getting local nursing staff engaged with the study was essential so that they would refer patients to the research nurse for screening for inclusion. However, getting staff initially engaged with the study was described as "like pulling teeth". This challenge was evident across all sites. This reluctance may have been a factor of the intervention being a new concept that required time to understand and to repeat the message. Indeed, there was an improvement over time and a gradual awakening of interest:

> *"because now I'm starting to get a lot of interest in it. …… and like—Today. "How can I get a patient on to this?" (nurse 6).*

The possible controversial nature of benzodiazepine prescribing may have been part of the initial reluctance:

> *".. I think, because again it was quite new, it was all a bit taboo, we didn't really know what was going on. It's like anything new, … no one really uses it until someone's brave enough to" (nurse 4).*

Research nurse enthusiasm

The enthusiasm and tenacity of the local research nurse was crucial in addressing any apathy in local services. Getting the interest of local clinical staff to aid recruitment through face-to-face contact proved successful as it allowed conversations to take place to determine where the problem lay:

> *"I tried emails first, got no response. So then we [nurse and clinical lead] just decided one day that we were going to come here and go to [other clinic] and physically go on the floor and start having conversations with people. A lot of the issue was that there was a lot of misconception about the criteria." (nurse 5).*

The particular research nurse communicated a clear plan of how she would screen patients, which paid off with further referrals:

> *"So I was like, "Right, okay, right, well what I would like you to do is I want you to put everything about the situation in an email and I want you to email it to me." I said, "And then what I will, I will look at that, I will look at all of our systems and everything else. And then I will email you back and I will say whether they are suitable or not suitable. And then I will give you a reason as to why currently they're not suitable so that there is a proper trail." And as soon as I started doing that, I was getting a lot more referrals and a lot more discussion. …And it really opened it up." (nurse 5).*

This clearly communicated process of referral and screening for suitability proved effective at increasing recruitment.

Suitability of patients

The issue of patient eligibility against inclusion criteria was discussed. The initial criteria had been for people in the first 3 months of OAT treatment but using street benzodiazepines, which was felt to be too restrictive and was changed to all OAT patients who were stable on OAT but using street benzodiazepines. As the first site to start recruitment, Grampian experienced the challenges of this potentially restricting inclusion criterion. Fife started recruitment after the change had been made and was able to recruit patients quickly. Despite this, there was still some difficulty in deciding whether a patient was suitable:

> *"Yeah, you could look on paper and be like, yes they do, no they don't, but there was also one or two that, they could be okay, was it just a blip [i.e. their benzodiazepine use]". (nurse 4).*

Where there was a close working relationship between the research nurse and clinician, the process of review for suitability was enabled but also provided some security in the clinical decision because there may have been a range of other prescribed medications to be considered.

> *"So, they [local nurse] would send me the information, and then I would send it—I would forward it to [clinician] and say, "I think this could be a goer. What's your thoughts?" And then he would get the same info that I got, then he would reply to me and say, "If you think that you could do something then I will support you with it." And I'd like, "Right okay. So, they're on this med, they're on that med. Am I okay to-" And then he'd be like, "Yes, you're okay" (nurse 5).*

Fidelity to the intervention

The protocol around the prescribing component of the intervention was interpreted differently in different settings. There was evidence that there was more of an earlier move to a tapering dose by the clinician in one site than in the other two. Whilst the intention was for a tapering dose to start only if and when the patient felt ready, and in response to progress with other components of the intervention, the clinician may have interpreted this as their decision.

> *"Well, the protocol basically didn't seem to state whether it was for maintenance or detox. It seemed to be suggesting that it was up to the individual clinicians involved as to what would be happening." (doctor 8).*

Another clinician described this in a more collaborative approach, as was the intention, albeit not on a par with opioid agonist treatment:

> *"We have a period of maintenance or stability until the person stabilises, but when you start them, there's always the intention that this is going to be this is not a forever like methadone, but it's going to be a detoxification. But we do it at the rate and pace of, so it's an agreement, frankly, with the, with the patient." (doctor 9).*

Discussion

Feasibility

This study demonstrated it was feasible to recruit, retain, and deliver a potentially effective bespoke intervention to people who are dependent on and/or regularly use high-dose 'street' benzodiazepines whilst in OAT. Recruitment proved feasible, although there were revisions to inclusion criteria such that there was no restriction on the time in OAT treatment prior to recruitment. This approach acknowledged that some people may start benzodiazepines or escalate street drug use whilst in treatment as treatment is not a linear progression. By expanding inclusion criteria, more patients became eligible. Recruitment was facilitated by positive and proactive research nurses, generally working closely with the local medical lead, which helped them address any uncertainty about inclusion decisions.

We were able to recruit participants across three sites. In one site, it was more difficult than the other two, and we did not recruit the full target of 15. This site was the first that was ready to recruit and where the original inclusion criteria were found to be too restrictive. Revised inclusion criteria—without the time restriction on the length of OAT treatment—were considered appropriate, but further guidance to define the term 'stable' will be required in any further trial. Length of OAT should be recorded as part of this assessment, but a stable dose and/or no requirement for re-titration in the immediate period prior to recruitment should be considered.

We deliberately approached this trial from the perspective of addressing high-risk benzodiazepine use rather than dependence per se. If a future RCT were to be undertaken, we recognise that the use of definitions of dependence such as DSM-5 would be necessary to tighten inclusion criteria for benzodiazepine use. However, the importance of reducing risky use should not be lost given the role that high-risk use plays in drug deaths.

Fidelity to the prescribing component of the intervention was mixed, and clarity regarding the protocol, including further research and good clinical practice training, would be essential in a large trial. The study highlighted the importance of a clear protocol around prescribing. Whether or not varying tendencies to move patients towards detoxification impacted retention is not clear from this small study, but a future trial should take this into account.

A limitation of our feasibility study is that we did not include prespecified progression criteria against which feasibility could be formally assessed, nor did we formally justify the sample size to assess feasibility outcomes. The retention rate was 77% over the 4–6 months of intervention. Only one person voluntarily withdrew, so patients were willing to be retained in the intervention.

Outcome measurement

Use of 'street' drugs

Changes in some 'street' drug use were reported by patients during interviews (publication in prep) but oral fluid testing data was incomplete and therefore inconclusive. Self-reported drug use showed reductions in the total number of different drugs used as well as a

reduction in 'street' benzodiazepine use. The method of self-report was insufficiently granular to identify reductions in quantity of use or frequency of binge use. A larger trial should explore and quantify 'binge' use as well as regular high-dose use.

Another challenge was that the nature of available 'street' drugs changed during the study with increased availability of 'bromazolam'. This was not specifically tested for in oral fluid tests. A full trial would need to monitor the emergence of 'new' drugs and patterns in street drug/benzodiazepine use to ensure testing includes emerging substances.

There were some challenges with oral fluid testing in that some people had very dry mouths due to insufficient saliva. In addition, some oral fluid tests went missing in the post from one site. Challenges in oral fluid testing could be addressed by advice on increasing saliva prior to testing and offering a urine drug screen as an alternative.

Mental health, cognitive function and recovery from drug use?

The GAD-7 has been validated in the addictions field [26] and widely used since as both a clinical tool and research outcome measure. It was found to be simple and efficient to use. The mean anxiety score was in the 'severe' band at baseline (< 15) and reduced to moderately severe at follow-up. The management of anxiety has been identified as a key driver to seek and use 'street' benzodiazepines [15]. Prescribed benzodiazepines are indicated for the management of anxiety, albeit for short-term use [27]. Therefore, addressing anxiety management and self-medication aspects of 'street' benzodiazepine use via the psychosocial aspect of the intervention shows promise for a future trial. The GAD-7 was considered an appropriate tool.

Similarly, using the PHQ, there was a high level of depression at baseline with the mean in the 'major' depression category (< 15). This reduced to 'moderate' at follow-up [28]. Whilst depression was not a target outcome, it is closely linked to anxiety and substance use and has proven validity in this group [29] so it may be that there is potential to reduce symptoms of depression secondary to improved anxiety, quality of life, and overall addiction management. Again, the PHQ was considered an appropriate tool.

The ACE III assessed cognitive functioning. There was no change, and mean scores indicated mild cognitive impairment. It is not possible to determine or differentiate in this study whether cognitive impairment for some individuals with lower scores had drug or alcohol-related brain injury, whether that is reversible, or whether it is an effect of the drugs taken (benzodiazepines, opioids, and possibly other substances such as cannabis). Only a longer study will be able to determine whether a safe and regular prescribed dose supports improved cognitive function or indeed whether long-term prescribing might have an adverse impact on cognitive function.

Self-reported substance use recovery was measured with the SURE measure, a validated tool to enable self-assessment of recovery from harmful substance use across a range of domains [30]. SURE scores improved over time, validating the improvement in EQ-5D-5L score and measures of anxiety, depression, and reduced 'street' benzodiazepine use.

Economic evaluation

The economic analysis considered the overall response rates, item completion rates, and the range of values provided in response to the questionnaires. There was good completion of the questionnaires (very low missing or non-item response) at the various time points, but this was dependent on the participant attending the appointment. There was no missing data on resource utilisation, and the highest resource use reported was the use of the outpatient department. Although no cost-effectiveness analysis was undertaken, the high completion rates and low level of missing data when participants attend the clinic suggest that it is feasible to collect resource use and quality of life data from participants as part of a powered randomised controlled trial.

Suitability for a full-randomised controlled trial

This feasibility study is small in scale, and findings cannot be generalised. However, it demonstrates it would be possible to undertake a full trial which compared this intervention against standard treatment, which currently is a tapered dose of a benzodiazepine (usually diazepam) with standard psychosocial support. Current 'standard' psychosocial support in drug treatment is variable and generally not specific to benzodiazepine drugs. A standard appointment through an addiction service is a maximum of half an hour, generally monthly (personal communication), which is less than this intervention. Whilst mental health nurses were used to deliver the intervention in this study, many services rely on support workers who have less specialist training and qualifications, and testing in this wider context would be pragmatic and have wider applicability.

In designing a future trial, there should be consideration of what the trial arms might be. Whilst there might be benefits from a maintenance benzodiazepine prescription alone, the bespoke and targeted nature of this intervention to address motivations for street benzodiazepine use was designed to complement the prescribing components as a package that could be considered a complex intervention. Testing such a package intervention

emphasising a maintenance dose prescription in the intervention arm versus a tapered dose control arm with psychosocial support in line with current recommended clinical guidance would be an appropriate way forward.

Conclusion

This single-arm feasibility study indicated that a larger controlled trial is feasible. There is a need for a two-arm randomised controlled trial to test the intervention as a package versus current recommended care of a reducing dose of diazepam with standard psychosocial support. Whilst other trial designs might be considered to determine the impact of the prescribing component of the trial versus the bespoke psychosocial package, it is our consideration that the bespoke psychosocial component was built around a maintenance approach to prescribing, albeit with capacity to reduce at the request of the patient and at a pace appropriate for the individual. A future Randomised Control Trial (RCT) would need to refine the toxicology testing to include emerging benzodiazepines as well as measuring both binge and regular use. Furthermore, a cost-effectiveness component to an RCT would enable the wider costs of intervention delivery, including NHS costs via overdose events, to be assessed.

Abbreviations

ACE	Addenbrookes Cognitive Evaluator
CARE	Consultation and Relational Empathy CARE Measure
OAT	Opioid agonist treatment
RCT	Randomised controlled trial
SURE	Substance Use Recovery Evaluator

Supplementary Information

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Additional file 1: CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*.

Additional file 2: Table S1. Anxiety and Depression. Table S2. Cognitive Function (ACE III). Table S3. SURE (Substance Use Recovery Measure). Table S4. Unit costs of study.

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Authors' contributions

CM, JS, DH, MT, TR, DS, MK, GM designed the study and obtained the funding. KB undertook fieldwork, data collection and project management. KB and CM analysed qualitative data. JS, CM, GM analysed quantitative data, while MK analysed the economic data. CM wrote the first draft of the manuscript; all other authors performed critical revisions of the manuscript and contributed to the writing. All authors read the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval was granted on 29/10/2021, by the North of Scotland Ethics Committee, ref: 21/NS/0135 (IRAS 304108). All methods were carried out in accordance with relevant guidance and regulations, including GDPR.

Consent for publication

Written informed consent was obtained from all participants prior to the commencement of data collection. All participants consented for data to be included in publications.

Competing interests

The authors declare that they have no competing interests.

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