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Insights for successful recruitment of people who actively use heroin to a pharmacotherapy trial: a case study

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ABSTRACT

Background: This paper reports on recruiting strategies in a study which aimed to examine the mechanism of intranasal oxytocin on cue-induced opiate craving and attentional bias in males using heroin in addition to substitute opiates from four UK community drug treatment services.

Methods: Recruitment took place during and post-COVID-19 periods of social distancing and lockdowns. Caseworkers obtained consent to contact from interested service users before an initial telephone screen. People were then scheduled for in-person screens, typically within seven days of the initial telephone call. Subsequent visits took place within 30 days of the previous visit. Each visit lasted one hour and participants received one £20 voucher per completed visit.

Results: Thirty participants were randomized from 113 referrals. We were unable to contact 36% ($n = 41$) of people. Of those eligible to start the study ($n = 44$), 68% ($n = 30$) agreed to start the study, retaining 82% ($n = 24$) to completion. Factors which positively influenced recruitment were having a research presence on site, the cultivation of relationships and demonstrating respect and gratitude toward the participants.

Conclusions: These results support the feasibility of recruiting males currently using heroin in addition to substitute opiates utilizing a person-first approach with service users and staff.

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Case study; methods; opioid use disorder; oxytocin; recruitment; substance misuse

Background

United Kingdom drug-related deaths continue to be considerably higher than the rest of Europe; of 4,859 registered drug-related deaths in 2021, 45.7% involved opioids (Office for National Statistics, 2022) and the leading cause of UK opioid-related deaths is accidental poisoning (Office for National Statistics, 2019). Aside from the addition of depot buprenorphine to the sublingual formulation, there have been no new pharmacotherapies for treatment of opioid dependence since Naltrexone in 1984 (Srivastava & Gold, 2018). To prevent opioid-related deaths, it is critical to improve treatment of opioid dependence.

There is relative paucity of UK-based pharmacotherapy research in this field despite the consequences to the person, the family and society. One of the factors making research challenging is the difficulty to recruit. Globally, 55% of all clinical trials are terminated due to low recruitment rate (Desai, 2020). Jacques et al. (2022) review of publically funded randomized controlled trial research in the UK found that the original recruitment target was achieved in just 53% of trials (207/388), reduced in a further 67% of studies (79/118) and a third of trials extended their recruitment period (128/388). Recruitment of people who use substances to clinical trials is thought to be more difficult than for other health conditions and remains a significant barrier to progress evidence based interventions (Demaret et al., 2014; Melberg & Humphreys, 2010; Sheard et al., 2006; Thomson et al., 2008).

A Canadian survey of 1,020 people who use illicit substances found 58.3% of people surveyed indicated willingness to participate in research. In multivariate analysis, factors which positively influenced willingness to participate included daily heroin injection and receiving opiate replacement therapy (ORT), whereas people who were homeless were negatively associated with willingness to participate in studies (Uhlmann et al., 2015). Further evidence of willingness to participate in opiate research was observed when clinic capacity was overwhelmed by response and recruitment had to be paused (Oviedo-Joekes et al., 2015). The studies reviewed so far indicate that people who are dependent on opioids are often willing to take part in research.

Some people are unwilling to engage in research. One UK feasibility study to assess recruitment to a randomized control trial for Baclofen to treat Gamma Hydroxybutyrate withdrawal was forced to discontinue after recruiting 7 participants from a planned 88 (Lingford-Hughes et al., 2016; EUDRACT number:2013–005319–28). Participant reasons for declining are unknown. To help improve recruitment to pharmacological trials for illicit opioid use, Neale et al. (2018) interviewed people who use opiates in the UK and proposed a checklist of considerations for study designs. Key considerations included reimbursement of travel and time costs, short clinic visits and

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overall study duration, flexible attendance, participation in the design of the study itself and understanding that some opioid users will take part for altruistic reasons rather than financial incentive.

The methods reported here were used within a double blind, randomized, proof of concept crossover study where participants attended four appointments, were given oxytocin/placebo and induced to crave heroin through exposure to a video of a man preparing and injecting heroin before measurements of opiate craving (McHugh et al., 2014) and attentional bias (Cox et al., 2006) were taken over a thirty minute period. On the final visit, participants were invited to an optional interview and to complete the Ravens brief cognitive task (Ravens, 2000). Each visit lasted approximately one hour, had fixed appointment times between 12:00 and 15:00, and could take place a maximum of 30 days since the last visit in line with usual attendance at the drug service. Participants received £20 in vouchers per clinic visit attended plus travel costs reimbursed. Ethical approvals were received from Brent NHS (REC: 20/LO/0758).

A case study method was chosen for this paper as the aim was to understand the barriers and share solutions for the recruitment of people currently using opioids to a pharmacotherapy study. The case study approach allows us to provide contextual analysis of recruitment variables beyond the final data set (Sayre et al., 2017).

Approach

Setting

Participants were recruited from four UK community treatment services who provided ORT. Services were chosen based on local population eligibility and existing professional relationships with the research assistant (RA).

Site one was operated by the NHS study sponsor in a county known for low levels of socioeconomic deprivation. The UK National Drug Treatment Monitoring System (2022) estimated 2,966 people who use opiates and crack cocaine within this region, with 1,255 people dependent on opiates accessing treatment throughout 2020/2021. Recruitment at this site (December 2020 – September 2021) was hindered by COVID-19 social distancing restrictions where service users were not routinely seen on site and contact was limited to mostly telephone-based interventions.

The remaining sites were operated by a national non-statutory drug and alcohol treatment provider. Recruitment from these sites (February 2022 – October 2022) was not limited by COVID-19 social distancing restrictions.

Site two was in a town north of London known for high unemployment, low income and high cost of living. The UK National Drug Treatment Monitoring System (2022) estimated that in 2019/2020, there were 1,515 people who used opiates in this region, with 710 people who used opiates accessing treatment throughout 2020/2021.

Site three was in an inner east borough of London known for experiencing significant problems with inequality and poverty. The UK National Drug Treatment Monitoring System (2022) estimated that in 2019–2020, there were 2,263 people who used opiates in this region, with 800 people who used opiates accessing treatment throughout 2020/2021.

Site four was a town in the south-east of England where the number of people homeless and in priority need is almost twice that of the remainder of the South-East and higher than England in general. The UK National Drug Treatment Monitoring System (2022) estimated that in 2019–2020, there were 1,091 people who used opiates in this region, with 740 people who used opiates accessing treatment throughout 2020/2021.

Participant recruitment

The RA was on site for 1.5 days a week due to time constraints. Our solutions to the known barriers of recruiting can be found in Table 1.

Presentations were held with each site less than one month prior to recruitment to explain the purpose of the study and build relationships. Caseworkers were asked to communicate the purpose of the study and to obtain consent for researcher contact to complete screening for eligibility only due to service delivery pressures. One member of staff per site was allocated to be the point of contact for the RA. The RA attended regular online meetings to give study updates, reintroduce the study to new staff members and answer any questions.

People who consented to be contacted were called within 48 hours to offer a first appointment, typically within one week of contact and answer any questions. Posters and the participant information sheet were also left in the reception areas. In order to minimize pressure, service users were called twice and sent one text message prior to being excluded. Service users were able to re-enter at a later date if they could not be contacted or later changed their mind.

Participants were offered text message or telephone reminders of study appointments prior to all appointments at a frequency of their choice. All participants were reminded the day before their appointment as part of procedure and others requested a reminder on the day or two hours prior to the appointment.

Data collection

Three different sources provided data on screening and recruitment;

- Quantitative data were collected as part of the original proof-of-concept study.
- Qualitative data were collected during a planned interview at the end of the original study.
- Observational data of day-to-day activities within each site which impacted recruitment.

All data were reported descriptively.

Results

Our recruitment target was largely met ($n = 30/34$), though numbers of people who consented to contact were below expectations and the relationship with each site influenced

Table 1. Evidenced barriers and our solutions to recruitment of people who use substances in research studies.

Participant Barriers		
Author	*Barriers*	*Our Solution*
Demaret et al.(2014); Melberg and Humphreys (2010); Sheard et al. (2006); Thomson et al. (2008)	Participants were resistant to randomization due to existing treatment preference	We explained through the participant information sheet and through verbal discussion at screening that the study is crossover, which means they will receive both medications
Demaret et al. (2014)	Participants held a fear of treatment ending or being left dependent on the new treatment	We transparently explained through the participant information sheet and through verbal discussion at screening that the study length is four appointments only and that they will not become dependent on oxytocin through one visits insufflation. It was explained there was no known risk of dependence or euphoria from using oxytocin. We explained verbally and through the written consent form that participation or withdrawing from the study will not affect their drug treatment in any way.
Melberg and Humphreys (2010)	Participants had preference for psychosocial trials rather than pharmacological trials due to concerns over side effects	We were unable to mitigate this due to the study design however this was not raised as a participant reason for declining consent to contact or a reason for declining participation.
Melberg and Humphreys (2010)	There was a wide difference in treatments offered during the trial	We explained through the participant information sheet and through verbal discussion at screening that only one medication, the oxytocin, would have any effect and the placebo will have no effects so there is no wide difference.
Thomson et al. (2008)	There was a lack of incentives for participating	We provided £20 in vouchers per session and reimbursed travel costs, including taxis where train tickets, bus tickets or taxi receipts were provided.
Brooker et al. (1999)	Inappropriate screening setting (during routine treatment for example)	Obtaining consent to contact took place during routine caseworker appointments where potential participants would be offered a range of services by the treatment providers. The research study was simply an addition to usual care, so there was no change or extra burden on staff or participants.
Brooker et al. (1999)	Staff did not believe in the research due to concerns with the original nursing manager who introduced the research	The original study site has a long history of research activities led by the Chief Investigator. Two of the non-statutory sites had existing positive relationships between members of the staff team and the research team.
Brooker et al. (1999)	Staff did not believe the extra work generated to screen participants should be within their role	We minimized the burden on staff members by asking for consent to contact only and emphasized they were not expected to explain the study beyond the basics.
Holland et al. (2014)	Recruited only 48% of the available pool due to subjective clinical assessments of individual participant safety	We recruited from multiple sites with participants referred by caseworkers rather than clinicians predominantly. The inclusion criteria was wide to represent the target population and the CI was consulted where safety concerns were raised by caseworkers or clinicians.
Sheard et al. (2006)	A lack of a comparable measure in clinical trials i.e., "participants should take part because it may be better than treatment x"	Our design meant we could not directly mitigate this however staff members were advised of the wider vision for the next study where a comparable measure would be possible. It was explained we cannot reach that point without the evidence from this trial.
Sheard et al. (2006); Thomson et al. (2008)	Staff held preconceived beliefs about the study	We continually joined morning meetings to discuss the study and answer questions. One to one discussions were also had with staff members.
Sheard et al.(2006); Thomson et al. (2008)	Complicated referral processes for staff	We agreed a process whereby staff would only need to obtain consent for the researcher to contact interested people. Once attained the staff simply gave the names and telephone numbers to the research assistant.
Thomson et al. (2008)	Lack of reward for staff referring in	We were unable to offer reward for staff referring in both due to financial constraints and the non-statutory provider approved the research on the basis it did not hinder core service delivery. By offering an incentive, this may have taken focus away from this.
Thomson et al. (2008)	Sites had a limited research culture	Our initial study site had a history of conducting research and so staff were used to the language and presentations. The non-statutory provider were identified due to the dedicated research department and organizational track record for research involvement.

Barriers identified from existing literature divided by barriers for participants and barriers for professionals with the solutions utilized in our study design.

recruitment success. The Chief Investigator was the lead psychiatrist at site one and so referrals were altruistic in nature. The RA had long standing personal relationships with staff members in sites two and four. There was no existing relationship in place at site three where high staff turnover and associated service delivery priorities contributed to a lack of consent to contact being obtained. In site four, the majority of referrals came from a single part-time staff member with the lowest case load but who had worked closely with the RA for a number of years previously. A handful of referrals from site four were through chance encounters or word of mouth amongst existing participants.

Sites differed in approach to gaining consent to contact. Site one allocated a single worker to screen electronic notes and call eligible participants. This was due to recruitment taking place during the COVID-19 pandemic where service provision was

prioritized was given to maintaining provision of ORT and less so psychological support, reducing opportunities to physically see service users and discuss the study. The approach to screen electronic case notes for eligibility was limited by individual differences in the detail of each note and so eligible people may have been missed. Site two placed posters throughout the building, within the needle exchange, and included discussion of the study as part of their daily meeting. Referrals were consequently spread out across multiple staff members. Site three, with high staff turnover, lacked consistent study visibility and were unable to gain consent to contact despite having the largest estimated pool of eligible clients from the non-statutory services.

In total, 113 participants consented to be contacted by the research team to learn more (Table 2). We were unable to contact 36% of the people. Of those confirmed eligible to start the study, a total of 68% agreed to start the study: site one 56%, site two 81%, site three 0%, site four 70%. The retention rate, excluding the participant randomized in error, was 82%; Site one 90%, site two 69%, site four 86%. There was an average 1.4 telephone calls and 1 text message per person to screen and arrange a first appointment for people who consented including those who subsequently declined and who were ineligible in comparison to 1.9 telephone calls and 1.2 text message attempts for people who consented to contact but were unable to be contacted.

Thirty-six percent of participants who consented to contact were unable to be contacted (41/113), possibly due to the protocol stating only two telephone calls and one text would be attempted. Case-workers identified a number of service users they had attempted to contact but who often put their telephones in pawnbrokers and so were difficult to contact. Interested participants may have been missed through this approach.

Participant experience

Participants reported no concerns with appointment length or number. It was not uncommon for participants to text or call the RA at unsocial hours to confirm their next appointment. Every contact was answered when the received meaning by the RA was often working out of conventional hours. Two appointments from two separate participants were rearranged due to attending observably intoxicated. All participants, including those who were ineligible due to abstinence, had no concerns about being induced to crave heroin, which was a key component of our study.

The Ravens measure of abstract reasoning completed at appointment four was off-putting to participants. One participant described this as "horrendous" whilst other participants similarly stated "No way, I would not have come back" had Ravens been completed at visit one due to the confusion surrounding the relevance, purpose and difficulty with which they found it. One participant declined to complete Ravens once started due to difficulties in understanding the task.

Reasons for taking part included understanding the problem which the research addressed, having personal experience with the problem which the research addressed, wanting to help others either now or in the future, wanting to do something different, giving them a purpose for the day, being interested in the background to the research, being skeptical in the research rationale, not wanting to let their caseworker down, not wanting to disappoint the RA and provision of voucher reimbursement though participants preferred cash in future studies.

Participants suggested recruitment could be improved by; increasing caseworker communication – "no one I know has heard about it, mentioned it or said anything about it," inclusion of females and meeting people at pharmacies when they collect ORT.

Barriers to referral

Safeguarding measures within our ethical approvals prevented us from approaching participants directly. Best practice supports patients and public to be actively

Table 2. Recruitment data per recruitment site.

Consented to Contact	Total (*n* = 113)	*Twitter* (*n* = 2)	*Site One* (*n* = 59)	*Site Two* (*n* = 30)	*Site Three* (*n* = 4)	*Site Four* (*n* = 18)
Unable to contact	41	2	20	10	3	6
Recruited – Complete	24	0	9	9	0	6
Recruited – Next Visit 2	0	0	0	0	0	0
Recruited – Next Visit 3	0	0	0	0	0	0
Ineligible – female	4	0	3	0	1	0
Ineligible – abstinent	17	0	16	1	0	0
Ineligible – psychiatric comorbidity	1	0	1	0	0	0
Ineligible – not stable on prescription	4	0	1	2	0	1
Ineligible – out of area	1	0	0	0	0	1
Ineligible – in custody	1	0	0	1	0	0
Declined – Family member unhappy with participation	1	0	1	0	0	0
Declined – unable to commit due to work	2	0	2	0	0	0
Declined – unable to commit to four appointments	5	0	2	1	0	2
Declined – anxiety	3	0	1	1	0	1
Declined – no reason given	3	0	2	1	0	0
Withdrawn – unable to contact post visit 1	2	0	1	1	0	0
Withdrawn – drop out of treatment	1	0	0	1	0	0
Withdrawn – OST dose change	1	0	0	0	0	1
Withdrawn – Randomised in error at screening	1	0	0	1	0	0
Withdrawn – Out of time	1	0	0	1	0	0

Total number of people who consented to be contacted per recruitment site along with final study status i.e., unable to contact, completed, ineligible (with reason), declined (with reason), withdrawn (with reason).

involved in the design of research (National Institute for Health Research, 2019) without intermediary introductions but to take part in research they helped design and people needed to be referred in by a third party. Adapting this requirement could eliminate burden on caseworkers, allowing researchers to recruit greater numbers of people. Service retendering hindered recruitment from site four where the initial patient and public involvement activities took place and thirty-seven people expressed interest. The number of people who eventually consented to contact was half this amount and less who then began the study. The RA undertook the patient and public activities and so had direct contact with service users, allowing trust to be built and all questions answered. When recruitment started, the RA was reliant on new caseworker communications, workload capacity of caseworkers and buy-in to the research from a new service provider following retendering. Site four offered to provide a volunteer with the sole focus of obtaining consent to contact but were unable to initiate due to volunteer shortages post COVID-19.

Existing relationships did not remove all barriers, suggesting gatekeeping between caseworkers and offering service users research opportunities. Caseworkers at all sites were asked for reasons why people had declined consent to contact but no caseworker provided any reason. One caseworker stated that they were unsure if service users would be able to commit to four appointments. It is therefore likely that not all caseworkers discussed the study with potential participants, perhaps due to personal preference, workload capacity or informal screening of likelihood to complete. One clinician with no previous relationship to the RA confused the medication with another leading to suspicion about the study. Following clarification the clinician continued to express doubt toward the validity of study results due to inclusion criteria and no referrals were made. Some caseworkers did not believe in the research rationale due to lack of neurobiological addiction knowledge. Once explained, although expressing interest and belief in the study, these caseworkers did not obtain consent to contact from anyone. One reason given for this was that within their treatment service model, caseworkers only signposted people to external support services beyond any clinical addiction-related need.

Relationship building with participants was critical to recruitment and retention in the study. Participants stated they were suspicious of who the RA was. One participant said they "needed to see if you knew what you were talking about" regarding addiction before committing to the study. Other participants researched oxytocin to understand more whilst others questioned aspects of the statistical analysis. During interviews participants highlighted the "personable" and interactive approach of the RA contributed to their engagement with the study.

Limitations

Records of the total number of people approached and reasons for decline were not collected and so only data for those who consent to contact are available. Each site differed in consent to contact methods despite being predominantly operated by the same service provider. This means that the approach may not be generalizable. Finally, we only recruited males using heroin. Our approach may not reflect recruitment of women who use heroin or people who use alcohol and other drugs aside from heroin.

Recommendations

To maximize recruitment and retention we have four recommendations. Firstly, ensure there is a research presence on site. Two sites reported workload hindered people remembering the study but seeing the RA reminded them. Secondly, obtain consent to contact during the patient and public involvement exercise where possible. In addition, allow researchers to directly approach service users. Confidentiality can be assured through the use of honorary contracts and pressure can be mitigated by not completing consent until 48 hours post contact. Thirdly, increase the number of telephone attempts, send appointments by letter and leave appointments at the pharmacy where participants collect their ORT. Finally, researchers should remember that this population typically have low self-esteem and participant experience should be at the forefront of study design (Hendy et al., 2018). Using complicated language or including tasks which have the potential to make people feel bad should be avoided where possible.

To cultivate relationships, we have three recommendations. Firstly, demonstrate appreciation for staff efforts and empathy for the pressures of service delivery to help build relationships. Secondly, researchers should approach the population with a perspective that the participants are the experts irrespective of the scientific literature. An expressed belief that evidence supersedes lived experience can create a power dynamic and barrier to acceptability. Thirdly, treat participants with gratitude to ensure they feel valued as people rather than data. Here, all participants were met by the RA in reception at the time of their appointment, offered a hot drink and given an agreed ten minutes with which they could be late unless they made contact out of courtesy. Participants were explicitly thanked and walked to the door by the RA. These small gestures demonstrated that "chaotic" opiate users can engage in structured appointments as observed by the retention rate and reasons for participation.

Conclusion

This case study demonstrates it is possible to recruit into clinical research from populations considered unstable. Such research would contribute to evidence based practice provision to those populations. Investment on developing relationships between the research team and care team is critical to success alongside a simple referral process. In addition, the study appointments must remain flexible to fit in with participant lifestyle. The high acceptability of eligible and ineligible participants in our study suggests that people who use opiates want to be involved in research. It is the responsibility of researchers to design studies which are representative, relevant and inclusive of the target population and for recruiting sites to inform people of research opportunities.

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Disclosure statement

BH was employed by the drug treatment service operating at site two in 2017 under a different non-statutory service provider. There are no other financial or non-financial competing interests to report.

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