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Improving recruitment to pharmacological trials for illicit opioid use: findings from a qualitative focus group study

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ABSTRACT

Aim To explore potential study participants' views on willingness to join clinical trials of pharmacological interventions for illicit opioid use to inform and improve future recruitment strategies. **Design** Qualitative focus group study [six groups: oral methadone (two groups); buprenorphine tablets (two groups); injectable opioid agonist treatment (one group); and former opioid agonist treatment (one group)]. **Settings** Drug and alcohol services and a peer support recovery service (London, UK). **Participants** Forty people with experience of opioid agonist treatment for heroin dependence (26 males, 14 females; aged 33–66 years). **Measurements** Data collection was facilitated by a topic guide that explored willingness to enrol in clinical pharmacological trials. Groups were audio-recorded and transcribed. Transcribed data were analysed inductively via Iterative Categorization. **Findings** Participants' willingness to join pharmacological trials of medications for opioid dependence was affected by factors relating to study burden, study drug, study design, study population and study relationships. Participants worried that the trial drug might be worse than, or interfere with, their current treatment. They also misunderstood aspects of trial design despite the researchers' explanations. **Conclusions** Recruitment of participants for clinical trials of pharmacological interventions for illicit opioid use could be improved if researchers became better at explaining clinical trials to potential participants, dispelling misconceptions about trials and increasing trust in the research process and research establishment. A checklist of issues to consider when designing pharmacological trials for illicit opioid use is proposed.

Keywords Clinical trials, ethics, opioid agonist treatment, opioid dependence, pharmacological interventions, qualitative study, study recruitment.

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INTRODUCTION

Pharmacological interventions play a critical role in the treatment of illicit opioid use. In 1964, methadone was first tested as a long-term maintenance treatment in two patients maintained previously on morphine [1–3]. Methadone subsequently became the dominant medical treatment for opioid dependence [4], but the search for alternative and more effective medications has continued. Over the years, different drugs and drug combinations (naltrexone, buprenorphine, combined buprenorphine and naloxone, levo-alpha acetyl methadol, morphine, dihydrocodeine), as well as different dosing regimens (detoxification, reduction, maintenance) and formulations (liquids, tablets, implants, injectables), have emerged. In response to rapid global increases in opioid use and poor adherence to existing opioid medications [5], novel long-acting formulations (e.g. slow-release implants, depot injections) are also now being developed.

Before new opioid medications receive regulatory approval they need to be tested in clinical trials, including volunteer Phase 1 studies as well as randomized controlled trials (RCTs) with opioid-dependent patients, to demonstrate safety and efficacy [6]. Difficulties recruiting participants to RCTs are common within most medical research [7,8]; indeed, one review of RCTs throughout a range of medical conditions found that nearly half received an extension due to recruitment problems [9]. Many addiction trials have also reported problems achieving their target sample sizes or taking longer to recruit than planned [10–14]. According to one review, fewer than 45 of every 100 potential participants in drug dependence RCTs were

actually eligible, consented and did not drop out immediately after randomization [12].

Researchers conducting trials of both pharmacological and psychosocial interventions for alcohol and other drug problems have sometimes published details of their recruitment difficulties. These data indicate that substance users can be deterred from participating in addiction trials because they do not like or cannot meet the conditions of treatment, such as having to attend appointments and services daily [11]; lack understanding of, or dislike, research [10,12]; have low motivation for treatment [10,14]; worry about their confidentiality, privacy or lack of choice as trial participants [10]; are reluctant to be a 'guinea pig' or part of an 'experiment' [10]; and are concerned about being assigned to a placebo treatment [14,15] or control condition [10].

In addition, recruitment to alcohol and other drug trials can be hampered because clinic staff have insufficient interest, time or capacity to conduct the research [10,14,16,17]; forget or become confused by complicated entry criteria and so do not refer patients to the trial [14]; and do not understand or are sceptical about the research or the trial drug [10,17,18]. Other recruitment challenges are more practical, such as strict eligibility criteria that limit the pool of potential participants [10–13,19]; fewer potential participants than expected or needed in a particular area or service [10,13]; and difficulty contacting potential participants because they lack stable accommodation, move around or change telephone numbers [13,20].

Responding to these problems, addiction researchers have already identified strategies that can be incorporated into their RCT designs to facilitate and enhance recruitment. These include offering financial reimbursements or incentives [14]; providing non-monetary incentives, such as coffee or bus tokens [21]; increasing the odds of receiving the experimental treatment [10]; simplifying the study referral processes [10,14]; providing treatments which appeal to the target population or are otherwise unavailable [13]; sending appointment reminders [10,14]; inviting trial participants to recruit others from their social networks [22]; highlighting the potential benefits of the study to patients and staff [14]; and engaging with peer and community organizations to secure their commitment to the research [13,21,22].

Very few studies have, however, asked people who are dependent on drugs or alcohol for their views on clinical trial participation. A rare exception is a quantitative survey of 1020 illicit drug users recruited from community settings in Canada. This research identified high rates of willingness to participate in a pharmacological addiction treatment trial (58.3%), with those engaged in high-risk drug and sexual activities expressing greater willingness [23]. In addition, a qualitative study of 37 African American crack cocaine users already enrolled in three different behavioural HIV prevention studies found that decisions to participate in HIV-related research (two behavioural interventions and a hepatitis vaccine project) were affected by the desire for information; scepticism and mistrust of research and researchers; perceptions of medical care and monitoring within the study; and participant control over decisions to enrol or not [24].

Lastly, a Belgian study of 52 heroin users who were eligible for, but not recruited to, a heroin-assisted treatment trial concluded that non-enrolment related to the trial conditions and fear of becoming more dependent because of the trial treatment [11]. The data were, however, quantitative, descriptive and related to one specific heroin-assisted treatment trial. Qualitative research is particularly suited to providing detailed insights into how and why people who use substances think and act as they do and has often been used, in related areas, to investigate drug treatment and its effectiveness [25]. Despite this, we are aware of no qualitative studies of recruitment to clinical trials of pharmacological interventions for illicit opioid use. The aim of our study was to explore potential study participants' views on willingness to join such trials in order to inform and improve future recruitment strategies.

METHODS

Data were collected via six focus groups (FGs) conducted with 40 people who were currently being treated, or who had been treated previously, with opioid agonist treatment (OAT) for heroin dependence (26 males, 14 females; aged 33–66 years). Groups were stratified deliberately by treatment drug and treatment status to prevent participants comparing their own treatment with other treatments and then becoming dissatisfied. The groups were: oral methadone (two groups); buprenorphine tablets (two groups); injectable OAT (one group); and former OAT (one group). Each group comprised four to eight participants (see Table 1 for additional participant details). The study received ethical approval from the UK NHS Research Ethics Service.

The groups were conducted in drug and alcohol services and a peer support recovery service in London, UK, during March and April 2017. To optimize recruitment, posters with the researchers' contact details were displayed in the services; researchers approached potential participants in person at the services; workers encouraged service users to contact the researchers; and participants from the earlier focus groups introduced the research to their peers ('snowball sampling'). Everyone who expressed interest in taking part (n = 75) answered a simple screening questionnaire that covered gender, age, ethnicity, substance use, prescribed medications and contact details. The researchers then used the screening information to

Table 1 Participant details.

Demographic characteristics	*FG[a] 1 Oral methadone (n = 4)*	*FG2 Oral methadone (n = 8)*	*FG3 Buprenorphine tablets (n = 8)*	*FG4 Buprenorphine tablets (n = 8)*	*FG5 Injectable OAT[b] (n = 6)*	*FG6 Former OAT (n = 6)*	*All (n = 40)*
Gender							
Male	2 (50%)	5 (63%)	6 (75%)	5 (63%)	4 (67%)	4 (67%)	26 (65%)
Female	2 (50%)	3 (38%)	2 (25%)	3 (38%)	2 (33%)	2 (33%)	14 (35%)
Ethnicity							
White/White British[c]	2	4	6	6	5	4	27 (68%)
Asian/Asian British	0	0	0	0	0	0	0 (0%)
Black/Black British	2	2	1	0	0	2	7 (18%)
Mixed or Multiple	0	1	1	1	0	0	3 (8%)
Other	0	1	0	1	1	0	3 (8%)
Age (years)							
Mean age (years) (range)	49 (42–59)	51 (43–58)	46 (33–55)	40 (34–47)	56 (47–66)	47 (39–58)	48 (33–66)
Street opioid use							
Mean age of first use (range)	23 (16–33)	18 (14–22)	24 (14–31)	23 (14–35)	18 (15–27)	22 (15–32)	21 (14–35)
Mean duration of use (range)	26 (22–30)	33 (25–39)	22 (2–37)	17 (0–33)	39 (27–50)	NA	27 (0–50)
Current street opioid use	4 (100%)	6 (75%)	4 (50%)	2 (25%)	2 (33%)	NA	18 (53%)
Current treatment[d]							
None	0	0	0	0	0	6	6 (15%)
Buprenorphine (tablets)	0	0	8	8	0	0	16 (40%)
Methadone (oral)	4	8	0	0	2	0	14 (35%)
Methadone (injection)	0	0	0	0	2	0	2 (5%)
Diamorphine (injection)	0	0	0	0	4	0	4 (10%)

[a]focus group; [b]Opioid agonist treatment; [c]19 participants identified as 'British', four as 'Italian', three as 'Irish' and one as 'European'; [d]two participants were prescribed a combination of opioid medications (injectable + oral). The denominator used for the calculation of percentages across all subjects was $n = 40$. Because two subjects from FG5 were included in the percentages for 'Current treatment' twice, the total percentage across all 40 subjects adds up to 105%. NA = not applicable.

identify and invite up to 10 people (both sexes and different ethnic backgrounds but with the same current medication) to each group.

Data collection was facilitated by two researchers who used a topic guide to steer the discussions gently while also allowing participants to raise issues spontaneously. The guide focused upon participants' willingness to join clinical trials of pharmacological interventions for illicit opioid dependence, including factors that might encourage or discourage participation. The researchers gave verbal explanations of trial methodology and presented three example study designs to increase participants' understanding and encourage discussion concerning technical issues, such as randomization, blinding and placebo treatment. The researchers also answered participants' questions. Groups were audio-recorded and participants were offered refreshments and £10 as a gesture of thanks.

The audio recordings lasted 44–64 minutes and were transcribed verbatim by a professional transcriber. All transcribed data were then analysed inductively through a process of Iterative Categorization [26]. No specialist coding software or deductive codes were used. First, each focus group was analysed in isolation within Microsoft Word. To this end, each transcription was reviewed line by line by the lead author to identify recurrent themes in the data. These themes were then grouped into categories, discussed within the team, and summarized in a new Word document. This process enabled us to (a) capture the nature of the discussion within each group, including the extent to which participants agreed or disagreed with each other and (b) assess whether the themes and categories identified were similar across the groups.

In practice, there were some differences of opinion between participants within individual groups but no notable differences of opinion when findings were compared across the groups. For example, within groups participants debated and often failed to agree on whether or not opioid users would participate in a trial without financial compensation. However, this same debate and lack of agreement was replicated across groups. Meanwhile, the themes and categories identified within each group were very similar, but not exactly the same across groups (an unsurprising outcome given that the focus group facilitators had used the topic guide flexibly and encouraged free

discussion within each group). In order to capture the full spectrum of responses, we therefore merged the themes from each of the six groups into a further Word document and then re-reviewed, re-ordered and re-categorized the themes inductively. By the end of this process, all identified themes had been categorized under one of five headings: (1) Study burden; (2) Study drug; (3) Study design; (4) Study population; and (5) Study relationships. Findings are presented descriptively and then reviewed more critically in the Discussion.

FINDINGS

Study burden

Participants reported that their willingness to join a clinical trial of an opioid medication would be undermined if involvement created too many demands for them (see Table 2). In particular, they felt that the financial costs of travel to and from a trial site, as well as the physical difficulty of travelling with pre-existing health and mobility problems, were important barriers to participation. Some emphasized that travel could leave them feeling exhausted, so limiting their ability to undertake other activities for the rest of the day. Others complained that trials requiring daily travel to a study site, or the completion of multiple tasks each time they attended a study site, were especially demanding.

Generally, participants believed that current and former heroin users would be reluctant to join trials if they had to provide blood samples, as poor venous access could make this difficult. Moreover, needles could trigger a desire to inject. In addition, some expressed concerns that urine drug screening was intrusive and positive test results could have negative consequences for them (e.g. existing treatment might be altered, reduced or stopped). Participants also tended to report that studies lasting longer than 1 month were less acceptable, as they locked people into treatment, limited treatment flexibility and choice and potentially interfered with people's own treatment goals by, for example, precluding the option of abstinence.

Despite these concerns, participants suggested various ways in which the burden of trial participation might be reduced. For example, many indicated that they would be more likely to enrol in a trial if the study site was near to where they lived, as this reduced their travel and associated costs. Some also suggested that study medications could be brought to their homes or dispensed via a mobile treatment van. Most participants felt that researchers should provide travel passes or a taxi to take them to the study site and, at the very least, reimburse all travel costs. Offering flexibility in terms of when people could attend for treatment and posting any questionnaires to them for home completion were also proposed as ways of making participation less arduous. Finally, participants frequently argued that trials should be as short as possible (ideally less than a month).

Study drug

Anxieties about the pharmacology of the study drug, with particular concerns that it might cause withdrawal symptoms, also seemed to discourage trial participation (see Table 3). Withdrawal symptoms were almost universally feared on the grounds that they were distressing, could prompt former heroin users to relapse and might expose pain that had previously been masked by opioids. Some participants argued that they would be reluctant to join pharmacological trials because they would be afraid of how a study drug might interact with any other medications they were taking or because of previous bad experiences after taking street or prescribed drugs. Indeed, some said that they would not participate personally in a trial under any circumstances if they did not like, or had heard bad things about, the trial drug. Meanwhile, nearly all emphasized that they would not join first-in-human

Table 2 Study burden.

Theme	*Example quotation*
Discouraging participation	
i. Travel	'Going to the chemist every day is a bind... It ties you to the chemist, you can't go away' (female, FG2)
ii. Daily attendance requirements	
iii. Numerous study components	
iv. Toxicology testing	'You've got to come every week to have a drug test, which is a bit intrusive' (male, FG3)
v. Study length > 1 month	
Encouraging participation	
i. Local study sites	'Send a cab around... to pick you up and take you there' (male, FG3)
ii. Free transport	
iii. Attendance flexibility	
iv. Minimal tasks per treatment site visit	'Shorter trials are more acceptable to our community' (female, FG5)
v. Minimal study duration	

Table 3 Study drug.

Theme	*Example quotation*
Discouraging participation	
i. Potential for withdrawal symptoms ii. Interactions with regular medication iii. Previous adverse drug reaction iv. Dislike of the treatment drug	'I've had bad, bad experiences with buprenorphine and Subutex. Because of that experience… I'd be scared to take a new trial drug now' (female, FG6)
v. First-in-human studies	'I don't think people like the idea of… [being] a guinea pig' (male FG1)
Encouraging participation	
i. Availability of 'rescue opioids' ii. Control over study dose iii. Direct access to medical care iv. Good information about trial drug	'There'd need to be… some kind of safeguard possibly, whether that be methadone or a morphine amp [ampoule] or something' (male, FG2)
v. Contract or 'opt out' clause	'I would want it written down, definitely, in black and white, that if I didn't get on with it [trial medication], for whatever reason… I can go back to my previous prescription' (female, FG3)

trials because of the lack of evidence on the medication and its side effects.

Nonetheless, participants volunteered strategies that researchers could deploy to mitigate their anxieties. For example, some explained that they would be more willing to participate in a trial, even if withdrawal symptoms might occur, if they were reassured that they would have access to their own 'regular' opioid medications; offered a special supply of 'rescue opioids'; given some control over the study dose; or promised direct and immediate access to medical care. Participants also often stated that having clear information about the trial drug might allay concerns. Specifically, they wanted to know the chemical structure of the trial drug, potential side effects and how it had performed in any animal or first-in-human studies. Participants additionally reported greater willingness to enrol in a trial if they had written agreement, a formal 'contract' or a note on their medical records that confirmed they could leave the trial and return to their previous medication at any time.

Study design

Aspects of the study design were also identified as barriers to recruitment (see Table 4). Participants occasionally reported that they would not enrol in a trial if the aim was unclear or if they thought that the study would not recruit. Others stated that they would be reluctant to participate if they believed that those recruited would be able to supplement the trial medication with illicit drugs, thus compromising the study results. Participants also

Table 4 Study design.

Theme	*Example quotation*
Discouraging participation	
i. Unclear study aim ii. Uncertain study feasibility iii. Randomization and blinding iv. Uncertainty over post-trial medication v. Unsuitable study site	'Unless you incarcerate me or hold me in a controlled environment, I'm going to abuse your test. I'm going to go and use other drugs, so it's going to affect it [the trial]' (male, FG4)
	'Blinding wouldn't work as people would be able to tell what medication they were getting from bodily functioning and how they are feeling' (female, FG2)
Encouraging participation	
i. Good study information ii. Controlled study environment iii. Reassurance about wrap-around support	'I need to know about this medication. I need to have more information. About everything. About side effects, about everything' (male, FG1)
	'As long as there's overseers and like doctors around, I wouldn't mind trying it' (female, FG1)

frequently questioned the feasibility of giving opioid users placebo drugs or blinding them to treatment, given that people who are dependent on opioids know the effects and side effects of opioid medications and would recognize if they were receiving a different drug.

Overall, participants were negative about randomization and blinding, arguing that they disliked not knowing what medication they would be receiving, the lack of choice and not feeling in control. Crucially, not knowing one's medication meant that they could not assess the likelihood that they would experience withdrawal symptoms or other adverse reactions, their ability to receive pain relief in the event of an accident or how they would feel more generally. Other participants reported that they would not enrol in a trial if there was uncertainty about the length of time it would take to return to their pre-trial medication once the study ended or if the trial required them to attend services where staff had previously exhibited negative or stigmatizing attitudes towards them.

Yet again, however, participants provided suggestions on how trials might be improved to increase recruitment. Most reported that current and former heroin users would be more willing to join a trial if the rationale for, and processes of, blinding and randomization were explained clearly. Some also stated that they would be more prepared to participate in studies (particularly those likely to induce withdrawal symptoms) if they took place in a safe, comfortable, controlled environment, such as a hospital, where there were activities (e.g. play stations and television), nurses or medical staff, round-the-clock monitoring and alternative medications if the treatment drug did not work. Lastly, one participant reported that she would be more likely to join a trial if she had reassurance that she would still be able to see her keyworker as usual.

Study population

Participants emphasized that readiness to join a clinical drug trial would invariably be influenced by an individual's treatment status prior to study enrolment (see Table 5). For example, most agreed that former heroin users who were happy with their current treatment would be less likely to enrol in a medication trial as they would not want to jeopardize a treatment that was already working for them, particularly if they had struggled to secure the treatment and were now stable and not using illicit drugs. In contrast, participants generally felt that opioid users would be more likely to participate in a trial if they were dissatisfied with their current treatment, thought that the trial treatment might be preferable to their current treatment or were desperate for treatment.

Study relationships

Lastly, participants reported that lack of trust in people, systems and organizations associated with drug trials would discourage study enrolment (see Table 6). In particular, they emphasized their distrust of the pharmaceutical industry, noting how pharmaceutical companies make mistakes when conducting research and yet still generate 'huge' profits. Some participants also highlighted their mistrust of doctors and the addiction treatment system, adding that service providers are constantly changing, the treatment system is unstable and they would be reluctant to trust anyone who promised them that their medication would be re-instated if they left a trial. Beyond this, there was a general concern that their personal details might be passed on to others not involved in the research.

Table 5 Study population.

Theme	*Example quotation*
Discouraging participation	
i. People satisfied with current treatment	'People that are stable, they've stabilised their dose already, they're not going to mess with it [current prescription]' (male, FG5)
	'The risk of losing your existing drug, or even reducing, outweighs any financial [incentive]' (male, FG4)
Encouraging participation	
i. People dissatisfied with current treatment	'I'd be always willing to try a new medication if it's different from methadone' (male, FG1)
ii. People desperate for treatment	'People that are struggling to get into rehabs… You're in trouble, you're on death's door, you've scratched the bottom of the barrel, you need help. You're probably going to go for things like this' (male, FG4)

Table 6 Study relationships.

Theme	*Example quotation*
Discouraging participation	
i. Lack of trust in the pharmaceutical industry	'It's about trust. Do I trust the medical industry?... At the end of the day they do make a lot of mistakes' (male, FG4)
ii. Lack of trust in the treatment system	
iii. Concerns about the confidentiality of personal data	'I don't want to be getting letters from every other drug company in the country' (male, FG3)
Encouraging participation	
i. Service-user involvement	'I have to be compensated for my time, so money' (female, FG1)
ii. Persuasion from a trusted other	
iii. Cash payments	
iv. Non-cash payments	'I'd do it to help others further down the line' (male, FG3)
v. Altruism	

Nonetheless, participants identified ways in which relationships with those conducting trials might be improved. For example, some reported that involving current and former heroin users in the design of a study would increase willingness to participate as it demonstrated that researchers were receptive to their views. Participants also felt that they might be encouraged to join a study after listening to peers or clinicians who were enthusiastic about the trial. Above all else, however, participants stressed the importance of cash incentives, explaining that these put them into a more formal contractual relationship with researchers but also showed that researchers valued their input. Indeed, some thought that cash payments were essential, given that trials could not occur without current or former heroin users, that participant reimbursement for opioid dependence trials should match reimbursement for other industry-sponsored trials and that the payment level should depend on the risks and discomfort likely to be experienced.

Although cash incentives were nearly always preferred, some participants still felt that non-cash payments (e.g. store vouchers, transport passes, food vouchers or gym memberships) were effective forms of incentivization and recognition, especially if study participants could choose the type of non-cash payment received. In addition, some suggested that promising current heroin users a fast track into treatment, or a place in residential treatment, on completion of the trial might increase recruitment. Lastly, a small number of participants stated that they would be prepared to join a trial without any compensation at all in order to help others; specifically, they wanted to contribute to research, facilitate better future treatment options and help to save lives.

DISCUSSION

We conducted a small qualitative study that focused upon recruitment to trials of pharmacological interventions for illicit opioid dependence. Data collection was narrow in scope and only involved people who had received OAT for heroin use. The analyses undertaken were exploratory, and caution should therefore be taken in generalizing from the findings. Despite this, themes identified supported international research on factors that hinder and facilitate recruitment to trials of both pharmacological and psychosocial addiction interventions. For example, participants reported that study enrolment was deterred by the burden and conditions of involvement [11,20]; concerns about confidentiality [10]; mistrust of researchers [24]; and reluctance to be a treatment 'guinea pig' [10]. In contrast, recruitment was encouraged by access to study information [24]; the presence of medical care and monitoring [24]; treatments being desirable [13]; and reimbursements or incentives [14,21].

Findings were not, however, entirely consistent with previous research. Participants did not express concerns about the placebo or control condition [10,14,15]; instead, they were more anxious about the treatment drug. They also did not seem to be worried by limited trial duration [11]; on the contrary, they recommended that trials should be as short as possible. Other issues that concerned the participants have not been well documented previously, including the side effects of the study drug (especially withdrawal symptoms and interactions with other medications); perceived weaknesses in the trial design (uncertainty about the aim, feasibility, randomization, blinding, setting and post-trial procedures); already being satisfied with, or making good progress on, a current medication; and lack of trust in the pharmaceutical industry and treatment system. In short, participants worried that the trial drug might be worse than their current treatment; a reminder that people already receiving medication for heroin dependence will probably have different concerns about trial participation than those not currently in treatment.

Table 7 Checklist to increase potential participants' willingness to enrol in clinical trials of pharmacological interventions for illicit opioid use, version 1.

A. Study burden
1. Minimize travel to the study site (distance and costs)
2. Provide transport to the travel site if possible
3. Consider home delivery of treatment medications or delivery by mobile treatment van
4. Consider home completion of questionnaires or routine data collection/trial monitoring
5. Reimburse any travel costs
6. Be flexible whenever possible in relation to attendance requirements at the study site
7. Minimize the number of study tasks per visit to the study site
8. Avoid unnecessary toxicology screening
9. Keep the study duration as short as possible

B. Study drug
10. Provide clear, comprehensive and accessible information on the trial drug (including any research evidence, particularly the potential for withdrawal symptoms and side effects)
11. Discuss potential drug/medication interactions on an individual basis
12. Provide information on the availability of 'rescue opioids' if needed
13. Provide information on the availability of other medical care if needed
14. Offer participants a written contract or formal note on their medical records regarding 'opting out' or leaving the study and returning to their previous treatment

C. Study design
15. Explain the study aims, methods, and recruitment strategy using a range of accessible media (in addition to any formal written study documentation)
16. Provide a clear explanation of the reasons for blinding and randomization
17. Provide clear information on what will happen at the end of the trial or if the participant leaves the trial
18. Ensure the study site is comfortable and welcoming, and that potential participants are not likely to feel uncomfortable or stigmatized
19. Ensure that participants have access to recreational activities during time spent at the study site (e.g. television, reading materials, computers, game consoles)
20. Ensure that medical professionals and the availability of medical care are visible at study sites
21. Provide participants with information about how the trial will or will not affect any other support or services they receive

D. Study population
22. Consider both scientific and ethical factors before targeting vulnerable or treatment dissatisfied subgroups of opioid users who might be more desperate for treatment and therefore more willing to participate

E. Study relationships
23. Consider the potentially negative impact on recruitment if the study is funded by the pharmaceutical industry or the treatment system is perceived as unstable
24. Work collaboratively with current and former illicit opioid users in designing the trial (patient and public involvement is often a requirement of health funding bodies)
25. Invite enthusiastic clinicians and illicit opioid users who have ever participated previously in research to talk about the study at events or via social media
26. Invite enthusiastic clinicians and opioid users who have ever participated previously in research to help recruit to the study
27. Offer financial payments that are respectful of the demands of participation and the level of risk involved
28. If non-cash payments are offered, allow participants some choice regarding the type of voucher or incentive
29. Consider whether, and if so how, payments (financial or non-cash) might bias the sample
30. Provide reassurances about the confidentiality of the data
31. Remember (and respect the fact) that some opioid users will participate in pharmacological trials for altruistic reasons
32. Express thanks when opioid users agree to participate

Crucially, participants also made some observations about clinical trials that seemed to be confused or misinformed. For example, many expressed concerns about having to take drugs with unknown effects, being trapped in trials without being able to leave, having a pre-existing valued treatment disrupted and not knowing what would happen to them once the trial finished. In practice, of course, trial protocols are reviewed carefully by funders and ethics committees and scrutinized subsequently by trial steering committees. Furthermore, all patients are given detailed information about the trial procedures and medication, and patient safety and confidentiality are paramount. Nevertheless, the concerns expressed by our participants were substantial. They suggested additionally that recruitment could be improved by restricting studies to less than a month in duration, allowing them to have control over the study drug, ensuring that they knew exactly what drug they were taking and targeting

recruitment at people who were dissatisfied with their current treatment or desperate for treatment. Trial protocols are, however, bound by strict methodological criteria and processes, including eligibility, randomization and blinding. Consequently, researchers cannot necessarily change study designs in the ways that participants suggested.

Misconceptions and misunderstandings about clinical trials occurred in our study, even though the focus group facilitators talked participants through example trials and answered any participant questions. Poor research literacy has been reported in other addiction pharmacological trials, and is known to hinder trial recruitment [10,24,27]. For example, one Australian survey revealed that many trial-naive injecting drug users did not understand key clinical trial concepts, such as blinding, placebo, equipoise and randomization, even after detailed verbal explanations. Meanwhile injecting drug users who demonstrated an understanding of placebo and double-blinding were significantly more likely to perceive those concepts as acceptable compared with those who did not [28].

Ensuring that trial participants understand fully what will happen to them is an ethical requirement, especially vital given that financial incentives could attract otherwise reluctant people into pharmacological research. Participant understanding is clearly hindered by the complexity of trial designs and technical terminology. However, lack of trust in those associated with the research process (in this study, the pharmaceutical industry and treatment providers) will probably compound misunderstanding as well as deter engagement. This is a difficult problem to overcome, but not insurmountable. Trial information does not have to be provided only via dense documents and formal information sheets delivered by researchers or clinicians. It can also be made available via informal media (such as video or social media) using accessible language and images which potential participants can view at the recruitment sites and elsewhere; enhanced consent forms or extended discussion during the consenting process [29]; or interactive events hosted jointly with opioid users (including those who have already participated in similar trials) as part of a collaborative research effort [30].

To help improve future recruitment strategies we have used our findings to develop a checklist that researchers may wish to consider when designing new pharmacological trials for illicit opioid dependence (see Table 7). The checklist comprises 32 issues relating to the five domains identified in the focus groups: study burden; study drug; study design; study population; and study relationships. We do not suggest that these are the only issues that researchers should consider, and we recognize that some issues will be more relevant to some trials than others. We also note that the checklist is likely to require revision following further research. Nonetheless, it should offer a useful and immediate starting point.

CONCLUSIONS

Recruiting to clinical trials of medications for illicit opioid use is a complex practical and ethical process. There are many pitfalls and barriers and whether or not any particular individual will enrol will depend upon a multiplicity of factors. Although many early clinical trials (Phases 0–II) do not require large numbers of participants to be viable, RCTs need bigger sample sizes, are expensive if they overrun and delay advances in treatment if they fail. Poor trial recruitment can also produce unrepresentative samples that undermine study results [12].

Despite the various difficulties identified, the overall message from our research is positive. First, participants in all six focus groups identified strategies to encourage and facilitate trial recruitment proactively, so demonstrating a basic desire to improve clinical pharmacological research. Secondly, some participants expressed a strong personal desire to participate in clinical trials without reimbursement or incentivization, simply because they wanted to help others. Thirdly, many reported that they could be encouraged to participate if the conditions and circumstances for involvement felt right; and fourthly, many more might be willing to participate if we become better at explaining trials to them, dispelling misconceptions and increasing trust in the research process and the research establishment.

Declaration of interests

J.N. receives honoraria and some expenses from *Addiction* journal in her role as Commissioning Editor and Senior Qualitative Editor. J.S. is a researcher and clinician who has worked with a range of types of treatment and rehabilitation service-providers. He has also worked with a range of governmental and non-governmental organizations and with pharmaceutical companies to seek to identify new or improved treatments from whom he and his employer (King's College London) have received honoraria, travel costs and/or consultancy payments. This includes work with, during the past 3 years, Martindale, Indivior, Mundipharma, Braeburn/Camurus and trial medication supply from iGen and from Camurus. His employer (King's College London) has registered intellectual property on a novel buccal naloxone formulation and he has also been named in a patent registration by a Pharma company regarding a concentrated nasal naloxone spray. For a fuller account, see J.S.'s web-page at http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx. R.M. has undertaken an unpaid student industry placement with Mundipharma Research Ltd. R.M. and J.S. have both worked as consultants for the United Nations Office on Drugs and Crime (UNODC). CNET has no disclosures to report.

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