Patient acceptability of three different central venous access devices for the delivery of systemic anticancer therapy: a qualitative study

Caoimhe Ryan, Hannah Hesselgreaves, Olivia Wu, Jonathan Moss, James Paul, Judith Dixon-Hughes, Evi Germen

ABSTRACT

Objective Three types of central venous access devices (CVADs) are routinely used in the delivery of intravenous systemic anticancer therapy (SACT): peripherally inserted central catheters (PICCs), subcutaneously tunnelled central catheters (Hickman-type devices) and totally implantable chest wall ports (Ports). This qualitative study, nested within a multicentre, randomised controlled trial, sought to explore patient acceptability and experiences of the three devices.

Design Eight focus groups were audio-recorded, transcribed and thematically analysed.

Setting Six outpatient cancer treatment centres in the UK.

Participants Forty-two patients (20 female, mean age 61.7 years) who had taken part or were taking part in the broader trial.

Intervention As part of the larger, randomised controlled trial, participants had been randomly assigned one of three CVADs for the administration of SACT.

Results Attitudes towards all three devices were positive, with patients viewing their CVAD as part of their treatment and recovery. Participants with PICCs and Hickmans tended to compare their device favourably with peripheral cannulation. By comparison, participants with Ports consistently compared their device with PICCs and Hickmans, emphasising the perceived superiority of Ports. Ports were perceived to offer unique psychological benefits, including a greater sense of freedom and less intrusion in the context of personal relationships.

Conclusions Patient experiences and preferences have not been systematically used to inform policy and practice regarding CVAD availability and selection. Our research identified patterns of patient device preferences that favoured Ports, although this was not universal. Results of this study could improve support for patients and offer greater scope for incorporating patient perspectives into decision-making processes.

Trial registration number ISRCTN44504648.

BACKGROUND

Three types of central venous access devices (CVADs) are routinely used in the intravenous administration of systemic anticancer therapy (SACT; drugs administered for the treatment of cancer, including but not limited to cytotoxic chemotherapy): peripherally inserted central catheters (PICCs), tunnelled central catheters (Hickman-type devices) and totally implantable chest wall ports (Ports). These devices obviate the need for repeated peripheral cannulation, which patients find painful and distressing and which becomes more fraught as the veins thrombose with repeated use. Yet the three devices differ in important ways: PICCs are inserted into a peripheral vein in the upper arm, under ultrasound guidance. The end of the line sits outside the chest wall, just under the skin. Ports, on the other hand, are surgically implanted under the skin of the chest wall. They are connected to subcutaneous reservoirs that are filled in an outpatient setting with catheters through which SACT is delivered.

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body, extruding above the elbow, Hickman-type devices are placed through an incision near the collarbone with the end of the catheter tunnelled under the skin, emerging from a second, lower chest wall incision. Ports are completely enclosed systems without external lines, implanted in the subcutaneous tissue of the chest wall. Needle puncture is required for access each time they are used.

While available evidence suggests that patients tend to be satisfied with all three types of device (PICC, Hickman and Port)\(^\text{7–12}\), there is little indepth knowledge about what it takes to live well with one of these devices in place. Moreover, the distinct characteristics of each device together with differing care and maintenance requirements could imply meaningful differences in patient experiences. To date, empirical evidence concerning differences and similarities in patient experiences remains scarce and inconclusive. In a prospective randomised controlled trial, Patel et al\(^\text{13}\) found no significant differences in terms of quality of life, yet participants commented that “the questionnaire did not ask about several aspects of quality of life which were affected by the central venous catheter, for example, showering, bathing and swimming.” Comparing experiences of Ports and Hickman-type devices, Wu et al\(^\text{14}\) found that Ports were associated with more positive and less negative patient-reported outcomes. Comparing patient-reported experiences of dual-lumen Ports and Hickman-type devices, Johansson et al\(^\text{15}\) found that while 4 out of 15 patients with Ports experienced extensive subcutaneous bleeding leading to premature study closure, patient questionnaires demonstrated that, overall, patients with Ports thought about their device less and reported less disruption when dressing and bathing.

Clinical and local service factors determine whether and which CVADs are made available to patients. Where more than one device is appropriate and available, and despite recent growth in patient-centred approaches, device selection and patient support tend to prioritise clinical aspects often to the exclusion of patient experience. In this paper, we report findings from a multicentre qualitative study which was nested within the Cancer And Venous Access (CAVA) trial. Involving over 1000 patients at 17 UK sites, CAVA constitutes the largest randomised controlled trial comparing PICC, Hickman and Port devices in terms of clinical efficacy, safety and cost-effectiveness. The present qualitative component incorporates patient experiences and perspectives into the outputs of the clinical trial.

**METHODS**

**Design**

This is a qualitative focus group study. Reporting is based on the Consolidated criteria for Reporting Qualitative research.\(^\text{16}\)

**Sampling and recruitment**

Forty-two patients who had enrolled in the CAVA trial participated in eight focus groups. As part of the trial, participants met the following criteria: aged ≥18 years, receiving or due to receive SACT of at least 12 weeks’ duration, and clinical team uncertain as to which CVAD is optimal for this indication. They had also opted to have their particular CVAD type allocated randomly. Participants were sampled from the six largest recruitment centres: Glasgow (lead centre), Leeds, Manchester, Newcastle, Durham and London. Three further participants who had agreed to participate were too unwell to attend, one each at Leeds, Durham and London. A purposive sample of participants was identified by local trial staff at each site (table 1). To include a range of perspectives and experiences, participants at each site were chosen for maximum variation in terms of age, sex, cancer diagnosis, device allocation, as well as positive and negative clinical experiences with CVADs. The largest group of patients had colorectal cancer as infusional regimens commonly used in this patient group frequently require long-term central venous access. To facilitate both comparison and device-specific examination, four groups were single-device groups (participants within each had been randomly allocated the same device type) and four were mixed-device groups (participants had been allocated different devices). After the eighth focus group, it was determined that data saturation had been achieved, that is, no substantive new information was generated and additional focus groups would be of no further benefit. Across groups, some participants had experiences of different lines prior to CAVA. Eligible participants were initially contacted by local trial nurses with whom they had prior contact and who provided information sheets in person or by mail.

**Procedure**

Focus groups were held between August 2016 and December 2017. Discussions took place in quiet meeting rooms in the trial centres and were moderated by the lead author (CR), a female psychologist (PhD) and experienced qualitative researcher who had no prior relationship with participants. A trial nurse attended part of one focus group (Leeds) to address patient queries, otherwise no other persons were present. Prior to each session, details about data collection, analysis and use were discussed, and informed consent was obtained. The moderator started by explaining her own background and role in the trial. She then reminded participants about the purpose of the broader trial and current focus group, using A4 cards depicting each device type and reiterating current clinical equipoise. A focus group guide was used to ensure that all relevant topics would be addressed (box 1). Topics included CAVA trial participation and day-to-day experiences relating to their device. To create a communication situation resembling a ‘naturally occurring interaction’,\(^\text{17}\) interference with the discussion was kept to a minimum. Focus group discussions lasted approximately 1 hour and were audio-recorded with participant permission. To assist with transcription and analysis, relevant field notes were compiled after each focus group.

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<thead>
<tr>
<th>Participant ID</th>
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<tr>
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<td>P2</td>
<td>PICC</td>
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<tr>
<td>P3</td>
<td>Hickman</td>
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<tr>
<td>P4</td>
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<tr>
<td>P5</td>
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\(^{1)}\) Topics included CAVA trial participation and day-to-day experiences relating to their device. To create a communication situation resembling a ‘naturally occurring interaction’,\(^\text{17}\) interference with the discussion was kept to a minimum. Focus group discussions lasted approximately 1 hour and were audio-recorded with participant permission.
Table 1  Demographic and clinical characteristics of study participants

<table>
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<td>At least one, inserted &lt;3 months prior to study entry</td>
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CAVA, Cancer And Venous Access; CVAD, central venous access device; PICC, peripherally inserted central catheter.

Box 1  Questions included in the focus group guide

Question 1: What factors did you take into account when considering whether to participate in this trial?
- Prompt: Did you have any doubts?
- Prompt: What discussion did you have with your clinician/family?

Question 2: How did you feel about your device/line being selected by randomisation (by chance)?
- Prompt: What previous experiences did you have with venous access before you had your line inserted?
- Prompt: Did you have a preference for any particular device prior to being randomised?

Question 4: What were the positive/negative aspects of your device?
- Prompt: How did you feel about your device? (What did it represent to you?)

Question 5: In what ways did your device affect your everyday life?
- Prompt: What sorts of adjustments did you have to make?
- Prompt: Did it have an effect on the social aspects of your life (eg, with family and broader)?
- Prompt: Did you experience any problems with your device?

Question 6: Is there anything else you would like to say about your device?
- Prompt: What is the most important thing for someone who is about to have a line implanted to know?
- Prompt: What would you like clinicians/NHS to know about your experience?

NHS, National Health Service.

Analysis

Recordings were transcribed, anonymised and uploaded to the QSR NVivo V.10 software. Data were analysed using thematic analysis, ‘a method for identifying, analysing and reporting patterns (themes) within data’. First, transcripts were read and reread to ensure familiarity. A coding framework was developed based on patterns and repeated topics identified in the data. Data were coded, and coded chunks of data were grouped into initial themes. These processes were conducted by a single researcher in the first instance and reviewed by two further researchers at different stages. Data were then reread and the appropriateness of themes interrogated. Particular attention was paid to similarities and differences across devices types, and to discrepancies between developed themes and the data. As a final step, the specifics of each theme were refined, and clear definitions for each theme were formulated.

Patient and public involvement

Patients were not directly involved in the design of this study. However, research aims, focus group materials and data analysis were closely informed by pretrial focus groups with patients who had experiences of CVADs in the context of SACT. These focus groups explored topics of importance to patients with respect to venous access and SACT, as well as their views on participation in a randomised controlled trial comparing CVADs.

RESULTS

Our analysis identified three main themes, presented in detail below.

Acceptability of CVADs

All devices were well accepted by participants, and attitudes towards all three were generally positive. CVADs were regarded as less impactful than other aspects of participants’ journeys (eg, SACT, surgical interventions) and the effects of their illness, more broadly. Patients who...
had experienced SACT via peripheral cannulation said that their device made administration less painful and easier (both for themselves and for the staff). Participants tended to frame satisfaction in terms of the role of their device in their treatment and in their overall journey: “It’s part of my treatment, so it’s part of my life, it’s there” (Female, PICC).

When expressing satisfaction with their device, many participants referred to having had a problem-free experience. Our sample also included people who had experienced various difficulties with each of the devices, including painful placement or unsuccessful placement attempts, thrombus, infection and device malfunction. Notably, even these patients reported being satisfied with their overall experience. Partial or minor malfunctions did not appear to affect acceptability or satisfaction, as long as the device remained functional.

Participant 1: It really doesn’t bother me. (Male, Port)
Participant 2: As long as you can have your treatment through, it doesn’t. (Female, Port)

Living with a CVAD

Notwithstanding acceptance, living with a CVAD presented distinct challenges, which necessitated meaningful adjustments and adaptations. While the experience of individual participants differed substantially, we provide an inclusive account of the wide range of experiences described, highlighting points of difference between devices.

Practical challenges

Participants with PICCs and those with Hickman-type devices described comparable challenges and responses, which centred on keeping their external line clean, secure and comfortable. At a minimum, most reported needing to change the ways in which they bathed or slept. To keep their line dry, participants described sourcing and using various waterproof covers, or innovating their own solutions using household items (eg, “I put cling-film on it” (Male, PICC)). Some described adopting a conscientious approach to choosing clothing that could both conceal and accommodate their devices: “I certainly think about what I’m going to wear” (Female, Hickman). Here too, they exhibited resourcefulness; they described improvising protective covers and finding ways of securing lines with underclothing or sterile dressings (eg, “I had an old pair of tights I used to cut them and I had different colours and that worked fine” (Female, PICC)). These difficulties were heightened when portable SACT infusion pumps were attached to devices for treatment, preventing participants from securing or covering their line in the usual way.

Quite often I slept downstairs on the couch because I was worried about my partner who does [big arm movements] you know in his sleep and I thought it’s better with these wires going from here and up through your jammies so I just slept downstairs so that’s what I did on those nights [when pump was attached]. (Female, PICC)

For participants with Ports, experiences varied more markedly depending on whether a portable SACT pump was attached to their device. With pumps in place, participants with Ports experienced the same challenges described by those with PICCs and Hickman-type devices. Most of the time, without a pump attached, participants experienced few concerns regarding everyday activities, although some reported feeling cautious about their device, especially early on and during sleep. In general, participants with Ports claimed that based on their observations or direct experiences (some had experienced different devices prior to CAVA), as compared with PICCs and Hickman-type devices, Ports were more discreet, more secure, less disruptive of hobbies and activities, and easier to live with and maintain.

It’s just ease of use and the fact that it’s not in usage 24/7 for months on end like the Hickman lines size of a packet of fags [cigarettes] hanging on your chest, or the cannula sticking out your arm constantly that you have to protect and worry about. (Male, Port)

Gaps in knowledge

Across all three devices, the adjustments and adaptations described by participants were often associated with moments of uncertainty regarding proper care of their device or moments where their device complicated ordinary activities.

Well, it’s like the showering. ‘Cause you don’t know until you’re home and you think ‘Oh, right. How am I gonna get around this now?’ So you suss it out for yourself. (Female, Port)

Where participants were unable to find a solution to a particular problem, they sometimes gave up and disregarded care advice: “I abandoned trying to keep it dry and I was just very naughty and I would shower regardless” (Female, PICC). Some of those who found that their device was affected by seat belts reported wearing their belt in unconventional ways, uncertain if what they were doing was safe or legal: “There is a question about eh, you know, is it safe? Is it legal?” (Male, Port). Participants with Ports demonstrated a unique knowledge gap; many were unclear as to how long their device would remain in place and what this might mean for ongoing care and support.

In all, participants received sufficient information concerning device placement and critical aspects of line care, but were generally underprepared for living with a device in place. Some explicitly called for better information provision for future patients.

When someone gets a line there should be some information. […] At least you should be told: ‘You need to keep it clean and dry so buy this thing for about £15. If you want, there’s a cover that makes it a bit more discreet’. That sort of thing. There’s no
support with that. I’d like to think the people that follow us will get advice that we’ve not been given.
(Male, PICC)

Clinical care
Participants spoke at length about interactions with clinical staff, particularly those encountered outwith oncology departments—mainly community (district) nurses, but also staff at local clinics or other hospital departments. These discussions centred on a lack of staff experience and knowledge regarding CVADs, which led to delays and inconveniences and was an additional source of worry for some. While this applied to all devices, it was especially pervasive in the case of Ports: “The biggest problem with me is the district nurses” (Female, Port).

Emotional and psychological impact
The practical benefits associated with their lack of external lines (ie, less visible, easier maintenance) meant that Ports appeared to be less psychologically burdensome. In particular, participants with Ports repeatedly stressed that it was easy for them to “forget” about their device for days or weeks at a time. Participants described feeling “free” between rounds of treatment.

This thing [Port] is kind of a plug and play approach. Plug it in, introduce the chemicals, take it out, chuck it away and you are free, it’s nothing, it’s as if it wasn’t there. (Male, Port)

While some participants with PICCs and Hickman-type devices also described being able to completely forget about their device, the majority were reminded of it several times daily, mostly when bathing and dressing. One participant compared his current Port and previous PICC in this regard, explaining that he had been aware of his PICC “24/7” and had come to resent his treatment because he conflated treatment and mode of delivery (PICC). By contrast, he could forget about his Port entirely and no longer resented treatment. In fact, he found the lack of external line so beneficial that he described the experience of having his portable pump disconnected in the following terms:

As soon as that [portable pump] came off, bang, that was it. You almost felt alive again. Because it just detaches everything. It all disappears. And mentally as well as physically you can begin to forget it because you don’t really know it’s there. And I think that’s a huge difference. It sort of lifts you back up again. (Male, Port—prior experience of PICC)

Participants also discussed the effects of CVADs on relationships and intimacy and found the Port to be beneficial in important ways. External lines, but not Ports, caused worry in the context of close physical contact. One participant with a Hickman-type device explained that it had affected her relationship with her husband because its external lines made her feel unattractive. Another explained that her external line had got in the way when she and her husband needed to comfort each. She talked about the importance of moments of physical comfort in the context of cancer.

But even, you know, my husband just putting his arm across me to give me a cuddle at night-time and we were denied that because he was so worried that he touched it and I was equally worried that it would be caught up as well. And it was when you need it most, some comfort, you were denied that comfort because of this line hanging out. (Female, Hickman—prior experience of Port)

Participants with different devices expressed different sets of emotions when discussing their decision to show their device to others or to conceal it. For instance, participants with PICCs and Hickman-type devices expressed discomfort regarding the appearance of their device and how it would make others feel to see it.

I don’t like seeing a tube going into my chest, so I don’t imagine other people want to see it either. (Female, Hickman)

In our sample, this sentiment was not echoed by participants with Ports. Among these participants, some talked about showing their device to others in terms of sharing a sense of awe or fascination with their device. Some even expressed humour; three participants with Ports (currently or previously) mentioned nicknames—based on the idea of a button—that they and others (friends, family) used for their device, for example, “She [young daughter] calls it my magic button!” (Male, Port).

Patterns of preference
Among our sample, participants tended to prefer their own device, and most stated that if they had to choose a CVAD they would choose the one they currently had. Noticeable differences between devices were evident with regard to how satisfaction and preferences were formulated and expressed. For instance, we observed differences in the comparators participants used when discussing device satisfaction. Participants with PICC and Hickman-type devices tended to compare their devices (favourably) with peripheral cannulation. Participants in a Hickman-only focus group compared Hickman and PICCs, preferring the former which they felt was less obtrusive. Unless prompted, participants with either of these devices tended not to make comparisons with Ports. When prompted, there was ambivalence. Some were unsure about the idea of a needlestick for device access or, among those with PICCs, a device in their chest. Some claimed to lack sufficient knowledge about Ports to compare. Others, while happy with their current device, professed an interest in Ports. By comparison, participants with Ports consistently compared them with PICCs and Hickman-type devices and explicitly regarded Ports as superior CVADs.

The whole three [CVADs] were an option and I was hoping that it would be the Port just because you didn’t see anything. (Female, Hickman)
Furthermore, participants with PICCs and Hickman-type devices tended to express satisfaction with their device in personal terms. In the following extract, when ‘Participant 1’ was asked if he would recommend PICCs to others, he was reluctant, stressing the personal nature of his preference. This was not the case with ‘Participant 2’ who had a Port device.

**Participant 1:** Well I wouldn’t suggest, I wouldn’t give anybody advice on it because it’s up to them what that they do, it’s everybody’s personal choice what they like, em, but I would just say, well I find this a lot easier you know, so that’s...[to Participant 2] obviously you’ve had a Port... (Male, PICC)

**Participant 2:** I would recommend the Port. (Female, Port)

As illustrated here, participants who preferred Ports were more forthright in their preferences, which tended to be based on characteristics of the device itself, rather than familiarity or personal factors. This forthrightness was noted with interest by one participant with a PICC:

Loving the fact that the Port owners are really enthusiastic, there is this sense of like evangelical ‘yeah this is great’. Whereas with the PICC line we are all indifferent, different experiences, it’s not as clear cut, whereas you guys are. (Male, PICC)

Participants who could directly compare Ports and other devices were unequivocal in their preference for Ports, and positive regard for Ports held, even among those who had experienced painful placement procedures and device complications.

So it [Port] hasn’t worked for me, but if it had worked I would think it was the best one. (Female, Port)

Reflecting on the provision of Ports by the National Health Service, participants advocated for greater access to Ports, arguing that benefits justify additional costs.

And I feel quite strongly the very small difference between the Hickman-line costs and Port costs and the overall benefits to people who are going, suffering enough anyway, their life should be made easier. And it’s a small difference, you know. And as I say I have had the benefit of trying these different things, and I find just, there’s no comparison. (Female, Hickman—prior experience of Port)

**CONCLUSIONS**

To the best of our knowledge, this is the first qualitative study concomitantly exploring patient experiences of the three most routinely used CVADs for the delivery of intravenous SACT, namely Ports, PICCs and Hickman-type devices. Our study was nested within a large-scale, randomised controlled trial and recruited a diverse sample of patients from six different UK centres. Our results resonate with prior findings suggesting that all three CVADs are generally well accepted by patients. More than that, our analysis allowed for meaningful comparisons between experiences of different devices. We found that, while participants were satisfied with all three devices, focus groups highlighted key practical benefits of Ports (ie, perceived to be less conspicuous, less disruptive and easier to maintain), which had important impact on psychological and emotional well-being. The unique psychological benefits of Ports, including a greater sense of freedom and less intrusion in the context of personal relationships, have not been previously described in the literature.

Prior qualitative work focusing on patient experiences with PICCs has suggested that continuing normal everyday activities (eg, bathing, dressing), although possible for most, can depend on disruptive adjustments and is not without worry. Participants in our study, regardless of device type, extensively discussed similar challenges, although these applied to a much lesser extent to patients with Ports (except when portable pumps were attached). Fundamentally, all three types of device necessitated meaningful adjustments, with implications for patient well-being, as well as device care and maintenance. Our work points to the resourcefulness and resilience of patients; when conventional solutions did not work or were inadequate, participants innovated ways to deal with practical problems (eg, using household items to keep their line dry). This also highlights important ways in which patients could be better supported with practical guidance regarding bathing, driving and other aspects of device maintenance, as well as locally available products and resources. Patients’ enthusiasm for speaking with fellow patients about their CVADs in the focus group context could indicate that providing forums for mutual support and knowledge exchange among patients might be one way to meet these needs.

In our sample, all participants with Ports, many of whom also had prior experience of other CVADs, were generally inclined to advocate for Ports and make the case that these should be more widely available. However, while a small number of participants with PICC and Hickman-type devices expressed preferences for or equal interest in Ports, participants tended to favour their own device over others. This suggests either that our participants had adjusted well to their device, or that preferences for Ports—although exhibited in a stronger and more consistent way—might not be universal. Thus, where medically appropriate, patients should be offered a choice, and device selection should be a collaborative process between patients and clinicians.

Qualitative research is context-bound, and a consideration of the context in which the study was carried out is essential for the interpretation of these findings. Our study context was the UK public health system. Within this system, Ports are less widely available than PICCs or Hickman-type devices and participants were aware of this situation. To some extent, the particular advocacy for Ports observed within our sample might have been a response to these circumstances (similar advocacy was also
observed at centres where Ports were more widely available). Relatively, the limited use of Ports within the public health system is closely associated with a lack of training and expertise among community nurses and other clinical staff—a factor identified by several participants with Ports as the most problematic aspect of their experience with the device. All of these factors might have affected, to some extent, how participants formulated and expressed their opinions and preferences. Further examination of this topic in different health service contexts is warranted.

**Study limitations**

The use of CVADs is heavily dependent on the type of SACT required. Our sample consisted mainly of patients diagnosed with solid malignancies, most frequently colorectal and breast cancers, the two cancers most commonly requiring a CVAD. Extrapolation of the findings of this study to other populations may not be appropriate. In addition, our sample is distinct in that all of our participants had agreed to have their particular device type allocated at random; a discussion of the process of device selection was outside the scope of this paper.

**Clinical implications**

This work comes at a time of expanding interest in the potential impact of CVADs. In the UK, cancer treatment has traditionally been associated with Hickman-type devices. More recently, there seems to be a shift in favour of PICCs, as more centres introduce nurse-led PICC services. In addition, Ports have tended to be less available to patients (primarily owing to greater upfront costs), but this seems to be changing too, especially in private healthcare settings. Our findings that Ports conferred unique benefits to and were advocated by patients in our sample are important in light of these trends. The results of this study could be used to improve support for patients living with CVADs and, where more than one device is available and clinically appropriate, offer greater scope for incorporating patient perspectives and needs into decision-making processes.

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**Contributors**

CR coordinated participant recruitment, designed and conducted focus groups, carried out thematic analysis of the data, and drafted this manuscript. HH contributed to the design of the focus groups and early data analysis and offered comments on the full manuscript draft. OW contributed to the design of the focus groups and offered comments on the full manuscript draft. JM contributed to study design and provided comments on full drafts. JP contributed to study design and provided comments on full drafts. JD-H contributed to study design, supported participant recruitment and provided comments on full drafts. EG contributed to data analysis and interpretation and offered comments on early and later drafts of the manuscript. All authors read and approved the final manuscript.

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**Competing interests**

None declared.

**Patient consent for publication**

Not required.

**Ethics approval**

Ethical approval was granted by West of Scotland Research Ethics Service, REC 1 (13/WS/0056).

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data sharing statement**

This study is a qualitative component of a multicentre, randomised controlled trial. While this component of the trial has been completed, the main trial is ongoing. Upon completion of the main trial, data will be made available in an online repository. In the meantime, data will be available upon request to the corresponding author.

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**REFERENCES**


