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Evaluation of the design, conduct and reporting of randomised controlled trials in the haemodialysis population: a scoping review and interview study

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ABSTRACT

Background Fewer trials are conducted in nephrology than any other specialty, often failing to recruit to target, resulting in unclear evidence affecting translation to clinical practice. This mixed-methods study aims to provide guidance for designing and reporting future randomised controlled trials (RCTs) in the haemodialysis population.

Method A scoping review was conducted. Five databases (MEDLINE, Cumulative Index to Nursing and Allied Health Literature, Embase, Cochrane Central Register of Controlled Trials and ClinicalTrials.gov) were searched for RCTs published between 2013 and 2019 involving prevalent adult haemodialysis patients. Reporting of sample size, recruitment, retention and statistical significance of primary outcome were assessed. Face-to-face semistructured interviews were conducted with individuals from a single centre during dialysis sessions. Interviews were analysed thematically.

Results Of 786 RCTs identified, 636 (80.9%) were parallel-group, 139 (17.7%) were crossover and 11 (1.4%) were cluster (including one stepped-wedge) design. Sample size justification was reported in 73.1%, 53.8% and 45.5% of parallel-group, crossover and cluster trials, respectively.

Target recruitment was achieved by 45.5% of cluster, 53.8% of crossover and 57.7% of parallel-group trials with patient retention at 75.6%, 83.1% and 87.8%, respectively. Primary outcome reached statistical significance in 81.8% of cluster trials, 69.2% of parallel-group and 38.5% of crossover trials.

Themes identified from individual interviews: perceptions of the convenience of trial participation; group allocation; perceptions of the benefits and adverse effects of taking part in clinical trials.

Conclusion The recruitment and reporting of RCTs involving people on haemodialysis could be improved. Involvement of all stakeholders and especially participants in the trial design process may address issues around participant burden and ultimately improve the evidence base for clinical practice.

Strengths and limitations of this study

- This scoping review includes a comprehensive collection of trials in the haemodialysis population over a 7-year period and is the first to assess by trial design.
- Semistructured interviews with individuals on dialysis complemented the review by identifying attitudes and perspectives to taking part in clinical trials.
- Not all parallel-group or crossover trials were included for review, but selection bias was reduced by using a random number generator.
- The interview size sample size was small, although purposive sampling was used to obtain a broad range of perspectives.
- The integration and synthesis of findings from the scoping review and interviews allows guidance to be suggested for future designing and reporting of clinical trials involving patients on haemodialysis.

INTRODUCTION

Nephrology has one of the lowest numbers of published randomised controlled trials (RCTs) across all medical specialities.[1–3] Furthermore, there has been no significant growth in the number of RCTs and compared with other specialties, the outcomes of these trials have had less impact in clinical practice.[2–4]

Inappropriate trial design, poor participant recruitment and retention, and inadequate reporting of trials have been identified as factors that can adversely affect trial outcomes.[5 6] Recent studies show poor reporting in nephrology trials,[2 7 8] despite the presence of Consolidated Standards of Reporting Trials (CONSORT) guidelines.[9] This is a particular problem when the number of RCTs performed is low (such as in nephrology) as each published trial has a greater contribution to the overall evidence base.[8] This led to the International Society of Nephrology (ISN) in 2016 identifying the need to increase the quality and quantity of trials in chronic kidney disease (CKD) by promoting conduct of clinical

trials, optimising trial design and increasing capacity for conducting trials.[10] One approach involves developing and using innovative trial designs.[11]

Previous qualitative studies exploring recruitment and retention in nephrology trials identified lack of knowledge, stress from participation,and feeling disconnected from the process affected participation.[12] Perceptions of RCT participation in the UK haemodialysis (HD) population requires further investigation to address barriers to participation and to shape future RCT design and implementation. The aim of this study was to explore how different trial designs can affect recruitment, retention and reporting of trials. We also sought the participant perspective on trial design and participation; these are priorities to address the need for more effective trials and in turn, to improve patient care.

METHODS

Study design

A mixed-methods study was conducted consisting of a scoping review and semistructured interviews. Due to the paucity of information currently published on this subject, a scoping review was chosen to allow a broad range of literature to be assessed using a systematic method.[13–15] We refer to non-standard trials as: cluster randomised parallel-group, crossover and stepped-wedge trials. The scoping review was complemented by semistructured interviews with people on maintenance HD to obtain participant attitudes and perspectives to taking part in clinical trials with a focus on recruitment and retention.

Methods of scoping review

Details of the scoping review protocol are available elsewhere.[16]

Eligibility criteria

Completed RCTs published between 2013 and 2019 were included, provided the trial design was one of the following: individually randomised parallel-group, crossover, cluster randomised parallel-group or stepped-wedge design. This period was chosen as the first stepped-wedge trial in patients with HD was published in 2013. Participants in the trials must have received HD for >3 months and be 18 years and older. All trials with any intervention, comparison and outcome were included. Publications solely of secondary and post hoc analyses were excluded.

Search strategy

Five databases were searched: MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature, Cochrane Central Register of Controlled Trials and ClinicalTrials.gov. The last search date was 8 October 2019.

No limits on language were set to reduce language bias. An example of a full search strategy for the MEDLINE database is shown in table A-1 (online supplemental text, Appendix 1).

Selection of sources of evidence

Search results were compiled using EndNote X9 and duplicate citations were removed.

Titles and abstracts were screened initially to assess eligibility by two reviewers (PK and DSM). If there was discrepancy or uncertainty from the initial screening, a third independent reviewer assessed titles and abstracts (JOB). If the abstract was unclear, the full text was accessed to understand the trial design.

Trials were categorised by design (ie, parallel group, cluster, crossover and stepped wedge). A sample of trials were selected using a random number generator, allowing for stratified sampling by design. Based on current literature, we expected cluster trials to be a small proportion of the total[17]; the number of cluster trials was therefore used to determine the numbers of other trials assessed. An equal number of crossover trials were assessed, and twice the number of parallel-group trials to account for the larger number of trials.

Publications within each trial design category were further subdivided by intervention type: 'Pharmacological' which included drug trials; 'Device' which included interventions such as choice of dialyzers; 'Procedure' involving interventions such as surgical procedures or changes in dialysis delivery; 'Lifestyle' consisted of dietary and exercise interventions and 'Other'. 'Other' consisted of 'Alternative Therapies' (Alt.), 'Psychological, behavioural and educational' (PBE) and a third 'Unclassified' subcategory. If a study compared two different intervention types, these were recorded twice.

The full text was only assessed to determine eligibility if the abstract was unclear.

Data collection process and data items

Data extraction was carried out independently by one reviewer (PK) and verified by the second reviewer (DSM). The full data extraction items can be found in the online supplemental text, Appendix 2. Authors of papers were not contacted for missing data, as one of the objectives of this review was to assess the reporting of trials.

CONSORT extensions for crossover trials and cluster trials were used to identify data items specific to sample size reporting (item 7a on the CONSORT checklist).[18 19]

Summary measures and synthesis of results

Papers were grouped according to trial design. Measures assessing reporting, achievement of target recruitment and achievement of significant primary end point were binary (Yes/No), summarised as raw numbers and percentages. Length of trial, number of participants recruited and number of finished trials were continuous outcomes, with the median and IQR calculated within the trial design category. Patient retention and attrition were calculated as percentages and the median percentage and IQR presented.

Data were synthesised using Microsoft Excel 16 and analysed using Stata 16 (Stata, College Station, Texas, USA).

Methods of interviews

Study design and participants

A pragmatic qualitative study was conducted using semi-structured interviews. Patients were recruited from a single dialysis unit in Leicester.

Inclusion criteria were the following: aged 18 years and older, on maintenance HD and ability to provide written informed consent. Participants were excluded if they were a hospital inpatient or if there was a language barrier. The aim was to recruit 10 participants; this sample size was chosen to reflect sufficiently diverse views and experiences within the time and resources available. Maximum variation purposive sampling was used to ensure a representative population reflecting differences in gender, ethnicity, age and previous research experience. Those who were screened as eligible to be interviewed were approached during their dialysis session and provided information about the study. Interviews were conducted the following week after being approached, at the same dialysis slot, and written informed consent was obtained prior to interview

Ethics and research approval was obtained from the London-Surrey Border NHS Research Ethics Committee (REC ref: 19/LO/1816).

Patient and public involvement

A patient and public involvement (PPI) meeting was held prior to interviews to ascertain general perspectives on taking part in clinical trials. Participants helped shape the interview topic guide and identified important themes and concepts to explore further during interviews (online supplemental text, Appendix 3). The method of undertaking interviews during dialysis was also explored. This meeting was held via Microsoft Teams in October 2020.

Following the PPI meeting, changes including increased use of lay terminology when referring to types of study design and further exploration of group assignment (intervention vs control) were made, as well as opting for interviews while on dialysis as this was highly favoured by the PPI group. Visual aids were used to provide further explanation of the different trial designs discussed (online supplemental text, Appendix 4).

Interview procedure

Data were collected via semistructured interviews conducted face-to-face on the dialysis unit.

Interviews were conducted and audio-recorded by one of two researchers (PK and SFA) between November and December 2020. Researchers kept a reflexivity diary and field notes throughout the interview process. The researchers PK and SFA are clinicians, but not involved in the care of the participants, while CJL is a non-clinical researcher.

Data analysis

All interviews were anonymised and transcribed verbatim by the same researcher who conducted the interview. QSR International NVivo12 was used to manage the data, which were analysed thematically using the principles outlined by Braun and Clarke.[20] One researcher (PK) read the complete data set and independently identified codes. A sample of interviews were read and coded independently by a second researcher (SFA). Both researchers reviewed and agreed on the final codes. Patterns in the codes were identified and collated, from which themes were developed inductively. Themes were reviewed and agreed by PK and CJL.

RESULTS

Results of scoping review

Selection of trials

The process of identification and selection of papers included in this review, as well as reasons for exclusion, is depicted by figure 1.

A total of 786 RCTs were identified in the prevalent HD population from 2013 to 2019. Six hundred and thirty-six (80.9%) were individually randomised parallel-group trials, 139 (17.7%) were crossover trials, 10 (1.3%) were cluster trials and 1 (0.1%) was a stepped-wedge trial. The stepped-wedge trial was also cluster randomised and therefore was included with cluster trials for analysis. In total, 50 trials were analysed for this scoping review.

Thirteen cluster trials, 13 crossover trials and 26 parallel-group trials were selected, the latter reflecting the larger proportion of parallel-group trials in total. Three cluster trials were excluded during data extraction (for reasons, see figure 1), resulting in 10 cluster trials. Trials included, organised by design, are presented inonline supplemental text, Appendix 5.

Characteristics of trials

Characteristics of all trials

All trials were categorised according to their intervention type as shown in table 1.

Characteristics of included trials

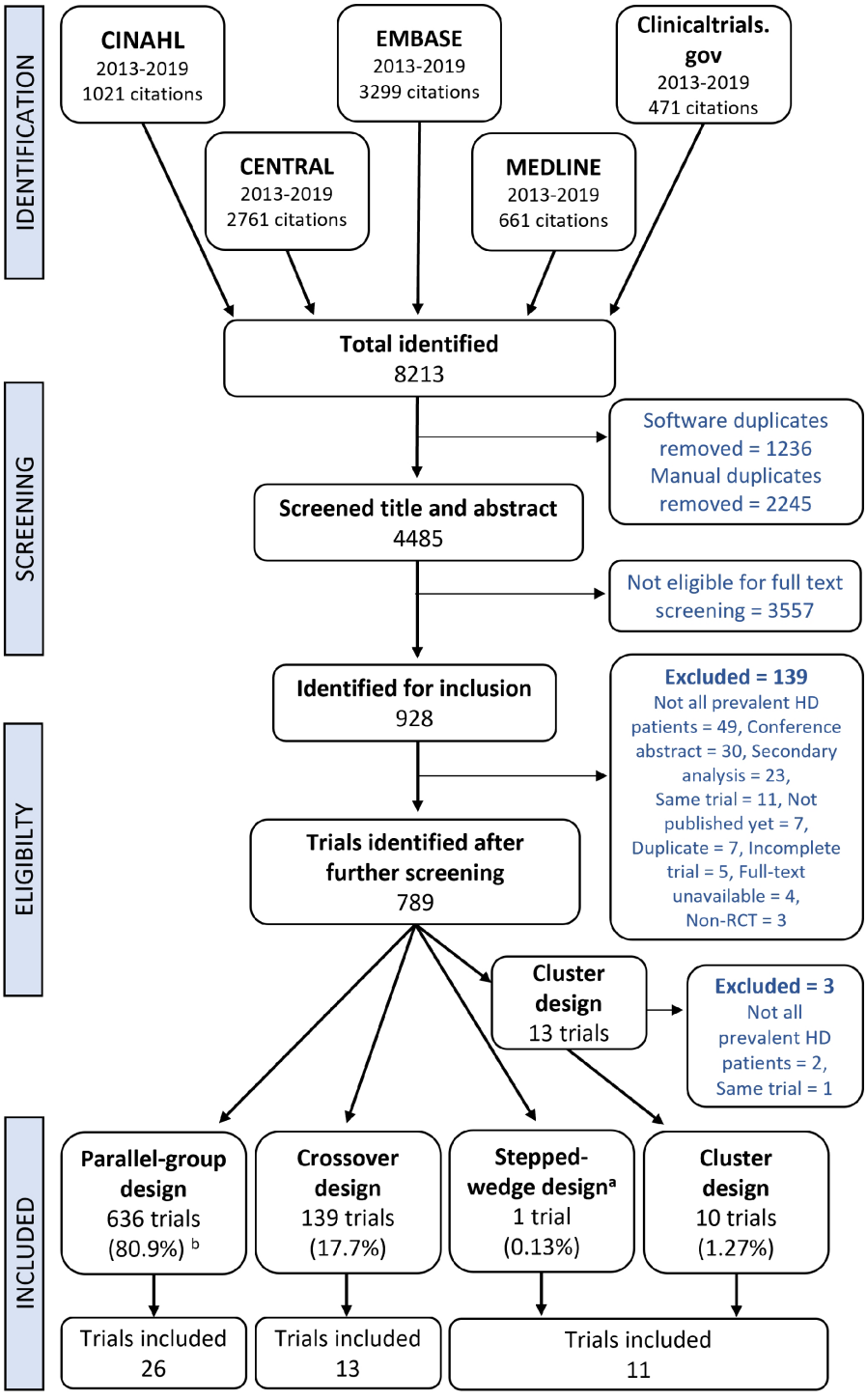
Cluster trials had the longest median duration (28 months, IQR: 12–39), followed by parallel-group trials (12 months, IQR: 5–25) and crossover trials (8 months, IQR: 6–12) (table 2). The duration of study was not consistently reported. Fourteen (53.8%) parallel-group and seven (53.8%) crossover trials reported the length of study, whereas only three (27.3%) cluster trials reported this (table 2).

The median number of participants recruited for cluster trials was 119 (IQR 90–259), 61 (IQR 45–100) for parallel-group trials and 33 (IQR 12–35) for crossover trials (table 2).

Reporting

Factors related to sample size

Sample size justification was provided in 19 (73.1%) parallel-group trials, compared with 7 (53.8%) crossover and 5 (45.5%) cluster trials (table 2). Table 3 shows the additional CONSORT requirements for crossover and cluster trials, which were poorly reported; one (7.7%) crossover trial and no cluster trials fulfilled all the requirements. Of the five additional items that cluster trials should report regarding sample size, cluster size was



[a] Trial was stepped-wedge and cluster randomised
[b] Percentages calculated from final number of trials = 786 (following exclusion of 3 cluster trials)

Figure 1 PRISMA flow diagram illustrating process of study identification and inclusion. HD, haemodialysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.

reported by two (18%) papers. The number of clusters in the sample size calculation and intracluster correlation coefficient (ICC) were reported by one (9%) paper. The two other parameters, assumption of equal or unequal cluster sizes and uncertainty in ICC, were unreported by all papers (table 2).

Other factors

Use of a CONSORT flow diagram to represent participant flow was seen in 9 (81.8%) cluster trials, 21 (80.8%) parallel-group trials and 9 (69.2%) crossover trials. Target recruitment numbers were not reported in six (46.2%) crossover trials and three (27.3%) cluster and seven (26.9%) parallel-group trials.

Table 1 Table showing trial design and intervention type of all trials

Characteristic	n	%
Trial design		
Individually randomised parallel group	636	80.9
Crossover	139	17.7
Cluster	10	1.3
Stepped wedge	1	0.1
Intervention type		
Pharmacological	290	36.9
Device	83	10.6
Procedure	58	7.4
Lifestyle	209	26.6
Other	149	19.0

'Pharmacological' included drug trials. 'Device' included interventions such as choice of dialysers. 'Procedure' involved interventions such as surgical procedures and changes in dialysis delivery (ie, high flow rate, temperature of dialysate). 'Lifestyle' consisted of dietary and exercise interventions. 'Other' consisted of trials that did not fit in any other category. This was further subdivided to include 'Alternative', such as acupuncture or music therapies which consisted of 74 trials and 'Psychological, Behavioural and Educational' which consisted of 43 trials. Some trials within 'other' did not fit any category and therefore remained 'Unclassified' which consisted of 32 trials. 'Unclassified' included interventions such as use of advanced care plans, nurse-led follow-ups or interventions and use of collaborative care models. If a study compared two different intervention types, these were recorded twice. Thus, the number of interventions is greater than the number of studies.

Recruitment and retention

Fifteen (57.7%) parallel-group trials achieved their target recruitment, the highest percentage of trials assessed, followed by seven (53.8%) crossover trials and five (45.5%) cluster trials. The median patient retention in parallel-group trials was 87.8% (IQR 79.5%–95.4%), 83.1% (IQR 74.3%–91.7%) in crossover trials and 75.6% (IQR 65.9%–84.4%) in cluster trials.

Two cluster trials (18.2%) used the HD centre as the cluster, with the remaining nine (81.8%) trials using dialysis shift for the cluster.

Trial outcomes

Cluster trials had the largest number achieving a statistically significant (p<0.05) primary outcome, n=9 (81.8%). Parallel-group trials had 18 (69.2%) and crossover trials had 5 (38.5%) achieving a statistically significant primary outcome.

Interview findings

Thirteen potential participants were invited to be interviewed. Of those, 10 participants agreed and consented to be interviewed (figure 2). Participant characteristics are shown in table 4. On average, interviews were 31 min (IQR: 30–33).

Table 2 Summary of data by trial designs

Trial designs	No of studies assessed	States how sample size was determined? % (n)	All sample size CONSORT requirements reported? % (n)	Did not state target recruitment % (n)	Use of CONSORT flow diagram? % (n)	Stated length of trial? % (n)	Length of trial, median months (IQR)	Number recruited, median number (IQR)	No of finished trial, median number (IQR)	Achieved target recruitment? % (n)	Patient retention, median % (IQR)	Studies achieving >80% retention? % (n)	% Lost to follow-up due to withdrawal of consent, median % (IQR)	Achieved significant primary end point? % (n)
Parallel group	26	73.1 (19)	–	26.9 (7)	80.8 (21)	53.8 (14)	12 (5–25)	61 (45–100)	55.5 (38.5–81)	57.7 (15)	87.8 (79.5–95.4)	65.4 (17)	0 (0–34)	69.2 (18)
Crossover	13	53.8 (7)	7.7 (1)	46.2 (6)	69.2 (9)	53.8 (7)	8 (6–12)	33 (12–35)	24 (11–30)	53.8 (7)	83.1 (74.3–91.7)	69.2 (9)	0 (0–75)	38.5 (5)
Cluster	11	45.5 (5)	0	27.3 (3)	81.8 (9)	27.3 (3)	28 (12–39)	119 (90–259)	87 (60–186)	45.5 (5)	75.6 (65.9–84.4)	45.5 (5)	22.7 (11.4–28.6)	81.8 (9)

CONSORT, Consolidated Standards of Reporting Trials; IQR, Interquartile range; n, number of trials.

Table 3 Reporting of crossover and cluster trials compared to CONSORT 2010 requirements

Trial design	No of studies assessed	States how sample size was determined? % (n)	States no of clusters in sample size calculation? % (n)	States cluster size? % (n)	States if equal or unequal cluster sizes are assumed? % (n)	States the ICC? % (n)	States uncertainty in ICC? % (n)	Within participant variability accounted for? % (n)
Crossover	13	53.8 (7)	N/A	N/A	N/A	N/A	N/A	7.69 (1)
Cluster	11	45.5 (5)	9.1 (1)	18.2 (2)	0	9.1 (1)	0	N/A

CONSORT, Consolidated Standards of Reporting Trials; ICC, intracluster correlation coefficient; n, number of trials; N/A, not applicable.

Theme 1: perceptions of the convenience of trial participation

Exemplar quotes are displayed in table 5.

Trial duration

Participants reported the ideal length of a trial was between a month and 18 months. A longer trial was considered acceptable if details about the trial were adequately explained, as participants acknowledged that kidney disease is a chronic condition thus longer trials maybe required. The length of the trial was not an issue to some participants as they felt they had 'all the time on dialysis'. Others felt that a long duration could be time-consuming and burdensome depending on the necessary involvement, consequently leading them to decline or dropout. Acceptability and burden of the intervention or follow-up were considered to more likely impact participants' adherence to the trial, including dropping out, than the duration and design of the trial.

Study visits

Most participants explained how they preferred trial visits to take place while they were receiving dialysis as it 'helps pass the time' or prior to their dialysis timeslot due to 'little enough free time now'. One participant stated that if visits took place during dialysis, they may drop out if they felt unwell postdialysis.

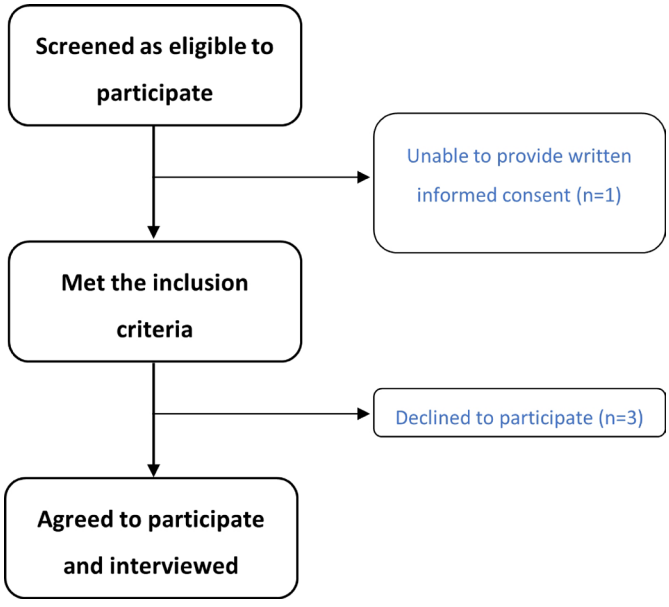


Figure 2 Flow diagram representing participant recruitment for semistructured interviews.

Theme 2: perceptions of equipoise

Exemplar quotes are displayed in table 6.

Clinical equipoise is the necessary belief that neither the intervention nor the control is 'better' during the design of an RCT. In our interviews, the intervention group was perceived to be the most desirable group, with participants describing feeling more involved in the study and gaining potential health improvements. Participants felt that they would not benefit from the study if assigned to the control group; one participant explained that they would only continue to take part in a trial if they received the intervention. Conversely, a small number perceived the control group as 'a contribution to the study, without the adverse risks', and thus a preferable option.

Parallel-group trials were believed to be fair and recognised as the 'standard way' trials are conducted. The concept of stepped-wedge and crossover trials were generally well received by participants as they liked the idea of being guaranteed the intervention at some point, even if initially allocated to the control group.

Theme 3: perceptions of the benefits and adverse effects of trial participation

Exemplar quotes are displayed in table 7.

Most participants perceived clinical trials to provide greater benefit to future patients rather than those participating in the trial. Motivating factors to participate in trials were discussed which included being able to continue with an intervention long term, feeling part of a community, a sense of pride or feeling they are 'giving back'. Some participants felt taking part in a cluster trial with others would be more motivating, with one participant reporting that talking to other participants would make him feel stronger. Participants believed having a personalised approach during the trial processes, such as having a good rapport with researchers, social events and newsletters, encouraged continued involvement. Participants who did not feel that they would benefit or who did not receive feedback reported being less likely to take part.

Table 4 Demographics of the participants Interviewed

Interview cohort (n=10)	Sex (M/F)	Age range (years)	Race	Dialysis vintage range (years)	Previous trial experience	
					Y/N	Trial design
P01	F	40–59	South Asian	5–10	Y	Parallel group
P02	F	>80	White	<5	N	
P03	M	60–79	White	<5	N	
P04	M	60–79	White	<5	Y	Parallel group
P05	M	>80	White	<5	N	
P06	M	20–39	South Asian	5–10	Y	Cluster
P07	F	40–59	White	<5	Y	Parallel group
P08	M	40–59	South Asian	<5	N	
P09	F	40–59	Mixed race	>10	Y	Parallel group, cluster
P10	M	60–79	Black	>10	Y	Parallel group, cluster

M, male; F, female; Y, yes; N, no

The adverse effects of participating in clinical trials were acknowledged, with participants reporting the concerns they had when enrolling or considering dropping out. One participant described the experimental nature of trials and feelings of being a 'guinea-pig'. Some participants recalled declining involvement because the intervention or investigations were not considered to be acceptable. Personal factors impacting trial participation were discussed; age and health at the time, especially daily fluctuations in health while on dialysis, were key factors. Taking part in trials while being on the transplant list was perceived to potentially jeopardise participants' chances of receiving a transplant.

DISCUSSION

The aim of this mixed-methods study was to evaluate the usage of different RCT designs in the HD population,

Table 5 Quotes showing perceptions of the convenience of trial participation (theme 1)

Subtheme	Quotation
Trial duration	"[longer than six months would be] too time-consuming… I wouldn't be prepared to do it for a very long time" (P02)
	"kidney disease is a long term issue anyway so I don't think [longer trials] would be a problem… It's probably what you are being asked to do, is probably more the reason why people are a bit worried and leave. Don't think the design has much to do with it" (P03)
	"If I knew it would be a long trial, then I wouldn't be so keen … and if it took up too much of my time. Then I may give it some thought [to leave the study early]" (P05)
	"Oh that doesn't matter, yeah because we've got all the time on dialysis… as long as it's on dialysis days, then we have all the time here" (P10)
	"No I think once you're on it, you know what's involved, you're committed to going through with it… I think people get concerned about longer term commitments than short term commitments" (P04)
Study visits	"I am always sick… I can't make any extra journeys than I already do… When I come here, Monday, Wednesday, Friday. I am here for 3 or 4 hours, then I am happy to take part. But to be invited on extra days, then I can't come, sorry… My body isn't prepared to come another time" (P01)
	"If [study visits] were fitted around dialysis, or done whilst we are on dialysis. Then it wouldn't take up any extra time" (P05)
	"I would leave the study [if visits were done whilst on dialysis]… because I don't feel well on dialysis and afterwards" (P06)
	"Patients don't want to be here, they want to do their best to help you but… when they finish, the first thing they want to do is leave, they want to get out and go. With research assessments and enquiries, it's the best time for you to participate with the patient while they're doing the dialysis… That is the main prime time, to do the research" (P09)
	"I wouldn't stay later but I'd come in earlier……. Maybe up to half an hour… Otherwise, I don't mind, plus when we're sat here for 4 hours, it helps us pass the time… when you have to come on another day, it affects work and everything" (P10)

Table 6 Quotes demonstrating patients' perception to equipoise (theme 2)

Subtheme	Quotation
Perception of intervention	"You're more active rather than passive… I don't think [as a control] I'm making much [difference] than just being there for a comparative basis… if you know that you're going to be a useful part of the intervention, I think that sounds more attractive to me" (P04)
	"I'd say significantly important [to get the intervention] because it could mean a change to your health, feel better and it could, if not for yourself, help other people, so that's always a good thing" (P07)
Preference to intervention	"I would prefer the studies where you get the treatment at some point … I would rather be the first person, so I get the treatment faster" (P06)
Perception of control	"It is a contribution towards the study, without the risk of adverse effects" (P05)
	"with the control side of things they're not really getting any benefit whatsoever as long as they're participating so they'll drop out more" (P08)
	"…like the potassium drug, I was, so excited about it, if I wouldn't have had the drug, I would have felt let down" (P09)
	"Well, I either get it [new treatment on offer] or I don't, it doesn't matter… as long as I'm here, I'm happy to help" (P10)
Preference to control	"I think I would like to be in group B [control]… because I have no idea what the treatment is doing" (P01)
Perception of parallel-group trials	"It's the normal way, to not be guaranteed the treatment" (P02)
Perception of non-standard trials	"I think it is better as far as the patient is concerned… because they get the treatment at some stage" (P02)
	"If you were in a control group, you'd want to carry on and get a different type of treatment. If you were in the intervention group you might not be happy about having to become a control…although, you're contributing by being just in a control group, I think anything that gives you an opportunity to be part of an intervention process, you would go for" (P04)

with a focus on reporting, recruitment and retention. The qualitative component aimed to explore the perceptions of individuals on HD towards trial designs and taking part in HD trials.

Our findings show that standard parallel-group RCT designs are the most frequently used in the HD population and is similar to a previous estimate of trials across medical specialties.[21] The reporting of sample size in trials assessed was poor, recruitment rates were low and retention varied by trial design. Themes extracted from the interviews were around trial duration and timing of study visits, perceptions of being allocated control or intervention arms (and how this related to perceived clinical equipoise), as well as perceptions of the adverse and beneficial effects of trial participation.

Figure 3 summarises some recommendations from the findings of the scoping review and interviews for improving recruitment and retention in future RCTs.

Implications for trial design

An important theme extracted from this study was the duration of trials. In our review, the longest and largest trials were cluster trials, which were also less likely to achieve their target recruitment number and retain participants. Discontinuation due to the burdensome trial duration was one of the main reasons cited by our interview participants and was also noted by Kotz *et al*.[22] Discussing expected trial duration when approaching a patient to discuss a trial may help manage participants' expectations and consideration of how to reduce the intensity of follow-up in longer trials may improve recruitment and retention rates.

Of the trials assessed, achievement of a significant primary end point was greatest in cluster trials (81.8%) and lowest in crossover trials (38.5%). Larger trials, such as cluster trials, were more likely to be adequately powered. For this review, achieving a significant primary end point was defined by a statistically significant result with $p<0.05$. However, trials may be successful or clinically significant without needing a statistically significant value.[23] Shochet *et al* concluded that p values may not provide the evidence required for evidence-based medicine and therefore larger RCTs with lower attrition are needed.[24]

Implications for trial conduct

Altering trial conduct to enhance the participant experience may improve recruitment and retention. Achievement of target recruitment in trials is poor across all medical specialties.[25] Trials involving patients on HD are no different, with between 46% and 58% of trials in this review achieving their recruitment target, in line with previous CKD literature.[12] The financial and scientific cost of under-recruitment to clinical trials is manifold; one institution estimated that low-enrolling trials may cost them close to $1 million a year but derive minimal scientific benefit.[26]

Table 7 Quotes demonstrating perceptions of the benefits and adverse effects of trial participation (theme 3)

Subtheme	Quotation
Individual benefits	"now the study is finished, but they kept me up on [the intervention], and it's such a good drug, it's helping me. Plus, they give you a newsletter, they let you know what's happening… Our research team is quite good. They give you that personal [touch]]. So you want to take part in research. Which makes you feel involved" (P09)
	"You will learn more, you can help yourself and other patients with what you learn" (P06)
Sense of giving back	"And I think I feel quite proud when I take part in a study, and it helps people" "When you do these studies, it's very important that the patient gets to know what's happening…I'd like to know what happened at the trial… sometimes we don't hear from them again" (P09)
Sense of community	"[regarding cluster trials] If you met up with a group of people that have the same problem, you will become stronger because you can talk about what affects each other" (P08)
	"[Doing cluster trials] might be better I think, more motivating" (P03)
	"[Doing cluster trials] wouldn't make a difference to me" (P04)
	"But [the research team] had a prize giving thing, and they all dressed up And then they had a little spread like sandwiches and cakes.…they gave out certificates" (P09)
Reasons to decline	"Sometimes there can be side effects of the new drugs or treatments" (P05)
	"you are a guinea pig. They could go wrong" (P03)
	"I did turn down one research project because that meant having to have regular body scans, and I'm not very keen on going into machines" (P04)
	"It depends at the time how I feel. Sometimes I don't feel well enough" (P06)
	"I am almost 91, so [taking part] depends on my health" (P02)
	"If I had a transplant… It's probably what you are being asked to do, is probably more the reason why people are a bit worried and leave" (P03)
	"But even if I was on a transplant list, as long as it was safe and it didn't affect chances of the transplant and everything, then you'd carry on, what's wrong with it. But I think it's important to have a transplant team that can liaise with a patient" (P09)

Literature suggests embedding research into clinical care to reduce participant burden may improve recruitment and retention.[27 28] Most of our interview participants preferred to have study visits during dialysis. Our interviews suggest that integrating clinical visits with study visits or using routinely collected data may reduce participant burden.

Retention for all trial designs was good. Our interviews revealed that previous good experiences of taking part in trials, such as physical benefits or 'feel-good' effects developed from a sense of community or fulfilment favourably influenced future participation. Focussing on fostering rapport and a sense of community may encourage continued participation in future RCTs. In our interviews, participants were disheartened to not receive feedback about outcomes from previous trial participation and felt deterred from taking part in future research.

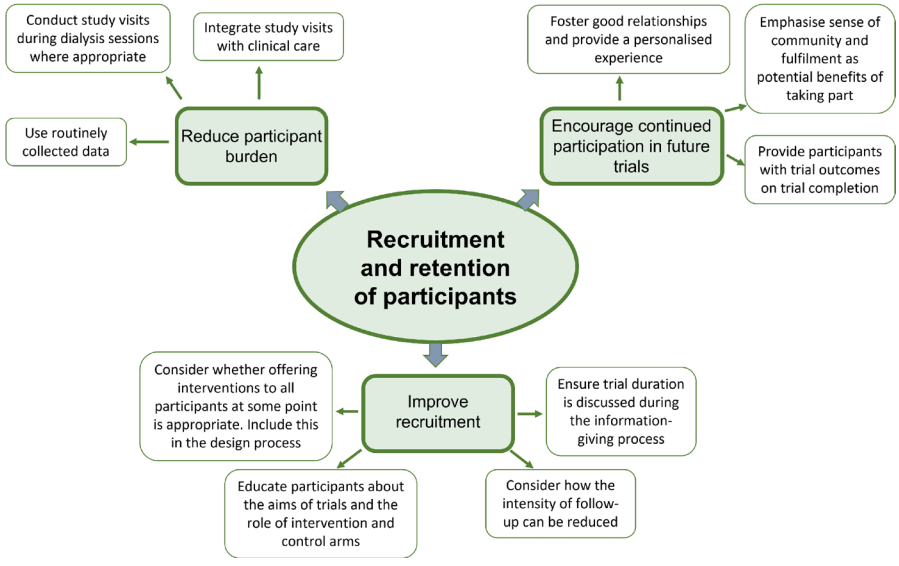


Figure 3 Recommendations to improve recruitment and retention of participants in randomised controlled trials in the haemodialysis population.

Ensuring participants have access to trial outcomes and are informed about which arm they received in a blinded trial demonstrates appreciation for their involvement.

Interestingly, our interviews suggest that participants perceive clinical equipoise differently to researchers. For many, getting the intervention was considered the 'best' treatment available and a reason to commit to a study; most did not understand the importance of a control arm and felt they were being denied treatment by being in this group. Participant-preconceived ideas can contribute towards 'resentful demoralisation', threatening the internal validity of a trial by leading to increased dropout rates or artificially increasing the difference in performance between the two arms of a trial.[29]

Post hoc review of the themes extracted found that there was little difference between the perspectives of participants with previous trial experience and those without. Those without experience seemed more wary about the effect of participation on potential transplantation. Both groups had similar preconceptions about equipoise in research; even some of those who had experienced randomisation in trials retained a belief that the intervention is better. It should be noted that this is an anecdotal observation on a small sample size and such subgroup comparisons should be viewed as hypothesis generating.

Our findings highlight the importance of educating participants about the role of the control and intervention arms and considering preconceptions about equipoise. Trials which ultimately offer the intervention to all participants during or, if possible, following trial conclusion may have better recruitment and retention. Post-trial access to interventions is recommended by the Declaration of Helsinki 2013 and should be part of the informed consent process, but the practicalities of implementation are complex.[30] Despite the views expressed in the interviews, the scoping review found little difference between recruitment rates of individually randomised parallel-group trials and crossover trials, where the intervention is trialled by all participants. Nevertheless, it is important to consider whether offering the intervention to all participants is appropriate and include this decision making in the design process of an RCT.

Implications for research dissemination

The reporting of sample size in non-standard trials assessed in this scoping review was poorer than individually randomised parallel-group trials. Poor reporting does not necessarily reflect the trial conduct; however, it does make it more difficult to assess the appropriateness of methodology and the extent to which bias was mitigated, weakening confidence in the outcome and limiting the interpretation of the hypothesis. The production of the CONSORT Statement in 1996 aimed to improve the conduct and reporting of RCTs, and there have been multiple updates and extensions since.[18 31 32] However, only 42% of biomedical journals that endorse CONSORT make its use compulsory, with 38% providing a checklist for authors.[33] Standards of reporting may improve if more journals endorsing CONSORT make using a checklist compulsory.

Reviews exploring reporting of clinical trials in nephrology, endocrinology and otolaryngology have identified that between 28% and 48% of trials justified their sample size.[2 7 34 35] In this scoping review, 57.5% of all trials provided sample size justification but less than half of cluster trials, which is similar to a previous review which found suboptimal reporting in cluster trials in patients on HD.[36] Of the 13 crossover trials selected, only 1 paper included the requirements from the CONSORT extension for crossover trials, although some were published prior to the CONSORT extension. Sample size justification and target recruitment was reported in seven crossover trials (53.8%). While specification of target recruitment is not required by CONSORT, credibility of a study is affected as achievement of recruitment target may show if a study was feasible, acceptable to patients and able to use resources efficiently. The use of flow diagrams, recommended to help assess reliability of a trial, was lower in crossover trials, potentially due to the more complex methodology.

Aiming to increase the number of high-quality trials in nephrology, the ISN developed an 'The ISN-ACT Clinical Trials Toolkit' in 2020 which provides guidance on design, ethnics, conduct and analysis of parallel-group, crossover, cluster and factorial trial designs.[37] Publicising the ISN-ACT toolkit to reach a wider audience may provide researchers with more guidance and support to develop clinical trials in nephrology, especially non-standard trials such as crossover trials, in turn improving the quality of the study conducted as well as the reporting and dissemination of findings.

STRENGTHS AND LIMITATIONS

This scoping review resulted in a comprehensive collection of HD trials from a 7-year period. Furthermore, this review assessed trials in the HD population by trial design, which has not been done previously. Databases were searched until 2019 as the pandemic postponed the interviews, delaying synthesis and integration of the data. It is unlikely that there will be significant changes in number and quality of RCTs published since 2019 as this is a much shorter timeframe than the initial search. While all cluster and stepped-wedge trials were assessed for this review, not all parallel-group and crossover trials were analysed. Nonetheless, attempts were made to reduce selection bias by using a random number generator to select the crossover and parallel-group trials.

Our interview sample size was small and from a single dialysis centre. Our data may be subject to biases related to geography, population and the types of research groups they may interacted with. However, purposive sampling was used to obtain a broad range of perspectives based on sex, age, ethnicity and previous research experience. Nevertheless, the findings from these exploratory interviews should be viewed as hypothesis generating and future research should include more participants from a wider pool of study sites.

CONCLUSION

HD trials need to be optimised with better design, conduct and reporting. Choice of trial design should be driven by the research question and hypothesis, while taking into account participant factors that affect acceptability. Greater patient involvement when designing and planning trials, as well as timely feedback on results, will improve recruitment and retention and ensure that participants feel acknowledged for their role.

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Patient consent for publication Not required.

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