Title:
Exploring obstacles to critical care trials in the UK: a qualitative investigation

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Background

Conducting clinical trials in critical care can be resource-intensive, with many challenges to participation. Clinicians in the US have identified several barriers to recruiting to critical care trials, including narrow recruitment windows and inclusion criteria[1]. Critical care research can create significant logistical issues during initial recruitment and subsequent study intervention. Specific challenges also relate to lack of mental capacity for patients to provide informed consent, relying instead on assent processes with family, out-of-hours recruitment, and potential conflict with provision of emergency critical care.

In the UK, most critical care research, backed either via a regional research network or direct funding, is supported through the National Institute of Health Research (NIHR). These studies are 'adopted' onto a national portfolio. The NIHR Clinical Research Network (NIHR CRN) portfolio of studies, holds a list of quality-appraised clinical research studies that are eligible for consideration for support from the Clinical Research Network in England. Recruitment is monitored centrally, with pre-defined targets for accrual. Recruitment data from the NIHR CRN Portfolio informs allocation of NHS service support costs for health trusts.

Among the NIHR portfolio studies, recruitment rates varies between studies and centre. The limitations to participation within the NIHR network are poorly defined and multi-factorial. There is limited research regarding the barriers which can hinder recruitment in critical care trials recruitment, and limited knowledge about facilitating factors. Availability of trained personnel able to take consent, is a known barrier[2,3], as is lack of continuity in physician staffing[1]. Patients' changing clinical condition also reportedly hinders recruitment[1]. Cook et al outlined a number of strategies to increase capacity, including: enhanced recruitment efficiencies, using alternative study designs and expanding consent procedures[4]. Public perception of research varies, with many misconceptions about informed consent and risk/benefit analysis[5]. Ethical concerns are a major issue, and have been dealt with in several studies[6,7,8,9]; however, additional influencing factors in other areas have also been identified. In studies of investigators in head and neck and gynaecology trials, several issues were identified, including patients' treatment preference leading to consent refusal, aversion to randomisation, amount of eligible patients, excess complexity/amount of information provided to patients and lack of support staff and time to accommodate research[10,11]. These issues arising from the literature[2-11] can be summarized as clinical factors (the patient's condition); study related issues (complexity of the protocol or information), resources (unit/study personnel; study requirements), unit-specific issues (such as research culture and staffing) and patient and family factors (including treatment preferences; understanding). This study aimed to explore the broad issues that facilitate or hinder critical care trials in the UK.

Objective

To identify facilitating factors and barriers to enrolling patients into established ICU clinical trials within UK National Health Service (NHS) critical care units.

Sample

Research active staff working in or with critical care units formed the sample. Participants were drawn from volunteer ICUs across the NIHR network. A sampling frame across the 25 CRNs was devised with a representative of a mix of smaller and larger ICUs, from teaching hospitals and district general type hospital ICUs. A sampling frame across the 25 CRNs was devised. We planned to interview no more than one person within each CRN to ensure region-wide representation.

Methods

The study design was exploratory using qualitative semi-structured interviews of research-active clinicians across the Clinical Research Networks (CRNs).

Telephone interviews

A telephone interview was undertaken with either a research nurse/coordinator or a lead clinician researcher/primary investigator (PI) from each participating centre using a loosely structured interview schedule. Written information about the study was sent via email beforehand and participants were assured of confidentiality. All transcripts were de-identified to maintain anonymity. Verbal informed consent was obtained both before and after the interview (processual consent) to ensure interviewees were content for the data from the interview to be used and to offer the opportunity to withdraw. Interviews were digitally audio-recorded. The NIHR group deemed this project did not require distinct ethical approval or written consent, as per the then National Research Ethics Service guidance for research with NHS staff (now Health Research Authority), and was not sponsored by NHS R&D or university, but by the NIHR.

Interviews were conducted with the aim of exploring the facilitating and hindering factors to enrolment of patients to ongoing studies. The interviews comprised a closed question demographic / audit section to elicit data about each ICU (which could be completed via email if preferred), followed by a more open topic schedule. The interview schedule was developed to capture elements of structure and process, and the topic schedule was refined as the interviews progressed, in line with changes to the data analysis framework. The research team used the interview schedule structure, which was agreed by team consensus. This enhanced dependability in research findings, as well as the qualitative concept of rigour in relation to reliability and replicability.[12] Refinement took place as a result of interviewees raising new issues not previously considered, and that did not fit within topics on the schedule.

These data were analysed for common themes using Framework Analysis[13], within each ICU and for overall themes across all the ICUs. Framework analysis interpretation involves thematic analysis, typologies and explanatory analysis, i.e. within case (each ICU) and cross case analysis (across ICUs). The themes were triangulated with the audit/demographic data[14,15], to provide explanatory detail to the issues raised in the audit/demographic data; and for later interviews, emerging themes were used to help explore and question audit issues. This added to qualitative notions of confirmability, whereby researchers look for distinctions and variability across the data to confirm or corroborate findings[12].

We explored common themes, themes specific to individual ICUs, and discordance between research nurses and clinicians to identify potential blocks within individual ICUs and at a system level, explore models of best practice that might inform other ICUs, ultimately describing the complexities related to trial recruitment.

Framework analysis

Five main categories were initially ascribed to the framework with five to eight sub-categories for each category; these were subsequently revised to six categories (see supplementary table 2). For the analysis, a preliminary matrix was developed in consensus with the research team; initially based on themes from the literature, as described. The analysis matrix was refined as initial data were analysed, with refinements agreed by two members of the research team to enhance confirmability[12], and tested across the data/cases to ensure data yielded in the qualitative interviews fitted within the matrix. Certain sub-categories were assigned to one of the six main categories but overlapped into more than one. Barriers and facilitators to enrolment into clinical research were considered *a priori* by the research team, based on both literature review and practice, under six broad categories: *Centre factors; Study factors; Unit factors; Patient factors; Clinician factors* and *Resources*. Each of these factors was also considered in the context of "structure" (eg. research staff; clinician time; ICU organization and characteristics; case mix of patients), "process" (eg. research staff rotas; clinician involvement; numbers of studies; local policies for prioritization; co-enrolment practices), and culture (clinician buy-in and engagement, research active ICUs). The framework provided a further degree of dependability in regards to analysis[12], and allowed for contextual differences to emerge. The matrix provided detail of within case and cross case analysis[15], which was developed into themes.

Audio data and interview notes were transcribed and each line of interview data was coded according to the framework, which was revised as the interviews progressed. Coding of the data led to a new core category, resources. Coding was checked within the team by the lead researcher, and a sample of the data was independently checked by a qualitative researcher outside the research team. Frequency of each code was also then recorded in a matrix to indicate how much each of the issues

arose (see supplementary Table 2). The framework analysis results were then refined into final themes with exemplar quotes provided to highlight critical issues.

Findings

Interviews were conducted across ten CRNs, representing one of the devolved nations, and regions across the UK (Table 1). Contact was attempted with a representative from every CRN, using the NIHR portfolio list contacts. No interviews were declined but obtaining contact was not always easy, since research staff turnover meant contacts were out of date, and not all responded to email contact (repeated once in each case to improve responses). Intensive care units (ICUs) from teaching hospitals and DGHs were included in the sampling frames. Interviews lasted between 27-79 minutes and a range of participants was interviewed; from senior intensive care clinicians, to specialty group leads, and band 5 research nurses.

Table 1 Demographics and setting

Demographics	Research nurse	Research nurse	Research nurse	Research nurse	Research nurse	Research nurse	Research nurse	Consultant	Consultant	Research nurse
CRN region	Wales	North west coast	South west peninsula	North east North Cumbria	East Midlands	Eastern	G. Manchester	Wessex	London South	W England
1. Level 3/2 beds	33	35	26	18	19	20	19	24	63	21
2. Annual admissions	1500	1880	1580	1000	1200	1890	1700	1200	3500	2000
3. Specialist/general unit	General/ neuro	General	General/ neuro	General	General	General	General	General	General/ neuro	General
4. Research staff numbers	5	2	1	2	3	4	0.8	3	9*	6
5. Research staff working* *some of these nurses work across all Division 6 studies	4 WTE research nurses	1 WTE band 7 shared 4 x band 6 (0.8)	-	1 band 3 res asst; 1 band 6	2.8 WTE	-	0.8	1.6	2 band 7; 7 band 6*	4 WTE (1 band 7; rest band 6)
6. Working patterns	8-4pm	7.30-3.30pm	8-4pm	9-5pm	8-4;8-7pm	8-8pm	8-4pm, 4/7		Across all Div 6 studies	7-7pm, short shift weekends 7/7 working
7. Consultant	14; 24/7	13; 8	14	9	-	-	9	14	-	12 (24/7

numbers and working patterns	consultant research									on call)
8. Details of consultant time for research	1 PA	0	0	0	2 PAs	1 PA	0	2 PAs	1	-
9. Number (total) of ongoing clinical trials (both NIHR and non- NIHR)	6	9	7	8	11	7	4	6	10	8
10. Underway/active	5	8	5	6	11	7	4	5	9	8

For each of the ICUs and research clinicians interviewed, there was an overarching sense of resource limitation that impeded how much time could be devoted to research. However, every centre described innovative ways in which to engage critical care unit staff, and to increase recruitment. Research staff were consistently committed to taking part in NIHR portfolio studies, despite barriers encountered in each of the six final themes outlined in Table 2 (detailed in the supplementary file) below: *centre factors; resources; unit factors; study factors; clinician factors and patient/family factors*.

Centre factors

Research and development (R&D) infrastructure influenced how much trials were part of the fabric of the critical care unit, whilst supportive on-site R&D departments facilitated access, and conversely, less supportive R&D departments had less engagement with non-income generating studies, providing little infrastructure to support research teams. This was reflected in the broader culture of the organisation, with certain ICUs lacking support for research at board and executive level. This manifested as trust boards not recognising the value of research, prioritising clinical practice over research and reassigning staff accordingly, at certain pressure point times. This specific issue is particularly noted in relation to the Resources theme.

It was easier to implement new clinical trials in units that promote active research participation, as engagement of the staff was easier; the lead investigators had less work to do to establish engagement, and it was easier to embed trials. Wider centre factors related to capacity of units to admit patients, which was a significant determinant of research implementation. For instance, during the winter bed pressures it was harder to dedicate time to undertake research as research staff were reallocated back to clinical practice, and unit clinicians were simply too busy to consider screening and enrolling patients. Where units were felt to be working at full capacity, it was harder to get engagement for research. However, opportunities for research were not seen as lost, but it depended on how research was prioritised:

> "When it's busy it can be ideal for recruitment as there are more potential trial participants, but it's not on people's radar." (Consultant Intensivist 1)

"No, research is not a priority. New ICU consultants [are] very keen, as are research SpRs. The resistance mainly comes from nurses. It is about perceived additional work or disagreement with the protocol. . .it's not part of routine care" (Research Nurse 4)

Resources

Centre factors and resources frequently overlapped as themes, and related to funding, as well as trial specific resources. Intensive-care based research nurses were frequently expected to work across the NIHR Division Six studies, the broader NIHR group including emergency department and anaesthetic studies, as well as very different groups like opthalmology. In addition to co-enrolment being a potential problem, this reduces focus and diminishes the ability to enrol in critical care studies. Whilst shared working and expertise could be helpful in certain cases, it was felt that ICU and ED trials were "a different kettle of fish" (Research Nurse 3).

Another significant issue was related to the funding of research nurses, with their employment varying from NIHR portfolio and study-based funding, to unit funded research nurses. All of the centres struggled with recruiting and retaining research nurses. This related to the low banding of research nurses, who are usually banded under the NHS Agenda for Change national pay system as a five or six (junior and senior staff nurse level), and equally to their employment under short-term contracts. Such contracts mean nurses are often reluctant to stay in research, as the short- term contracts lack career and financial stability. Moreover, long-term career prospects for research nurses is limited; usually a band seven would be the maximum a nurse could hope to achieve, and band six would be the maximum in certain areas. To recruit experienced intensive-care nurses who are happy to remain at this grade with limited career options; and to retain them appeared to be a real problem.

". . .these research nurses are highly motivated nurses but the career ladder is limited for them and so they move to management or work in R&D roles, and the use of temporary contracts is demoralising and a disincentive. I've had nurses not able to work as research nurses because they couldn't guarantee they can get a mortgage working under a temporary contract and so couldn't take on the role." (Consultant Intensivist 1)

Research nurses were also often a casualty of resource limitations, often compelled to return to clinical practice in the ICU at critically busy times, leading to suspension of research studies and demotivation.

Some centres circumvented shortfalls in funding (either wholly/partly) using the ICU budget to pay research nurses and additional trial costs (such as nutrition). Furthermore, the disparity in funding from R&D budgets, which was short-term, versus the CRN budgets, which had the capacity to be

longer-term in certain cases, using contingency funding for example in order to meet shortfalls in research staff funding and contractual difficulties (such as a hiatus between studies), was also raised by two participants. Some research teams carried out trial coordination themselves, with no trial managers/co-ordinators, and instead liaising where needed with the central trials offices for support. There was a general description of insufficient research staff, which impeded research capacity. These were small, often tight-knit, teams of staff which, despite often consisting of one or two research nurses still managed to recruit to, or exceeding, targets for NIHR portfolio studies. Commercial studies were sometimes used as income-generators to support wider critical care research activity, but were viewed as more onerous, often related to laboratory requirements. For non-commercial studies not on the portfolio, such as health services research, or trainees' studies, these were carried out with no resources, and research nurses would support wherever they could.

Unit factors

Unit factors and centre factors were also closely aligned, with unit engagement highlighted as a critical factor. There was an issue regarding clinician reluctance to engage in clinical trials, often at an individual level. This was dealt with by a senior investigator addressing any reluctance to participate, or doubts about the study. Methods used to engage other clinicians included speaking on a one-to-one level with reluctant clinicians, reflecting at multidisciplinary team meetings (MDT), undertaking unit-based research teaching, addressing consultant meetings, undertaking extensive pre-trial ground work to engage clinicians and knowing when to leave colleagues alone. This category linked in with clinician factors, described later.

For clinical staff that were reluctant to engage, innovative measures were undertaken to try and increase engagement. Measures included: loyalty cards to win small prizes, competitions with voucher prizes for referring nurses, offering to cover ICU nurses for breaks to show willingness and demonstrate clinical credibility, posters in clinical areas to help identify prospective patients, bedside posters about research, designated display boards and a culture within the critical care unit where it was explained (by staff, via posters) to patients and families that they would routinely be approached about research. Another approach was the use of "research champions"; nurses based in the ICU who were used to help identify patients particularly out of hours. Each of these innovations required little resource, and was deemed by many nurses to inspire commitment and enthusiasm.

One centre took an unusual approach to dealing with new studies and those with low recruitment. A unique method used to deal with new studies was to perform "a simulated run of the study to make sure it's embedded" (Consultant Intensivist 2). Information systems were tested, consents taken, and this was performed at different times of the day to ensure there were no differences in the ability to recruit.

Motivation of the unit was also highlighted as an important factor, particularly when "it can seem that each study feels like the first study. . . The first one [patient] can be nerve wrecking for consultants to put in [to the trial] and then they're happy and fine after that…" (Research Nurse 3)

> "You need a willing team to have a research active ICU. Our ICU is very research active, the whole ICU, the consultants are very keen and the nursing staff don't have to do much because we do all the screening, but most people are proactive and let you know regarding potential patients." (Research Nurse 2)

Periodic staffing crises in ICUs made it hard to encourage nurses to identify and screen patients. In certain units, ICU clinical nurses helped identify patients for trials. However, where the ICU nurses were often working a ratio of 1:2 with level 3 patients; involvement in clinical trials was not a priority. This was compounded by the culture of the unit, where units that acknowledged the embedded value of research were more likely to participate in clinical trials.

> "local pressure on service means there are no spare hours research . . . and people have prior opinions about the embedded value of research." (Consultant Intensivist 2)

> "Clinical commitments come first. Others don't think about it during the busy working hours." (Research Nurse 6)

This was reflected in the time allocated for research at a senior level, with only the minority of intensive care units allowing consultant PA sessions for research, even for clinicians with additional NIHR responsibilities, such as being specialty group lead. This element of the theme links in to the resources theme; where units had a research-active culture, they fought hard to ensure resources, such as protected time, were made a priority for all staff.

Registrars and junior doctors were not supported with time to undertake research. Certain areas had introduced initiatives such as the anaesthetic and critical care trainee research networks to help support specialist registrar undertake research and audit locally. However, there was still no allocated time for this, and required individual-level motivation and commitment over and above ICU clinical duties.

Building on how new studies were embedded, participants described the barriers that had to be anticipated to make the studies work. Knowing that there would be differences in the value of research, and lack of equipoise, early discussions with ICU consultants was considered crucial in gaining consensus support. Having a presence on the 'floor' was mentioned as critical by several participants. Two participants discussed building trust around research with ICU colleagues.

> ". . .you learn not to take it personally and they have to trust us, even if you don't agree they have to have the final say as clinicians, and as we get more experienced this gets better. For

example there was a neurological study, everyone was signed up for it but two consultants then withdrew their support. But I have noticed they speak in a different way to me [compared to research nurses] and they will come round after discussion." (Consultant Intensivist 2)

Where there were studies that were problematic in terms of recruitment it was important to learn lessons and feedback to the research and ICU teams, making things more stringent in the future. Target-setting for recruitment was usually done at a local level, with strategies such as under-estimating accrual used to ensure numbers were achieved to target and time.

Screening practices varied, but usually took place during normal working hours on a daily basis, and sometimes over the phone if out of hours. One nurse described how they would screen several times day electronically.

Study factors

The protocol complexity of the study was an issue in terms of recruitment for certain trials, particularly for non-Clinical Trial of Investigational Medicinal Product (CTIMP) intervention trials. A non-invasive ventilation trial was highlighted as an example in several interviews. Participants described how as a team they would not take on a trial if it was too 'complex' or beyond their resources. Furthermore, pharmacist availability also hindered certain studies with lack of trial or CCU pharmacy support regarding study drug supply out of hours. Some units had got around this by keeping drugs in ICU fridges, but this was less easy for commercial and certain time-sensitive studies. Clinicians also often had doubts about equipoise, which impaired enrolment:

> "they say they have equipoise, but when it comes down to it, they don't, you get surreptitious opposition and stark persuasion is used in those situations." (Consultant Intensivist 1)

Senior investigators had to emphasise that where individual equipoise did not exist, national equipoise existed. Consultant and ICU meetings were used to decide on which studies to participate in, with the aim of achieving consensus as a unit.

Co-enrolment agreements were the norm for each centre, with agreements established for each trial. For the simpler observational studies it was easier, and families were usually happy to agree. Several of those interviewed said often people were open to co-enrolment.

> "People are often not bothered if they're in more than one trial, if they're happy to be in research". (Research Nurse 3)

Tight inclusion criteria was a factor in poor recruitment, with teams having to work hard to deal with these issues. Certain studies were more attractive to families/patients, such as sepsis shock CTIMPs, and less concern was described in these trials than in certain intervention studies. Where studies involved usual care but randomised to an alternative order of receiving care, these recruited well. Novel interventions, seen as fairly benign, were also attractive to families/patients. One centre focused on conducting nurse or AHP-led portfolio studies that provided quick wins for clinicians, to enhance engagement with clinical staff, as well as patients/families. Conversely, studies with multiple visits or return to the hospital after discharge were problematic to recruit to.

Strategies for embedding studies included:

Having a step-by step guide of process and mechanism of approach was useful, with practice phases and scenarios, as were teaching sessions for clinical staff. One nurse found it useful to meet other research nurses across the region to discuss upcoming studies, as well as those underway.

> "We get in touch with other centres with trial up and running to find about teething problems." (Research Nurse 4)

Clinician factors

Interviewees describe how research was not always considered a priority for some clinicians, especially those less research-focused.

> "Clinical commitments come first. Others don't think about it during the busy working hours." (Research Nurse 5)

> "Clinical staff tend not to refer to research nurses as they are too busy and it is not on their mind." (Research Nurse 4)

Permission was routinely sought from the clinicians' responsible for care to approach patients for inclusion, even in research-active units.

> "At the end of the day it's their name on the end of the bed so it would be rude not to ask them [consultants] . . . but you have to maintain a balance and know when to back off . . . I check in advance to ensure they wouldn't break protocol, find out the issues and reassure them." (Consultant Intensivist 2)

The ability of research nurses to undertake consent, which also relates to centre factors, was an inhibiting factor because most R&D departments did not allow nurses to consent with CTIMPs, and

this in turn impeded certain trial recruitment. However, where nurses could consent for CTIMPs, this facilitated recruitment. Moreover, this team also worked seven days a week:

> ". . .the (clinical) consultants are not as au fait with the studies as we are, so it makes sense for us to consent" (Research Nurse 8)

Out-of-hours working was generally problematic as there was rarely extra funding for this, so research teams worked with a lot of goodwill, working on-call unpaid at times (or taking back time in lieu), sharing screening and recruitment across Division Six. Usually research nurses would come in for trial interventions out of hours, but not always for recruitment.

A lot of one-to-one work around communicating the trial was carried out to ensure nurses and clinicians could be persuaded to consider studies, in addition to regular unit-based and research-team based meetings, and innovations described previously. This again related to whether there was a research culture in the ICU. One centre's research lead ensured all consultants were ICH GCP trained so that they could all take consent, even out of hours, which enhanced recruitment and engagement.

Patient/family factors

Critical care trials were often regarded as very complex and, therefore, the verbal explanation of patient information sheets was seen as much more important than the printed literature. A lot of families asked for clarification, and needed further explanation. Ethical factors also played a role, with timing of approach a careful consideration, at a difficult and vulnerable time for families, particularly for the research nurses interviewed.

There were reports of patient and family concerns about uncertainty in regards to receiving a placebo but refusals related to potentially receiving a placebo were not common, instead there was talk of hope about receiving the medication. Patient and families did sometimes express a wish for treatment preference, but this issue did not significantly impact on recruitment. Research staff were careful to stress the altruistic nature of research. The following research nurse summarises the issue:

> "It's down to individual choice and preference, the majority are keen and it's a research active unit. They are happy to be involved, in fact our screening logs show that we only ever had three or four patients/families decline." (Research Nurse 3)

Timing and consent issues were a problem in studies with narrow recruitment windows, and conveying the complexity of intervention studies, both CTIMP and Non-CTIMP, could be difficult, with

families finding it hard to understand. Protracted and lengthy information sheets were also seen as an obstacle.

> "We've got savvier about taking consent and have learnt lessons; you don't gain it by giving more paper." (Consultant Intensivist 1)

Over-burdening patients' families was seen as an issue:

> "Patient relatives are beside themselves with worry and you feel awful approaching them; you say the word 'research', and they think 'guinea pig'. So to get it across to relatives you need good communication skills." (Research Nurse 2).

> ". . .the easiest are those with least requirements, such as an extra blood sample." (Research Nurse 8)

Cultural factors included recruitment issues in one hospital in part of the country with a high density ethnic minority population, and this research nurse regarded culture rather than language as an issue here:

> "Refusal from ethnic minority populations is a problem. This may relate to time to recruit and getting hold of a family member to say yes/no is difficult. More cultural issues rather than language issues as there were often lots of family members involved." (Research Nurse 4)

Few patients had capacity to consent to the studies the interviewees discussed and there was concern over perceived capacity, possibly related to ICU memory deficits and lack of recall, which emerged as an issue at deferred consent at a later date. Nobody reported withdrawal of consent. Most of these units described over half of all families who were approached agreed to participate and there were relatively low refusal rates across the CRNs.

Discussion:

This research noted six different themes related to barriers and facilitators, namely: centre factors, resources, unit culture, study complexity, clinician factors and patients and family factors.
Centre factors referred to how the infrastructure and research culture of individual ICUs significantly influenced engagement in research. Executive and board level support was essential in facilitating this. The findings also pointed to a broader issue in regards devolved funding, alluded to by certain participants, and the difficulties of negotiating CRN funding for divisional activity from R&Ds. Funding of research nurses was associated with significant challenges, particularly in relation to short-term

contracts, lack of maternity cover, low pay banding of research nurses, having to work across other NIHR Division Six trials and limited career opportunities. This lack of opportunity limits the attractiveness of the research nurse role[16], in turn affecting recruitment to such positions. A clear career pathway, and working toward independent researcher status, could help this situation.

Despite these centre challenges, small teams of committed staff worked effectively to recruit to or exceed targets on NIHR portfolio studies. Innovative measures were employed at unit level to facilitate clinical staff engagement to improve recruitment and enhance clinician engagement. Simple, often nurse-led, measures facilitated recruitment. Examples included loyalty cards, covering clinical breaks and helping out, maintaining clinical credibility, research champions, posters to identify prospective patients, display boards, simulated recruitment runs, regular patient screening, and step-by-step guides and regular meetings, within an overall culture of routine family approaches about research.

Additional resource implications were noted with laboratory work, and out-of-hours staffing which could impair recruitment or even a centre's ability to undertake the study. Interestingly, set-up support from the CRNs did not emerge as an issue, with R&D support reported as critical for success. Concerns regarding accrual-based funding, or devolved funding (where trust R&D departments receive CRN monies but have to allocate and share across pre-determined broader research divisions, of which critical care is a small element) were not identified, but would be worthy of exploration in future research. Study-specific factors such as tight inclusion criteria and narrow recruitment windows were particularly a problem out-of-hours, due to inadequate staffing and capacity to recruit, reflecting similar issues found in Bruce et al[1]. Ensuring all clinicians are GCP trained and nurses able to consent for CTIMPs at weekends aimed to address this issue.

Recognised resource and clinician barriers included: staffing crises and clinicians viewing research as additional work. With regards to individual studies, complexity was problematic. This related to patient/family factors and the length of patient information, as described by Dickson et al[10]. Lack of equipoise among clinicians also impaired enrolment, as others have found[17,18]. As identified in previous research[1], ICU consultant continuity is a potential problem for recruitment, differing from "specialty based" medicine where patients remain under the care of a single consultant and potentially exacerbating any lack of consensus or equipoise.

Any perceived lack of willingness to recruit patients into trials by clinical staff was often related to conflicting clinical priorities and heightened out-of-hours. Although ensuring more clinicians were GCP trained facilitated enrolment, the research nurses' ability to obtain consent had a greater impact, as highlighted previously by Burns et al[2,3]. It has been proposed that more professionals should be trained to obtain patient consent. However, R&D departments should recognise that research nurses are specialised clinicians who can take this duty on with training, to facilitate work out of hours and narrow recruitment windows. Consent waivers helped recruitment, particularly where there were narrow recruitment windows, such as septic shock trials [2,17,20].

In relation to patient/family factors, complexity of studies was problematic. The number of eligible patients has been highlighted as a limitation to recruitment into clinical trials[10,11], and although this

was not reported as a limiting factor, it is certainly the case that eligibility limitations affect CRN accrual. Aversion to randomisation was not a significant issue for poor recruitment in contrast to previous findings[10,11], nor did we find that treatment preference was a significant issue[10,11]. Concern about 'burdening' families at a difficult time is echoed by others[21], especially when decisions need to be made for time-sensitive research. Researchers have to find a balance between perseverance and pressurising families. Most ICUs we interviewed found that half of all families approached agreed to participate and there were relatively low refusal rates across the CRNs. We found that approaching the family for consent where the patient lacks capacity is not without its concerns[21-24], especially with regard to over-burdening families. Majesko et al suggests that good communication is essential to ensure family confidence in decisions, which was in keeping with our findings[25]. The limitations of this study relate to the small number of people interviewed, predominantly nurses, however '*moderatum generalisations*' are possible from such qualitative work[26], and the fact that it was difficult to access less research active ICUs in order to gain their perspectives. This reflects issues related to ease of contact, likely to be symptomatic of broader issues in terms of staff turnover and workload. Furthermore, we might have found different barriers if we had interviewed different staff from the same research team, however, we reasoned that we might also encounter similar issues, which might not add much to the data.

The depth of study and analysis can be criticised, since we chose to look at a broad range of factors related to barriers and facilitators, as raised by participants, as opposed retaining a narrow focus. These issues warrant greater exploration across a broader sample encompassing more disciplines and in more depth.

As a result of these findings, a summary checklist is suggested, in order to help clinicians identify facilitating factors and pre-empt barriers, ultimately enhancing recruitment to critical care trials (Table 2).

The key recommendations for facilitating trials can be summarised as:
- Principal investigators early scoping of capacity and funding pre-trial
- Consider novel approaches to recruitment using ICU staff, supported by research teams
- Address potential equipoise issues at the scoping stage to enhance engagement
- Encourage broader GCP training with ICU staff, so out-of-hours recruitment is possible
- Negotiation of funding arrangements, using R&D and CRN offices to leverage research nurse funding, thus ensuring continuity
- Encourage reciprocal working between ICU staff and research teams to enhance recruitment opportunities
- Consider trial amendments to reduce trial burdens in studies that are difficult to recruit to
- Consider how approaches to families and patients and how complexity is conveyed using peer review and communication crib sheets

Table 2. Summary checklist of issues to consider in relation to optimising critical care trials/study recruitment

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1. Centre/Organisational Factors
   a) Can high-level agreements be established regarding research staff time at board and executive level to avoiding mandatory relocation of research staff to the 'floor' in staffing crises?
   b) Is there scope to allow research staff a degree of flexible working across unit, in times of need, to reciprocate for unit staff helping to recruit to trials, enhancing unit cohesion?
   c) Can the research leads negotiate with NIHR CRN leads to get portfolio contingency funding to bridge gaps or negotiate with R&D for 'soft monies'?
   d) Has capacity (unit and R&D) been assessed prior to a new trial?
   - Can the unit reasonably cope with more studies?
   - Do the research team have capacity to run more studies? Will R&D infrastructure support new trials and regulatory and approval processes?
   e) If problems are anticipated embedding trials, can a pilot phase for the trial be considered?
   f) When research staff allocated to support studies are based outside the critical care team (for example Clinical Research Facilities) has agreement to provide adequate screening time and frequency been reached?

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2. Unit factors
   a) Staffing:
   - How have funding arrangements been negotiated at a local level?
   - Could research staff be funded from critical care budgets if portfolio funding is
   - problematic?
   - Could secondments or rotational posts be used to aid research staff
     numbers?

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   b) Communication and support from staff team:
   - How will patients be identified and who will identify? How can unit staff aid this screening process?
   - Has the research teams addressed unit concerns regarding equipoise, uncertainty or consent prior to commencing study?
   - How will intra-trial communication (research team and central study co-ordinators) be considered?
   - Are there regular, formalised contact meetings and/or teleconferences?
   - How will intra-ICU communication (research team and clinical team) be considered? Is there regular contact (e.g. via MDT presentations/posters) with clinical colleagues?

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   c) Logistics
   - How has protocol compliance been addressed at the outset and throughout the study?
   - Has a co-enrolment agreement been considered with existing and/or other planned trials ?
   - How often is screening undertaken? How can screening be organised to take place more than once a day?

3. Study factors
   a) Have all the trial resources been accounted for (drug supply/drug storage/out-of-hours laboratory services etc)?
   b) Have numbers of potential patients been scoped at a local level for studies with narrow recruitment windows?
   c) What are the burdens and scheduling of the study and how might this affect potential recruitment?
   d) Are there any potential concerns about randomisation/placebo or treatment arm preferences that could impinge on recruitment?
   e) How have trial complexity and understanding been conveyed (to staff and participants); is it easy to understand?
   f) Who is able to undertake out of hours consent?
   - Can unit clinicians be trained and GCP-compliant to be able to undertake this?

4. Resources
   a) Can the research nurses be recruited into/placed on full-time permanent contracts to enhance retention and recruitment? (Local CRNs may be able to help with this).
   - How can research staff be supported in career development opportunities (e.g Masters in clinical trials/MRES)?
   b) Can team initiatives to optimise recruitment be implemented, such as simulation of study recruitment and procedures; unit-based teaching; motivational small reward incentives for unit staff screening?
   c) How have underlying issues of unit workload been considered within the proposed trial context?
   - Can additional resources (such as research staff covering staff breaks) be used to encourage a collaborative culture?
   d) Can the research nurses be trained, through competency-based assessment, to take consent (challenging R&D policy where required) or be Principal Investigator?

5. Clinician factors
   a) Can critical care consultants who are leading research negotiate PA/SPA session time to facilitate research?
   b) Have local lead investigators negotiated with senior clinicians to promote engagement, encourage buy-in and address potential opposition at the outset?

6. Patient/family factors
   a) Have the wider trial/study burdens for families and patients been fully considered; there may be unforeseen local issues (e.g. transportation for follow-up)?
   b) Could the scheduling be altered in an amendment submission, without affecting the primary outcome?
   c) Are there specific randomisation/placebo or treatment preference concerns that need focused attention and education from the research team, including research lead?
   d) Is the initial approach being carried out by clinicians or researchers? Which is the best for the trial in terms of optimal recruitment potential?
   e) Is the trial understandable to patients and families; could a trial amendment be made where it is evident that it is difficult to recruit because of understanding?
   f) Is there a documented process for communicating trial/study information to patients/families?
   - Are there any peer-assessment/reflective processes that could be used to enhance communication?

The supplementary file (Figure 1.) provides visual representation of the main factors that enhance recruitment.

Key messages/Conclusion: Research teams are highly committed to providing cover in recruitment to critical care trials. Significant background work in order to anticipate barriers is undertaken, ensuring clinical staff are amenable to facilitating recruitment. However, several factors impede recruitment, which are beyond researchers' control. These include: organisational support, research nurse employment and retention, out-of-hours employment, and study complexity. Research teams have to be innovative with funding and employment, to ensure continuity of studies and retention of research staff. Several innovations are described which may optimise recruitment, and how these can have a positive impact on unit culture, as well as study recruitment. Equipoise concerns continue to be a factor at clinician level, but experienced researchers are able to deal with this in a variety of ways. Patient and family factors regarding treatment preference were not a significant issue, and over half of families approached by researchers usually agreed to participation.

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(Supplementary) Table 2 Framework analysis

Factors	Frequency of codes in transcripts* (*oft repeated more than once per respondent)	Framework theme
1a. Unit capacity	8	CENTRE FACTORS
1b. Embedding trials (piloting etc)	3	
1c. Unit culture (research active v less active)	15	
1d. Competing studies	7	
1e. Local R&D approval	4	
2a. Staffing	23	UNIT FACTORS
2b. Funding for staffing	4	
2c. Intra-ICU communication (research team v clinical team)	21	
2d. Intra-trial communication (research team v co-ordinators)	2	
2e. Screening capacity/frequency	10	
2f. Patient identification	8	
3a. Trial complexity	10	STUDY FACTORS
3b. Consent timing (eligibility/out of hours)	18	
3c. Screening issues	14	
3d. Co-enrolment	6	
3e. Ease of central trial contact	2	
3f. Trial resources (e.g. drug supply)	9	
3g. Recruitment targets	11	
4a. Consultant PA time	6	RESOURCES
4b. Nursing workload ICU	15	
4c. Team initiatives to increase access	10	
4e. Research nurse retention	17	
4f. Inclusion criteria restrictions	5	
4g. Funding culture/practicalities	10	
5a. Personal (consultant/team) buy-in	3	CLINICIAN FACTORS
5b. Concerns re: equipoise/uncertainty/consent	7	
5c. Protocol compliance	4	
6a. Burdens/scheduling	12	PATIENT/FAMILY FACTORS
6b. Randomization/placebo concerns/ preferences	9	
6c. Trial understanding	12	

6d. Information/communication (Patient/family)	20	