Ethical Issues in the Design and Conduct of Pragmatic Cluster Randomized Trials in Hemodialysis Care: An Interview Study With Key Stakeholders

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Abstract
Background: Pragmatic cluster randomized trials (CRTs) offer an opportunity to improve health care by answering important questions about the comparative effectiveness of treatments using a trial design that can be embedded in routine care. There is a lack of empirical research that addresses ethical issues generated by pragmatic CRTs in hemodialysis.
Objective: To identify stakeholder perceptions of ethical issues in pragmatic CRTs conducted in hemodialysis.
Design: Qualitative study using semi-structured interviews.
Setting: In-person or telephone interviews with an international group of stakeholders.
Participants: Stakeholders (clinical investigators, methodologists, ethicists and research ethics committee members, and other knowledge users) who had been involved in the design or conduct of a pragmatic individual patient or cluster randomized trial in hemodialysis, or their role would require them to review and evaluate pragmatic CRTs in hemodialysis.
Methods: Interviews were conducted in-person or over the telephone and were audio-recorded with consent. Recorded interviews were transcribed verbatim prior to analysis. Transcripts and field notes were analyzed using a thematic analysis approach.
Results: Sixteen interviews were conducted with 19 individuals. Interviewees were largely drawn from North America (84%) and were predominantly clinical investigators (42%). Six themes were identified in which pragmatic CRTs in hemodialysis raise ethical issues: (1) patients treated with hemodialysis as a vulnerable population, (2) appropriate approaches to informed consent, (3) research burdens, (4) roles and responsibilities of gatekeepers, (5) inequities in access to research, and (6) advocacy for patient-centered research and outcomes.
Limitations: Participants were largely from North America and did not include research staff, who may have differing perspectives.
Conclusions: The six themes reflect concerns relating to individual rights, but also the need to consider population-level issues. To date, concerns regarding inequity of access to research and the need for patient-centered research have received less coverage than other, well-known, issues such as consent. Pragmatic CRTs offer a potential approach to address equity concerns and we suggest future ethical analyses and guidance for pragmatic CRTs in hemodialysis embed equity considerations within them. We further note the potential for the co-creation of health data infrastructure with patients which would aid care but also facilitate patient-centered research. These present results will inform planned future guidance in relation to the ethical design and conduct of pragmatic CRTs in hemodialysis.
Trial Registration: Registration is not applicable as this is a qualitative study.

Abrégé
Contexte: Les essais pragmatiques randomisés par grappes fournissent une occasion d'améliorer les soins parce qu'ils répondent à des questions importantes sur l'efficacité comparative des traitements en utilisant des modèles pouvant être intégrés aux soins courants. On constate toutefois un manque de recherche empirique abordant les questions éthiques générées par ces essais en contexte d'hémodialyse.
Objectif: Connaître le point de vue d'intervenants sur les questions éthiques liées aux essais pragmatiques randomisés par grappes en contexte d'hémodialyse.
Introduction

Fewer trials are conducted in nephrology than in any other internal medicine specialty.1 The trials that have been conducted are limited by poor recruitment, inadequate sample size, nonadherence to the allocated therapy, missing data, and reliance on surrogate outcomes.1-6

The clustered randomized trial (CRT), in which intact groups (such as all patients within a dialysis facility) are randomly allocated to study arms,7 has been proposed as a potentially useful design that may facilitate the conduct of more pragmatic trials in hemodialysis.8,9 For example, cluster (rather than individual) randomization may better mimic the clinical (“real-world”) context in which treatments will be used, may promote adherence to the intervention due to the universal adoption of an intervention at the site, and may reduce the complexity of allocating multiple individuals within the same facility to differing interventions.7 Moreover,
it may not be possible to evaluate certain interventions in an individually randomized trial due to the mechanism of delivery or logistical infeasibility. When routinely collected data are available for outcome assessment, cluster randomization may facilitate the cost-efficient inclusion of whole clusters, potentially increasing generalizability.\textsuperscript{10}

However, CRTs may not be appropriate in all circumstances; cluster randomization introduces methodological issues, such as the need for larger sample sizes, due to the fact that outcomes are correlated within clusters, making CRTs statistically less efficient than patient randomized trials.\textsuperscript{11} In addition, CRTs are more prone to bias than patient randomized trials. Consequently, there must be a clear justification for the use of a CRT design.\textsuperscript{12,13}

Pragmatic CRTs may also raise ethical challenges, and particularly so in the context of hemodialysis.\textsuperscript{7} For example, in a CRT the unit of allocation may be the hospital or dialysis center, the intervention delivered to health professionals, and data are collected from patients. The multi-level nature of the trial may, therefore, complicate questions regarding who are research participants and from whom informed consent is required.\textsuperscript{13} Existing research ethics guidelines, developed with explanatory, patient randomized, trials in mind, provide little guidance on such issues\textsuperscript{14} and are thus difficult to interpret and apply to pragmatic CRTs.\textsuperscript{15-17}

Furthermore, while guidelines do exist for CRTs broadly,\textsuperscript{13} there may be additional challenges when conducting pragmatic CRTs in the hemodialysis context. A recent ethical analysis used the Time to Reduce Mortality in End-Stage Renal Disease (TiME) trial as a case study for a preliminary exploration of ethical issues in pragmatic CRTs in hemodialysis.\textsuperscript{7} The authors identified seven key ethical issues: justification of the use of cluster randomization, the adoption of individual-level interventions as local standard of care, the complexity of benefit-harm analyses, the role of gatekeepers and their responsibilities, how informed consent is approached (including the potential for waivers of consent), the role of notification, and the potential inclusion and protection of vulnerable participants.

While empirical research exploring ethical issues in pragmatic trials, and CRTs more broadly, has begun to emerge,\textsuperscript{18-23} there is a paucity of research with those who are actively involved in the design and conduct of pragmatic CRTs in hemodialysis. The aim of the present study was to address this gap and identify stakeholder perceptions of ethical issues in pragmatic CRTs in hemodialysis.

**Methods**

We conducted semi-structured interviews with key stakeholders in the design and conduct of pragmatic CRTs in hemodialysis. Potential interviewees were eligible if they had been involved in the design or conduct of a pragmatic individual patient randomized trial or CRT in hemodialysis, or their role would require them to review and evaluate pragmatic CRTs in hemodialysis. These inclusion criteria and sample frame were chosen to ensure that participants would be familiar with pragmatic and cluster trials, compared with clinical trials more generally, and consequently that the identified challenges would be grounded in experience. Patient partners were not included in the present study, but were the subject of a separate study which used a scenario-based group-discussion approach to elicit their perspectives. Given the differences in design and data collection, patient perspectives will be reported elsewhere.

**Identification and Recruitment**

Participants were identified through a range of sources including (1) our study team’s professional network, (2) a search of the clinicaltrials.gov website to identify principal investigators of ongoing CRTs in hemodialysis, (3) authors of published CRTs or CRT protocols in hemodialysis settings identified from a recent systematic review,\textsuperscript{24} (4) publicly available information on funded hemodialysis trials, or (5) other publications discussing pragmatic trials or CRTs in hemodialysis settings. Sampling was not limited by geography or publication year. Only English-speaking participants were eligible.

**Sample Size**

We purposively sampled individuals to obtain a broad range of perspectives based on role, jurisdiction, and clinical interests in hemodialysis. Based on prior experience, logistical considerations, and likely saturation of themes,\textsuperscript{25-29} our target sample size was 12 to 20 participants.

**Data Collection**

Data were collected through semi-structured interviews. The interview guide was informed by prior work on the ethics of CRTs\textsuperscript{20} and pragmatic trials,\textsuperscript{30} as well as a review of the literature. We piloted the interview guide with members of the team. The interview covered (1) experiences of trials in hemodialysis settings, CRTs, or pragmatic trials; (2) existing ethics resources used (generally) and those which would be valuable for pragmatic CRTs in hemodialysis settings; and (3) specific ethical issues arising from pragmatic CRTs in hemodialysis. Given the semi-structured nature of the interviews, and the differing stakeholder roles, the interview guide was adapted depending on participant role. Novel topics or themes were explored with in-depth questioning. A copy of the interview guide template is provided in Supplementary File 1.

All interviews were conducted by a member of the team (S.G.N.) with experience and training in qualitative research methods. Interviews were conducted either in person or by telephone.

Interviews were audio-recorded with consent; if someone consented to participate but did not wish to be recorded, contemporaneous notes were taken. Audio-recordings were transcribed verbatim by a professional transcription service. Two individuals did not wish to be recorded, and field notes were taken with consent. Transcribed, interviews and field notes
were de-identified and interview participants assigned a unique identifier. Participants whose interviews were transcribed were subsequently provided with a copy of their interview transcript, which allowed them to verify its accuracy and provide any additional comments. One participant provided comments on their transcript and these were included within the final documentation for analysis. Final copies of transcribed interviews and field notes were imported into qualitative data analysis software (NVivo 11) to assist with coding.

The study was approved by the Ottawa Health Sciences-Research Ethics Board (Ref: 20180133-01H).

Data Analysis

The examination of the interview transcripts followed a thematic analysis approach. Initial coding used a codebook developed for a previous study of ethical issues in pragmatic trials which was then expanded in an inductive manner, based on additional issues identified in the transcripts. Issues were then grouped into larger themes organized around a core concept (such as challenges with informed consent). Transcripts were coded by one researcher (S.G.N.) and verified by a second (K.C.). Any discrepancies were discussed until consensus was achieved. Coding was conducted using the constant comparison method to compare and modify themes across interviews.

Results

From 28 invitations, a total of 16 interviews were conducted with 19 individuals (response rate 66%). One interview involved a group of 3 individuals, and another involved 2 individuals. Interviews took place between November 2018 and April 2019. Interviews were 64 minutes in duration on average (range: 31-78 minutes). A total of 14 interviews (involving 17 individuals) were audio-recorded.

Participants’ experience spanned a wide array of trial designs and hemodialysis interventions, including exercise, hemodialysis duration, professional education, and drugs. Most participants were based in North America (16 of 19; 84%), with clinical investigators comprising almost half of the sample (8 of 19; 42%). Eleven interviewees were female (58%). Table 1 provides a description of participant demographics.

A common point of discussion, albeit not specific to pragmatic CRTs in hemodialysis, was the need to develop a research culture in nephrology. Participants indicated that many treatments in nephrology are opinion-based or supported by low-quality evidence. Strongly held beliefs regarding treatments supported by low-quality evidence was identified as both a source of variation in practice and an impediment to the conduct of pragmatic CRTs.

Ethical issues raised by pragmatic CRTs in hemodialysis were identified within six themes: (1) patients treated with hemodialysis as a vulnerable population, (2) appropriate approaches to informed consent, (3) research burdens, (4) roles and responsibilities of gatekeepers, (5) inequities in access to research, and (6) advocacy for patient-centered research and outcomes (see Table 2).

Patients Treated With Hemodialysis as a Vulnerable Population

Participants viewed patients treated with hemodialysis as complex and vulnerable because of co-morbidities and general ill health. In part this was due to the care trajectories that patients receiving hemodialysis experience because of their underlying kidney disease, as well as care needs due to other health conditions (e.g., diabetes, cancer). Several participants indicated that patients may be vulnerable due to cognitive impairment, which is prevalent in patients undergoing hemodialysis treatment. Participants also indicated that some patients receiving hemodialysis, such as Indigenous Peoples, may be vulnerable due to social and system-level factors.

Participants noted that patients receiving hemodialysis face constant judgment; they are subject to both clinical and personal evaluation on a regular basis. One participant highlighted how patients are viewed as “good” and “bad” based on their compliance with clinical recommendations. As a result, some participants questioned whether such judgments could lead patients to feeling obligated to participate in research.

Others observed how some patients undergoing hemodialysis live in a state of precarious medical stability. Such patients may be reluctant to participate in a trial so as not to disrupt that stability, or as one participant put it, so as not to “rock the boat.”

Appropriate Approaches to Informed Consent

Participants questioned when it is appropriate to deviate from written informed consent for participation in pragmatic CRTs. They asked, under what circumstances are different...
Table 2. Key Themes.

| Theme | Quote |
|-------|-------|
| 1. Patients treated with dialysis as a vulnerable population | 1.1 “Our patients are sick there’s no doubt about it. The (in particular) end stage renal patients are very sick individuals with very high morbidity and mortality and I think there’s a true concern . . . more experimentation may lead to worse outcome for a population that’s already quite sick.” HE005, Clinical investigator, USA |
| | 1.2 “So they can go from being on haemodialysis to peritoneal dialysis to receiving a transplant. There’s a number of competing risks that might impact the probability of observing endpoints so they’re it’s just a very complex group of patients that will require more complex methodology I suspect.” HE015, Methodologist, Canada |
| | 1.3 “Because I think [First Nation’s] needs are very different from other people’s needs and I think they’re often very disenfranchised and their physical vulnerability enhances their social vulnerability and they feed into each other and they’re in this vicious cycle that they can’t get out of. And so I think in Canada there’s enormous obligations especially since kidney disease is so disproportionately prevalent in the First Nations population.” HE006, Clinical investigator, Switzerland |
| | 1.4 “(Patients) in a highly, highly vulnerable situation are judged all the time for dialysis. They are constantly being told; you don’t eat this, don’t eat that. Don’t drink too much water . . . They get a lecture from every Tom, Dick and Harry that they come across in that dialysis unit every single time . . . And then I think they would probably feel that . . . because they get judged as bad patients and get labelled quite quickly . . . I would imagine that there is not that much freedom to decline because they would then feel this is another thing that’s going to label me as a bad patient.” HE006, Clinical investigator, Switzerland |
| | 1.5 “So for example, unlike cardiovascular disease trials where there’s an acute event, usually, and . . . They appreciate that they’re very sick and they’re very motivated to be in any trial that might improve their outcomes. In dialysis trials patients are generally doing okay with their dialysis. The ones who are doing okay have been sick enough once in their life at least to know that they don’t want to rock the boat if you will and participate in any research that might rock the boat and make them sick. The ones who are not doing well and who are sick say that they don’t want to do research studies because they don’t want to get sicker . . . But the perception I get is that they are reluctant to participate in research studies because they don’t think that it will benefit them.” HE003, Knowledge user, Canada |
| 2. Appropriate approaches to informed consent | 2.1 “We may want to consider things like cognitive ability because as patients get older, there’s the potential for the onset of cognitive impairment through dementia and whatnot. So those may be things to consider in terms of eligibility that when in a pragmatic trial if you’re just trying to reach everyone that can complicate things in terms of being able to recruit them into the study and have them understand their care.” HE015, Methodologist, Canada |
| | 2.2 “Well I think patients need to be informed. I think they definitely need to be informed and I don’t know how much they are really explained all this when they get on to dialysis. And then I think a lot of these patients are elderly. They’re sick, they might be explained things before dialysis, during dialysis they might have an event low blood pressure, you know, even fainting and things like that. Who knows if they even remember after the dialysis what the conversation was and why they signed consent.” HE006, Clinical investigator, Switzerland |
| | 2.3 “In [STUDY] they’re going to get individual consent because although the current management is not evidence-based actually they are deviating from what is standard care . . . So as a result, because people will be treated in a way that varies from the general standard, they felt they needed to get individual consent. And how they do that may be an expedited approach using consent via tablets or other approaches that sort of reduce the burden. Because it could be very, very time consuming and you’re talking about a large number of patients.” HE008, Knowledge User, USA |
| | 2.4 “I think with cluster randomized trials basically you’re trying not to recruit participants specifically or at least . . . the implementation of the intervention doesn’t necessarily depend on the patient agreeing to have the intervention. If the patient needs to agree to take part, then probably you’ve lost your advantage of not needing consent because then you’re going to have to go to the patient and explain it anyways . . . But it’s truly a cluster RCT then basically the reason to do that is because it’s a lot easier to get patients into a trial because you don’t need to recruit them so to speak. They will just be naturally selected because they’re already in that primary care practice or in that dialysis unit.” HE007, Clinical Investigator, Canada |
| | 2.5 “I’ve heard that a lot of people will say oh they want to do a cluster randomization trial to avoid patient level consent (laugh) which is kind of something that maybe isn’t communicated effectively enough or it could just be that people don’t have the experience with cluster trials. Because you read any of the textbooks or articles and it obviously squashes that myth. But I am always surprised when I hear that kind of perspective that well it’s a cluster trial so that we wouldn’t need patient level consent and that is definitely not true.” HE015, Methodologist, Canada |

(continued)
3. Research burdens

3.1 “[T]his is a patient population that’s got a huge treatment burden. There’s probably no other condition out there that requires people to attend hospital for or centres for up to 15 hours/week just to stay alive. And so that is a massive burden on the individuals involved and it does mean that we need to think very carefully when we’re trying to impose any additional burden on them. It also means that they are likely to be very reluctant to accept any additional burden related to trials. The sort of things that we typically do in terms of creating an entirely parallel universe of data collection and analysis is arguably in most circumstances inappropriate in patients who are on dialysis. And I’d argue is probably unethical . . . .” HE002, Clinical investigator, Australia

3.2 “And not just to them [patient] but also to their relatives and all their carers who we impact in small ways . . . . [T]ake dialysis patients for example: they are in hospital three days per week anyway. If they come for a research study it might well be that they have to take an extra day off work or that their partner or carer has to do the school run on a fourth day of the week which affects their work.” HE004, Clinical investigator, UK

3.3 “And so I think they [patients] see how much the staff are busy and going from place to place and patient to patient, answering the phone and all that sort of thing. And, you know, the message that we got is that the patients are very, very observant of the environment and they see that the staff are just rushing around all the time. And unless there is something serious they don’t like to ask about anything . . . . a lot of them feel that they don’t want to be a burden.” HE004, Clinical investigator, UK

3.4 “[W]hen you embed research into clinical care delivery, in a way, it’s more respectful of the participants’ needs and limited time available. So by embedding research you’re reducing the burden to patients of having to go to separate study visits.” HE001, Clinical investigator, USA

3.5 “So I think pragmatic trials with minimal follow up visits are good because they help to ensure that you’re going to get the primary outcome in all your participants because you don’t get burden of follow up visits contributing to your dropouts.” HE003, Knowledge user, Canada

3.6 “[T]he other thing is about research fatigue for patients ultimately . . . . I think the number of research questions being asked of that population is not slowing down and it’s quite fatiguing for patients from a research point of view. And some of the projects are fairly low impact. They might be questionnaire studies or observational studies where they just consent and then it’s followed up, the results are followed up through registry. But I think there’s quite a lot we ask a lot of our patients and I think there’s research fatigue.” HE004, Clinical investigator, UK

3.7 “… how many competing trials can you have within one health system without breaking it? While still maximizing benefits for everybody involved will require lots of collaboration among lots of different groups of researchers who may or may not have traditionally worked together before or at least acknowledged each other’s similar trials or different trials. So I think it will be a paradigm shift in the way these trials may be delivered within health systems and will require a fair amount of governance and oversight.” HE005, Clinical investigator, USA

4. Roles and responsibilities of gatekeepers

4.1 “I think in our system it [key stakeholder buy in] would be the medical clinic director—well first off, the primary care leadership. So we embedded that initial trial in two different primary care clinics within a network of about 12 different clinics, and so making sure that the Chief Medical Officer for the primary care clinic network was onboard as well as his or her group or C3 leadership; followed by the individual Medical Directors of the individual clinics and those Medical Directors worked as a team with quality improvement directors and the Chief Nursing Officer and just the clinic operations leadership. So, we needed buy-in from both of those levels and once we had buy-in from those levels then we presented to the physicians and presented to the staff and it was more just to make sure everybody was onboard once we had the clinical leadership.” HE005, Clinical investigator, USA

4.2 “Because you can’t do any trials in the hospital without the approval of the hospital and, and they won’t give that to you unless— they won’t give that to you if there’s some increase in cost to them . . . . So, we had to negotiate with them how we would come up with the funds and so on and so forth. And so, I can’t remember all the logistics of what we finally came up with but we did come up with some hybrid model where the study would provide some funds and industry would provide some other funds and so on and so forth and we did do that. But if we didn’t come up with that solution the trial wouldn’t have run at our centre.” HE003, Knowledge user, Canada

4.3 “And again sometimes if doctors feel that a certain thing is a bit too time consuming because sometimes in private units it’s very time sensitive and so if a study took an extra 30 minutes and delayed the next patient by 30 minutes or somehow impacted your workflow, probably private units would be less likely to join” HE006, Clinical investigator, Switzerland
Table 2. (continued)

| Theme | 
| --- | 
| 5. Inequities in access to research | 4.4 “But the entire area of kidney disease and the study of kidney disease is greatly distorted by the large dialysis providers and by pharma. And those are real challenges. I think one of the ways of pushing back is to have publicly funded large pragmatic trials to really test some of these things, but it’s still a challenge to do those. And for dialysis it’s, it’s tricky. Because that the priorities of the large dialysis organizations are just really different” HE008, Knowledge user, USA

5.1 “. . . but actually dialysis care is pretty protocolized . . . And so standard care [within one institution] is pretty standard if you want the honest answer . . . if you’re looking [across institutions] at care bundles for example: if you go to ten different centres for managing that [a fistula] is going to be different in all centres.” HE004, Clinical investigator, UK

5.2. “One is their access to trials because of the way again dialysis services are all set up in the UK, which is probably not unique to the UK, but we tend to have hospital-based dialysis units, satellite and community units and the further you are away from an academic centre the less likely if you’re a dialysis patient that you are to have access to taking part in clinical trials . . . And the further you move away from that university teaching hospital environment . . . then the ability or the opportunity to enrol in clinical trials is just less.” HE004, Clinical investigator, UK

5.3 “[I]n my view every dialysis patient or every patient with a condition should be offered access to trials out there and I think that’s not happening for a large proportion, particularly of the dialysis patients. And partly that relates to capacity and workforce at the centres involved, but also interest of the clinicians.” HE002, Clinical investigator, Australia

5.4 “So I think this issue of . . . what the effects of the trial conduct are on other aspects of care that are not being studied in the trial or, you know, patients who are not even in the trial may be getting less attention because all the effort’s going into implementing the trial.” HE001, Clinical investigator, USA

6.1 “I think the other thing that would be really helpful is to have a way to get greater input from people on dialysis . . . and that hasn’t really existed to date, I think. So growing that would be really helpful.” HE002, Clinical investigator, Australia

6.2 “I think one of the issues is the idea of public engagement—the idea of studying things that are important to the patients. And generating questions with the patients. It’s not only about physical survival but a huge amount in dialysis is about quality of life and how they feel their dignity is maintained or respected. How they can still feel meaningful contributors to society and all that kind of thing. And so often for patients you wonder are they that interested in all these minutiae (meaning blood levels etc.) or would they rather have something else that’s going to make them feel more human on some level. So, I think just from the ground up, rather than top down studies and study design is probably important especially since these patients are so knowledgeable about themselves and their disease, the treatment and everything.” HE006, Clinical investigator, Switzerland

6.3 “And we’ve also found that in some cases patients will identify outcomes that we would have never considered that are important to them. So it might be things like, if I’m hospitalized with it what would be my time and how many days would I be stuck in hospital? Which actually is an important question from a Ministry perspective because every day that you’re in hospital can be quite expensive. But that’s what the patients want to know.” HE015, Methodologist, Canada

6.4 “The issue about surrogate outcomes: I don’t know if there’s specific ethical issues except to say that a lot of times people do the surrogate outcome trial and based on the surrogate outcome something becomes the standard of care and then it’s no longer eligible to be tested in a proper trial looking at hard outcomes because there’s no longer equipoise. So if the surrogate outcome is not going to be followed up with a trial looking at least at quality of life or one hard outcome or some outcome that’s important to patients, then I’m not sure that we need that trial.” HE003, Knowledge user, Canada

6.5 “. . . if you have more technology-based or EHR-based trials the desire is often to get EHR-based data as a primary outcome . . . . I think the concern is not a lot of patient reported outcomes are embedded in the EHR.” HE005, Clinical investigator, USA

6. Advocacy for patient-centered research and outcomes | approach appropriate, and when is the use of a waiver of consent acceptable?

As noted above, participants reported the prevalence of cognitive impairment in the hemodialysis population. This raised concerns about vulnerability, eligibility for research, and ability to provide informed consent (Quote 2.1). Cognitive impairment is an issue for trial eligibility in terms of initial recruitment, but also retention, as incident cases of impairment may occur over the course of the trial. The loss of decision-making capacity was flagged as an issue of concern for continuing informed consent (Quote 2.2).

Factors impacting the perceived need for informed consent included risks of the study intervention, study deviations from routine clinical care, research burdens on patients, as well as the approach to informed consent and its feasibility (Quote 2.3). Some participants associated the use of a CRT
with alternate approaches to consent (e.g., verbal consent only) or waiver of consent (Quote 2.4), whereas others believed that written informed consent is required (Quote 2.5). Indeed, most participants identified the need for further guidance on informed consent.

**Research Burdens**

Participants identified the burdens of research participation as an issue for pragmatic CRTs in hemodialysis, noting that trials can pose burdens to patients, family, friends, caregivers, and clinical care staff (Quotes 3.1-3.2). Some commented that additional workload for clinical staff may be a reason for patients to decline research participation (Quote 3.3).

Participants emphasized that design features which are more closely aligned with the clinical care context could reduce system-level burdens (by minimizing organizational and setting-related workload) and patient-level burdens (by not requiring additional visits for follow-up or tests for data collection) (Quotes 3.4-3.5). Making use of routinely collected patient data and samples was one example given to reduce patient burden.

However, participants raised two cautionary notes. First, the widespread adoption of pragmatic CRTs may lead to a higher volume of research and this may impact the capacity of hemodialysis facilities to conduct further research. Second, multiple ongoing trials in a hemodialysis unit may lead to “research fatigue” among patients and health care providers and affect their willingness to participate in research (Quotes 3.6-3.7).

**Roles and Responsibilities of Gatekeepers**

Participants recognized that various stakeholders act as gatekeepers in pragmatic CRTs, and these gatekeepers facilitate the implementation of the trial. Participants identified clinicians as key gatekeepers insofar as they facilitate the recruitment of patients and the conduct of the trial. Other gatekeepers identified by participants included dialysis center managers, regional managers within health systems, nurses, and allied health professionals (see, for example, Quotes 4.1-4.2). Gatekeeper support was deemed a key predictor of success for a pragmatic CRT.

Pragmatic CRTs conducted in for-profit hemodialysis facilities face additional challenges (Quotes 4.3-4.4). Participants noted in a for-profit dialysis facility there are potential conflicts among the facility’s clinical functions, its responsibilities as a business, and the needs of a trial.

**Inequities in Access to Research**

While some participants said that within-center clinical care is highly protocolized, others reported substantial variation in care between centers (Quote 5.1). Participants identified equitable access to research as an ethical issue. Both the organization and funding of hemodialysis care were thought to impact access to trial participation. For example, trials may not be as accessible to patients in satellite centers or community settings as they are in academic hospitals (Quotes 5.2-5.3). Other participants questioned whether an ongoing trial could negatively affect nonparticipating patients due to trial demands on resources such as health provider time (Quote 5.4).

**Advocacy for Patient-Centered Research and Outcomes**

The final theme identified was the need for patient-centered research and the use of patient-centered outcomes. Participants indicated that training and resources to support patient-centered research are needed (Quotes 6.1-6.2).

The importance of patient-relevant outcomes in research was highlighted often by participants (Quote 6.3). Traditional research endpoints, such as mortality, are commonly infeasible in hemodialysis given the timeframe of trials. This has led to the use of surrogate endpoints such as biomarker levels with variable clinical utility. As a result, treatments are often adopted in practice without evidence of impact on patient-relevant outcomes (Quote 6.4).

Another barrier to patient-centered research is that patient-relevant outcomes are not captured in routinely collected data sets (Quote 6.5). To capture patient-centered outcomes, additional efforts may need to be made to collect these directly from patients participating in a pragmatic CRT. However, this is in tension with the pragmatic aim of relying on routinely collected data and using existing staff and data infrastructure for outcome assessment.

**Discussion**

In the present study, we interviewed a range of stakeholders involved in hemodialysis research to identify ethical issues in pragmatic CRTs. Much of the discussion was prefaced by concerns regarding the lack of high-quality trial evidence, and the potential for strongly held opinions to impede trials. Participants identified six themes: patients being treated with hemodialysis as a vulnerable population, appropriate approaches to informed consent, research burdens, roles and responsibilities of gatekeepers, inequities in access to research, and advocacy for patient-centered research and outcomes.

These findings should be considered within the limitations of the study. First, while the response rate of those invited was almost 70%, the sample was largely drawn from the United States and Canada. While this reflects the geography of completed trials in hemodialysis, almost 85% of the articles in a recent systematic review were from the United States, United Kingdom, or Australia and New Zealand. Participants from other countries may have raised additional
issues informed by their own regulations and health care systems. Second, the interviews were only conducted in English, and non-English speakers may have contributed additional perspectives. Third, our sample did not include nurses or research coordinators. Given their day-to-day interactions with patients, we believe future studies seeking to further our analyses should include nurses and research coordinators. Finally, no patients or families were included in this study. Given the complexity of the study designs for pragmatic CRTs we adopted a different vignette-based approach to engage patients and this work will be reported separately.

Many of the six themes identified are consistent with previous ethical analyses of pragmatic CRTs in hemodialysis (see Table 3). However, participants identified issues of equity in access to research, and the need for patient-oriented research and patient-centered outcomes, as key themes. These issues have been emphasized to a lesser degree in the literature compared with other themes identified, such as informed consent.

The ethical principle of justice requires fair participant selection procedures. Injustice occurs when patients are unduly excluded from research participation, leading to systematic gaps in knowledge and evidence-based treatments. Unlike previous work on the ethics of pragmatic CRTs, our study identified equitable access to pragmatic CRTs as a key ethical issue.

This lack of discussion within previous analyses is surprising given the established literature illustrating that participants recruited to trials testing hemodialysis interventions may not reflect the broader clinical population from which they are drawn and broader inequities in hemodialysis care. Notably, patients enrolled in hemodialysis trials have also been found to be younger and have fewer comorbidities than patients in the clinical setting, with many trials systematically excluding patients above the age of 65. The relatively high prevalence of cognitive impairment in patients being treated with hemodialysis presents a special challenge for pragmatic CRTs: there is a need to balance individual rights and respect for persons with social justice concerns and the inclusion of patients normally excluded from trials.

We believe that equity requires greater efforts to ensure that both trial participants and hemodialysis facilities are representative of the target clinical population and setting for treatments. Going forward, pragmatic CRTs should avoid excluding patients, such as those with comorbidities or lacking decision-making capacity, who would likely receive the treatment in clinical practice. The need to include a broader patient population and diverse hemodialysis facilities is consistent with recent statements by funders to ensure equity considerations in health research.

Our study also indicates the perceived need to develop and embed patient-relevant outcomes within pragmatic CRTs in hemodialysis. Participants highlighted the problems associated with the use of surrogate outcomes for mortality due to the cost of trials large enough to detect mortality outcomes. Indeed, the inclusion of patient-relevant outcomes has been low: a recent scoping review found that only 23% of registered randomized controlled trials relevant to dialysis addressed an important research topic as established by a priority setting partnership, and only 16% of the trials assessed clinical outcomes as part of the primary outcome of the study.

This highlights the need for the creation of networks of hemodialysis facilities that can serve as a platform for large, pragmatic CRTs. The feasibility of pragmatic CRTs may be
further enhanced by making use of routinely collected clinical data and reducing the need for dedicated research personnel. Second, the identification of other patient-relevant outcomes in hemodialysis trials is a key priority. Patient outcomes are beginning to receive attention in the literature and recent efforts to standardize outcomes for nephrology trials have included patients, family members, and other caregivers. Other examples include work by BC Renal Agency and Ontario Renal Network and through which the Edmonton Symptom Assessment Scale (ESAS) (known as My Symptom Checklist) is reported and recorded in routine care.

Despite this, few studies in nephrology report patient engagement and there is a lack of experience and knowledge about how to engage patients. A lack of awareness and resources have been identified as key barriers to greater patient involvement in kidney research. We suggest that the resources have been identified as key barriers to greater patient involvement in kidney research. We suggest that the resources have been identified as key barriers to greater patient involvement in kidney research. We suggest that the resources have been identified as key barriers to greater patient involvement in kidney research.

Checklist
My Symptom
Symptom Assessment Scale (ESAS) (known as
Chronic Kidney Disease (Can-SOLVE CKD) (Canada) and
Canadians Seeking Solutions and Innovations to Overcome
Chronic Kidney Disease (Can-SOLVE CKD) (Canada) and
the Kidney Patient Involvement Network (UK).

Finally, we note that our study failed to identify some ethical issues reported by other publications. Discussion of methodological aspects of CRTs was notably lacking in our study. Participants did not discuss the need to justify cluster randomization or controversies in the adoption of individual-level interventions as the local standard of care. The analyses by Dember et al and Goldstein et al, both used the TiME trial as a case study, and this may have shaped their findings. In the present study, individuals drew upon their own experiences with a range of different trials, which included a variety of interventions that differed from the TiME trial intervention (see Table 3 for a comparison of issues raised).

Conclusions
The treatment of patients who require hemodialysis lacks an adequate evidence base and further research is urgently needed. Pragmatic CRTs offer a methodological approach to address these concerns. However, if such trials are to proceed ethically a variety of ethical issues must be addressed, including patient vulnerability; appropriate informed consent; the burdens of research on patients, families, and clinical staff; and gatekeeper roles and responsibilities. Our study highlights that greater attention needs to be paid to inequities within research and the ongoing need to advocate and provide resources for patient-centered research and outcomes.

Ethics Approval and Consent to Participate
The study was reviewed and approved by the Ottawa Health Sciences Research Ethics Board (REF: 20170435-01H) and all individuals provided informed consent to participate in the study.

Consent for Publication
All authors have approved the manuscript for publication.

Availability of Data and Materials
The data sets generated and/or analyzed during the current study are not publicly available due potential identifiability.

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Author Contributions
M.T., C.W., J.M.G., and A.X.G. conceived the project idea and co-led the funding application. S.G.N., K.C., J.C.B., C.W., C.E.G., E.B., M.S., developed the interview guide and E.B., M.S., A.A-J., A.X.G., J.M.G., C.W., and M.T. facilitated recruitment. S.G.N. conducted the interviews. S.G.N. and K.C. conducted the analysis. S.G.N. wrote the initial draft of the manuscript with input from M.T. and K.C. S.G.N., K.C., C.W., C.E.G., J.C.B., M.S., A.A-J., E.B., J.M.G., A.X.G., M.T. all contributed critical revisions and approved the final manuscript.

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Supplemental Material
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