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Cultivating Innovative Pragmatic Cluster-Randomized Registry Trials Embedded in Hemodialysis Care: Workshop Proceedings From 2018

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on behalf of the Gardner's Grove Participants

Abstract

Hemodialysis is a life-sustaining treatment for persons with kidney failure. However, those on hemodialysis still face a poor quality of life and a short life expectancy. High-quality research evidence from large randomized controlled trials is needed to identify interventions that improve the experiences, outcomes, and health care of persons receiving hemodialysis. With the support of the Canadian Institutes of Health Research and its Strategy for Patient-Oriented Research, the Innovative Clinical Trials in Hemodialysis Centers initiative brought together Canadian and international kidney researchers, patients, health care providers, and health administrators to participate in a workshop held in Toronto, Canada, on June 2 and 3, 2018. The workshop served to increase knowledge and awareness about the conduct of innovative, pragmatic, cluster-randomized registry trials embedded into routine hemodialysis care and provided an opportunity to discuss and build support for new trial ideas. The workshop content included structured presentations, facilitated group discussions, and expert panel feedback. Partnerships and promising trial ideas borne out of the workshop will continue to be developed to support the implementation of future large-scale trials.

Abrégé

L'hémodialyse constitue un traitement essentiel au maintien de la vie pour les personnes atteintes d'insuffisance rénale. Les patients hémodialysés voient cependant leur qualité et leur espérance de vie réduites. Des données de recherches probantes, provenant de vastes essais cliniques contrôlés à répartition aléatoire, sont nécessaires pour améliorer l'expérience, les résultats et les soins des patients hémodialysés. Grâce au soutien des Instituts de recherche en santé du Canada (IRSC) et de leur Stratégie de recherche axée sur le patient (SRAP), l'initiative sur les essais cliniques novateurs (ECN) en centres d'hémodialyse a réuni divers intervenants en santé rénale (chercheurs, patients, fournisseurs de soins et administrateurs), du Canada et de partout dans le monde, lors d'un colloque qui s'est tenu à Toronto les 2 et 3 juin 2018. Ce colloque a permis d'accroître la sensibilisation et les connaissances sur la conduite d'essais cliniques novateurs, répartis en grappes,

pragmatiques et intégrés aux soins d'hémodialyse de routine. Cette rencontre a également fourni une occasion de discuter de nouvelles idées d'essais cliniques et de susciter les appuis nécessaires à leur réalisation. Le colloque s'est déroulé sous forme de présentations structurées, de discussions animées en groupe et de rétroaction de la part d'un comité d'experts. Les idées de recherche prometteuses et les partenariats issus de ce colloque continueront d'être développés pour soutenir la réalisation d'essais cliniques futurs de grande envergure.

Keywords
chronic kidney disease, hemodialysis, pragmatic, cluster randomized, registry-based, randomized controlled trial, patient-oriented research, workshop

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Background

Kidney disease places a heavy burden on patients, their families and caregivers, and the health care system. For persons whose kidneys have failed, dialysis represents a treatment that can prolong life. However, those on dialysis face a poor quality of life, have high morbidity and mortality, and incur high health care costs.[1-11] Furthermore, they are challenged by a high prevalence of debilitating symptoms.[5,12]

The field of kidney medicine has the unfortunate distinction of conducting the fewest randomized controlled trials (RCTs) of any medical discipline.[13,14] Furthermore, these RCTs are limited by the following:

1. Enrolled patients who do not represent the average dialysis patient.
2. Low recruitment and retention rates resulting in an insufficient number of patient participants and outcomes.
3. Poor adherence to the allocated treatment resulting in a loss of statistical power.
4. Missing data and health economic analyses resulting in difficulty informing health decision-making.[13-21]

Consequently, best practices for dialysis care are largely informed by expert opinion (ie, "eminence-based" medicine), physiology expertise, and observational studies rather than by evidence from high-quality RCTs—the gold standard for evidence-based medicine.[22]

The Innovative Clinical Trials (iCT) in Hemodialysis Centers initiative, funded in 2017 as a Canadian Institutes of Health Research (CIHR) Strategy for Patient-Oriented Research (SPOR) Multi-Year Grant ("An Integrated Platform for Innovative Pragmatic Cluster-Randomized Registry Trials in Hemodialysis"), was established to address these critical issues in hemodialysis care and research. The foci of this activity are to

- plan, design, and conduct large-scale pragmatic trials embedded into routine hemodialysis care, where the intervention is delivered by routine health care providers (rather than research coordinators);
- use cluster-based randomization at the hemodialysis unit level;
- perform modified procedures for patient informed consent; and
- use existing data-rich registries with linked health care data for all baseline and follow-up information, including government expenditures.

The iCT in Hemodialysis Centers initiative is governed by a Steering Committee consisting of a health professional (Dr Amit Garg), a new Faculty member (Dr Amber Molnar), a health care administrator (Dr Peter Blake), 2 patients (Mr Hans Vorster and Mr Michael McCormick), and a health researcher (Dr Jeremy Grimshaw). The Steering Committee takes overall responsibility for all aspects of the initiative, including the workshop. Aligned with the vision of CIHR's SPOR, the grant activities are undertaken in full partnership with persons on hemodialysis (including family and caregivers), as well as health care providers and health administrators.[23] Guided by their priorities in every stage of the research process, needed and meaningful clinical trials in hemodialysis can be implemented for successful knowledge translation and uptake in care settings.[15,20,24,25] As many clinical decisions in hemodialysis care are made at the program/unit level (eg, setting the level of calcium in dialysis fluid), rather than from individual clinician-patient discussions, the trials in this initiative use cluster-randomization of entire hemodialysis units to assess the benefits and risks of intervention. With these considerations, pragmatic trials can test the effectiveness of promising interventions in real-world hemodialysis settings and broad patient groups.[18,26] The results produced are then generalizable and applicable for a diverse population of persons on hemodialysis. Furthermore, critically needed trials can be conducted with the same quality as traditional trials with individual randomization, but with less time and at a fraction of the cost. The knowledge gained from these new trials is ultimately expected to improve the health and care of those undergoing hemodialysis.

A key objective of the iCT in Hemodialysis Centers initiative is to support the development of at least 2 new promising interventions so that by the end of the 4-year grant period (2017-2021), they are ready for large-scale trial implementation in hemodialysis centers. With the involvement of patients, health care providers, and health care administrators, trial planning will be advanced in a manner that builds consensus on research priorities and considers the challenges to implementing different trial concepts. To fulfill this objective, a stakeholder engagement and research development workshop was held in Toronto, Ontario (Canada) on June 2 and 3, 2018. The workshop emcee was Dr Amit Garg, nephrologist, Program Lead of the ICES Kidney, Dialysis and Transplantation (ICES KDT) Ontario provincial program (London Health Sciences Center, Western University), and the nominated principal investigator of the funded iCT CIHR SPOR grant. Through structured presentations, facilitated group discussions, and expert panel feedback (see Supplemental Appendix Table A1 for workshop agenda), workshop attendees shared knowledge and opportunities to develop and collaborate on innovative, pragmatic, cluster-randomized registry trials embedded in hemodialysis care.

Workshop Participants

The workshop brought together 111 individuals of diverse disciplines and backgrounds (see Supplemental Appendix Table A2 for list of participants): patients, caregivers, physicians (practicing in community and academic settings), non-nurse allied health professionals, nurses, nurse practitioners,

renal program officials, researchers, research personnel, trainees, health charity representatives, industry partners' representatives, and one director of research ethics. Participants were Canadian as well as international, and came from 5 Canadian provinces (Alberta, British Columbia, Manitoba, Ontario, and Quebec), Australia, Europe, and the United States. Participants included representatives from several organizations: the CIHR, the Canadian Nephrology Trials Network, the Canadian Society of Nephrology, the Canadians Seeking Solutions and Innovations to Overcome Chronic Kidney Disease (Can-SOLVE CKD) Network, the Ontario ICES KDT provincial program, Kidney Foundation of Canada, the Ontario Renal Network (ORN), and the Ontario SPOR SUPPORT Unit.

Nine patients, family members, and caregivers attended the workshop, after a call for involvement through Patient Partnerships Coordinator Ms Leah Getchell. Ms Getchell reached out through the ORN, Patient and Family Advisory Councils, Can-SOLVE CKD, and patient partners from the iCT in Hemodialysis Centers initiative to identify participating patients. To ensure that patients, family members, and caregivers were fully included in the conference, a patient and caregiver discussion and networking meeting was held as a pre-workshop opportunity and multiple opportunities were provided for patients to provide feedback (see "Workshop Introduction" section). These actions were planned by the patient partners on the iCT in Hemodialysis Centers Steering Committee (Mr Hans Vorster and Mr Michael McCormick).

Workshop Goals

Aligned with the overall objectives of the iCT in Hemodialysis Centers initiative, the workshop had 3 goals:

1. Increase awareness and knowledge of innovative, pragmatic, cluster-randomized registry trials in hemodialysis.
2. Foster opportunities to partner and collaborate on the development of current and future trials across stakeholder groups.
3. Identify at least 2 new trial concepts that would be appropriate to develop further and launch as large-scale innovative trials by 2021.

The trials are meant to test promising interventions with the potential to improve the health and well-being of persons on hemodialysis, help manage their disease symptoms, and improve the delivery of their care through the optimal use of health care resources.

Process

Patient-Oriented Research Training

"How do we incorporate our patients in every step of our research program, so that we can make sure that the questions we are actually answering are important to the people who live the illness?" Quote from Deborah Zimmerman, MD, FRCP(C), Associate Professor, Division of Nephrology, The Ottawa Hospital and the University of Ottawa.

Module 1 of CIHR's Foundations in Patient-Oriented Research training was provided to 54 of the workshop's participants as a pre-workshop opportunity. Participants were physicians, researchers, research personnel, and industry partners' representatives alongside patients with lived experience of hemodialysis and their caregivers. The 4-hour session reviewed CIHR's SPOR[23] and provided practical considerations for those wishing to engage with persons on hemodialysis as research team members as well as examples of the roles patients can play within the research process. Participants found the session helpful in providing insight into the needs and concerns of persons on hemodialysis, the challenges of research, and the ways in which researchers and patients can collaborate.

Workshop Introduction

Initially, a status update for an ongoing trial, titled "Major Outcomes With Personalized Dialysate TEMPerature: Cluster Randomized Controlled Trial" (MyTEMP), was presented by Dr Garg (principal investigator) to inform workshop attendees on how innovative, pragmatic, cluster-randomized registry trials embedded in hemodialysis care can be designed, successfully implemented and conducted, and address potential challenges.[27] A summary of the details of the MyTEMP trial (ID: NCT02628366) that were presented at the workshop is included in Supplemental Appendix B, and a protocol of the trial is published elsewhere.[28]

Feedback and knowledge sharing were emphasized as being critical to the workshop's success, especially from workshop attendees with diverse perspectives and backgrounds. Several discussion platforms were also provided to encourage engagement from all those attending

- facilitated group discussions, where there was protected time for workshop attendees to provide in-person feedback;
- expert panel discussions, where panels of patients, researchers, health care providers, and health administrators were invited to be seated together on stage to lead group discussions; and
- a live online feedback and polling platform, through which attendees could anonymously provide comments during discussions.

The online platform was reviewed in detail with participants to ensure that everyone (including patients, family members, and caregivers) had a chance to provide feedback. In addition, protected time was allotted for online feedback and staff members were available to help with technical issues. Finally, feedback and discussion given during the presentations were recorded and transcribed by notetakers. These

were later compiled and provided to the trial presenters to inform further development of their trials.

Patient Voice

Mr Hans Vorster, a person on hemodialysis and an investigator on the iCT in Hemodialysis Centers CIHR SPOR grant, was invited to provide his perspective on cluster-randomized registry trials in hemodialysis and what they may mean for persons on hemodialysis and their health care needs. Mr Vorster believed that, by helping to better understand fundamentals within hemodialysis, such trials and their findings would be of great significance to the future of hemodialysis care. Provided that the interventions studied in these trials were minimally intrusive and had a good potential to help patients feel better, he felt confident that the trials would be highly valued by patients on hemodialysis.

Ethical Considerations in Innovative, Pragmatic, Cluster-Randomized Registry Trials

As innovative, pragmatic, cluster-randomized registry trials still lack consensus ethics guidelines on how they should be conducted, researcher Dr Charles Weijer of Western University discussed ethical issues for these trials. Feedback was solicited to inform future ethics guidelines, led by an expert panel discussion. Furthermore, all workshop attendees were given an opportunity to provide feedback in person or through an anonymous live online poll.

Dr Weijer discussed his team's work on the following relevant ethical considerations:

- How should we protect vulnerable persons on hemodialysis?
- Are usual care interventions research or practice?
- When, how, and from whom is informed consent required?
- What are the goals of notification and how are they best achieved?
- What research ethics oversight is required?

The first international ethical guidance for cluster-randomized trials (The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials) provided guidance on many ethical issues.[29] However, further work is needed to clarify the ethical issues related to individual cluster-randomized trials, which are the type of trials to be implemented in hemodialysis units. Developing an ethics consensus for the iCT in Hemodialysis Centers initiative requires ethicists, patients, and other stakeholders to work together as partners to develop ethical guidelines informing the conduct of innovative, pragmatic, cluster-randomized registry trials embedded into routine hemodialysis care. Empirical studies (eg, interviews and systematic reviews), ethical analyses (ie, identifying questions and potential solutions), and a process for developing consensus guidelines need to be developed.

Considerations for how research ethics boards (REBs) will adapt to these changes are also critical. In research ethics review, the first step is to distinguish clinical practice from research. In pragmatic trials, routine medical treatments may be compared with one another, and/or a treatment may be assigned to a cluster unit as its usual standard of care. It becomes difficult to distinguish between practice and research when usual standard of care interventions are assigned randomly for research and are not a result of joint physician-patient deliberation or a physician's individualized judgment. Future consensus guidelines will be needed to help navigate such complex issues.

The expert panel discussion was led by nephrologist Dr Manish Sood of the University of Ottawa, patient Mr Charles Cook, nurse practitioner Ms Betty Hogeterp of Lakeridge Health, nephrologist Dr Sanjay Pandeya of Halton Healthcare, and Office of Human Ethics Director Mrs Erika Basile of Western University. The discussion centered on the following themes:

- Patient or caregiver perspective (Mr Charles Cook): Building trust with patients, asking for their input, and involving them throughout the research process resonate strongly with patients and should be continued for developing a consensus on research ethics.
- Ethical oversight of clinical practice differs from that of research and lacks upfront review.
- Vulnerable persons on hemodialysis need to be given more opportunity to be involved, to be engaged, and to indicate interest in participating in research.
- There is limited value of having multiple REBs reviewing the same trial; stakeholders need to cooperate to delegate research ethics oversight.
- In studies comparing the effectiveness of interventions within the current scope of hemodialysis care, there may be minimal or no marginal difference in risk to the trial participants compared with routine care. However, the complexity of research methods and the inclusion of vulnerable persons on hemodialysis are additional qualifying factors in determining ethics oversight. Using proportionate review, a sliding scale of risk versus oversight can be implemented where these factors can be taken into consideration to determine the level of scrutiny needed.
- Consent documentation and procedures need to be concise to avoid limiting patient participant recruitment.

Workshop attendees provided feedback on the ethics presentation and its expert panel discussion, summarized as follows:

- Patient or caregiver perspective: Persons on hemodialysis need to be involved as partners in the development of

ethics guidelines, to ensure that research ethics review processes can be improved without violating their rights. This is critical when trials omit individual participant consent for the sake of research quality, which risks disempowering persons on hemodialysis and disregarding the aim of patient-oriented research. They will need to be kept informed on these ethical issues.
- Current clinical practices in hemodialysis may be arbitrary decisions made on limited evidence. A systematic approach to determining best practices is needed. In contrast, clinical research may be overregulated, where REBs may be hindering the ability to produce high-quality evidence.
- To improve ethics approval processes, REBs need assistance in being updated on innovative scientific research methods and procedures. This requires commitment from researchers and other stakeholders to participate in and contribute to REB discussions.
- Individual hemodialysis units may not receive local REB ethics approval and may not be able to participate in research studies, despite high-level REB approval. Better guidelines are needed to determine when high-level ethics clearance is sufficient for individual units.

As part of the overall initiative's goal to develop a responsible ethical framework with ethicists, patients, and other stakeholders, the feedback and discussion of the workshop will be used to guide a series of empirical and ethics studies to ascertain ethical challenges and issues in conducting these trials in hemodialysis centers. These will produce documentation that will be used by an international panel of experts to reach a consensus for production of a final ethics guidance document.

Panel Presentations

Six trial proposals were presented. In each case, there was an initial presentation on the intervention being proposed, followed by an expert panel discussion, feedback from audience members, and an anonymous live online poll where all audience members could provide feedback through comments and assess the intervention on the following 3 criteria:

1. Does this intervention have real potential to improve the health of patients receiving in-center hemodialysis or improve the system caring for them, where the intervention's benefits likely outweigh any risks and where the intervention, if proven beneficial, can be incorporated broadly into routine care?
2. Is a pragmatic hemodialysis-center-based cluster-randomized trial, with an efficient method of patient consent, where most baseline and follow-up information comes from existing health care databases and where the intervention is delivered within routine health care without research coordinators, an appropriate design to test this intervention?
3. Would you enthusiastically support this trial?

In addition, to ensure that the implementation and conduct of trials are guided by the needs and experiences of persons on hemodialysis and stakeholders, workshop attendees were encouraged throughout the discussions to think about the following 7 considerations for the interventions presented:

1. Benefits and risks of the intervention for persons on hemodialysis within the health care system.
2. Quality of evidence for the proposed intervention.
3. Values—*Will persons on hemodialysis have the choice of participating? Will most prefer receiving the intervention? Will most care providers prefer delivering the intervention?*
4. Availability of funding, human resources, and personnel.
5. Feasibility and scalability.
6. Acceptability to key stakeholders.
7. Ethical considerations for implementing the intervention.

As an example, the proceedings are reported from one of the 6 presentations in detail. The other 5 are summarized in Supplemental Appendix C1.

Intervention proposal: Bringing diabetes care expertise to the hemodialysis unit. Endocrinologist and researcher Dr Kristin K. Clemens of Western University shared her proposal for a diabetes care trial that would investigate whether better coordination of diabetes and hemodialysis care would lead to improved diabetes-related patient outcomes and care. The trial idea was informed by a qualitative patient-oriented research study, where persons with diabetes and advanced kidney disease identified several challenges with their health care.[30]

One quarter to half of persons with diabetes have chronic kidney disease.[31] Those undergoing hemodialysis face many reoccurring challenges, including poor glycemic control, a low quality of life, and difficulty balancing a busy dialysis schedule with diabetes-related tasks (eg, insulin injections, strict diet, medication). They are also more likely to face diabetes-related complications (eg, cerebrovascular disease, cardiovascular disease, foot ulcers).[32] Consequently, they are burdened by numerous health care appointments and procedures. This care burden can make it financially and logistically impractical for persons with diabetes and chronic kidney disease to meet all their needs, which lead to gaps in their health care and decreased overall quality of care.[30]

Persons with diabetes and chronic kidney disease can be provided better coordinated care by integrating diabetes-related care resources into the hemodialysis unit. Certified diabetes educators (CDEs), trained to provide clinical support

for persons with diabetes, can be embedded into hemodialysis units' health care teams to implement a diabetes case management program developed with patients. Guided by a chronic care model, which is beneficial for persons with diabetes, the program could include self-management support, diabetes-related education, treatment adjustment support, foot screening and monitoring, screening reminders, care coordination, and resource navigation.[33] The CDE also brings improved access to other specialists, care professionals, and diabetes-related community resources.

The intervention would be implemented as a 2-year, innovative, pragmatic, cluster-randomized registry trial, investigating the following question: Do Ontario hemodialysis units that adopt the intervention of a CDE-delivered diabetes case management program have a lower rate of diabetes-related complications compared with hemodialysis units operating under standard care?

To investigate this question, participating Ontario hemodialysis units will be randomized into an intervention or control group. Units randomized to the intervention group will be assigned a CDE, who will provide individualized treatment plans to be carried out by the unit's health care team, in addition to providing routine/as-needed care (eg, insulin titrations). Units randomized to the control group will operate at a standard level of care. A composite outcome will be generated using diabetes-related complications: hospital encounters for hyperglycemia and hypoglycemia, foot ulcers, amputations, cardiovascular and cerebrovascular events, and retinopathy treatment. Secondary outcomes will involve average blood sugar levels in the past 2 to 3 months (hemoglobin A1c [HbA1c]), annual vision screening, quality of life, and number of health care appointments.

To be successfully implemented at a large scale, the trial will first undergo a preparation phase that includes

- sourcing baseline and follow-up trial data from existing administrative data holdings;
- assessing CDE availability and accessibility for Ontario-wide hemodialysis units;
- developing a diabetes case management program with CDEs, patients, and stakeholders;
- designing management pathways (eg, blood sugar–level management, foot screening);
- implementing a pilot RCT at a local hemodialysis unit to assess feasibility and identify potential barriers;
- performing economic analyses (eg, CDE costs, health care costs);
- collaborating with patients, health care providers, and researchers for research development and patient care coordination; and
- receiving ethics approval for a notification method of modified consent based on identified low risk.

If these considerations are addressed, Dr Clemens expects that the trial will test a promising strategy to improve the outcomes and coordination of care for persons with diabetes undergoing hemodialysis while minimizing the burden on them to meet their health care needs. The trial may illustrate how a chronic care model for diabetes and chronic kidney disease can be deployed by leveraging and coordinating existing health care resources (as opposed to new resources funded by a research budget). The trial may also produce data to inform and justify health care funding for implementing such a program across Canadian clinics (as CDEs are not currently available in all jurisdictions).

The expert panel discussion was led by nurse educator Ms Channing Liberty of The Ottawa Hospital, nephrologist Dr Rey Acedillo of Thunder Bay Regional Health Sciences Centre, nephrologist Dr David Berry of Sault Area Hospital, nephrologist Dr Ron Wald of St. Michael's Hospital, and patient Mr Craig Lindsay. The discussion focused on the following themes:

- Patient or caregiver perspective (Mr Craig Lindsay): The intervention aligns closely with patient-oriented care and research, by addressing the difficulty persons face coordinating diabetes and kidney care. However, they will always need care, which may conflict with the scheduling of CDEs, health care providers, and the diabetes case management program. In addition, they may not be interested in undergoing diabetes-related care during hemodialysis. Patient needs and expectations will need to be taken into account during program development.
- Persons with comorbidities face difficulties managing their symptoms due to extended wait-times for health care providers. Through reducing wait-times, the intervention has the potential to relieve their care burden and prevent a multimorbidity cascade effect leading to hospitalization and other complications.
- A significant portion of First Nations, Inuit, and Métis persons have diabetes, are on hemodialysis, and have difficulty managing blood sugar levels; they may particularly benefit from the program given that the program is culturally sensitive. A key challenge will be implementing the program in smaller and more remote hemodialysis units, which will be difficult to access for CDEs.

Workshop attendees provided feedback on the panel presentation and its expert panel discussion, summarized as follows:

- Patient or caregiver perspective: Better education help patients make informed decisions.
- The study's outcomes of interest need to ensure that they are a result of diabetes-related complications (eg, hospital encounters for hypo- and hyperglycemia may be due to acute illnesses and not from a diabetes-related cause).

- Some health regions are geographically large with widely interspersed satellite hemodialysis units. These regions may require many available CDEs, to ensure that all units can be visited a sufficient number of times per week.
- CDEs may need to dedicate counseling time with individual patients, to ensure that their concerns are addressed regarding their individualized treatment plan. Otherwise, they may be resistant to changes in their care (eg, medication) which they perceive as troublesome or not helpful.
- To address potential financial costs for implementing the study, a factorial approach could be used to determine which components of the intervention are most cost-effective (eg, foot care vs glycemic control).

Overall, workshop attendees supported the intervention by Dr Clemens for further development as a promising innovative, pragmatic, cluster-randomized registry trial embedded in hemodialysis care based on the assessment criteria. Based on feedback, Dr Clemens decided to conduct a series of studies and surveys to inform implementation of her program (see "Activities Following the Workshop" section).

Rapid Fire Proposal Presentations

The valuable experiences of those gathered provided an additional opportunity to launch informed discussions on new ideas for future interventions and trials. Six researchers briefly presented proposals for research interventions in hemodialysis and received feedback through anonymous live online polling (summarized in Supplemental Appendix Table C2). One of the rapid-fire proposals is described in detail as an example of the proceedings.

Researcher Dr Marisa Battistella of the University Health Network (UHN) presented her proposal on deprescribing medications in hemodialysis units. Persons on hemodialysis face an increased likelihood of polypharmacy due to having the highest pill burden of all patients receiving chronic care.[34-36] As a consequence of polypharmacy, they face a higher risk of negative outcomes, including adverse drug events, increased health care costs, hospitalization, and mortality.[37-43] However, many medications used for those on hemodialysis are poorly substantiated by evidence.[44-46]

To identify potentially inappropriate medications, databases in Alberta, British Columbia, and Ontario were used to determine the most common medications used by persons on hemodialysis (eg, proton pump inhibitors [PPIs]). Literature searches were then performed to determine the safety, efficacy, and appropriateness of these medications. Ultimately, 9 deprescribing algorithms were developed and validated. Each of these evidence-based decision-making tools will be a component of a medication-specific deprescribing toolkit. These toolkits are designed to help clinicians, in collaboration with persons on hemodialysis, identify potentially inappropriate medication use for each person and to guide safe deprescribing of that medication.

Going forward, these decision-making tools will undergo clinical testing to determine whether they lead to improved outcomes for persons on hemodialysis. Feedback was invited on how to best implement these tools into practice, including whether a large-scale, pragmatic, cluster-randomized registry trial would be an appropriate study design. Audience feedback (through anonymous live online poll) agreed that while reducing pill burden is an important issue for those on hemodialysis, cluster-randomized clinical trials may not be the best approach for this proposed intervention. The audience recommended that the decision-making tools be implemented in clinical practice as an observational trial so that patient-reported outcomes could be followed. Finally, Dr Battistella received the support of several clinicians at the workshop who agreed to help in the validation of the deprescribing algorithms.

Next Steps

The workshop successfully brought together people of diverse backgrounds to share knowledge of innovative, pragmatic, cluster-randomized registry trials in hemodialysis, collaborate on current and future trials, and develop promising solutions as new trials. Participants provided feedback and recommendations for the workshop and its overall scope. To continue to advance these innovative trials, promising trial proposals will be supported for trial development and a follow-up workshop will be held in the coming years.

Overall, most participants were highly satisfied with the workshop (Figure 1), opportunities to provide feedback, and the new format of crowdsourcing information through anonymous live online polling and panel discussions. There were a total of 507 comments logged through the online polling system (of which 36 were provided by patients). The workshop's gardening theme, relaxed atmosphere, and online polling were praised for being enjoyable and engaging. Patients were particularly appreciative of being listened to and valued for their personal experiences and feedback. Furthermore, patients found the workshop to be promising and encouraging for the future of kidney research and care. Feedback on the workshop is summarized below.

What the workshop did well:

- The gardening and nurturing theme of the workshop provided a relaxed atmosphere, which made it easier for participants to contribute to discussions—many participants wore gardening and farming outfits to support the theme. Networking and patient-oriented events (eg, patient-caregiver sharing circle) were also helpful in making participants feel comfortable and engaged.

Figure 1. Word cloud of overall workshop experience.

- The anonymous live online polling and commenting platform was well received for being engaging and effective for crowdsourcing feedback and ideas. Participants who were less likely to participate in person welcomed the anonymous nature of online commenting.
- Expert panel reviews of the trial presentations were effective in providing valuable feedback on the trials from different perspectives.
- Stakeholders, particularly patients and their families and caregivers, felt that they were heard, valued, and provided a great opportunity to contribute their experiences, opinions, and perspectives. The workshop's events were found to be meaningful for those living with hemodialysis and promising for the future of patient-oriented hemodialysis care and research.
- Overall, the workshop was scheduled and organized well, providing sufficient time and multiple perspectives for presentations and discussions.

What the workshop could improve on:

- As a patient-oriented research workshop, the following changes could make the workshop more patient-friendly:
  - Meals and refreshments provided could be more suited for persons with kidney disease and on dialysis.
  - Hand sanitizer can be placed at strategic points (eg, entrance/exit) to protect those who are immunocompromised.

- To ensure discussions are not dominated by physicians and nephrology researchers, the workshop could benefit from more participating patients, experienced trial leaders in other specialties, and allied health care members.
- Based on related experience and interest, patients may be matched with trial presenters, to collaborate on trial development and co-present trial ideas.
- Rapid fire proposal presentations could benefit from being structured similarly to panel presentations and fewer in number to ensure that the audience is able to provide sufficient feedback. Feedback was not given for all presentations due to limited time.
- Changes to panel discussions could better facilitate engagement: semi-circular seating to encourage interaction among panel members, reduced number of presentations with more time for discussion, and opportunity for the presenter to respond to online and in-person comments.
- Networking events were invaluable but limited in number. More opportunities could be created by increasing the duration of breaks and providing networking events after trial presentations.
- A survey can be conducted to formally assess whether the next workshop achieved its goal of raising awareness and knowledge of pragmatic cluster-randomized registry trials in hemodialysis.
- Additions to the next workshop's agenda were suggested:
  - Initial survey to determine the goals and content of the workshop;
  - Peer-review process to determine trial proposals to be presented at the workshop (eg, are they appropriate as a pragmatic, cluster-randomized registry trial);
  - Written publication summaries of successful trials;
  - Dedicated discussions on trial preparation (eg, methodology, analyses); and
  - More detailed information on how trials are selected to proceed to the next step of applying to granting agencies for funding.

Activities Following the Workshop

Ethics Activities

The iCT in Hemodialysis Centers initiative is finalizing a systematic review of how pragmatic cluster-randomized registry trials in hemodialysis are reported, with respect to their ethical conduct and justification of trial design. A paper was published summarizing the ethical issues in pragmatic cluster-randomized trials in dialysis facilities.[47] Structured interviews are also being conducted with trial experts, hemodialysis patients, and key informants (trialists, regulators, methodologists, clinicians, ethicists, and research ethics chairs) to guide the ethical conduct of these types of trials (ethics approval for this qualitative study was obtained in November 2018). This includes having developed and evaluated educational material and scenario-based interview guides/scripts for interview use. Ethics approval for these interviews was obtained in November 2018. Based on interviews completed to date, manuscripts on identifying ethical issues and notification (of patients and the public) strategies in these trials are being prepared for publication.

Trial Activities

Audience feedback was compiled and returned to the trial presenters to inform and strengthen their proposals. The presenters were then surveyed to determine how the feedback influenced their decision to proceed with development of their trials. The feedback process was found to have helped in identifying patient priorities and stakeholder concerns within the trial protocols. The feedback was used to determine whether the trial was acceptable to the nephrology community and whether it was considered feasible or of interest. Of the trial proposals presented at the workshop, the following are in active development for securing funding:

1. *Implementation of deprescribing and patient education tools in hemodialysis units to decrease polypharmacy (Dr Marisa Battistella, UHN)*: It has determined that the baselines, outcomes, and database updates available would lead to a feasible trial. A grant to finance the trial is currently under peer-review.
2. *Dialysate magnesium outcomes (DyMo) study (Dr Eduardo Lacson, Jr, Dialysis Clinics Inc)*: This trial concept was further developed with patients and health care administrators over the subsequent 12 months. The protocol with discussed extensively with the REB, and received ethics approval through Clinical Trials Ontario in September 2019. Analytics of health care administrative data in Ontario were conducted to inform the trial. The trial will be submitted for peer-review funding in November 2019 for funding to run the trial in 160 hemodialysis centers across 4 Canadian provinces.
3. *Bringing diabetes case management into the hemodialysis units (Dr Kristin Clemens, Western University)*: To inform this trial, analytics were conducted for the following: baseline rates in primary and secondary outcomes and the total expected number of trial participants. Dr Clemens is collaborating with Dr Justin Presseau (Ottawa Hospital Research Institute) on a study to determine barriers and facilitators to implementing the program, where CDEs, patients, and hemodialysis center staff will be invited to be interviewed. Funding has also been provided by St. Joseph's Healthcare Foundation to examine the program through a quality improvement project at London Health Sciences Center, which has been found useful in streamlining the CDE care package and determining local barriers to the program. A baseline assessment will be completed at the Kidney Care Center's (London, Ontario) hemodialysis unit and a CDE has been hired to start running the program in November 2019. Finally, a survey study is in progress with Ontario CDEs to gauge their interest in participating in this type of program and determine the type of diabetes management (eg, education) that they believe patients would most benefit from.

Further collaborations on new research initiatives are underway, which includes the following:

- Dr Amber Molnar, with
  - Dr Charmaine Lok (University of Toronto) on the development of trial protocol on a washing technique and catheter-related infections.

- Dr Samuel Silver, with
  - Dr Amber Molnar on a trial proposal to investigate outcomes for suboptimal initiation of hemodialysis;
  - the ORN on the evaluation of patient outcomes from the use of sick-day medication protocols in chronic kidney disease.

Conclusion

Overall, participants found the workshop to be enlightening, exciting, and inspiring. The workshop was able to achieve its purpose in increasing awareness, dialogue, and knowledge of innovative, pragmatic, cluster-randomized registry trials and the opportunities they present in improving the health and well-being of persons on hemodialysis. Expert panel discussions, structured group evaluation, and feedback clearly showed that the effectiveness and suitability of research interventions are highly contextual and need to address issues of feasibility, sustainability, implementation, and patient-oriented concerns. The workshop provided a means

for collaboration between people of diverse disciplines and backgrounds, which will be leveraged to develop new trial ideas and inform the standard of care for hemodialysis in the future. A follow-up workshop will be held in the future to continue the collaborative research development of hemodialysis interventions and to develop a consensus ethics statement on the conduct of these trials.

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Supplemental Material

Supplemental material for this article is available online.

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