Challenges in Hemodialysis

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ABSTRACT

Background

Chronic kidney disease prevalence is increasing globally. Those with end-stage kidney disease may require hemodialysis, a complex and costly treatment modality, which is associated with many challenges.

Objectives

This thesis focuses on four objectives, each addressing a different challenge in research among chronic kidney disease patients on hemodialysis: (1) examining dietary mobile app intervention feasibility and effectiveness in changing user behavior; (2) analyzing the impact of arteriovenous access type and risk of maturation failure on the total costs of attaining and maintaining patency of arteriovenous access over one, three, and five years post creation; (3) determining the feasibility of conducting a randomized controlled trial to evaluate the impact of a novel catheter care protocol on the rate of catheter-related bacteremia; and (4) evaluating the completeness of reporting in pilot randomized controlled trials.

Methods

Study 1: A systematic review was conducted, which included a search of scholarly databases, as well as the gray literature, for all randomized controlled trials, observational studies, needs assessments, and pilot testing/studies/trials focused on the development or evaluation of chronic kidney disease dietary mobile app interventions. The characteristics, user satisfaction with, usability/feasibility, and effectiveness in changing dietary behavior of the mobile application were summarized using descriptive statistics and in a narrative manner.

Study 2: A cost analysis was conducted in which all first arteriovenous access creations (January 1, 2002 – January 1, 2018), revisions, removals, and interventions from a single academic institution were prospectively captured. The present value of total vascular access related costs from a third-party payer perspective was calculated and the potential associations of arteriovenous access type and risk of Failure to Mature stratum with arteriovenous access cost were examined using Loglinear models and generalized estimating equations.

Study 3: A pilot randomized trial was conducted in which adult hemodialysis patients using catheters were recruited from 11 hemodialysis units. Patients were randomized to receive Hemodialysis Infection Prevention Protocols Ontario—Shower Technique or standard care and were followed up for 6 months. Only catheter related bacteremia outcome assessors were blinded. For the study to be considered feasible, 4 of 5 feasibility outcomes, each with its own statistical threshold for success, must have been achieved.

Study 4: A methodological survey was conducted of Pubmed for all pilot trials conducted in HD patients. Reporting quality was assessed against the 40-item Consolidated Standards of Reporting Trials (CONSORT) Extension for Pilot Trials. Potential associations between study factors including year and country of publication, intervention, number of centers, type of funding, and journal endorsement of CONSORT with reporting quality were also examined.

Results and conclusions

Study 1: Thirteen full-text studies were included: of the 7 pilot studies that measured usability/feasibility, all found at least some aspects of the application feasible/useful and of the 5 pilot studies that reported an evaluation of changes in behavior/diet related to

self-management, all reported some positive change. According to current studies, nutritional apps show promise in chronic kidney disease self-management.

Study 2: A total of 906 patients were included in the study, 696 fistulas and 210 grafts. The costs of attaining and maintaining arteriovenous access were increased among patients with high/very high risk of Failure to Mature.

Study 3: A total of 68 patients were randomized (33 shower technique and 35 control) and were followed up to 6 months. Of 5 measures of feasibility, 4 were achieved. The pilot study demonstrated the feasibility of the larger study, especially given the high levels of education success with the shower technique arm and the low levels of contamination in the control arm.

Study 4: The mean number of items reported from the CONSORT extension for pilot trials across all included articles was 18.4 (standard deviation [SD] = 4.4). In the adjusted analysis, studies reported in later years (incidence rate ratio [IRR] = 1.026, 95% confidence interval [CI] [1.018, 1.034], $p < 0.001$) and an increase of 20 persons in sample size (adjusted IRR = 1.021, 95% CI [1.010, 1.031], $p < 0.001$) were associated with a significantly higher number of CONSORT pilot items reported. Current reporting completeness of pilot trials in hemodialysis patients is suboptimal.

PREFACE

This thesis is a "sandwich thesis" which combines four individual studies prepared for publication in peer-reviewed journals. The primary author of all the studies and of this thesis, S.D. Kosa, made the following contribution to all four studies: conception of the research idea, development of the research question, design of the study, conduct of the analyses, drafting of the manuscript including figures and tables, and revision of the manuscript based on co-author feedback. The contributions of co-authors vary for each of the four studies and includes but is not limited to: the collection of data, support and review of the study design, and revision of the manuscript. The work in this thesis was conducted between September 2014 and March 2020. All four paper have been published.

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CHAPTER ONE
BACKGROUND

INTRODUCTION

Chronic Kidney Disease Prevalence and Burden

Chronic kidney disease (CKD), defined as abnormal kidney structure or function impacting health persisting more than 3 months, is estimated to have a global prevalence of 13.4% (11.7–15.1%).[1,2] CKD is classified into five stages of increasing severity based on multiple criterion including: elevated protein in the urine (i.e., albumin excretion rate greater than or equal to 30 mg in 24 hours or an albumin–creatinine ratio of 3 mg/mmol or greater), abnormal sediments or electrolytes in the urine, atypical histology or kidney structure, or persistent kidney dysfunction represented by an estimated glomerular filtration rate lower than 60 mL/min/1.73 m^2.[3] The two tests used most often to classify CKD patients are a blood test for creatine levels used to estimate the glomerular filtration rate (i.e., G1, normal/high > 90 mL/min/1.73 m^2; G2, mildly decreased = 60-89 mL/min/1.73 m^2; G3a, mildly to moderate decreased = 45-59 mL/min/1.73 m^2; G3b, moderately to severely decreased = 30-44 mL/min/1.73 m^2; G4, severely decreased = 15 - 29 mL/min/1.73 m^2; G5, kidney failure <15 mL/min/1.73 m^2) and a urine test to estimate the albumin to creatinine ratio (i.e., A1, normal to mildly increased <30mg/g; A2, moderately increased, 30-300mg/g; A3, severely increased, >300 mg/g).[1,4] The prevalence, associated burden, and management of CKD varies by stage, as well as with co-morbid conditions such as, commonly, hypertension, cardiovascular disease, and diabetes.[3]

Stages 1 to 3 are generally considered ‘early’ stages of the disease. In stage 1 and 2 there is evidence of mild damage to the kidneys but they are almost or fully functional and there are generally no symptoms. The prevalence of stage 1 and 2 is 3.5% (2.8–4.2%) and 3.9% (2.7–5.3%), respectively.[5]

In Stage 3 there is some damage to the kidneys and they are not working optimally, which may result in the presentation of some symptoms such as irregular urination, swelling of the hands and feet, or back pain. Stage 3 is divided into two subcategories, G3a and G3b. Stage 3 is the most prevalent at 7.6% (6.4–8.9%).[5,6] Early stage CKD patients generally experience greater frailty, as well as specifically, they are burdened with cardiovascular risk, bone deterioration and fracture, susceptibility to infection, and cognitive decline.[3,4] It is recommended that early stage patients be followed by a non-specialist physician or, if symptomatic, a nephrologist, to develop a treatment plan which may include pharmacological intervention (e.g., angiotensin-converting enzyme inhibitors, statin therapy) as well as lifestyle and dietary recommendations to preserve kidney function and delay disease progression.[3,4,6] The dietary restrictions in particular can be very challenging for CKD patients to manage, and they report being constantly concerned about eating a type of food that could do them considerable harm.[16]

In Stage 4 CKD, the kidneys are moderately to severely damaged and not functioning properly, with increasingly severe symptoms including include those of stage 3, as well as fatigue, impaired cognition, anorexia, and sleep disturbances.[6,7] Stage 4 CKD is less common than the earlier stages with a prevalence 0.4% (0.3–0.5%) globally.[1,6]. Complications include elevated blood pressure, anemia, and bone disease.[6,8] At this stage, referral to a nephrologist is recommended and patients are sometimes managed in specialized clinics with teams of healthcare providers including dieticians, nephrology nurses, pharmacists, and others who can more fully address their complex complications and risks, as well as prepare patients for the potential progression of their disease including future options and interventions to prepare for kidney replacement therapy.[4,7]

In Stage 5, or end-stage kidney disease the kidneys have either failed completely or have severe impairment of their function requiring kidney replacement therapy. This stage is the least prevalent at a rate of 0.1% (0.1–0.1%).[1,9] Though a small absolute percentage, over 2 million people across the globe

require kidney replacement therapy, which requires significant resources and places a significant burden on the patient and their families.[10] There are two options for kidney replacement therapy: 1) dialysis using either an external membrane (hemodialysis) or internal membrane (peritoneal dialysis) that filters to replace some of the functions of the kidney, or 2) transplantation of a donated kidney into the patient.[4] While transplantation offers significant long term quality of life benefits and cost savings as compared to dialysis, there are limited kidneys available for transplant.[11,12] Approximately 7 in every 10 patients on kidney replacement therapy are on hemodialysis,[13] a very costly treatment modality.[5,14]

Hemodialysis Vascular Access

A hemodialysis vascular access is a necessary connection between the patient's vascular system and the hemodialysis machine and is required to provide hemodialysis therapy. There are significant challenges in the creation and maintenance of hemodialysis vascular access, which can take the form of a fistula, graft, or central venous catheter (catheter). Fistulas and grafts are both forms of arteriovenous access, a surgically created anastomosis between an artery and vein, which strengthens the vein sufficiently that it can be punctured (cannulated) to connect to the dialysis machine for treatments a minimum of three days a week, or more frequently if indicated. The length of time required for fistulas to be ready for use is two to six months, in which time the vein 'matures', increasing in diameter and wall thickness due to pressure from arterial flow.[73] A graft can be ready for use within 24 hours, but typically in two to four weeks, because graft connections are reinforced with polytetrafluoroethylene or other synthetic materials.[73] There are very specific benefits and limitations of each of these two access types.

Arteriovenous access (fistula or graft) use is associated with considerably lower morbidity, mortality, and costs than use of a catheter.[18-25] However, the time required for an arteriovenous access to mature and be ready for use precludes them as an immediate option for many patients starting

hemodialysis urgently. These urgent start patients initiate hemodialysis with a central venous catheter, often with plans to remove the catheter once an arteriovenous access is mature enough for use. For other patients, a catheter remains their primary vascular access, despite its' associated risks, due to unsuccessful attempts to place or use an arteriovenous access or comorbidities and life circumstances that preclude arteriovenous access creation.[24,26-28] In North America, the majority of patients initiate hemodialysis with a catheter,[29-32] a flexible synthetic tube inserted through the skin into a large central vein whose distal end rests in the right atrium of the heart. The proximal end of the catheter protrudes from the skin and is connected to the dialysis machine for hemodialysis treatments. The proximal end has a cuff that becomes endothelialized, creating a seal preventing extraluminal organism entry.[33-37]

Much of the additional morbidity, mortality, and cost associated with catheter use is driven by its' associated infections,[5] with estimates of the average costs of the associated hospitalization per infection ranging from US$17,000 to US$32,000.[19,38-40] Catheter-related infection includes entry site infections, tunnel infections, and bacteremia; however, the latter is the most clinically important due to the risk of progression to sepsis and death.[18] Strategies to care for catheters must minimize infection risk, inconvenience and discomfort to the patient, and cost.

CLINICAL ISSUES AND METHODOLOGICAL CHALLENGES

This thesis addresses four key issues in hemodialysis which require the simultaneous consideration of clinical outcomes, resource utilization, and patient preferences, and each present their own methodological challenges (see figure 1).

This thesis first addresses the need for technology that can support hemodialysis patients in the management of their nutrition and encourage their adherence to often complex dietary restrictions. While several mobile applications (apps) have been developed for this purpose, a systematic review was conducted to capture information from the wide-range of study designs that have been used in their

development and evaluation including the features of these apps, whether patients like them or are willing to use them, and how effective they may be in changing behavior. Ultimately, the hope is such an app could empower patients to better manage their diet and reduce the burden of nephrologist and dietician visits on the patient and the healthcare system.

The second issue addressed in this thesis is the selection of the appropriate arteriovenous access for use on hemodialysis. Despite their advantages over catheters, the placement of the two forms of arteriovenous access, fistulas and grafts, remain low in North America. While many policies in North America favor the placement of fistulas as the first arteriovenous access choice, citing longer term patency and lower costs, these policies often do not consider patients' specific circumstances and risks. Indeed, certain patient-related factors have been shown to be associated with higher risk of fistula failure (i.e., presence of peripheral vascular disease and cardiovascular disease, ethnicity, and age). A more nuanced approach to arteriovenous access selection may be more appropriate. The cost analysis conducted to address this issue compares the costs associated with arteriovenous access creation and use, not only by access type, but also by the risk of fistula failure.

The third pressing issue addressed in this thesis is the need for a hemodialysis central venous catheter care protocol that minimizes infection risk and cost while allowing the patient to shower. As an initial step in addressing this issue, a pilot study was conducted to determine the feasibility of conducting a larger trial to evaluate such a protocol. The major methodological challenges in addressing this issue included the standardization of the catheter care protocol flexible enough for use across multiple program/centres and the creation of tests of catheter entry site healing for use as randomization criteria as there were none pre-existing in the literature.

This thesis also considers the significant issue of a lack of strong evidence to inform clinical practice in hemodialysis, owing in part to the lack of positive randomized clinical trials. While pilot

studies offer considerable promise in informing and optimizing the design of these trials, until recently little guidance was available on their conduct and reporting. A methodological review was conducted to better understand what gaps may exist in the reporting of pilot clinical trials in hemodialysis, in order to ultimately inform their design and implementation, which in turn may lead to more successful definitive clinical trials in hemodialysis.

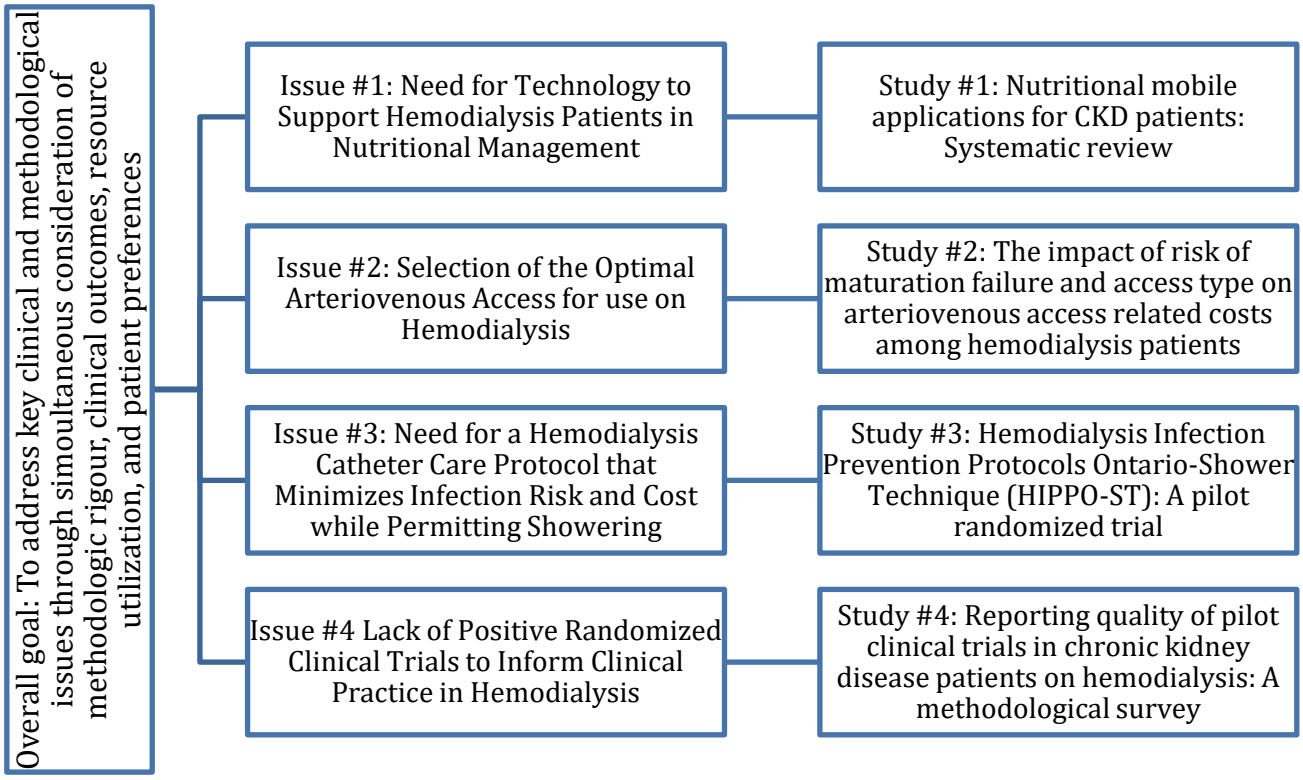

Figure 1. Key Methodological and Clinical Issues Addressed in this Thesis

Issue #1: Need for Technology to Support Hemodialysis Patients in Nutritional Management

Clinical Problem

Nutritional management of CKD patients is complex and differs for each patient over time based on their disease progression, co-morbitidies (e.g., diabetes, heart disease) and other clinical markers.[15] Restrictions may include limitation of their intake of protein, fluids, sodium, potassium, and

phosphorus.[15] Patients have reported feeling overwhelmed and confused by these restrictions and being poorly/uncompassionately supported by healthcare providers (e.g., being scolded or patronized).[16] Mobile applications show promise in overcoming some of these challenges, by offering features to monitor intake of key parameters and aid in taking greater control of their diet to increase quality of life and satisfaction.[17]

Methodological Challenges

A systematic review was conducted examining mobile app types, characteristics, feasibility, and effectiveness in changing behavior, as well as user satisfaction with dietary mobile apps, specifically in both adult and pediatric CKD populations. This systematic review included a wide range of studies from needs assessment and design studies to non-randomized and randomized pilot and feasibility studies focused on the development and/or evaluation of all types of mobile applications designed to assist individuals living with CKD manage their nutritional intake. The main methodological issue was designing a standardized data extraction spreadsheet that could function well for extracting data from a wide range of study designs. An excel based form, with a data dictionary was used. Key domains included study characteristics, characteristics of the intervention including app features, app process related outcomes including satisfaction, feasibility, and usability, and changes in dietary behavior, nutritional markers, and fluid intake of the patient with CKD using the app. Prior to piloting the data extraction form, a meeting was held with all those extracting the data in which the use of the form was demonstrated, feedback was obtained, and the form further revised. The form was then piloted, with all those extracting data providing feedback in an in-person meeting after the first four records, and then further revised, and where necessary the data were re-extracted. All extracted data were then reviewed by two other reviewers and inconsistencies/disagreements were resolved. This process, while time

consuming initially, reduced the number of inconsistencies in extraction and ensured completeness in extracted data.

Issue #2: Selection of the Optimal Arteriovenous Access for use on Hemodialysis

Clinical Issue

A prominent policy related to hemodialysis vascular access in North America for the past 2 decades, called "Fistula First", is based on the perception that fistulas have superior patency, the fewest complications and are less costly compared with other vascular access types.[74,75] Observational study data comparing fistulas and grafts suggests however, that each type of access has their own risks and benefits, the former is associated with high rates of maturation failure but longer-term patency, while the latter is more likely to mature and mature quickly, but with shorter patency. [76-81] There are a few previous cost studies which detail the costs associated with attaining and maintaining patency among fistulas and grafts, though being based on observational (non-randomized) samples, they are subject to some limitations.[81] Patients in whom grafts were placed may have not been eligible for a fistula, as fistulas are generally not placed in patients with a shorter life expectancy or significant heart failure, or they may have needed a more urgent start on dialysis and therefore may be at greater risk for complications.[81-83] Finally, most of these studies are not analyzed according to the intention-to-treat principle, that is not according to the intended access, but rather the created access.[84]

Methodological Challenges

There are limited studies which detail the costs associated with attaining and maintaining patency among fistulas and grafts.[85-87] An earlier study by Lee et al (2002), found that maintenance costs, which ranged from CAN$600 to $5000 per year among prevalent dialysis patients, were lower among those with a fistula. However, this study did not consider the costs associated with attaining patency, costs which, given the higher rates of maturation failure among fistulas, are likely to be higher

as compared to grafts.[87] Manns et al., in their 2005 study, did consider both the costs of attaining and maintaining patency in a single centre prospective cost analysis among incident hemodialysis patients.[85] The mean cost of access care per patient-year at risk was lowest for patients in whom a fistula was attempted at $7989, then higher in catheter-only patients at $9180 and highest among patients with a graft $11,685 ($p = 0.01$, log-transformed ANOVA).[85] The authors concluded overall that "…results support clinical practice guidelines that recommend preferential placement of a native fistula" (p. 201) based on their primary analysis which was unadjusted for comorbidity and compared mean cost per patient-year at risk. However, in secondary analyses, comparing patients with Charlson comorbidity scores <5 with those ≥5, the mean access cost (unadjusted for follow-up time) was $11,571 versus $7109, respectively, in patients in whom a graft was attempted ($p = 0.14$). The relatively large magnitude of the difference in cost, albeit not statistically significant, suggests that co-morbidities may be salient to consider in such comparisons of cost by access type.

Further, Leermakers et al. (2013), used a decision tree and markov modelling to compare the cost effectiveness of fistulas and grafts.[86] Data for their clinical outcomes on a retrospective chart review of 230 fistulas and 92 grafts. Overall they concluded that fistulas were more cost-effective than grafts, however, in sensitivity analyses they found if the base-case fistula early maturation failure rate of 19% adjusted to 30%, as has been observed in other samples,[88,89] the outcomes would be similar for both types of AV-access. The authors acknowledged that maturation failure was a challenge and that their maturation failure rate was lower than that reported in other studies.[86] Drew et al (2015) constructed a decision analytic model from multiple data sources and found that while a fistula first approach seems associated with better survival and lower annual per patient costs overall, in certain subgroups of patients, particularly those over the age of 60 years, women, or with diabetes, the differences in survival and cost become very small.[77] Taken together the cost studies described above

demonstrate that significant resources, including diagnostic and interventional radiology and surgical revisions are required to facilitate and maintain AV-access patency.

In the cost study conducted as part of this thesis, the costs associated with both attaining and maintaining patency for fistulas and grafts were captured. However, unlike previous studies which generally conducted an undifferentiated comparison of fistula and graft cost comparison, the risk of maturation failure was also considered.[88,89] This approach may inform a more nuanced approach to arteriovenous access selection, which considers patient-specific factors.

Issue #3: Need for a Hemodialysis Catheter Care Protocol that Minimizes Infection Risk and Cost while Permitting Showering

Clinical Problem

Standard catheter care has three main components performed by hemodialysis personnel a minimum once weekly: 1) cleansing of the catheter entry site with an antiseptic cleansing solution such as chlorhexidine or poviodone-iodine solution,[33,37,41-44] 2) placement and changing of a dressing, either occlusive or transparent dressing, at the catheter entry site, typically once weekly or if it becomes 'damp, loosened, or visibly soiled'[33,36,37,45,46] and 3) locking the catheter lumens with a solution that minimizes the risk of clot formation and the risk of infection from intraluminal sources.[47-58] Additionally, some centres have hemodialysis personnel apply an antimicrobial ointment at each dressing change such as Mupirocin, Medihoney, and Polysporin Triple ointment.[59-64] It is also recommended that patients are educated to preserve the integrity and dryness of their catheter dressings,[33,36,37,46] particularly with respect to personal hygiene practices, where submerged baths and showering are typically discouraged.[65]

Catheter care varies considerably across dialysis programs in Canada, particularly with respect to personal hygiene recommendations with 75% of centres recommending patients to clean themselves

by bathing (non-submerged) or sponge bath and 38% recommending showering (categories non-mutually exclusive).[66,67] Similarly, when the patients themselves were asked, 77% indicated that they shower and 71%`reported that the recommendation not to shower bothered or inconvenienced them moderately to extremely, despite widely not adhering to it, findings which are consistent with reports from nurses that many patients present with wet and non-intact dressings from showering.[68] Indeed, in a previous study of hemodialysis patients, the level of dissatisfaction was markedly higher for patients with catheters, as compared to those with fistulas and grafts.[69] To address the disconnect between catheter care protocol recommendations and the patient's desire to shower for hygiene and quality of life issues, several "shower techniques" have been developed though not yet formally evaluated.[68,70,71] There is a clear need for a standardized and evaluated shower technique.

Methodological Challenges

We determined the feasibility of conducting a large randomized controlled trial comparing the rate of catheter-related bacteremia in adult satellite hemodialysis patients using a novel standardized shower technique, called *Hemodialysis Infection Prevention Protocol Ontario- Shower Technique*, versus standard catheter care over 6 months in a pilot study.[72] We secondarily compared the rate and proportions of catheter related bacteremia, entry site and tunnel infections, and vascular access−related satisfaction between the groups receiving the shower technique protocol and standard catheter care.

The shower technique protocol itself needed to be developed in advance of the pilot study. Several different centres participated in the study, each with their own catheter care protocols, which as per above, represented the considerable variation in practice across Canada. The nephrologist and nurse leaders of the participating centers met and the standard catheter care protocols were compared. Those components which were key to standardize, including the number of dressing changes and cleansing agent were agreed upon. The use of prophylactic use of triple antibiotic ointment, however, was

optional at the program level as it was thought this might be important to compare across programs in the full trial. Additionally, the 'shower techniques' of London Health Sciences and Credit Valley Hospital were compared and components from each, as well as the Toronto General Hospital catheter care protocol, were used in the final shower technique protocol. Supporting educational tools in lay language for training patients were also developed, including an educational pamphlet, video, and demonstration mannequin. There was input from a panel of nephrologists, vascular access and hemodialysis patient education experts, and hemodialysis patients. Following training, including successful demonstration of the shower technique protocol, the study participants were given the necessary supplies, as well as the educational pamphlet for reference.

Prior to conducting the pilot study, tests of catheter entry site healing tests also needed to be developed and piloted. It was important that prior to randomization to the study intervention or control, the catheter entry site be sufficiently healed to minimize any potential risks of extraluminal organism entry associated with the additional dressing changes conducted as part of the shower technique protocol. A panel of vascular access experts determined that the catheter entry site healing tests should capture three indicators: the stability of the catheter ingrowth, appearance of the catheter entry site, and integrity of the seal. The stability of the catheter was the most objectively measurable, as a stable catheter should have little to no movement as the patient breathes. The assessor need only measure the distance from the hub of the catheter to the entry site before and after the patient took a deep breath. The catheter entry site appearance, while less objective, is routinely assessed by hemodialysis nurses as part of clinical care. The presence of redness, discharge, or swelling, signs of irritation or infection, indicate healing is not complete. The study coordinator only had to document the nurses' routine assessment. The final indicator was the most challenging to assess, the integrity of the skin seal around the catheter. This was assessed by the hemodialysis nurse or nephrologist. In the pilot of these tests, the

latter two indicators were also independently assessed by two of the vascular access experts who developed the tests, who agreed with the hemodialysis nurses assessment in every case. While these tests were not formerly validated, they do offer an initial step in standardizing how catheter entry site healing is assessed.

Issue #4: Lack of Positive Randomized Clinical Trials to Inform Clinical Practice in Hemodialysis

Clinical Problem

Over last 40 years there has been significant resources and efforts in research in hemodialysis, however, survival and quality of life of patients on hemodialysis remains low.[90] Well-designed randomized clinical trials are required to address many pressing clinical problems in hemodialysis,[90] particularly with respect to how to manage vascular access.[91] However, as is reflected in the above delineation of clinical issues, there remains few positive randomized trials in this population.[9091]

Methodological Challenges

Pilot studies are important to improving the design of RCTs as they can help standardize and ultimately optimize trials processes, including screening, recruitment, coordination, intervention delivery, and inform power calculations.[91] However, in order to inform larger trials, pilot studies themselves must be well designed and reported.[92] The Consolidated Standards of Reporting Trials (CONSORT) extension for reporting randomized pilot and feasibility trials was published in 2016 can be used to inform pilot study design and implementation.[93] However, as these standards were only recently available, it is likely that significant gaps and inconsistencies in the reporting of pilot studies in hemodialysis exist. As part of this doctoral thesis, a methodological review was conducted to identify these gaps to inform initiatives to improve pilot trial design, implementation, and reporting.

The Objectives and Scope of the Thesis

This thesis includes four studies, three published and one unpublished (in press), which each address the clinical issues and methodological challenges outlined above.

The first study, published in *Kidney International Reports* in 2019 entitled "Nutritional mobile applications for CKD patients: systematic review" examined the characteristics, feasibility, and effectiveness in changing user behavior, as well as user satisfaction, of CKD dietary mobile app interventions.

The second study, published in *Kidney360* in 2020, entitled "The impact of risk of maturation failure and access type on arteriovenous access related costs among hemodialysis patients", describes the analyses of the impact of AV-access type and FTM risk on the total costs of attaining and maintaining patency of AV-access over one, three, and five years post creation, among incident hemodialysis patients.

The third study, published in *Kidney International Reports* in 2017, entitled "Hemodialysis Infection Prevention Protocols Ontario-Shower Technique (HIPPO-ST): A pilot randomized trial" describes the development of the Hemodialysis Infection Prevention Protocols Ontario—Shower Technique to permit hemodialysis patients with central venous catheters (catheters) to shower without additional infection risk. The pilot study aimed to determine the feasibility of conducting a parallel randomized controlled trial to evaluate the impact of shower technique on catheter-related bacteremia in adult hemodialysis patients.

The fourth study, published in *Pilot and Feasibility Studies* in 2019, entitled "Reporting quality of pilot clinical trials in CKD patients on hemodialysis: a methodological survey" evaluates the completeness of reporting in pilot randomized controlled trials in CKD patients on hemodialysis and explores factors associated with better completion of reporting.

The final chapter summarizes the key findings, limitations, and implications of the above studies. This thesis work collectively addresses important clinical problems in the management of patients on hemodialysis with a diverse range of appropriate methodological approaches.

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CHAPTER TWO
NUTRITIONAL MOBILE APPLICATIONS FOR CKD PATIENTS: SYSTEMATIC REVIEW

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ABSTRACT

Introduction

Mobile health applications offer the potential to help people living with chronic kidney disease (CKD) manage diet-related challenges. This systematic review examined CKD dietary mobile app interventions; specifically, app characteristics, feasibility, and effectiveness in changing user behavior, as well as user satisfaction.

Methods

This review was reported in accordance with PRISMA guidelines. We searched scholarly databases, as well as the gray literature, for all randomized controlled trials, observational studies, needs assessments, and pilot testing/studies/trials focused on the development or evaluation of CKD dietary mobile app interventions. The characteristics, user satisfaction with, usability/feasibility, and effectiveness in changing dietary behavior of the mobile application were summarized using descriptive statistics and in a narrative manner.

Results

Thirteen full-text studies were included, of which 11 were single center, with a mean sample size of 23. Of the 7 studies that measured usability/feasibility, all found at least some aspects of the application feasible/useful. Of the 5 studies that reported an evaluation of changes in behavior/diet related to self-management, all reported some positive change.

Conclusion

According to current studies, nutritional apps show promise in CKD self-management.

Keywords: application, chronic kidney disease, mobile app, nutritional, patient-centered care, systematic review

BACKGROUND

CKD prevalence is on the rise and is a complex condition to manage for patients, families, and providers.[1]Dietary monitoring and modification are vital components of treatment for individuals living with CKD to prevent disease progression and to manage symptoms. Generally, nutritional management of CKD requires balancing the intake of energy, protein, sodium, potassium, phosphorus, and fluid with biochemical markers and weight changes.[2] Because of complex nutrition guidelines and consideration of coexisting conditions, dietary monitoring and modification can be significant and present daily challenges for people living with CKD.

It has been suggested in the literature that mobile health applications (apps) are promising vehicles to deliver health information and interventions to people living with chronic health conditions. By 2020, it is estimated that 6.1 billion people around the world will own a mobile phone,3 and as of 2017, 79,298 health and fitness apps were available on iTunes.4 Apps are accessible, convenient, and customizable.3, 5 Other reported advantages of mobile health apps include affordability, ability to reach traditionally hard-to-reach groups and overcome geographical barriers,3 improved treatment compliance,6 increased access to care,3increased accuracy of data collection due to built-in features such as global positioning systems and image recognition,7 and potential to reduce barriers to seeking health care, such as stigma and discomfort.3

Mobile apps offer the particular potential to assist individuals living with CKD address unique challenges related to their individual diet. For example, to monitor and adhere to the nutritional recommendations provided by a health care professional, it is often advised to keep a food diary. This tool has its challenges; patients may forget to record a meal, have difficulty estimating serving sizes, or lack the time or ability to keep a diary. A study by Franco *et al.*7 identified 9 existing apps that provide a food diary feature to record food intake. They report that patients prefer digital recording of food

intake over using pen and paper, as it saves time and resources.7 The authors also discuss the potential of technology to simplify food and portion selection processes. Some existing apps have features such as text search and a barcode scanner for data input, as well as a camera feature for taking pictures of meals. This could be useful for recognizing food items and estimating portion sizes for more accurate data collection and monitoring.7 Although a mobile app would not replace the role of the dietician in helping patients with CKD manage their nutritional needs, the app offers potential to help health care providers overcome some of the potential barriers to consistent and optimal nutritional management, such as cost of dietician appointments, if not covered by insurance plans, and availability of dieticians and patients for frequent follow-up. Given the suggested promise of mobile applications in addressing some of these issues in nutritional management, this systematic review aims to examine mobile app types, characteristics, feasibility, and effectiveness in changing behavior, as well as user satisfaction with dietary mobile apps, specifically in both adult and pediatric CKD populations.

Go to:

METHODS

This systematic review was reported in accordance with PRISMA guidelines (see Supplementary MaterialPRISMA Checklist), and the protocol, although prespecified, was not published in advance of this review.8

Search Strategy

Scholarly Literature

To retrieve scholarly articles examining mobile app types, characteristics, feasibility, and effectiveness in changing behavior, as well as user satisfaction with dietary mobile apps, in both adult and pediatric populations living with CKD, the scholarly databases PubMed, Embase, and Google Scholar were searched in July 2017 using search terms related to nutrition [i.e., dietary OR nutritional], mobile

application [i.e., mobile applications, mobile apps, OR smartphone apps], AND Chronic Kidney Disease [i.e., Renal failure–chronic, Chronic renal insufficiency, Chronic kidney failure, Chronic renal failure, OR Chronic Kidney Disease].

Gray Literature

The gray literature was searched by entering keywords in the search bar on multiple general and targeted Web sites. The first 100 records retrieved were reviewed. The search terms for the gray literature included the following: "kidney disease" AND eHealth, mobile health, health information technology, mobile health apps, telemedicine, mHealth, mobile health apps for patients, apps, applications, OR mobile health technology. The Web sites searched included Google, iMedical Apps (using the Web site search bar to enter the search term "kidney" for information on kidney apps currently available), Canadian Medical Association, National Kidney Foundation, Nephcure Kidney International, MyHealthApps, Athena Health, and Mobi Health News.

Types of Participants

Patients of any age diagnosed with any stage of CKD who are able to use the mobile application (patients with end-stage renal disease on any form of renal replacement therapy were included).

Types of Interventions

Mobile application designed to assist individuals living with CKD manage their nutritional intake.

Types of Records

This systematic review includes randomized control trials, observational studies, and pilot testing/studies/trials focused on the development or evaluation of all types of mobile applications designed to assist individuals living with CKD manage their nutritional intake.

Article Selection

Title and abstract screening was performed in duplicate (MD, AJ, KP, SR, SS, BS), and disagreements were resolved by a third reviewer (SK) using predefined inclusion and exclusion criteria.

Criteria for Considering Studies for This Review

Records were included if (i) the publication date was available; (ii) available in English; (iii) available free of charge; (iv) focused on apps used by patients, not medical professionals; (v) focused on a randomized controlled trial, observational study, or pilot testing/studies/trials, or needs assessment/design of a nutritional application in patients with CKD; and (vi) not a review/systematic review of other studies.

Types of Outcome Measures

The types of outcomes collected included the following:

(i) Dietary behavior: Immediate changes in dietary behavior, nutritional markers (e.g., sodium, glucose, and cholesterol levels), and fluid intake of the patient with CKD using the app

(ii) Mobile application feasibility: Feasibility of application to use for patients and sustainability of use

(iii) User satisfaction: Satisfaction with the content/functionality of the application, suggestions/feedback for improvements

Data Extraction

Data extraction was performed in duplicate (MD, AJ, KP, SR, SS, BS), with all data entries reviewed by a third reviewer (JM), and disagreements resolved through consultation with the study lead (SDK). A standardized data extraction spreadsheet was created and piloted by the review team. After piloting and further revision of the data extraction sheet, the following items were extracted: author; title; year of publication; journal in which the study was published; reviewer who extracted data; link from which the record was retrieved; intervention under study; sample size; number of sites; start date of the study;

primary completion date of the study; study type; study design; study arms paper; primary objective/goals; secondary objectives/goals; whether the app provides dietary recommendations regarding carbohydrates, protein, fat, vitamins (A, D, E, K, B-complex), or minerals; whether the app provides a calorie-counting function; whether the app provides personalized Dietary Reference Intake (DRI) values for users based on age; whether the app allows users to track their food intake (e.g., food diary); whether the app contains a section for healthy recipes; whether users found the app user-friendly; whether the app has been evaluated; how long the app has been in use; use of a data-monitoring committee; study sponsor; and clinical trial registry number. Although risk of bias assessment was planned, given the variable and largely exploratory nature of the study designs, no risk of bias assessment was conducted.

Analysis

The level of agreement between reviewers was estimated using the kappa statistic. The characteristics, user satisfaction with, usability/feasibility, and effectiveness in changing dietary behavior of the mobile application were summarized using descriptive statistics and in a narrative manner.

Go to:

RESULTS

Of the 284 records retrieved, 13 full-text studies were admissible for the purposes of this evaluation based on the inclusion criteria (see Figure 1 for PRISMA diagram).

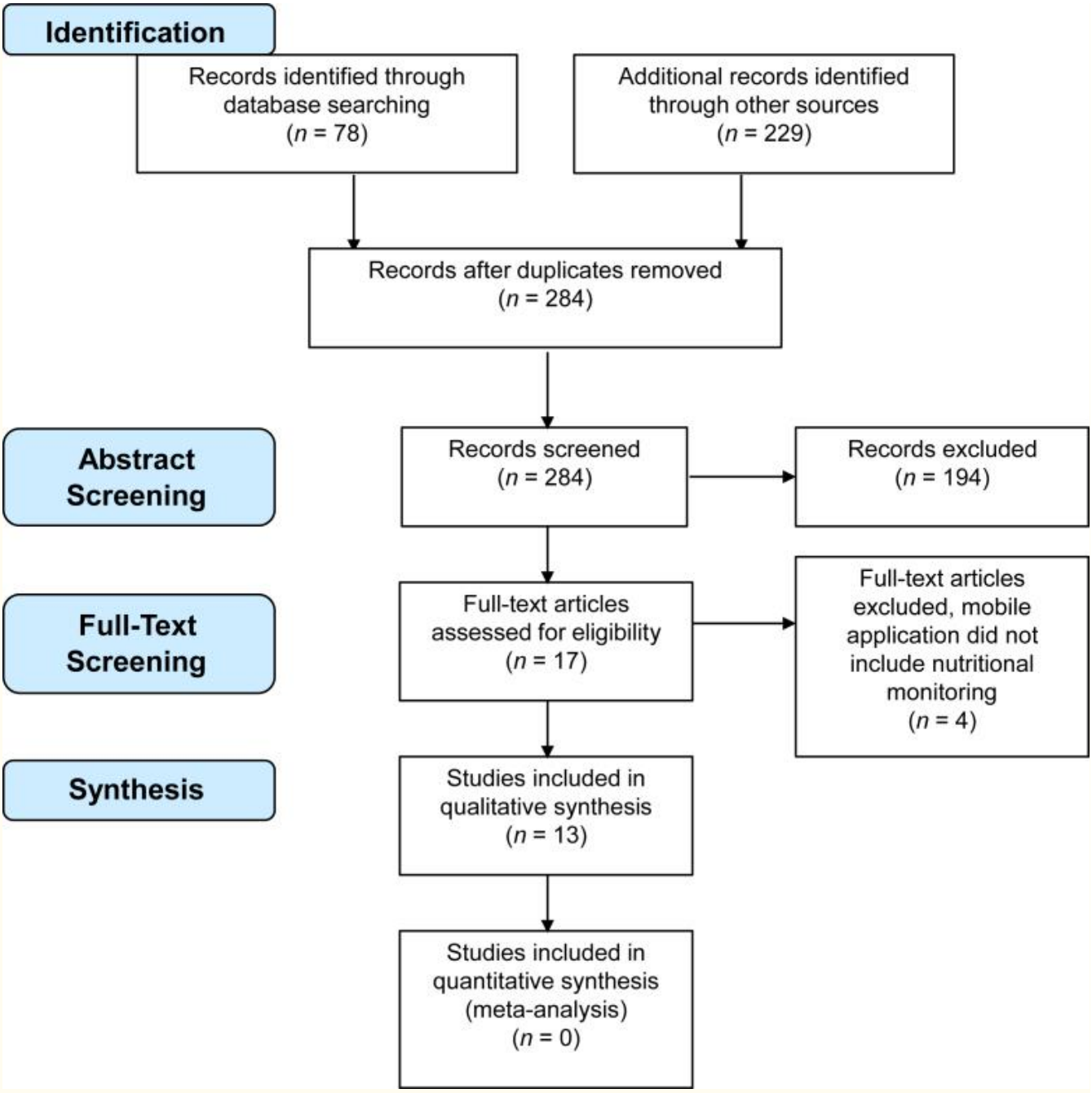

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Figure 1

PRISMA 2009 flow diagram.

Characteristics of Included Studies

Eleven of the 13 included studies were single center. The mean sample size was 22.7 and ranged from 1 to 48 participants. Two of the 13 studies were industry funded, and 2 reported having a data-monitoring committee. Four of the included studies were needs assessment/design studies, 2 were case studies, 5 were nonrandomized pilot studies, and 2 were randomized pilot studies.

Summary of Key Features of Mobile Applications

Reported features of the 9 studies testing a developed app varied widely: 8 allowed patients to track their food intake like a food diary, 7 had a calorie-counting function, 7 provided dietary recommendations regarding minerals, 6 provided dietary recommendations regarding protein, and 6 provided personalized DRIs. No apps contained a feature that recommended CKD-friendly recipes (see Table 1).

Studies Focused on the Design of a Mobile Application for Patients With CKD to Monitor Their Own Dietary Intake

Of the 13 full-text articles included, 4 were design studies (i.e., did not evaluate an already developed app) (see Table 2).

Huby *et al.*9 developed an online resource to provide reliable information and support to parents of children with CKD stages 3–5. Interviews were conducted for the purposed online application, and confirmed that such an application is needed and would be useful, especially if easily accessible (i.e., can be accessed on different platforms, regardless of device and location).

The objective of the study by Lin *et al.*10 was to understand the needs of the CKD population they were working with to inform the creation of a personal mobile health diary using a simulated prototype. The primary goal of the mobile health diary was to improve communication channels between the

patients and members of the health care team. Although all of the participants found the prototype easy to learn, they felt that if errors or system malfunctions arose, this might reduce the utility of the app. Nightingale *et al.*11 conducted a study in the pediatric population and facilitated interactive child-led interviews to gather user input to inform the development of a child-focused, efficient, cost-effective digital application that provides safe, supportive, and timely care management to children with CKD. According to their findings, gaps exist with current online information and support, and there is a need for reliable sources of CKD information tailored to engage and empower pediatric patients. Participant suggestions for an app included diverse colors and interactive games, as well as a decision-making tool for food/meal selection tailored to children.

Welch *et al.*12 described the computer, informational, numerical, and visual literacy considerations relevant to the development of a Dietary Intake Monitoring Application to facilitate self-management and improve clinical outcomes regardless of literacy levels. Forty participants of an urban inner-city hemodialysis facility were recruited to take part in this iterative participatory design approach. Participants were approached during scheduled dialysis appointments to discuss computer literacy for using an interactive app. In particular, items discussed included the ability to read and interpret informational, graphical, and numerical data within the app, and visual screenshots of these proposed components were shared with participants. The study found that having words associated with food icons helped patients confirm dietary selections for the day. They also found that the use of more than 1 application/device (such as a scanner) would complicate dietary self-management. Overall, participants indicated that the Dietary Intake Monitoring Application could be helpful and usable.

Studies Focused on the Evaluation of a Mobile Application for Patients With CKD to Monitor Their Own Dietary Intake

Of the 9 studies noted that evaluated the mobile app in some way, 7 measured usability/feasibility, and all found some aspect of the applications feasible/useful. Among the 5 studies that measured changes in dietary behavior, all reported some positive change, although different measures were used (see Table 3).

Case Studies

Examples of the impact of nutritional-based apps on CKD patient care and outcomes are reviewed. Sevick *et al.*13 described a case study of one patient's self-monitoring using a Personal Dietary Assistant programmed with a software called BalanceLog. This was paired with dietary counseling based on social cognitive theory over the 16 weeks of intervention. This hemodialysis patient saw reductions in interdialytic weight gain, as well as intake of sodium, phosphorus, and potassium.

In an earlier study, Sevick *et al.*14 conducted a case study in 5 hemodialysis patients to determine whether BalanceWise, an individualized dietary adherence enhancement program, could improve patients' adherence to CKD diet and reduce information burden associated with adhering to the hemodialysis dietary regimen. For a 4-month period, 5 patients received dietary counseling sessions based on social cognitive theory, as well as training on using Personal Dietary Assistants with BalanceWise. Serum albumin levels, phosphorus, and potassium levels and average monthly interdialytic weight gain were successfully monitored.

Nonrandomized Pilot Studies

Connelly *et al.*15 conducted a pilot study of 18 hemodialysis patients to assess the usability of a Dietary Intake Monitoring Application to assist with self-management of prescribed dietary regimens. Interdialytic weight gain was recorded 3 times per week and at study completion, 2 face-to-face

questionnaires were administered to assess usability. All participants used a Dietary Intake Monitoring Application and agreed that the food icons were helpful in monitoring their dietary intake; however, 1 participant noted that feedback from the app was not easy to understand.

The pilot study by Cueto-Manzano *et al.*16 aimed to determine whether mobile phone text messages would improve lifestyle, adherence, and clinical outcomes in 23 patients with CKD. When evaluated, users rated the usefulness of the text messaging application as 9.6 on a scale of 0 to 10.

Dowell and Welch17 conducted a pilot study in 4 hemodialysis patients to record intake patterns of fluid, sodium, potassium, phosphorus, protein, and calories over a 3-month period using a Palm Pilot Zire 31 Personal Dietary Assistant, programmed with an application designed by Diet Mate Pro. Patients in this pilot study were compliant with their recommended dietary regimen. The fluid, sodium, potassium, and phosphorus intakes of these patients fell within the recommended intakes, whereas 3 of the 4 patients fell below the suggested intake for calories and protein.

Welch *et al.*18 conducted a pilot study among 4 patients with CKD to test the feasibility of a Palm Personal Dietary Assistant programmed with software DietMate Pro to electronically self-monitor fluid and dietary intake (calories, sodium, phosphorus, potassium, and protein) over 3 months. Although participants found the Personal Dietary Assistant to be helpful in creating shopping lists and developing weekly menus, they had navigation difficulties 33% of the time, especially when trying to find specific food items. Participants also found the font to be too small, and had difficulties in using the stylus pen of the Palm Personal Dietary Assistant. Compliance for capturing each meal after eating ranged from 22% to 31%.

Welch *et al.*19 conducted a pilot study of 44 hemodialysis patients to examine the feasibility of using the Dietary Intake Monitoring Application to help design a randomized trial with sufficient power to assess changes in intradialytic weight gain, changes in self-efficacy, perceived benefits, and perceived

control. Twenty-four participants were assigned to the Dietary Intake Monitoring Application and 20 were assigned to a Daily Activity Monitoring Application (i.e., does not monitor dietary intake). Data collection in both the control and intervention groups occurred during patient visits at 2 urban outpatient dialysis units at baseline, 6 weeks, and 8 weeks after study completion (14 weeks after baseline). No changes in interdialytic weight gain were seen in either group, but users of the Dietary Intake Monitoring Application did see a decrease in calories, sodium intake, and protein. At the end of the self-monitoring period, patients using Dietary Intake Monitoring Application were found to have higher perceived control than participants assigned to Daily Activity Monitoring Application. On a scale of 1 to 5, the mean acceptability score in the Dietary Intake Monitoring Application group was 3.93.

Randomized Pilot Studies

Koprucki *et al.*20 conducted a randomized controlled trial of 26 peritoneal dialysis patients over 4 months to determine if adhering to an individualized Personal Dietary Assistant dietary program with BalanceLog software would reduce sodium intake. Participants in both groups received computer-based, dietary education. Participants in the intervention arm also received counseling and feedback based on the daily dietary targets from the Personal Dietary Assistant dietary program. Outcomes were measured at baseline and at 4 months. Those using the Personal Dietary Assistant were able to reduce their sodium intake by 187 mg, whereas patients assigned to the control group saw an increase in sodium intake of 44 mg. Most (86.7%) participants in the intervention group said they would use the Personal Dietary Assistant to self-monitor their diets.

Stark *et al.*21 conducted 2 randomized trials of 48 patients, 22 hemodialysis patients, and 30 peritoneal dialysis patients to determine whether a Personal Dietary Assistant, PalmOne Tungsten/e2 Personal Dietary Assistant, programmed with BalanceLog software by MicroLife could moderate sodium intake

in hemodialysis and peritoneal dialysis patients over a 16-week period. On average, hemodialysis patients entered 244.9 meals, whereas peritoneal dialysis patients inputted an average of 212.1 meals during the intervention period. Study findings suggest that the intervention is feasible and may be useful for assisting dialysis patients in adhering to a complex dietary regimen.

DISCUSSION

Given the complexity of managing diet in CKD, there is a need for interventions that can not only help patients navigate daily challenges but that could also be integrated into clinical practice to support the work of dieticians and other health care providers. This systematic review aimed to examine the characteristics, user satisfaction with, feasibility of, and effectiveness in changing dietary behavior of mobile app interventions in patients with CKD. Eleven of the 13 included studies were single center and all were relatively small, with a mean sample size of approximately 23. The most common mobile application feature was allowing patients to track their food intake like a food diary. Interventions varied from more general text messaging applications to specialized applications, such as Dietary Intake Monitoring Applications and Personal Dietary Applications. In the 7 studies that measured app usability/feasibility, all found at least some aspects of the application feasible/useful; however, a few studies noted the difficulty some end-users experienced with using their assigned application/device. Noncompliance was a commonly reported issue. Of the 5 studies that evaluated changes in behavior/diet related to self-management, all reported some positive change, particularly with respect to sodium intake.

Our findings indicate that a mobile application focused on engaging patients and encouraging healthy self-management of CKD may be helpful in improving adherence to dietary restrictions pertaining to sodium, potassium, phosphorus, protein, calories, and fluid. Our findings are consistent with those of Campbell and Porter,[2(p750)] who found in their systematic review of 5 studies that there is “potential for

clinical benefits of dietary mobile app interventions in a CKD population." In addition to helping individuals living with CKD, mobile apps also can serve as a knowledge translation tool to provide friends and family members with trustworthy information about CKD, particularly with respect to pediatric populations, as identified by Nightingale *et al.*11

This systematic review has several limitations that are important to acknowledge. The search was restricted to English-language studies and some relevant studies therefore may not have been found. Among included studies, there was a lack of randomized controlled trials. Most included studies were pilot studies, which are largely exploratory in nature. The time frame of included studies was often short (less than 6 months). Some of the apps used are not currently available (e.g., were used on Palm Pilots), so although proof of concept was demonstrated, those apps evaluated in the study are out of date. Because of the wide range of study designs and outcome measures, a meta-analysis could not be conducted. Therefore, definitive conclusion of the efficacy of mobile apps for CKD dietary management cannot be drawn. Finally, although reporting quality of included pilot trials was assessed, the quality of the study conduct itself could not be evaluated due to a lack of validated measures for this purpose.

CONCLUSION

This systematic review found that development and testing of apps was often informed by not only behavioral/dietary outcomes, but also patient-reported usability/feasibility. Future research is required to study apps in pediatric and adolescent populations, how to address different types of learning styles to effectively use apps, and how (and to what extent) apps can complement the work of health care provider teams to optimize dietary adherence. The results of the included pilot studies provide a foundation for future research, which should use more rigorous study design and study larger and more diverse samples.

DISCLOSURE

All the authors declared no competing interests.

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TABLE, FIGURES, & SUPPLEMENTARY MATERIALS

Table 1. Features of nutritional mobile applications for people living with chronic kidney disease (*n* = 9)

Features	*n*
Recommendations on macronutrients:	
Carbohydrates	0
Protein	7
Fat	0
Recommendations on micronutrients:	
Vitamins (e.g., A, D, E, K, B-complex)	0
Minerals (e.g., sodium, potassium, phosphorus, copper, zinc, iodine, selenium, fluoride)	8
Calorie-counting function	8
Personalized Dietary Reference Intake	7
Allows users to track their food intake (e.g., food diary)	9
Provides examples of healthy recipes	0

Table 2. Studies focused on the design of a mobile application for patients with chronic kidney disease to monitor their own dietary intake

Author (yr) sample size	Primary goal of study	Main findings including desired features
Huby *et al.*9(2017) *n* = 26	Develop an online parent information and support internet application for parents of children with chronic kidney disease (CKD) stages 3–5 that is a trustworthy source of information; also provide support to children living with CKD	Participants indicated that an application would be useful if it can be accessed across many platforms regardless of where users were and on any device they choose to use.
Lin *et al.*10(2014) *n* = 20	Develop a mobile application to increase communication channels between patient and case management health care teams	All participants found the system prototype (paper-based) potentially easy to understand; however, participants were concerned about errors arising from system malfunctions.
Nightingale *et al.*11(2017) *n* = 37	To determine the desirable components for a child-focused and interactive	Participants suggested an app that made use of colors and includes interactive games and a decision-

	child-led application to support home-based CKD management	making tool for food/meal selection, which may be more accessible and usable for children and young people, than an online resource.
Welch *et al.*12(2010) *n* = 40	Develop a Dietary Intake Monitoring Application for adults receiving hemodialysis to self-manage dietary intake regardless of health literacy levels	Participants indicated that a word associated with food icons helped to confirm dietary selections for the day. They also suggested that the use of more than 1 application/device, such as a scanner, would complicate the use of dietary self-management. Overall, participants indicated that the Dietary Intake Monitoring Application could be helpful and usable.

Open in a separate window

Table 3. Studies focused on the evaluation of a mobile application for patients with CKD to monitor their own dietary intake

Author (yr) sample size	Description of mobile application	Goal of the application	Feasibility/user satisfaction	Dietary/behavioral change
Case study				
Sevick *et al.*14(2005) *n* = 5 Adult hemodialysis (HD) patients	A behavioral intervention based on social cognitive theory to enhance self-efficacy, paired with a dietary self-monitoring PDA with BalanceWise software	To improve patients' adherence to chronic kidney disease (CKD) diet and reduce information burden associated with adhering to the HD dietary regimen	Not reported	• 4/5 study participants had an increase in serum albumin level. • 4/5 participants experienced a small increase in serum phosphorus level. • Mixed results with regard to serum potassium and average monthly interdialytic weight gain

Sevick *et al.*13(2008) *n* = 1 Adult HD patient	A PDA programmed with BalanceLog software for self-monitoring paired with dietary counseling based on social cognitive theory	To help patients evaluate content of foods, track their dietary intake, and evaluate the percentage of dietary targets achieved by meal; ultimately to reduce interdialytic weight gain and increase adherence to a complex kidney diet	• The participant was highly compliant. • The intervention did not place a high burden on the participant.	• Reduction in sodium intake • Reduction in interdialytic weight gain • Alleviation of hyperphosphatemia • Alleviation of hyperkalemia
Pilot study (nonrandomized)				

Connelly *et al.*15(2012) *n* = 18 Adult HD patients	Dietary Intake Monitoring Application is a mobile application that uses touch-screen, visual interfaces, barcode scanning, and voice recording.	To help patients self-manage dietary intake regardless of health literacy levels	• 14/18 users reported ease of finding food using icon interface. • 6/18 used voice recordings. • 15/18 used disease-specific interface components. • 18/18 reported that feedback icons were	Not reported

			useful in monitoring dietary intake. • • 10/18 reported difficulty finding a food the first time using the scanning feature. • • 15/18 reported it easier to find the same item the next time.	
Cueto-Manzano *et al.*16(2015) *n* = 23	Mobile phone text messages generated by a	To improve lifestyle, treatment	• • Participants rated the	Not reported

CKD patients older than 14	multidisciplinary group of experts in nephrology, internal medicine, family medicine, general medicine, and nutrition about kidney disease risk factors, medical alert information, healthy diet and lifestyle, as well as recommendations to improve adherence to treatment and attendance of	adherence, and clinical outcomes in patients with kidney disease	usefulness of the text messages (on a 0–10 scale) as 9.6 (SD 0.7). • • Medication reminders as 9.8 (SD 0.5) • • Appointment reminders as 9.8 (SD 0.6) • • Perceived the tool as helpful • • Considered	

	follow-up appointments		that it could be implemented widely	
Dowell *et al.*17(2006) *n* = 4 Adult HD patients	PDA, Palm Pilot Zire 31, with application designed by Diet Mate Pro in which participant inputted dietary and fluid intake	To test the feasibility of the intervention to electronically self-monitor dietary (calories, sodium, phosphorus, potassium, and protein) and fluid intake over 3 months	Not reported	• Participants were fairly adherent to their dietary intake of measured micronutrients and fluid. • Reduced intake of protein and calories • Dietary and fluid intake varied considerably over 3 months.

Welch *et al.*18(2007) *n* = 4 Adult HD patients	Electronic self-monitoring diary, Palm PDAs (Zire 31) that were programmed with software designed to collect diet and fluid information (DietMate Pro)	To collect diet and fluid information	• Participants found the PDA to be helpful in making shopping lists and developing weekly menus. • A total of 33% had navigation difficulties, especially in trying to find specific food items. • Found the font to be too small	Not reported

			• Had difficulties in using the stylus pen part of the Palm hardware • Actual compliance for capturing each meal after eating ranged from 22% to 31%	
Welch *et al.*19(2013) *n* = 44 Adult HD patients	The Dietary Intake Monitoring Application based on mobile technology to	To assess changes in intra-dialytic weight gain and self-efficacy, perceived	• Patients using Dietary Intake Monitoring Application had higher	• No changes in interdialytic weight gain • Decrease in calories, sodium intake, and protein using

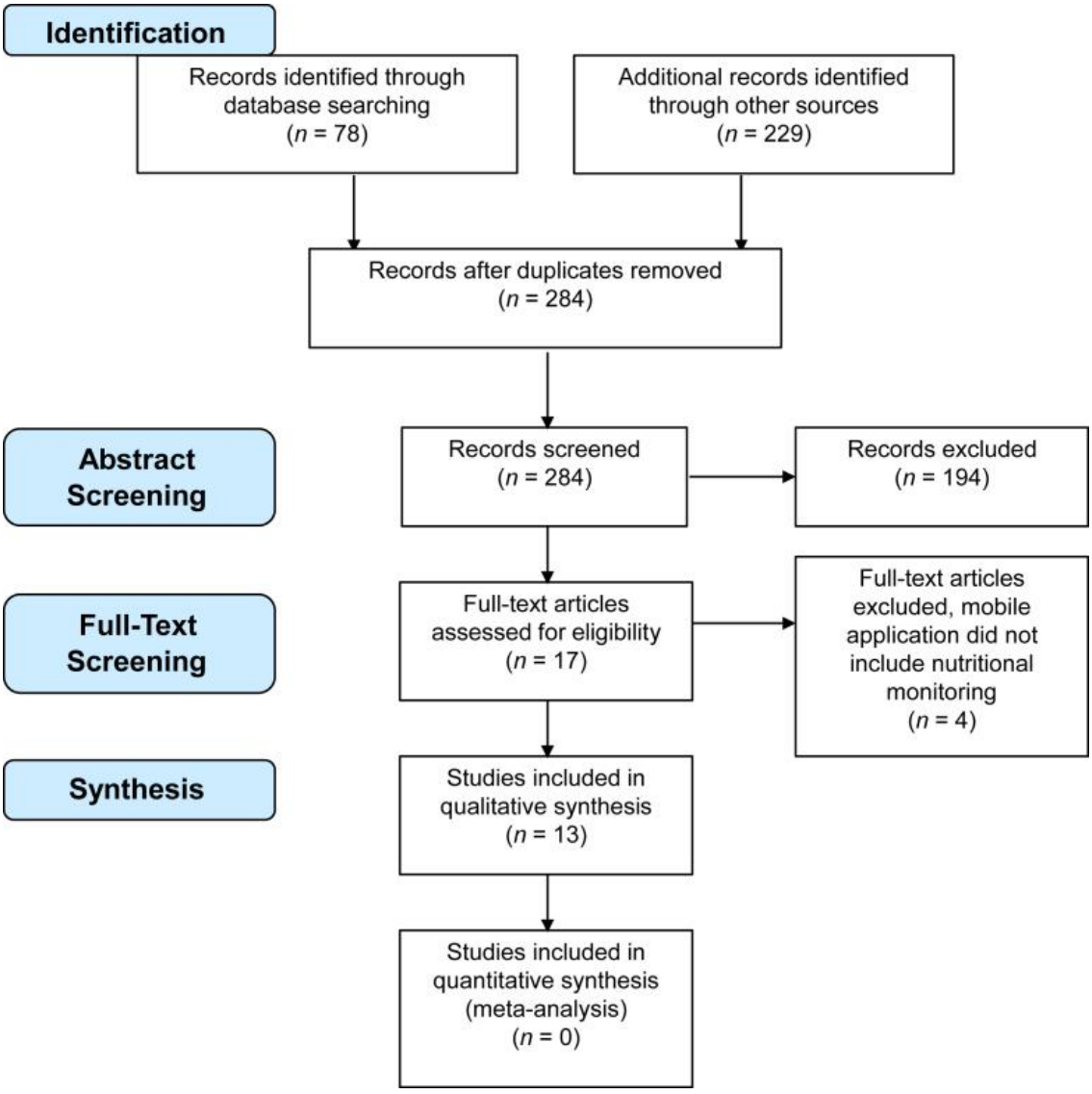
	facilitate self-monitoring for patients	benefits, and perceived control	perceived control than participants assigned to Daily Activity Monitoring Application . • On a scale of 1–5, the mean acceptability score in the Dietary Intake Monitoring Application group was 3.93.	Dietary Intake Monitoring Application
Pilot studies (randomized)				

Koprucki *et al.*20(2010) *n* = 26 PD patients	An individualized PDA with BalanceLog software which delivers counseling and feedback based on the daily dietary targets	To determine if adhering to an individualized PDA dietary program would reduce sodium intake	• A total of 86.7% of intervention participants said they would use the PDA with BalanceLog to self-monitor their diets.	• Reduction in sodium (187 mg in intervention vs. 44 mg in control)
Stark *et al.*21(2011) *n* = 48 HD and PD patients	PDA, PalmOne Tungsten/e2 PDAs programmed with BalanceLog software by MicroLife	To determine whether a PDA, PalmOne Tungsten/e2 PDAs programmed with BalanceLog	• On average, HD patients entered 244.9 meals. • PD patients averaged	Not reported

		software by MicroLife can moderate sodium intake in patients over a 16-week period	212.1 meals. • The intervention is feasible and may be useful for assisting dialysis patients in adhering to a complex dietary regimen.	

Note: CKD, chronic kidney disease; HD, hemodialysis; PD, peritoneal dialysis; PDA, Personal Dietary Assistant.

Figure 1. PRISMA 2009 flow diagram



Supplementary Material 1. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			

Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4-5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

CHAPTER THREE
THE IMPACT OF RISK OF MATURATION FAILURE AND ACCESS TYPE ON ARTERIOVENOUS ACCESS RELATED COSTS AMONG HEMODIALYSIS PATIENTS

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ABSTRACT

Background and objectives

Several studies report lower costs associated with attaining and maintaining patency for arteriovenous (AV) fistulas as compared to AV grafts among hemodialysis patients. However, these costs may vary according to the AV access's risk of failure to mature (FTM). To analyze the impact of AV access type and risk of FTM on the total costs of attaining and maintaining AV access patency over one, three, and five years post creation, among incident accesses.

Design, setting, participants, and measurements

All first AV-access creations (January 1, 2002 – January 1, 2018), revisions/resections, and interventions from a single academic institution were prospectively captured. The unit costs (2011 CAD) were estimated primarily through the provincial patient Ontario Case Costing Initiative database. The present value of total vascular access related costs from a third party payer perspective was calculated by multiplying specific unit costs by the number of AV access creations, revisions/resections and interventions from the date of creation to one, three, and five years post creation. The potential associations of AV access type and FTM risk stratum with AV access cost were examined using Loglinear models and generalized estimating equations.

Results

A total of 906 patients were included in the study, 696 fistulas and 210 grafts. The median present value of total costs to attain and maintain AV access over one, three, and five years was positively associated with the highest FTM risk stratum in all models. It was not associated with AV access type when the interaction between AV access type and FTM risk stratum was considered.

Conclusions

The costs of attaining and maintaining AV access were increased among patients with high/very high FTM risk. Risk of FTM, related interventions and costs should be considered when choosing vascular access type for an individual patient.

BACKGROUND

For adequate hemodialysis, a reliable vascular access is essential and remains the "Achille's Heel" of hemodialysis. The United States' national quality initiative to improve vascular access outcomes, originally called "Fistula First", was based on the perception that arteriovenous (AV) fistulas have superior patency, the fewest complications and are less costly compared with other vascular access types (1, 2). Indeed, central venous catheters (catheters) have been established as associated with the highest rates of complications, particularly infection (3-10), although they are often needed as a temporary measure, such as until an AV access (fistula or graft) can be created and used, or as a valid long-term option in select circumstances (11, 12). The validity of Fistula First has been recently been challenged in comparisons of outcomes of fistulas and grafts (12-16).

A systematic review of observational studies comparing clinical outcomes between fistulas and grafts found that the former is associated with high rates of maturation failure but longer-term patency, while the latter is more likely to mature and mature quickly, but with shorter patency (17). The review noted that the included studies are subject to significant risk of bias (17), particularly in the form of selection bias from several sources: 1) patients in whom grafts were placed may have not been eligible for a fistula, as fistulas are generally not created in patients with a shorter life expectancy or significant heart failure (18); 2) patients in whom grafts are placed may have needed a more urgent start on dialysis and therefore may be at greater risk for complications (19), and 3) most of these studies are not

analyzed according to the intention-to-treat principle, in other words, they are analyzed by the created access rather than the intended access (20).

There are limited studies which detail the costs associated with attaining and maintaining patency of fistulas and grafts (AV access) among incident and prevalent patients (12, 21-25). These studies demonstrate that significant resources, including diagnostic and interventional radiology and surgical revisions are required to facilitate and maintain AV access patency. In the current study, we build on the work of Manns et al., 2005, by capturing the costs associated with both attaining and maintaining patency for fistulas and grafts (21). However, unlike previous studies that generally conducted an undifferentiated comparison of fistula and graft cost comparison, we will also adjust for the risk of fistula maturation failure using the Failure to Mature (FTM) risk score (24, 25) and the interaction of the FTM risk score with access type. The FTM risk score has been previously validated and considers several factors in its computation of risk (i.e., age, peripheral vascular disease (PVD), coronary artery disease (CAD) and ethnicity). The goal of this study is to analyze the impact of AV-access type and FTM risk on the total costs of attaining and maintaining patency of AV access over one, three, and five years post creation, among incident hemodialysis patients.

The specific objectives of this study are to: 1) Compare the rates and proportions of AV access creations, revisions, removals, and other interventions among fistulas and grafts; 2) Describe the total AV access related costs from a third party payer perspective at one, three, and five years post creation among fistulas and grafts; and 3) Examine whether the total AV-access related costs were associated with AV access type and their FTM risk stratum as determined by their FTM risk score.

METHODS

Population

The University Health Network-Toronto General Hospital (UHN) is a large academic based institution in Toronto, Ontario, Canada, that serves 250-350 patients in its in centre hemodialysis program. Patients with a first AV-access created from January 1, 2002- January 1, 2018 at UHN with their access in situ for at least one year were included in this study. The patient could have been pre-dialysis or have already started dialysis with a catheter (see clinical data collection below for details). This study was approved by the UHN research ethics review board.

Clinical Data Collection

At University Health Network-Toronto General Hospital, a hemodialysis vascular access clinical and research database (VASPRO) is maintained which prospectively captures key patient characteristics, the date of all vascular access creations, removals, related endovascular and surgical interventions at University Health Network-Toronto General Hospital (any care occurring elsewhere not captured), and the reasons for vascular access failure. This database collects data as long as the patient is a patient in the hemodialysis program at Toronto General Hospital and also captures reasons for leaving the program (e.g., change of modality, death). The first day of costing was the day of surgical creation of the AV-access. For the duration of the AV-access, all AV-access history including date of AV-access creation and subsequent interventions required to facilitate and/or maintain patency (i.e., angiograms, angioplasties, thrombolysis, revisions), date of access termination, reason for access termination, and central venous catheter use are captured.

For the purposes of this study, data on all hemodialysis patients who had a vascular access created from January 1, 2002 - January 1, 2018 were retrieved from VASPRO. The patients' primary access during the study period was selected so that there was only one access captured per patient, ensuring independence of the unit of analysis. Specifically, sociodemographic data collected at the time

of access creation including age and ethnicity, chronic kidney disease etiology, comorbidities were extracted (see Table 1 for full list of baseline characteristics). For the duration of the AV access, all AV access history including date of AV access creation and subsequent interventions required to facilitate and/or maintain patency (i.e., angiograms, angioplasties, thrombolysis, revisions), date of access termination, reason for access termination, and central venous catheter use were retrieved.

For the analyses related to access days and access related interventions, the cohort of patients included all primary AV access during the study period and all retrieved data from the surgical creation of the AV access to the termination of the primary access or the end of the study period were included.

For the cost analyses, three cohorts of patients were included, only those patients for whom there was complete follow-up data (i.e., their access had not been terminated, or the study period had not ended) at one, three, and five years post creation were included in the analysis for each time point, respectively, with the first day of costing being the day of surgical creation of the AV access. This prevents potential bias associated comparing accesses with differing longevity, as accesses with a shorter observation period would potentially accumulate less costs, as was observed in Manns et al. 2005 study (21).

Quantifying the catheter use while the AV access was in situ included computing based on the start and end date of all catheters: 1) the number of catheter insertions during, 2) the number and date of catheter removals, and 3) the number of catheter days from the date of AV access creation to AV access removal. The burden of catheter related complications while the AV access were then computed by drawing on rates per 1000 days from clinical trials previously conducted at TGH-UHN including bacteremia (0.383)(26), exit site infections (0.595)(26), malfunctions requiring TPA use (3.3)(27), and hospitalizations (0.28)(27).

Any secondary AV access creation/use were not included so as to focus this analysis on primary AV access related cost, the population in which the FTM risk score was developed.

The costs of bacteremia related to AV accesses were not included in this analysis as these were not consistently captured in the VAS-PRO database. However, a recent large prospective study in 177,875 prevalent and 11,290 incident hemodialysis patients, found no difference in vascular access infection rates between patients with a graft or fistula among both incident and prevalent patients and the rate of infection with both types of access was very low (28).

Estimating Unit Costs

In order to obtain an estimate of the unit costs of vascular access related events and complications, five separate sources were used: 1) Aggregated estimated costs from the Ontario Case Costing Initiative (OCCI) database, 2) TGH-UHN interventional radiology and surgery department costing records, 3) TGH-UHN Pharmacy cost records, 4) TGH- UHN Ward costs, and 5) previous costing study in TPA use (29).

1) The OCCI is an undertaking of the Ontario Ministry of Health and Long-Term Care; its primary objective is to collect case costing data in support of improved management decision-making and resource allocation. OCCI collects case cost data for acute inpatient, day surgery and ambulatory care cases, as well as complex continuing care, rehabilitation, mental health and community care centres cases (30). The OCCI makes aggregate data for the province of Ontario publicly available using the online Costing Analysis Tool. In this study, the median total costs, direct costs, and indirect costs in Ontario for 2011 were obtained by entering the procedural codes for each type of vascular access related complication or event into the cost analysis tool as this is the last year for which the costs were publicly available.

2) TGH-UHN interventional radiology and surgery department records were used to obtain an itemized cost estimate of catheter removal and new catheter insertion, which includes the costs of the catheter, use of the interventional room, and equipment required.

3) TGH-UHN Pharmacy cost records were used to obtain an estimate of the cost associated with the outpatient management of catheter-related bacteremia (CRB).

4) TGH-UHN costing records were used to estimate the cost per day on the ward to obtain an estimate of the cost of hospitalizations for catheter associated complications (including infection).

5) For this study, we obtained a point estimate for the use of a rescue thrombolytic, recombinant Tissue Plasminogen Activator, for catheter malfunction from a cost analysis of the prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator (PRECLOT) study (29).

Analysis

Baseline Characteristics

Descriptive statistics were calculated for all baseline characteristics including sex, age, ethnicity, etiology of end-stage kidney disease, and co-morbidities. Patient ethnicity, age, cardiovascular, and peripheral vascular disease statuses were used to determine each patient's risk of fistula maturation failure according to the FTM risk score (25) as low (24%), moderate (34%), high (50%), or very high (69%).

Access Days and Access Related Interventions

The mean number of AV-access days was calculated based on the number of days the access was in situ, that is, from the creation date to the access end date of the patients' primary AV- access during the study period. Rates (events/1000 access days) of AV-access related interventions were calculated based on the number of AV-access related interventions during the time the access was in situ. The rates of catheter related interventions were calculated by determining the number of catheter days while each

AV- access was in situ. The proportions and rates (events/1000 access days) of fistulas versus grafts requiring angioplasties, angiograms, thrombolysis, revisions, catheter placement, and having an infection (fistula and graft or catheter related) were compared using Fisher's Exact Test and Exact Poisson Method, respectively. The mean number of access days, both AV-access and CVC days while the AV-access was in situ, were compared between fistula and grafts using independent samples t-tests.

Cost Analyses

This study took the perspective of the health care purchaser and includes only direct health care-related costs. Societal costs (e.g., time costs for patients and relatives, patient transport costs), though important to consider, were not captured in VAS-PRO and therefore were not included. The total costs reported in 2011 Canadian dollars at one, three, and five years post access creation were calculated by multiplying the unit cost for each intervention by the number of complications requiring intervention from creation to one, three, and five years post creation. To take into account time preference, we used discounting to calculate the present value at a rate of 3% per annum (31). Median costs were reported by access type.

The potential association of year of access creation, access type and FTM risk stratum with access related cost was compared at one, three, and five years using Loglinear models and access type and FTM risk with access related cost over time using generalized estimating equations. Both the main effects of access type and FTM risk stratum on costs, as well as the main effects and interaction of access type and FTM risk stratum were reported. Due to small cell counts in the very high risk stratum, the patients were collapsed in with high risk for these analyses. All analyses were conducted using SPSS 22.

RESULTS

There were 1343 primary AV-accesses created and captured in VAS-PRO from January 1, 2002 to January 31, 2018, of whom 437 were excluded for this study as they were not incentre UHN patients (received dialysis at other centres). Of the 906 remaining accesses, 662 were in situ for a minimum of one year, 419 were in situ for a minimum of three years, and 275 were in situ for a minimum of five years. The mean number of access days (length of follow up) for fistulas was 1539.2 and for grafts was 1038.5.

Baseline Characteristics by Vascular Access Type

A total of 906 patients were included in the study, 696 fistulas and 210 grafts (see figure 1 for access type by year). The characteristics used to calculate the risk score are listed in table 1 for patients with fistulas and grafts including: being aged 65 or older (33.8% vs 38.1%, respectively), being Caucasian (54.6% vs 55.7%, respectively), having coronary artery disease (17.5% vs 19.5%, respectively), and having peripheral vascular disease (7.6% vs 8.1%, respectively). When stratified by risk of failure, among fistulas 28.3% were in the low risk category, 45.7% in the medium risk, 20.0% in the high risk and 6.0% in the very high risk. Among grafts, 23.7% were in the low risk category, 49.0% in the medium risk, 21.4% in the high risk, and 5.7% in the very high risk.

Vascular Access-related Interventions over the Access Lifetime

The proportion of fistulas requiring radiologic imaging was higher than that of grafts: angiogram (13.6% versus 8.1%, $p = 0.034$). The proportion of fistulas requiring endovascular interventions to promote or maintain patency was generally lower than that of grafts: angioplasty (34.3% versus 41.9%, $p = 0.045$) and thrombolysis (8.0% versus 34.3%, $p < 0.001$). The insertion of a new CVC during the AV-access's lifetime was higher in fistulas than grafts (22.1% versus 14.3%, $p = 0.014$) (Table 2). Similar trends were reflected in the rate (frequency) of events over the AV-access lifetime span (events /1000 access days) (see Table 2).

Median Vascular Access-related Costs

For unit cost estimates see Table 3. The median vascular access-related costs, undifferentiated by FTM risk, were lower for fistulas than grafts at one year ($3,822.21 versus $4,172.34, see Figure 1), three years ($4,765.22 vs $7,953.31, see Figure 2), and five years ($5,856.21 vs $8,324.39, see Figure 3) post creation.

Impact of FTM Risk Score and Access Type on Vascular Access-related Costs

The potential association of access type, FTM risk stratum, and year of access creation with access related cost was examined at one, three, and five years, as well as access type and FTM risk stratum with access related cost over time. The highest risk stratum and decreasing year of access creation was consistently associated with higher cost in all models at all time points. However, access type was not significantly associated with higher cost in any of the models that considered the interaction between access type and risk stratum (Table 4).

DISCUSSION

The main finding of this study is that the costs of attaining and maintaining patency increased with increasing risk of fistula maturation failure at one, three, and five years. Those AV accesses that were likely to be at high risk of failure also had the greatest need for interventions and consequent increased costs to achieve and maintain access patency, which is consistent with other studies (12, 32-34). However, AV access type was not a significant predictor of cost when the interaction between access type and risk of fistula maturation failure was considered. Year of creation was negatively associated with cost, which suggests that more recent advances in technologies and strategies to inform vascular access placement may have been effective in reducing AV access related costs over time.

Other previous cost studies have indicated fistulas are less costly compared with grafts (21, 22). The primary reason for the difference in findings likely relate to the difference in how costs were

compared. Rather than an undifferentiated comparison of fistula and graft cost comparison, we stratified our analyses according to risk of AV access maturation failure. Indeed, we did find that the undifferentiated median cost is lower for fistulas than grafts; however, when we adjusted for FTM risk stratum and access type, as well as the interaction, we found that FTM risk stratum was associated with increasing cost, and access type was not. The differences in the magnitude of the median cost in this study as compared to others may be attributable to the variance in unit cost estimates globally, however, the unit costs estimates in our study generally fall within the range of those in the literature: angiograms from $90-$404 (22, 35, 36), angioplasties from $571-$1939 (22, 35-38), and thrombolysis from $1,381.00 – $6,802.00 (36, 38-41).

Thus, the findings of this study highlight the need for careful consideration of vascular access choice based on the patient's risk of fistula maturation failure from not only a clinical but also an economic standpoint. While fistulas were once thought to be associated with the lowest morbidity and mortality of all types of vascular access, this may be true only if they mature enough to be used to deliver adequate dialysis. If fistulas are created in patients in whom there is likely to be significant difficulties in attaining patency, resulting in greater interventions, catheter use and their complications (42-44) their main advantage over grafts may be lost. This may be particularly important to consider in subsets of the hemodialysis population such as the elderly, diabetics, or female, where fistula and grafts have been shown to have equivalent outcomes (12, 45).

This study has potential implications related to policy on hemodialysis vascular access in North America as lower costs are one of the cited reasons for the promotion of fistulas in the 'Fistula First' quality initiative which has been widely adopted (1, 2). Given that fistulas tend to have greater rates of maturation failure but better longer term patency than grafts (12-14, 17) costs may vary based on FTM risk. In this study, we found that increasing FTM risk score was associated with increasing cost. When

FTM risk is considered in the model, AV access was not a significant predictor of cost. Therefore, if resource utilization is a concern, both fistulas and grafts should be considered, particularly in those patients in whom maturation failure is highly likely, a graft may be a better choice, as recent studies have shown that they have a shorter maturation time (less exposure to a catheter), require less interventions to attain patency, and offer comparable patency rates (43, 44, 46, 47). Indeed, catheter use was lower among grafts in our study. Catheter use, even as a bridge for a maturing AV access, can be associated with complications that puts patients at risk for additional morbidity and mortality and secondarily, place a heavy drain on health care resources (3-10). Catheter related infections in particular are very costly; estimates of the total direct and indirect costs associated with hospitalizations due to catheter-related infection range from $17,000 USD to $32,000 USD (4, 48-50). In our analysis, we did not include the costs of ICU stays for patients with catheter-related sepsis, thus underestimating the costs of treating catheter related infections.

This study has certain limitations that should be noted. Given the cost analysis was conducted at 3 time points (see analysis below), one, three, and five years post creation, only those patients whose AV-access was still in situ at one, three, and five years post creation were included in the analysis at each time point, respectively. While this prevents potential bias associated comparing accesses with differing longevity, as accesses with a shorter observation period would potentially accumulate less costs, as was observed in Manns et al. 2005 study (21), the costs associated with access that failed in less than a year were not captured. Secondly, while our study prospectively followed AV-accesses from creation to abandonment and determined their actual events upon which we calculated the costs, the exact costs accrued for each patient was not used in this study. Rather, we used unit costs and multiplied them by the number of events, yielding a modeled estimate of the cost. Most of the unit costs used for this study represent the cost estimates obtained from the OCCI database, to which a large

majority of the hospitals in Ontario, Canada contribute. This province has a single payer health system and therefore the generalizability of these findings may be limited for areas with different payer models. Thirdly, the number of events was drawn from a single centre with multiple surgeons in Toronto, Ontario, Canada, also limiting the generalizability of the findings to other jurisdictions. Fourthly, the FTM risk score was used to compare groups due to its validated ability to predict maturation failure; however, there are other risk factors such as need for an urgent start on dialysis (51) which might be important to adjust for in analyses to minimize the bias in an examination of cost that were not considered. It is important to acknowledge that the FTM risk equation was itself was developed prior to the use of many modern surgical techniques and maturation assisting procedures and requires further validation in more current samples, however, the finding in this study that the FTM risk equation predicted costs does suggest that the FTM risk equations' predictive value has withstood the test of time. Finally, the outcome of total present value vascular access related costs from a third-party payer perspective used in these analyses did not consider any patient-related costs such as costs associated with patient transportation for additional vascular access related interventions (52). Prospective capture of such costs in the long term in future research is critical to more fully capturing all facets of vascular access choice and consequences.

Conclusion

While lower costs are one of the widely cited reasons for the promotion of fistulas (1, 2), our study found that this varies based on the risk of fistula maturation failure. Higher present value of total vascular access related costs was associated with elevated FTM risk scores, but vascular access type was not. Consistent with previous clinical studies (12-14, 17), fistulas had higher rates of interventions associated with attaining patency, whereas grafts had higher rates of intervention associated with maintaining patency. Rather than promoting only one type of vascular access, policies related to

vascular access should encourage thinking about the patient's risk of fistula success/failure. Use of the FTM risk score is one aid that can be used in clinical decision-making and patient education, but we encourage research to update the FTM risk score, to encompass other important variables that impact the success and cost of vascular access creation and use. Indeed, there must be careful consideration of other dimensions including overall health status, life expectancy, support systems, and functional capacity as well as their personal goals and preferences when deciding on what vascular access is optimal for a given patient.

DISCLOSURES

The authors have no conflict of interest to declare. This project was unfunded.

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TABLE, FIGURES, & SUPPLEMENTARY MATERIALS

Table 1 - Baseline Characteristics of All Primary Permanent Accesses (n = 906)

Characteristics		Access Type			
		Fistula N = 696		Graft N = 210	
		Count	%	Count	%
Age (years)	<65	461	66.2%	130	61.9%
	≥65	235	33.8%	80	38.1%
Ethnicity	Caucasian	380	54.6%	117	55.7%
	Other	316	45.4%	126	44.3%
Etiology of End-Stage Kidney Disease	Hypertension	66	9.5%	16	7.6%
	Diabetes	130	18.7%	48	22.9%
	Glomerulonephritis	122	17.5%	28	13.3%
	Interstitial nephritis	4	0.6%	6	2.9%
	Other[a]	169	24.3%	45	21.4%
Co-morbidities	CHF	52	7.5%	20	9.5%
	COPD	38	5.5%	12	5.7%
	Diabetes mellitus	199	28.6%	76	36.2%
	CAD	122	17.5%	41	19.5%
	Hypertension	412	59.2%	136	64.8%
	PVD	53	7.6%	17	8.1%
	Other[b]	324	46.6%	94	44.8%

Risk Stratum[c]	Low	197	28.3%	50	23.8%
	Moderate	318	45.7%	103	49.0%
	High	139	20.0%	45	21.4%
	Very High	42	6.0%	12	5.7%

Note: CHF = Congestive Heart Failure; COPD = Chronic Obstructive Pulmonary Disease; CAD = Coronary Artery Disease; PVD = Peripheral Vascular Disease; [a]e.g., combination diabetes and hypertension; polycystic kidney disease and other genetic, ischemic and toxic injuries ; [b] e.g., cancer, amyloidosis, liver cirrhosis and other GI disorders,;

[c] Calculated based on FTM prediction score = 3 + 2(age) +3(PVD) + 2.5(CAD) -3(Caucasian)

Table 2- All Primary Accesses- Comparing Proportions and Rates of Accesses Requiring Interventions (n = 906)

Access lifetime intervention	**Vascular Access Type**				**Comparison**		
	Fistula n = 696		Graft n = 210				
Proportions	n [a]	%	n [a]	%	% Difference	95% CI	p-value[b]
Angioplasty	239	34.3%	88	41.9%	7.6%	0.19% - 15.2%	0.045
Angiogram	95	13.6%	17	8.1%	5.5%	0.44% - 9.6%	0.034
Thrombolysis	56	8.0%	72	34.3%	26.3%	19.8% to 33.2%	<0.001
Revisions	58	8.3%	11	5.2%	3.1%	- 1.2% - 6.3%	0.137
Catheter Insertion	154	22.1%	30	14.3%	7.8%	1.7% - 13.0%	0.014
Catheter Removal	236	33.9%	79	37.6%	3.6%	-3.6% - 11.1%	0.338
Catheter Use[c]	398	57.18%	112	53.33%	3.9%	-3.7% to 11.6%	0.318
Rates	n[d]	/1000 access days	n[d]	/1000 access days	Incident rate ratio	95% Confidence Interval	p-value[e]
Angioplasty	684	0.64	345	1.58	0.40	0.0020 - 81.69	<0.001
Angiogram	127	0.12	20	0.09	1.29	1.07 - 1.49	0.285

Thrombolysis	79	0.07	174	0.80	0.09	0.00019 - 45.32	<0.001
Fistula or Graft Revisions	58	0.05	11	0.05	1.07	21.19 - 0.051	0.829
New Catheter Insertion	207	0.19	36	0.17	1.17	1.4941 - 0.8967	0.383
Catheter Removal	263	0.25	86	0.39	0.62	0.042 - 9.27	<0.001
Access Length		Mean		Mean	Mean Difference	95% Confidence Interval	p-value[f]
AV Access Days		1539.21		1038.53	500.67	289.40 - 711.94	<0.001
Catheter Days		214.74		145.40	69.34	12.10 - 126.58	0.018

Note: [a] n is the number of accesses and % is the proportion of accesses with at least one intervention during the access lifetime; [b] proportions compared using Chi-square test; [c] had a catheter in situ anytime during the access lifetime; [d] n is the total number of procedures performed in all accesses of that type; [e] rates compared using fisher's exact test; [f] means compared using independent samples t-test

Table 3 - Unit Costs of Vascular Access Surgery from Ontario Case Costing Initiative Costing Analysis Tool (2011)

Permanent Access-related Surgery and Interventions	Total Cost Per Case ($)		Indirect Cost Per Case ($)		Total Cost Per Case ($)	
	Median	Std Dev	Median	Std Dev	Median[a]	Std Dev
Access Creation [a]	$1,631	$719	$497	$220	**$2,128**	$849
Access Revision [a]	$1,223	$800	$464	$255	**$1,687**	$1,053
Angioplasty [a]	$1,954	$621	$675	$221	**$2,629**	$841
Angiogram [a]	$1,346	$480	$488	$139	**$1,833**	$617
Thrombolysis [a]	$1,121	$785	$375	$164	**$1,496**	$904
Catheter-related Interventions (Catheter Use while Permanent Access In Situ)					Point Estimate[a]	
Outpatient treatment for vascular access associated bacteremia per event[b]					**$262**	
Catheter removal and new insertion[c]					**$1,121**	
Cost of hospital per day related to catheter related complications (non-ICU) (price per day)[d]					**$700**	
Cost of rescue Tissue Plasminogen Activator for patients who develop catheter malfunction[e]					**$533**	

Note: [a] Source: Ontario Case Costing Initiative Costing Analysis Tool (2011), the median total costs obtained from OCCI are derived from the sum of the direct costs (i.e. costs directly related to the

provision of patient care, such as nursing in the operating room, diagnostic imaging, pharmacy and labwork required), and the indirect costs (i.e. costs which includes overhead expenses, such as those related to managing relevant facility operations) of all hemodialysis patients who had their vascular access related complications or events in all OCCI hospitals in Ontario during 2011;

[b] Source: TGH-UHN pharmacy costing records, the dose and duration of antibiotic treatment as well as the cost of laboratory monitoring for the antibiotics were based on the out-patient hemodialysis diagnostic and treatment algorithm as follows. For this study, we assumed that once a CRB is suspected, two sets of blood cultures, which cost $102.00 CAD per set, are obtained as per guideline recommendations (53). Empiric parenteral Vancomycin and an aminoglycoside, Tobramycin, are initiated at 3 administrations per week, until sensitivities and cultures return. The list price of Vancomycin and Tobramycin were used; the duration of antibiotic use estimated was two weeks; [c]TGH-UHN interventional radiology department costing records; [d]Source: TGH-UHN costing records for ward, the cost of hospitalizations for catheter associated complications were included in this analysis, but not permanent access related complications as these were not consistently captured in our database [e]Source: Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator study

Table 4- Association of Access Type and FTM Risk Stratum with Access Related Cost at One, Three, and Five Years and Over Time (n=662, n= 419, n=275, n = 275, respectively)

Log Cost	Factor	Main Effects		Main and Interaction Effects	
		Effect Estimate (95% CI)	P-value	Effect Estimate (95% CI)	P-value
1 year[a]	Year of Creation	0.99 (0.99, 0.99)	<0.001	0.99 (0.99, 0.99)	<0.001
	High Risk[b]	1.11 (1.06, 1.16)	<0.001	1.19 (1.09, 1.31)	<0.001
	Moderate Risk[b]	1.02 (0.98, 1.06)	0.243	1.07 (0.99, 1.17)	0.100
	Fistula[c]	0.96 (0.92, 1.00)	0.054	1.02 (0.94, 1.10)	0.674
	High Risk*Fistula[d]			0.91 (0.81, 1.01)	0.074
	Moderate Risk*Fistula[d]			0.94 (0.85, 1.04)	0.218
3 years[a]	Year of Creation	0.98 (0.97, 0.99)	<0.001	0.98 (0.97, 0.99)	<0.001
	High Risk[b]	1.14 (1.05, 1.24)	0.002	1.27 (1.06, 1.52)	0.011
	Moderate Risk[b]	1.07 (1.01, 1.14)	0.035	1.15 (0.99, 1.36)	0.069
	Fistula[c]	0.82 (0.76, 0.88)	<0.001	0.89 (0.77, 1.03)	0.104

	High Risk*Fistula[d]			0.88 (0.72, 1.08)	0.219
	Moderate Risk*Fistula[d]			0.91 (0.77, 1.08)	0.290
5 years[a]	Year of Creation	0.98 (0.97, 0.99)	<0.001	0.98 (0.97, 0.99)	<0.001
	High Risk[b]	1.22 (1.08, 1.38)	0.001	1.64 (1.14, 2.36)	0.008
	Moderate Risk[b]	1.08 (0.99, 1.18)	0.068	1.27 (0.98, 1.66)	0.072
	Fistula[c]	0.86 (0.76, 0.96)	0.008	1.00 (0.79, 1.27)	0.993
	High Risk*Fistula[d]			0.72 (0.49, 1.06)	0.092
	Moderate Risk*Fistula[d]			0.84 (0.63, 1.11)	0.209
Over time[e]	5 Years[f]	1.24 (1.20, 1.27)	<0.001	1.24 (1.20, 1.28)	<0.001
	3 Years[f]	1.16 (1.13, 1.19)	<0.001	1.16 (1.13, 1.19)	<0.001
	High Risk[b]	1.14 (1.03, 1.27)	0.011	1.44 (1.09, 1.91)	0.011
	Moderate Risk[b]	1.04 (0.97, 1.11)	0.311	1.14 (0.93, 1.39)	0.211
	Fistula[c]	0.92 (0.84, 1.02)	0.095	1.02 (0.85, 1.21)	0.849
	High Risk*Fistula[d]			0.77 (0.57, 1.04)	0.093

	Moderate Risk*Fistula[d]			0.90 (0.73, 1.12)	0.353

Note: [a] Loglinear model, [b] Reference is Low Risk, [c] Reference is Graft, [d] Interaction term, [e] Generalized estimating equation, [f] Reference is One Year

Figure 1 – Access Type by Year of Access Creation (n=906)

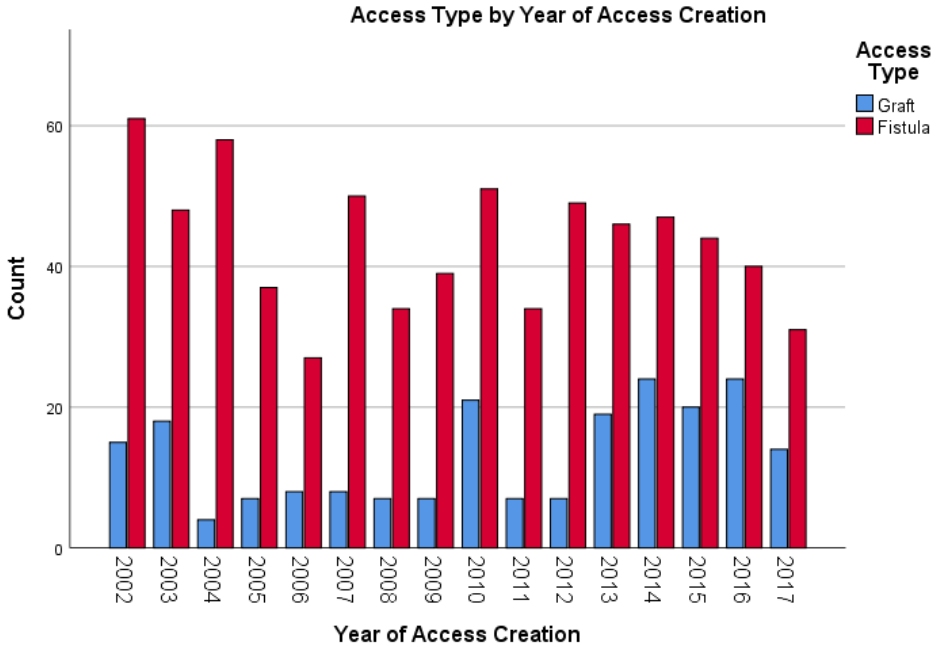
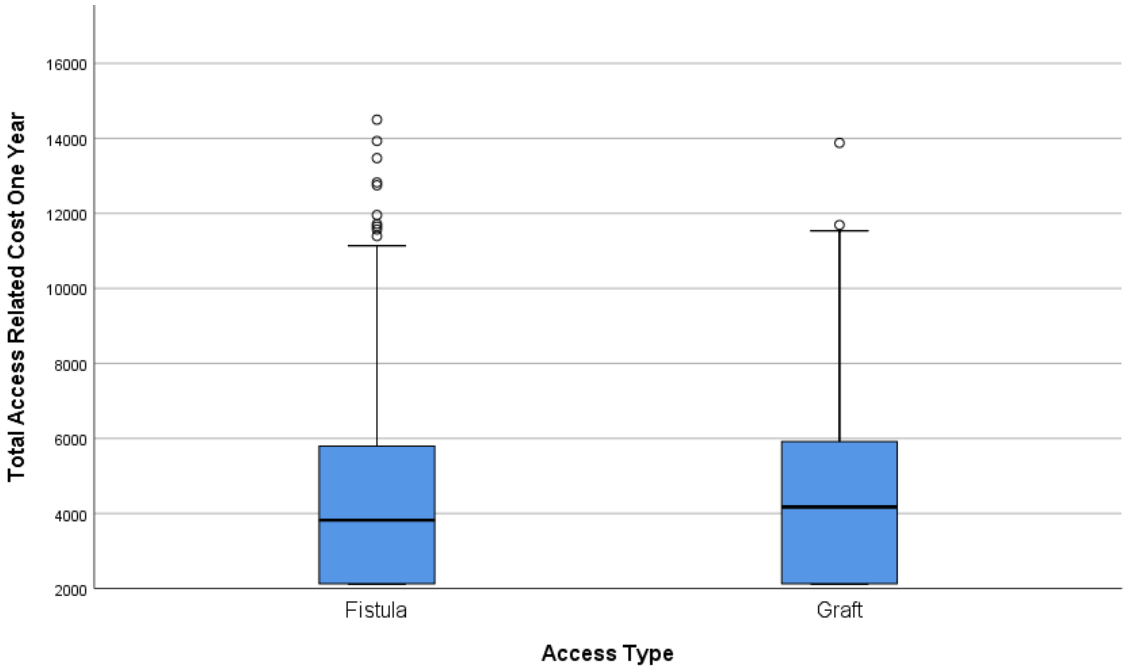
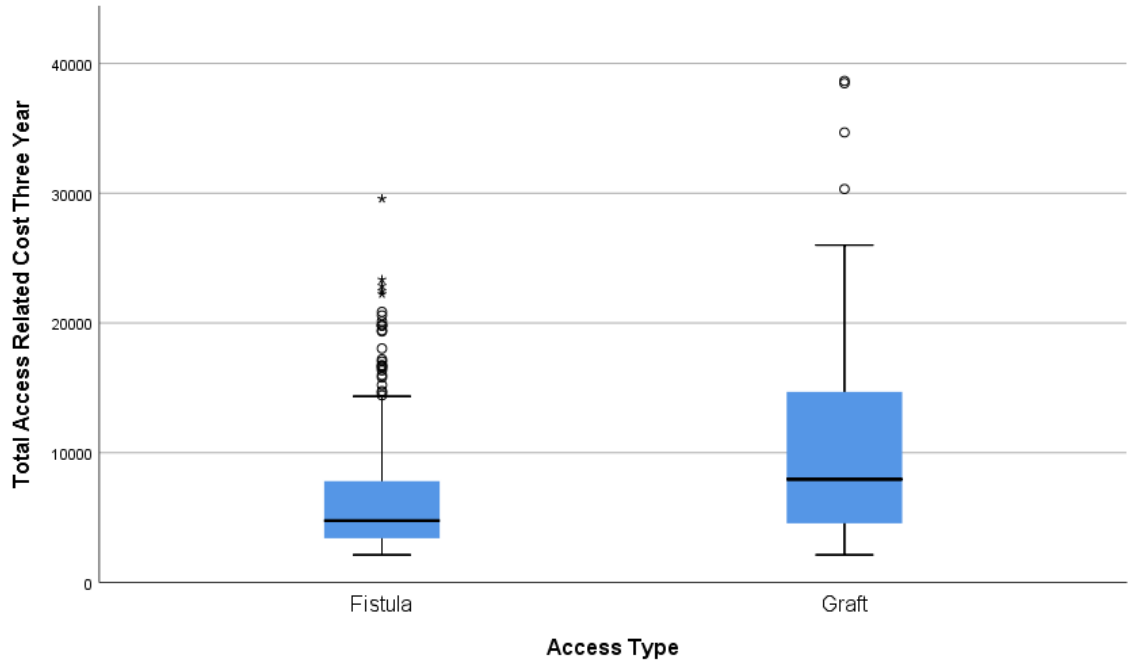


Figure 2 – Simple Boxplot of Access Related Cost at One Year (n=662)



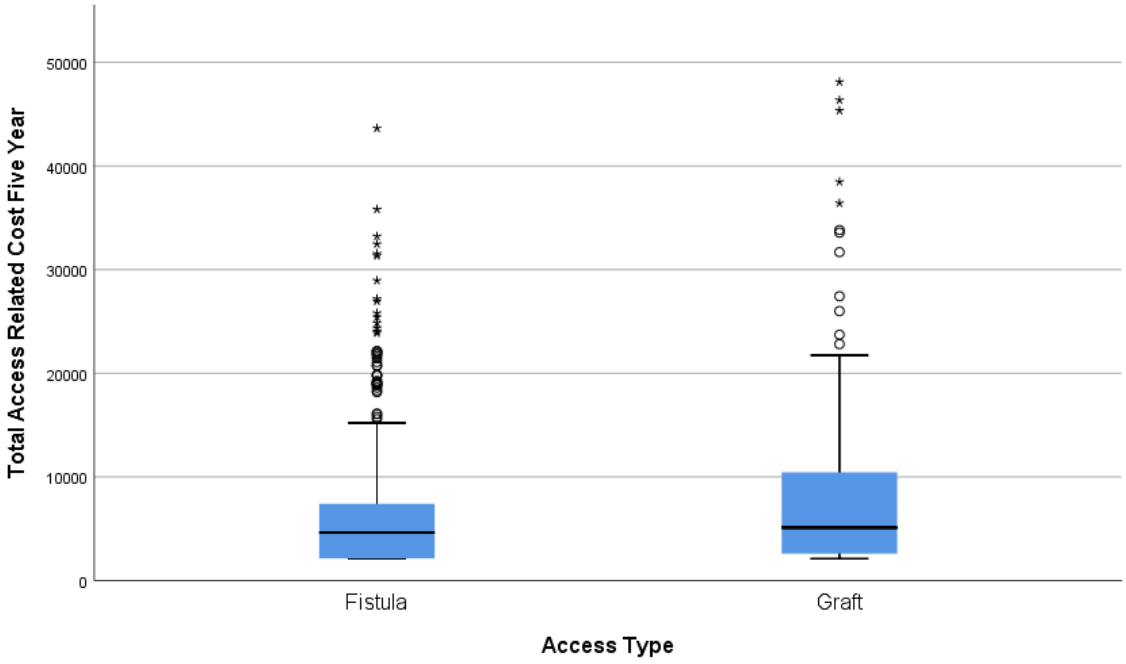
Note: Fistula n = 510, median = $3,822.21, Graft n = 152, median = $4,172.34

Figure 3 – Simple Boxplot of Access Related Cost at Three Years (n= 419)



Note: Fistula n = 338, median = $4,765.22, Graft n = 81, median = $7,953.31

Figure 4 – Simple Boxplot of Access Related Cost at Five Years (n=275)



Note: Fistula n = 239, median = $5,856.21, Graft n = 36, median = $8,324.39

CHAPTER FOUR
HEMODIALYSIS INFECTION PREVENTION PROTOCOLS ONTARIO-SHOWER TECHNIQUE (HIPPO-ST): A PILOT RANDOMIZED TRIAL

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ABSTRACT

Introduction

We developed the Hemodialysis Infection Prevention Protocols Ontario—Shower Technique (HIPPO-ST) to permit hemodialysis (HD) patients with central venous catheters (catheters) to shower without additional infection risk. Our primary objective was to determine the feasibility of conducting a parallel randomized controlled trial (RCT) to evaluate the impact of HIPPO-ST on catheter-related bacteremia (CRB) in adult HD patients.

Methods

Adult HD patients using catheters were recruited from 11 HD units. Patients were randomized to receive HIPPO-ST or standard care and were followed up for 6 months. Only CRB-outcome assessors were blinded. For the study to be considered feasible, 4 of 5 feasibility outcomes, each with its own statistical threshold for success, must have been achieved.

Results

A total of 68 patients were randomized (33 HIPPO-ST and 35 control) and were followed up to 6 months. Of 5 measures of feasibility, 4 were achieved: (1) accurate CRB rate documented (threshold: κ level >0.80); (2) 97.8% (279/285) of satellite HD patients with catheters were screened (threshold: >95%); (3) 88% (23/26) in the HIPPO-ST arm were successfully educated by 6 months (threshold: >80%); and (4) 0% (0/29) patients in the control arm were "contaminated," that is, using HIPPO-ST (threshold: <5%). However, only 44.2% (72/163) of eligible patients consented to participate (threshold: >80%). The rate of CRB was similarly low in HIPPO-ST and control groups (0.68 vs. 0.88/1000 catheter days).

Discussion

This HIPPO-ST pilot study demonstrated the feasibility of the larger HIPPO-ST study, especially given the high levels of education success with the HIPPO-ST arm and the low levels of contamination in the control arm.

Keywords: catheter, hemodialysis, pilot study, randomized controlled trial, vascular access

BACKGROUND

Arteriovenous fistulas (fistula) are associated with the lowest morbidity and mortality of the 3 vascular access types, if they mature to be used to deliver adequate dialysis.[1], [2] However, hemodialysis (HD) central venous catheters (catheters) are the predominant choice of vascular access for patients requiring immediate HD until either a synthetic arteriovenous graft (graft) or a fistula can be placed. Currently, despite efforts to promote increased arteriovenous-access creation and use,[3] up to 80% of incident and 50% of prevalent patients in North America dialyze via a catheter.[4], [5] Catheter use represents a burden on health care resources; it is associated with both the highest financial costs and the highest associated morbidity and mortality of all vascular access types.[6], [7], [8], [9], [10], [11], [12], [13]

Catheter-related infections drive much of this increased cost,[14] with estimates of $17,000 USD to $32,000 USD for the total direct and indirect costs associated with hospitalizations due to catheter-related infection.[7], [15], [16], [17] Catheter-related infections encompass catheter entry site infections, tunnel infections, and bacteremia; however, HD catheter-related bacteremia (CRB) are considered the most clinically important, as they have the potential to progress to sepsis and death.[6] Thus, it is critically important to have effective prophylactic strategies as part of routine catheter care to limit catheter-related infection overall, and CRB specifically, with minimal complication risk, inconvenience, and discomfort to the patient, and at minimal cost.[18]

Currently, in most guideline recommendations on routine catheter care, wet submersion of the catheter or catheter entry site is not advised, including swimming, submerged baths, and showering, as it is not possible to ensure full protective coverage of the catheter entry site with dressings, ointments, or other protective barriers during these activities.[19], [20], [21], [22], [23] Exposure to nonsterile, dirty, and/or damp environments may facilitate microrganism colonization and entry at the catheter entry site, potentially leading to subsequent catheter-related infection, especially if the catheter entry site is not fully healed.[20], [21], [22], [23] Yet despite the potential infection risk associated with showering, patient compliance with the recommendation not to shower with their catheter is poor. Up to 77% of patients shower despite being advised not to by their health care team.[24]

To address the patient's desire to shower for hygiene and quality of life reasons and to simultaneously adhere to infection prophylactic measures, several "shower techniques" have been developed as an alternative method of catheter care[24], [25], [26]; however, "shower techniques" have not yet been formally evaluated to ensure that they do not increase catheter-related infection risk. We developed the Hemodialysis Infection Prevention Protocols Ontario—Shower Technique (HIPPO-ST) to permit HD patients with catheters to shower but not increase infection risk. The primary objective of this pilot study is to determine whether it is feasible to conduct a large randomized controlled trial (RCT) comparing the rate of CRB in adult satellite HD patients using HIPPO-ST versus standard catheter care over 6 months. Our secondary objectives include comparing the rate and proportions of CRB, entry site and tunnel infections, and vascular access−related satisfaction in adult HD patients using HIPPO-ST versus standard catheter care over 6 months.

Go to:

MATERIALS AND METHODS

Details of this pilot parallel randomized controlled trial protocol are published and registered at ClinicalTrials.gov (NCT02002169), with key study conduct information consistent with that described below.27 One major change from the published protocol was expanding recruitment into some in-center HD units due to recruitment challenges (see Discussion) as we originally planned to recruit only in satellite HD units. The rationale for this initial recruitment decision is that historically, satellite patients were more "independent"; thus we envisioned them to have a greater ability to learn and to shoulder the responsibility of performing the shower technique with minimal assistance if they were randomized to it. However, as we found that some in-center patients had characteristics similar to those of satellite patients, and as we had difficulties with recruitment, we expanded our recruitment criteria and the number of sites (different from published protocol). To fully reflect the contributions of all the centers across Ontario that developed the HIPPO-ST, the study title was also altered. The design, conduct, and reporting of this study adheres to Consolidated Standards of Reporting Trials (CONSORT) guidelines (Supplementary Material 1).28 This study took place in 3 in-center and 8 satellite HD units affiliated with 2 academic centers, University Health Network−Toronto General Hospital (UHN-TGH) and London Health Sciences Centre and 3 community centers: the Scarborough Hospital, Trillium Health Centre−The Credit Valley Hospital, and Mackenzie Health Hospital in South Central Ontario, Canada. Research ethics board approval was obtained before study initiation at all participating sites.

Eligibility Criteria

Individuals were screened by the study coordinator using predefined inclusion and exclusion criteria (Table 1). The main inclusion criteria included use of a tunneled HD catheter for >6 weeks and the ability to take a shower (with or without assistance). The main exclusion criteria included use of antibiotics at the time of enrollment and limited life expectancy.

Interventions

Participants with healed catheter entry sites were randomized to either the Control group, which involved standard catheter care provided by HD nurses at the HD center, or to the HIPPO–ST Intervention group, which involved training and use of the HIPPO-ST when the participant showered plus standard catheter care provided by HD nurses at the HD center. In both the control and HIPPO-ST arms, participants whose HD center used a prophylactic barrier, polysporin triple ointment (PTO), at the catheter entry site as part of their standard catheter care protocol, continued to have it applied according to guideline recommendations[23] or as per HD unit policy and procedures for HD patient and catheter care, a practice supported by high-level RCT evidence.[29] The duration of the interventions was 6 months from the time of randomization.

Control Group

In the control group,[27, 29] standard catheter care was performed by trained HD nurses and consisted of cleansing with chlorhexidine 2% or povidone (if allergic to chlorhexidine) at the catheter entry site, followed by placement of a dry gauze dressing once per week or when clinically indicated.

HIPPO-ST Group

In the HIPPO-ST group,[27] participants randomized to the HIPPO-ST received a 30-minute personalized HIPPO-ST training session with the study coordinator, using the HIPPO-ST training tools (see below) in which they were taught how to do the following: (i) prior to showering, prepare all the supplies required to change their catheter entry site dressing; (ii) carefully shower to clean their body and to avoid the catheter entry site; no coverage of the catheter dressing was required; (iii) after showering, dry their body, again avoiding the catheter entry site; (iv) wash their hands with soap thoroughly; (v) carefully and gently remove and discard existing catheter entry site dressing; (vi) remove the chlorhexidine-soaked cotton swab applicator (supplied by the study) from its packaging and

then cleanse the skin around the catheter entry site and catheter tube; (vii) if using PTO, apply the PTO (this PTO had the participant's study number affixed, and participants were taught that this PTO is strictly not to be used for other reasons or to be shared by other household members); and (viii) apply new dry dressing at the catheter entry site. At the end of the training session, the participant had to successfully demonstrate the HIPPO-ST on a demonstration mannequin, evaluated against a test checklist by the study coordinator (HIPPO-ST Test), before proceeding to independent showering. If the participant passed the HIPPO-ST Test, they were provided an educational pamphlet on the HIPPO-ST, not to be shared with other participants, to be kept as a reference and placed in their bathroom/household. They were also given the necessary supplies for the HIPPO-ST, itemized in individual sequentially numbered kits, to take home. Twelve kits were given to each patient at a time, enough for 3 showers per week for 1 month. New kits were distributed monthly. Study personnel were available to answer any questions during HD or by telephone for both study arms any time throughout the study.

Shower Technique Protocol Training Tools

The HIPPO-ST protocol was developed at an in-person meeting of nephrologist leaders of the participating centers in which several pre-existing catheter care protocols were carefully examined and revised until consensus was reached. The HIPPO-ST training tools, including an educational pamphlet, video, and demonstration mannequin, were then developed specifically for use in the HIPPO-ST pilot study by a panel of nephrologists, vascular access and HD patient education experts, and HD patients. The pamphlet and video use lay term language (education level, grade 5) with clear visual aids to explain the HIPPO-ST, as well as signs and symptoms of infection of which participants should be aware.

Recruitment

Each site had 6 months to recruit patients, from which a recruitment rate was determined. All satellite HD patients with a catheter *in situ* for at least 6 weeks were approached. A screening log was maintained and evaluated weekly. Participants could rescind consent from the study at any time. The target sample size was 78 participants and was calculated based on 50% eligibility, 30% refusal, 10% noncompliance, <1% loss to follow-up, and previous trials in the HD setting.[24, 27, 29]

Allocation Process

Once written informed consent was obtained, the participant underwent formal testing for catheter entry site healing.[27] As no tests of catheter entry site healing for HD patients were found in the literature, the catheter entry site healing tests were developed for the HIPPO-ST pilot study by a panel of vascular access experts, including an expert nephrologist on HD vascular access,[30, 31, 32, 33, 34, 35] a vascular access coordinator (a co-leader experienced as the first vascular access coordinator in North America),[33, 36, 37, 38, 39, 40, 41, 42, 43] and an experienced HD nurse. The panel established 3 components to evaluating the entry site for healing: (i) stability of the catheter ingrowth, (ii) appearance of the catheter entry site, and (iii) integrity of the seal.[27]

Stability of the catheter was quantified by measuring the distance from the hub of the catheter to the entry site with a small disposable paper ruler before and after the patient took a deep breath. The catheter is generally inserted into the internal jugular vein, and protrudes from the chest just below the collar bone. If the catheter is not endothelialized *in situ,* the catheter may move as the patient takes a deep breath due to the muscles in the chest wall contracting. The measurement was taken during the catheter dressing change routinely conducted once weekly by the nurses. A difference between full exhalation and full inspiration of >0.23 cm indicated a failed test. The appearance of the catheter entry site was measured using a visual assessment of the skin around the point of catheter entry into the chest

for signs of irritation and infection (e.g., redness, discharge, or swelling) by the HD nurse with the assistance of the study coordinator. The presence of any 2 of the following present constituted a failure of this test: redness, discharge, or swelling. The integrity of the skin seal was measured using a visual assessment of how tightly the skin is sealed around the catheter tube by the HD nurses with the assistance of the study coordinator. The integrity of the skin seal around the catheter is rated in the test as good, fair, or poor, and a rating of poor constituted a failure of this test. If two-thirds or more of the above catheter entry site healing tests were failed, standard care was applied and dressings changed once per week on dialysis as per protocol, and the catheter entry site–healing tests were repeated once weekly until two-thirds of the tests were passed, and the patient could proceed to randomization, or the study ended. As with other criteria, such as for exit site infection, the above tests have not been validated; however it was an attempt to standardize and objectively determine entry site healing, rather than have no criteria aside from the current subjective evaluation by nurses.

Upon passing two-thirds of the catheter entry site healing tests, participants were randomized via a 24-hour, telephone-accessed independent central randomization facility. Randomization involved a computer-generated randomization sequence using random block sizes with stratification by study site. Allocation of participants to the intervention was concealed to the randomization desk; however, participants and the study coordinator could not be blinded to allocation status due to the nature of the intervention. As participants were stratified by site, the number of patients from each site allocated to each arm was balanced, and potential differences in outcomes owing to site-specific practices (e.g., brand of dressings, polysporin triple ointment use) should consequently also be balanced. We therefore did not control for use of prior regimens in the analysis (regimens are determined by individual site policies).

Outcomes

Feasibility objectives and their corresponding outcome measures are listed in Table 2. The primary clinical objective (exploratory) was to compare the rate of CRB in patients with healed catheter entry sites using HIPPO-ST in addition to standard care versus standard catheter care alone over 6 months (hypothesized to be non-inferior). Catheter-related infections were adjudicated by a blinded outcomes committee, the HD Infection Control Subcommittee (HICS),36 at UHN-TGH, for confirmation and classification of the diagnosis of CRB according to the Health Canada definitions.44 The secondary clinical outcome, determining patient satisfaction with their vascular access, was measured using the Short Form Vascular Access Questionnaire (SF-VAQ), which contains 13 items, 1 item relating to patient satisfaction with the vascular access overall as measured using a 7-point Likert scale. The other 12 items involve the patient indicating their level of agreement with individual statements about having problems with physical symptoms (including pain, bleeding, swelling, bruising, social functioning, which includes daily activities, appearance, sleep, and bathing), and complications, including problems on dialysis, vascular access care, hospitalization, and concerns about vascular access longevity (Supplementary Material 2).16 For those 12 items, when the 7-point Likert scale results in low scores, this indicates satisfaction, a score of 4 indicates neutrality, and high scores indicate dissatisfaction. For example, in a previous study of hemodialysis patients,16 the item associated with the highest level of dissatisfaction overall in the social functioning domain was bathing, with values of 3.27, 1.60, and 1.29 for catheters, fistulas, and grafts, respectively, suggesting that hemodialysis patients were satisfied with their current bathing protocol overall; however, dissatisfaction was markedly higher for patients with catheters.

Data Collection

Study visits took place at baseline and 3 and 6 months postrandomization. Baseline clinical, demographic, and vascular access information was obtained from the chart and/or a short interview with the participant. The catheter care survey, a measure of participant compliance and contamination with their catheter care protocol, and the SF-VAQ were administered to all participants at each study visit.45, 46 At the once-monthly monitoring visits, the study coordinator tracked use of all HIPPO-ST patients' supplies and checked dialysis treatment sheets (resource use data will be reported separately). Feasibility outcomes were evaluated at each phase of the study (e.g., screening, recruitment, education, event determination, and documentation), with successes defined in Table 2.

All participants were clinically evaluated 3 times per week on HD by their HD nurses, who were all experienced at recognizing and managing patients with a suspected catheter-related infection, especially a CRB.27 When an infection was suspected, swabs were sent for organism identification and growth and antibiotic sensitivities. A provider (nurse practitioner or physician) and the study coordinator were notified and subsequently completed a data collection form and submitted it to the HICS36 for outcome adjudication (above).44

All baseline and outcome data were collected by study coordinators and entered into the computerized HIPPO-ST database. Only the principal investigator, study coordinator, and monitors from the research ethics boards had access to the final dataset.

Data Analysis

Descriptive statistics were calculated for all feasibility outcome measures, with the corresponding hypotheses and thresholds of success/statistical test listed in Table 2. For all clinical outcomes (deemed exploratory in nature), estimates of effect are presented as mean values for HIPPO-ST and control groups with confidence intervals only, in accordance with a checklist for the conduct of pilot studies, as

this pilot study is designed to assess feasibility and not statistical significance.48 Data from the SF-VAQ are presented as means due to the ability of Likert scales to approximate interval level measurements.47, 49All analyses were based on an intention-to-treat approach and conducted using SPSS 22 software (IBM, Armonk, NY).

RESULTS

Recruitment and Baseline Characteristics

A total of 72 patients consented to participate, and 68 participants met the criteria for healed tunneled catheter entry site. Of the participants, 35 were randomized to control and 33 to HIPPO-ST (Figure 1). The recruitment period was from November 2012 until December 2014. Recruitment was stopped before the target recruitment number of 78 was reached due to non−study-related practical limitations (i.e., funding was depleted). The participants in the HIPPO-ST and control groups were similar in their baseline characteristics (Table 3).

Primary Outcome: Feasibility of a Larger Trial

Four of the 5 objectives of feasibility were achieved at 6 months, as reported in Table 2 and detailed by each objective below.

Feasibility Objective 1: To Accurately Capture the CRB Rate Within the Satellite HD Setting

The level of agreement between the dates of (1) suspected CRB and notifying the study coordinator within 72 hours and (2) the date the catheter entry site was swabbed and sent to the microbiology laboratory was excellent ($\kappa = 1.0$; success threshold: $\kappa > 0.80$). The study coordinator was notified within 72 hours regarding all 11 cases of suspected catheter-related infection.

Feasibility Objective 2: To Determine the Percentage of Eligible HD Patients Who Were Screened

There were 285 patients with catheters during the screening period, of whom 279 patients (97.8%) were screened for eligibility to participate in the study (success threshold, >95%). Some patients were

not screened due to the logistical difficulties of research staff traveling to the satellite units. Of the 279 patients screened, 163 were deemed eligible to participate (Figure 1).

Feasibility Objective 3: To Determine the Percentage of Eligible Satellite HD Patients Who Consented

Of the 163 eligible patients, 72 (44.2%) consented to participate in this study (success threshold, >80%).

Feasibility Objective 4: To Determine the Percentage of Patients Who Passed the HIPPO-ST Test

Of the patients randomized to HIPPO-ST, 100% (33/33), 100% (31/31), and 88.4% (23/26) in the study at baseline, 3, and 6 months passed the HIPPO-ST test (success threshold, ≥80%). Figure 1 provides reasons for loss to follow-up in the intervention arm. Over the study period, 3 patients in the HIPPO-ST arm who had suspected infection stopped using the HIPPO-ST during the time that the infection was suspected; however, they were still administered the HIPPO-ST test and included in the descriptive statistics above, as per intention-to-treat. All 3 patients who had a suspected infection were given the option to resume using the HIPPO-ST; however, all 3 patients declined to continue using the HIPPO-ST.

Feasibility Objective 5: To Determine the Percentage of Participants in the Control Arm Who Used Aspects of the Intervention (HIPPO-ST)

At both the 3-month (n = 32) and 6-month (n = 29) study visits, no participants in the control arm (0%) were using any aspect of the HIPPO-ST that they were not using at baseline (n = 35), as determined by the catheter care survey (success threshold, <5%). Figure 1 presents reasons for loss to follow-up in the control arm.

Catheter-Related Infection

The proportions and rates of patients with different types of catheter-related infections are reported in Table 4. The proportion of patients with a CRB in the HIPPO-ST group was 12.1% (4/33) and in the

control group was 11.4% (4/35), with a mean difference between groups of 0.007 (95% confidence interval [CI] = −0.16 to 0.17). The rate of CRB in HIPPO-ST group was 0.88/1000 catheter days and in the control group was 0.68/1000 catheter days, with a mean difference between groups of 0.16 (95% CI = −2.25 to 2.65). No unexpected harm using HIPPO-ST was observed.

Patient Satisfaction With Vascular Access

The change in patient satisfaction as measured by the Short Form Vascular Access Questionnaire (SF-VAQ) scores[45], [46] are shown in Supplementary Material 2. Mean scores for both the HIPPO-ST and the control group indicated high levels of satisfaction with their vascular access overall over the course of the study (5.73 vs. 5.94, 6.24 vs. 6.25, and 5.73 vs. 6.68 at baseline, 3 months, and 6 months, respectively). The HIPPO-ST group had a similar improvement in SF-VAQ scores compared with the control group over 6 months for the item “During the past 4 weeks my vascular access caused me problems when I was bathing or showering” (Figure 2).

DISCUSSION

The key finding in this study is that criteria for feasibility success (4/5 criterion) were met and the full HIPPO-ST study is feasible to conduct. The results from this pilot study’s exploratory analysis of the primary clinical outcome (CRB rate) indicated similar CRB rates between the intervention and control arms, suggesting that a noninferiority design for the full study would be appropriate. The percentage of patients with a CRB was similar in the HIPPO-ST group (12%) compared to the control arm (11%); the rate of CRB was slightly higher in the HIPPO-ST Group (0.88/1000 catheter days) compared to the control arm (0.68/1000 catheter days), although both were under the threshold of an excellent CRB rate (1.0/1000 catheter days).[50] In addition, analysis of a secondary clinical outcome, SF-VAQ score, showed an improvement within the HIPPO-ST group in terms of their satisfaction with their catheter care relating to problems when bathing or showering; however, satisfaction was not a relatively greater

improvement than the control group condition. We found that compliance with the catheter care protocol was high, and contamination of patients in the control arm (i.e., using aspects of the HIPPO-ST) was not detected. The results of the HIPPO-ST pilot study indicate that on HIPPO-ST, patients are satisfied and compliant with the HIPPO-ST, which was designed specifically to meet their needs and minimize infection risk.[27]

Our findings are consistent with other studies of HD catheter care with a shower component.[51, 52] Both of these previous studies used a "no-dressing" shower technique in which the patients shower freely and do not have a dressing placed over the catheter entry site as part of their catheter care.[51, 52] However, the HIPPO-ST in the current study differs in that patients were trained, using the HIPPO-ST tools, on how to correctly cleanse the entry site and apply a dressing following a shower up to 3 times per week. Although these studies are not directly comparable, the investigators have consistently found that a patient showering with an HD catheter *in situ* did not demonstrate an increase in infection risk, and patients' quality of life was improved by not restricting their ability to shower.[51, 52, 53]

Another unique difference is that both prior studies did not test catheter entry site healing before introducing a shower component into catheter care, but instead used various time thresholds from the time of catheter insertion to determine shower technique eligibility.[51, 52] The use of the catheter entry site healing tests prior to randomization are a critical feature of the HIPPO-ST design. For unhealed catheter entry sites, there may be a potential increased risk of infection using any shower technique, including HIPPO-ST, by extraluminal exposure to microorganisms compared with standard catheter care due to the higher number of risk exposures from showering with or without dressing changes conducted by patients. As 4 patients failed to meet entry site healing randomization criteria despite

using a catheter for >6 weeks, our results suggest that duration of catheter use itself is not a reliable factor to ensure entry site healing.

A prior study in HD patients dialyzing via catheters demonstrated that patients were 3.8 times more likely to be compliant with their catheter care protocol (i.e., not to shower with a catheter *in situ*) if they recalled a health care provider educating them not to, compared with having no such recollection (95% CI = 1.2−4.5).24 This is consistent with the high compliance with the catheter care protocol found in our study after patient education and regular reinforcement of proper catheter dressing care and infection prevention.

From both clinical and research perspectives, it is critical to understand the infection rates and patient satisfaction associated with the HIPPO-ST in HD patients with healed catheter entry sites as a prophylactic strategy. The Centers for Disease Control and Prevention (CDC) guidelines state that the optimal method of catheter infection prophylaxis in patients with healed entry sites is an unresolved issue.54 This is reflected in a Canadian survey of 68 dialysis centers across Canada in which practice was found to be very inconsistent surrounding the recommendations made to patients for personal hygiene: 75% of centers recommended that patients clean themselves by bathing (nonsubmerged) or sponge bath, 38% recommended showering, and 5% made no recommendation at all (categories non−mutually exclusive).55Therefore, HD patients across Canada receive conflicting, inconsistent, or no recommendations about personal hygiene care techniques and whether or not they should preserve the dryness of their dressings to prevent catheter-related infection.

Lessons Learned About How to Design the Main Trial

Given the burden of catheter-related infection and the reduced quality of life of patients from restricting their ability to shower, the study question of whether the CRB rate for HD using HIPPO-ST is noninferior to that of patients using standard catheter care remains a pressing issue that the full HIPPO-

ST trial will ultimately address. Although the outcome of the CRB rate addresses the morbidity and mortality associated with the intervention being studied, we submit that equally important is patients' satisfaction with their vascular access and its care. Thus, the full potential benefit of the HIPPO-ST is best captured by including the SF-VAQ. This insight will be helpful in designing the full HIPPO-ST study, in which both hard and surrogate, clinical and patient-focused outcomes will be crucial to fully understanding the impact of the HIPPO-ST.45 When designing the full HIPPO-ST trial we will not aim to show a large difference in a single outcome; rather, we will be evaluating several dimensions of the patient experience to incrementally improve care. In addition, we originally planned to conduct the pilot study only in satellite units due to the perception that the satellite population may be more eligible (i.e., tend to be younger and have fewer co-morbidities) than in-center patients. However, this was not so, and recruitment rates were similar in both satellite and in-center units. Therefore, in the full trial, in-center units should be considered for inclusion.

Study Limitations

There are several limitations to this study. First, this study was a pilot study, and any examination of clinical outcomes is only exploratory. The full HIPPO-ST trial is needed to answer these clinical questions. In addition, there are no fully validated vascular access−specific questionnaires, including the SF-VAQ; however the full HIPPO-ST may provide an opportunity for construct validation of this measure.56, 57Moreover this study may be limited by selection bias, as many eligible patients declined to participate. Although we collected data on their reasons for declining to participate (Figure 1), constraints placed by the study REB prohibited collection of any additional sociodemographics or clinical data on these patients. Therefore we cannot examine whether these patients were systematically different from those who decided to participate. It is possible that patients at highest risk for infection, for example, were self-selecting out of participating in the trial. Recruitment is challenging when

conducting any clinical research study but is particularly difficult in RCTs. Indeed, we failed to meet our feasibility criteria on recruitment, despite using multiple strategies to facilitate recruitment, including identification of a nurse leader (such as a vascular access coordinator at each center), extensive in-servicing with all unit nurses, and expanding recruitment into some in-center units (as we originally planned to recruit only in satellites). However, the availability of the pilot study data to patients may help alleviate patient concerns, and facilitate recruitment in the future full HIPPO-ST study.

Conclusion

Overall, we found that the full HIPPO-ST study is feasible to conduct, with a high level of compliance with the HIPPO-ST, and low levels of contamination in the control arm. The conduct of the full HIPPO-ST study will address the current paucity of evidence surrounding showering aspects of catheter care allowing patients, HD personnel, and nephrologists to make informed choices about HD catheter care.

DISCLOSURE

All the authors declared no competing interests.

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TABLE, FIGURES, & SUPPLEMENTARY MATERIALS

Table 1. Criteria for participating in the Hemodialysis Infection Prevention Protocols Ontario—Shower Technique (HIPPO-ST): pilot randomized trial

Inclusion criteria
1. English speaking
2. Age ≥18 years
3. Required a catheter for vascular access: a) end-stage kidney disease (ESKD) without a functioning surgically created access; b) ESKD patient whose peritoneal dialysis problems required transfer to HD for an anticipated prolonged period
4. Was willing and able to take a shower as the standard form of body cleansing if randomized to HIPPO-ST
5. Trisodium citrate (4%) as standard catheter locking solution
6. Catheter has been *in situ* for >6 weeks
Exclusion criteria
1. Acute kidney failure, likely to be reversible with recovery of renal function
2. Nontunneled catheter
3. Antibiotic use by any route in the week prior to enrolling in the study, including intranasal mupirocin
4. On immunosuppressant therapy
5. Use of the catheter for purposes other than access for HD (e.g., TPN)
6. Involvement in another interventional study related to their vascular access

7. Catheter or patient life expectancy <6 months (e.g., active malignancy; serious comorbidity such as hepatic failure)
8. Routine use of TPA or antibiotic as a locking solution
9. Catheter insertion in location other than the neck/chest region (internal jugular or subclavian acceptable)

Note: ESKD, end-stage kidney disease; HD, hemodialysis; TPA, tissue plasminogen activator; TPN, total parenteral nutrition.

Table 2. Feasibility of Hemodialysis Infection Prevention Protocols Ontario—Shower Technique (HIPPO-ST): pilot randomized trial

Objective	Outcome measure	Criteria for success	Results
Primary objective is to determine the feasibility of the HIPPO-ST study design defined by 5 outcomes below:			
1. To assess the accuracy of capturing the CRB rate within the satellite HD setting	The level of agreement between the date the nurse contacts the coordinator to inform them of a suspected infection[a] and when the culture was sent to the laboratory	$\kappa > 0.80$	1.0
2. To determine the percentage of satellite HD patients with catheters who are screened[b]	The percentage of HD patients with catheters who are screened for eligibility among all HD patients	>95%	97.8%
3. To determine the percentage of eligible HD patients who consent	The percentage of consented eligible patients among all eligible patients	>80%	44.2%
4. To measure the success of HIPPO-ST teaching	The percentage of patients in the intervention arm passing the Shower Technique Test at 3 and 6 months	≥80% of patients randomized to HIPPO-ST	88.4%

5. To determine the percentage of participants in the control arm who are using aspects of the intervention	The percentage of controls who are using aspects of the HIPPO-ST that they were not using at baseline	<5% of participants in the control arm	0%

Note: HD, hemodialysis.

[a]Catheter-related infection defined by the Health Canada guidelines and determined by the independent event adjudication committee (see previously published protocol for full details27).

[b]Screening was challenging in remotely located satellite units (compared to in-center HD).

Table 3. Baseline Characteristics of Hemodialysis Infection Prevention Protocols Ontario—Shower Technique (HIPPO-ST) pilot study participants

Characteristic at baseline	Control % (n)	HIPPO-ST % (n)
Sociodemographics		
Mean age (yr)	53.00	58.41
Sex		
Male	58.8 (20)	64.5 (20)
Female	41.2 (14)	35.5 (11)
Ethnicity		
White	63.6 (21)	61.3 (19)
Black	6.1 (2)	12.9 (4)
East Asian	18.2 (6)	12.9 (4)

South Asian	12.1 (4)	12.9 (4)
Comorbidities		
Hypertension	64.7 (22)	80.6 (25)
Diabetes	55.9 (19)	61.3 (19)
Peripheral vascular disease	8.8 (3)	6.5 (2)
Coronary artery disease	32.4 (11)	38.7 (12)
Congestive heart failure	26.5 (9)	22.6 (7)
Stroke	8.8 (3)	9.7 (3)
Gastric bleeding	15.2 (5)	0.0 (0)
Chronic obstructive pulmonary disease	0.0 (0)	3.3 (1)
Malignancy	26.9 (7)	16.0 (4)
Chronic skin condition	11.8 (4)	6.5 (2)
Other conditions[a]	54.5 (18)	48.4 (15)
Catheter characteristics		
Mean length of follow up (catheter days)	167	172
Previous catheter use	67.9 (19)	52.2 (12)

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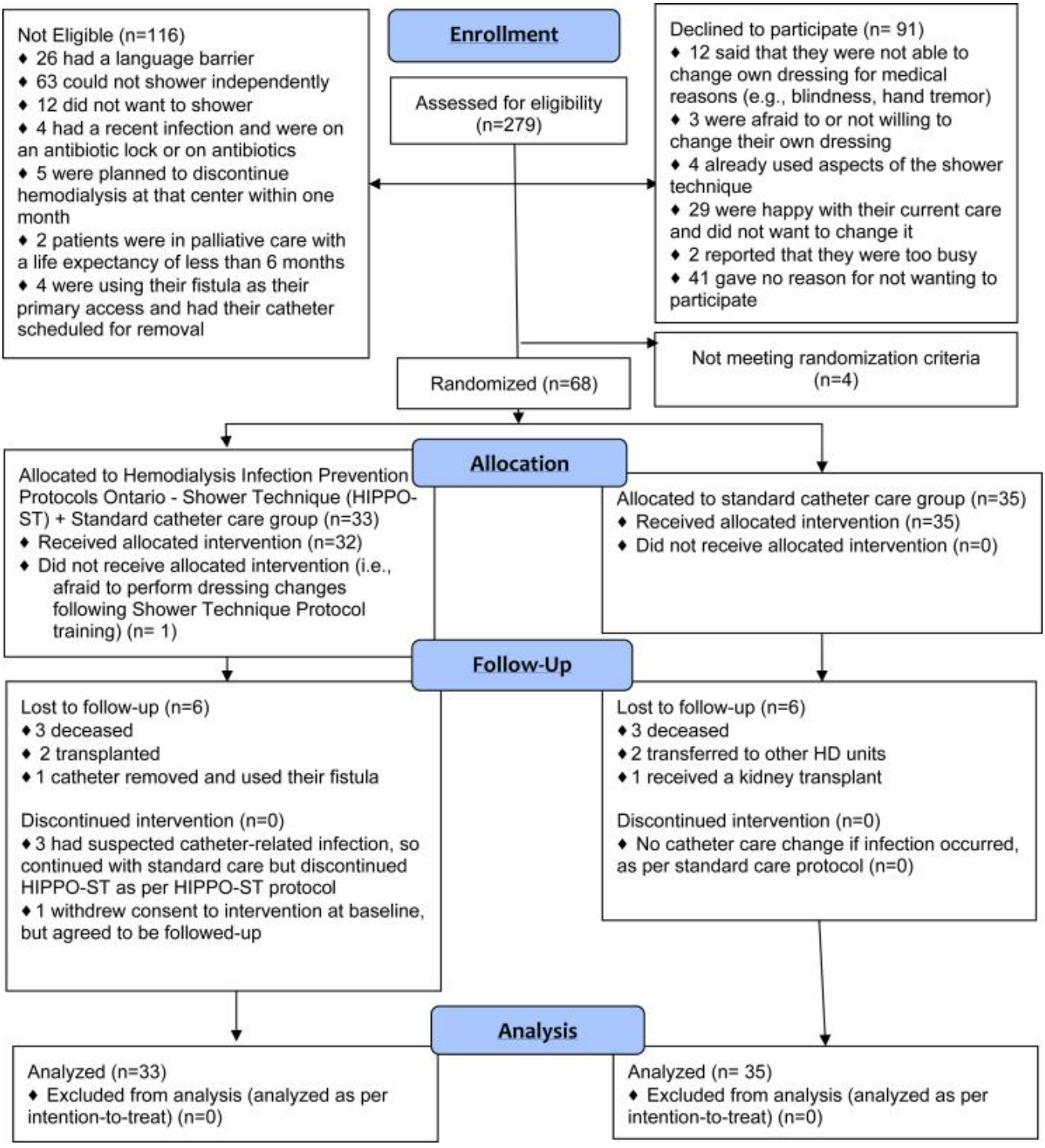
[a]Some other comorbidities included psychiatric disorders, rheumatologic conditions, gastrointestinal disorders, head injury, intracranial hemorrhage, and hematologic conditions.

Table 4. Rates and proportions of catheter-related infection in hemodialysis patients with healed catheter entry sites using Hemodialysis Infection Prevention Protocols Ontario—Shower Technique (HIPPO-ST) versus standard catheter care over 6 months

Catheter-related infection type	HIPPO-ST (n = 33)	Standard Care (n = 35)	Mean difference (95% CI)
Bacteremia			
Rate/1000 catheter days	0.88	0.68	0.16 (−2.25 to 2.65)
Proportion % (SD)	12.1 (0.33)	11.4 (0.318)	0.7 (−16 to 17)
Entry site			
Rate/1000 catheter days	0.88	0.68	0.16 (−2.25 to 2.65)
Proportion % (SD)	12.1 (0.33)	11.4 (0.318)	0.7 (−16 to 17)
Tunnel			
Rate/1000 catheter days	0.35	0	0.35 (−0.81 to 1.51)
Proportion % (SD)	6.1 (0.24)	0 (0)	6.1 (−2.1 to 14)

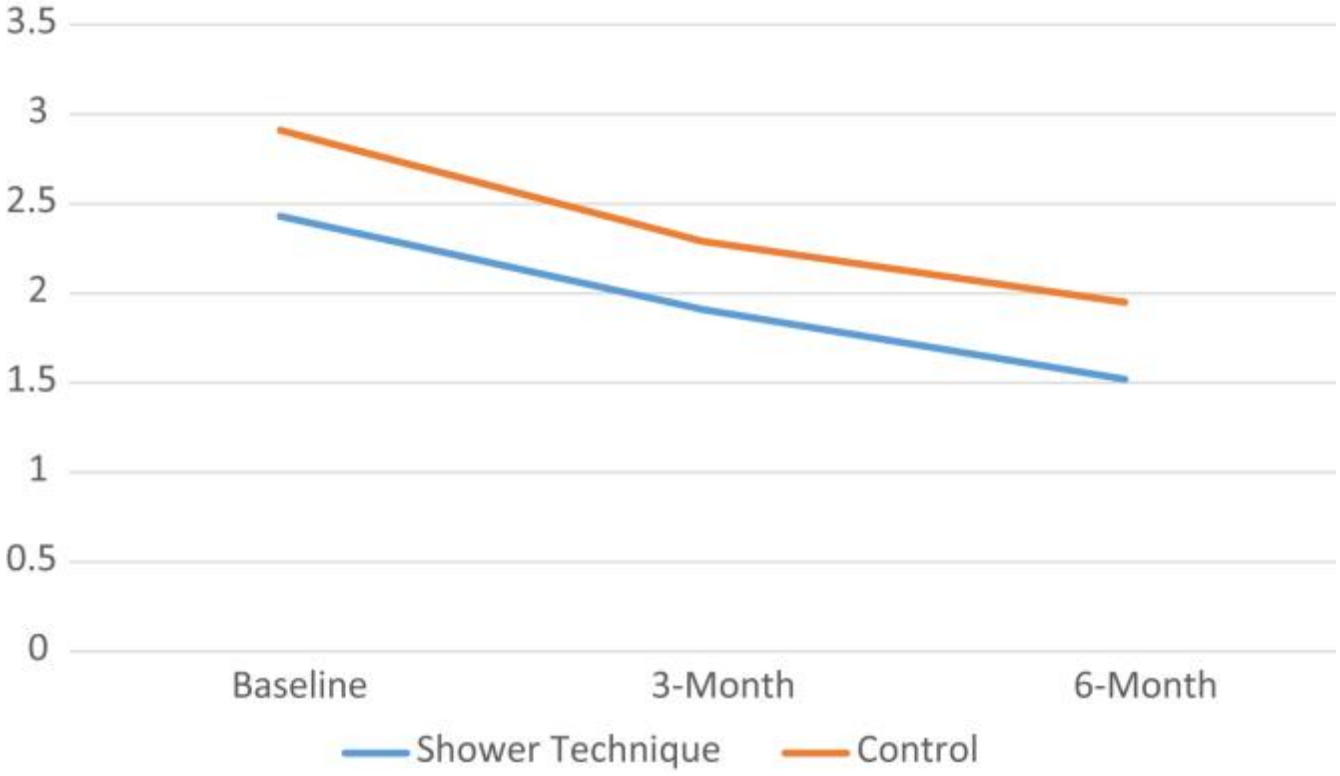
Note: Rates and proportions compared with Poisson distribution. CI, confidence interval.

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram



Note: HD, hemodialysis; HIPPO-ST, Hemodialysis Infection Prevention Protocols Ontario—Shower Technique

Figure 2. Patient-reported levels of problems associated with vascular access when bathing or showering in hemodialysis patients with healed catheter entry sites using Hemodialysis Infection Prevention Protocols Ontario—Shower Technique (HIPPO-ST) versus standard catheter care over 6 months



Note: The y-axis represents the level of agreement with the item "During the past 4 weeks my vascular access caused me problems when I was bathing or showering," which was rated by using a 7-point Likert scale from 1 (strongly disagree) to 7 (strongly agree).

Supplementary Material 1. CONSORT 2010 checklist of information to include when reporting a randomized trial.

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	4,15
Participants	4a	Eligibility criteria for participants	Table 1

	4b	Settings and locations where the data were collected	4-5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5-6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8 (Table 2)
	6b	Any changes to trial outcomes after the trial commenced, with reasons	4
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7-8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7-8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps	7-8

		taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7-8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	7-8
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9, Table 2
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1

Recruitment	14a	Dates defining the periods of recruitment and follow-up	9
	14b	Why the trial ended or was stopped	9
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 2, Table 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Supplementary material 2

Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	11
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13-14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12-13
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1, 16

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are

forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Supplementary Material 2. Self-reported satisfaction with vascular access measured on Short-form Vascular Access Questionnaire (SF-VAQ) in hemodialysis patients with healed catheter entry sites using Hemodialysis Infection Prevention Protocols Ontario - Shower Technique (HIPPO-ST) versus standard catheter care over 6 months.

SF-VAQ Item	Baseline		3 month		6 month	
	HIPPO-ST	Control	HIPPO-ST	Control	HIPPO-ST	Control
Overall satisfaction with vascular access	5.73	5.94	6.24	6.25	5.73	6.68
During the past 4 weeks I was bothered by pain associated with my vascular access	1.27	1.41	1.45	1.25	1.24	1.09
During the past 4 weeks I was bothered by bleeding associated with my vascular access	1.03	1.31	1.45	1.25	1.19	1.00
During the past 4 weeks I was bothered by swelling associated with my vascular access	1.07	1.03	1.27	1.21	1.14	1.05
During the past 4 weeks I was bothered by bruising	1.33	1.56	1.45	1.46	1.14	1.00

associated with my vascular access						
During the past 4 weeks my vascular access interfered with my daily activites	1.83	2.63	1.95	2.29	1.57	1.64
During the past 4 weeks I was bothered by the appearance of my vascular access	2.43	1.87	2.41	1.96	2.24	1.73
During the past 4 weeks I my vascular access interfered with my sleep	2.57	2.41	2.14	1.93	2.29	1.55
During the past 4 weeks my vascular access caused me problems when I was bathing or showering	2.43	2.91	1.91	2.29	1.52	1.95
During the past 4 weeks my vascular access had problems	2.47	2.28	1.68	2.07	2.52	1.95
During the past 4 weeks my vascular access was difficult to care for	1.50	1.63	1.27	1.71	1.48	1.23
During the past 4 weeks I was worried about being	2.07	1.63	1.91	2.14	1.95	1.23

hospilitized because of my vascular access						
During the past 4 weeks I was worried about how long my vascular access will last	3.03	2.69	2.41	3.30	2.76	1.91
Overall degree of dissatisfaction	1.92	1.94	1.78	1.91	1.75	1.44

Note: The Vascular Access Questionnaire is a measure of patient satisfaction with their vascular access that is previously not validated in this population. Satisfaction is measured using the above items, rated on a 7 point Likert scale from 1 (strongly disagree) to 7 (strongly agree).

CHAPTER FIVE
REPORTING QUALITY OF PILOT CLINICAL TRIALS IN CHRONIC KIDNEY DISEASE PATIENTS ON HEMODIALYSIS: A METHODOLOGICAL SURVEY

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ABSTRACT

Background

The conduct of high-quality pilot studies can help inform the success of larger clinical trials. Guidelines have been recently developed for the reporting of pilot trials.

Objective

This methodological survey evaluates the completeness of reporting in pilot randomized controlled trials in chronic kidney disease patients on hemodialysis (HD patients) and explores factors associated with better completion of reporting.

Methods

The authors searched Pubmed on July 1, 2018, for all pilot trials conducted in HD patients. Reporting quality was assessed against the 40-item Consolidated Standards of Reporting Trials (CONSORT) Extension for Pilot Trials. Study factors including year and country of publication, intervention, number of centers, type of funding, and journal endorsement of CONSORT were also examined.

Results

The mean number of items reported from the CONSORT extension for pilot trials across all included articles was 18.4 (standard deviation [SD] = 4.4). In the adjusted analysis, studies reported in later years (IRR = 1.026, 95% CI [1.018, 1.034], $p < 0.001$) and an increase of 20 persons in sample size (adjusted IRR = 1.021, 95% CI [1.010, 1.031], $p < 0.001$) were associated with a significantly higher number of CONSORT pilot items reported.

Conclusions

Current reporting completeness of pilot trials in HD patients is suboptimal. Endorsing the CONSORT extension specific to pilot and feasibility studies and ensuring that pilot trials focus on the feasibility objectives may improve reporting completeness of these trials.

BACKGROUND

Chronic kidney disease (CKD) is a significant and growing global health problem, with a prevalence estimated to be between 11 to 13% [1]. CKD is defined as having a decreased kidney function for at least 3 months, regardless of the etiology, and has many serious complications such as uremia, volume overload, and hematologic and metabolic disturbances [2, 3]. Risk of mortality, largely due to cardiovascular disease, is significantly increased in the CKD population and increases as kidney function declines [2]. An estimated two million CKD patients with very little or no residual kidney function require kidney replacement therapy [4]. Kidney replacement therapy is very costly, consuming 6.7% of the total Medicare budget to care for less than 1% of the covered population. The costliest modality is hemodialysis (HD), estimated at over US$87,000 per year per patient [5]. Despite significant investment into research in the last 40 years, survival and quality of life of patients on HD remain low [6].

There are many pressing clinical questions in HD which require a definitive, well-powered randomized clinical trial (RCT) [7]. Health care providers and patients alike have identified the need for further research across a range of priorities in HD including how to best address vascular access problems, reduce fatigue, risk of mortality, and cardiovascular disease and to improve dialysis adequacy [6]. However, the immense quantity of information and resources required for the conduct of adequately powered RCTs across these clinical areas in HD can act as a barrier to their conduct [7, 8]. Pilot studies can facilitate designing such definitive RCTs by assessing feasibility of screening, recruitment, coordination and acceptability, safety, and fidelity of the intervention and the study protocol, as well as informing power calculations [7, 9, 10].

However, pilot trial methodology is often criticized for inadequacies, mainly critiquing the emphasis on hypothesis testing and the lack of criteria for evaluating feasibility [11, 12]. To address these issues, the

Consolidated Standards of Reporting Trials (CONSORT) extension for reporting randomized pilot and feasibility trials was published in 2016, which builds on the statement published in 2010 [13]. The 2016 CONSORT extension, which will be utilized in this study, lays the groundwork for the reporting of pilot trials, as well as informs their design and implementation. This is expected to enhance the completeness and transparency in the reporting of pilot RCTs and establish a standardized approach to this area of research [13].

Until recently, standards for the reporting of pilot studies have been unavailable and it is likely that there are significant gaps and inconsistencies in the reporting of pilot studies in HD—as similarly identified in other areas of clinical research [14]. Identification of these gaps may not only help inform initiatives to improve reporting, but also potentially raise awareness among clinicians and research about pilot trial design and implementation. Using the newly published CONSORT extension for pilot trials, we undertook a methodological survey to assess reporting completeness among pilot trials investigating interventions in CKD patients on hemodialysis (HD patients) and explored factors associated with better completion of reporting. A methodologic review is a type of study designed to examine methodologic quality of a sample of articles, generally within a certain discipline or study design [14,15,16].

METHODS

Study eligibility

Inclusion criteria: (1) the words “pilot” or “feasibility” used to describe its design, (2) randomized control trial, (3) examine interventions in HD patients, and (4) published in English.

Exclusion criteria: (1) single-arm observational pilot or feasibility studies, (2) quasi-randomized trials, and (3) studies among nonclinical or acute populations.

Search strategy

In order to survey the medical literature for pilot trials in HD patients, we searched Medline/Pubmed and included studies published before July 1, 2018, using the following strategy: (1) feasibility studies/ or pilot projects/; (2) pilot stud*.mp.; (3) exp Randomized Controlled Trial/; (4) randomized controlled trial.pt.; (5) controlled clinical trial.pt.; (6) randomized controlled trials.sh.; (7) random allocation.sh.; (8) double-blind method.sh.; (9) single-blind method.sh.; (10) 3 or 4 or 5 or 6 or 7 or 8 or 9; (11) (animals not humans).sh.; (12) 10 not 11; (13) 1 or 2; (14) 12 and 13; (15) exp Renal Dialysis/; (16) renal dialysis.tw.; (17) 15 or 16; (18) hemodialysis.tw.; (19) haemodialysis.tw.; (20) 17 or 18 or 19; (21) exp peritoneal dialysis/; and (22) 20 not 21.

Study selection

One author (SK) screened all titles and abstracts based on the inclusion and exclusion criteria and conducted a full-text review of randomly selected citations to assess eligibility. The full-text articles were then screened independently and in duplicate for eligibility by three teams of reviewers (AL and SL, DS and SV, and SS and SS).

Outcome measures

The primary outcome of this survey was the completeness of reporting of each of the items on CONSORT statement extension for randomized pilot and feasibility trials checklist, measured as a number and proportion of studies reporting each of the 40 items. The secondary outcome was the completeness of reporting of the CONSORT statement extension for randomized pilot and feasibility trials checklist, as measured by the total number of applicable items reported.

Data extraction

The Excel-based data extraction form was developed based on a previous methodological survey [16] and collected study characteristics including year and country of publication, sample size, number of

sites, type of funding (i.e., industry, non-industry), type of intervention (i.e., pharmaceutical, behavioral/educational, dialysis technology/technique, nutritional supplements, vascular access technology/technique, and other non-pharmaceutical interventions), whether the manuscript explicitly stated the pilot study to be prelude to definitive study (i.e., yes, no), journal endorsement of CONSORT statement if the article was published after 2010 (i.e., yes, no), and reporting of individual items on the CONSORT extension for pilot and feasibility studies (Additional file 1). For the reporting of individual items on the CONSORT extension for pilot and feasibility studies, each item on the checklist was scored as either "reported" or "not reported," indicating whether or not the article reported the appropriate information as per the criteria outlined in the original publication (Table 1). Exceptions to this are items 6c, 7b, 11a, 11b, 18, and 19a, all of which had "not applicable" as an option [13].

Data analysis

All statistical analyses were performed in SPSS version 25.

Descriptive statistics

The completeness of reporting was summarized using descriptive statistics percentages for the general characteristics and number of articles reporting each CONSORT statement item (for items 6c, 7b, 11a, 11b, 18, and 19a, the percentage was calculated based on the total number of studies for which the item was applicable). The mean, standard deviation, and range for the total number of CONSORT statement items reported, sample size, and number of sites were also calculated. To calculate the mean number of CONSORT items reported, "not applicable" responses to reporting items 6c, 7b, 11a, 11b, 18, and 19a were excluded.

Inferential statistics

We conducted a Poisson regression to explore factors, including year of publication, sample size, multisite study (yes or no), industry funding (yes or no), prelude to a definite trial (yes or no), and

journal endorsement of CONSORT (yes or no), associated with completeness of reporting as measured by the number of reported CONSORT items ("not applicable" items were excluded). Based on previous research, we hypothesized that a later publication date [17], larger sample size [18], multisite study [16], industry funding [16, 18, 19], and journal endorsement of CONSORT [20] would be associated with better reporting. The results of the Poisson regression were reported as unadjusted and adjusted incidence rate ratios (IRR) including 95% confidence interval (CI) and *p* value ($\alpha = 0.05$). Journal of publication was also considered as a potential factor to include in the Poisson regression as some clustering has been observed in prior studies on reporting [16, 18]; however, no clustering within journals was noted in exploratory analyses, likely due to the wide breadth of journals in which the included studies were published, with no more than 10 studies published in the same journals (see characteristics of included studies below).

RESULTS

Our initial search retrieved 593 records, of which 86 were included in the synthesis (see Fig. 1 for PRISMA diagram).

Characteristics of included studies

The studies examined a wide range of interventions (see Table 2) including pharmaceutical (33.7%, e.g., magnesium carbonate plus calcium acetate, oral cholecalciferol), behavioral/educational (19.8%, e.g., cycling, resistance, or cycling and resistance, chairside meditation), dialysis technology/technique (17.4%, e.g., equilibrated kt/v goal of 1.4, fx-e membrane), nutritional supplements (14.0%, e.g., fish oil), vascular access technology/technique (12.8%, e.g., dialysis needles placed 2.5 cm and then 5 cm apart, u clip anastomosis), and other non-pharmaceutical interventions (2.3%, i.e., acupuncture, low-intensity vibration device). The majority of the studies were single center (68.6%) and had a sample

size of 50 or less (74.4%). The mean sample size was 44.0 (standard deviation (SD) = 55.1, range = 4–448) and number of sites was 2.2 (SD = 2.7, range = 1–15).

The studies were conducted across the globe, including Africa (1.2%), Asia (15.1%), Australia/New Zealand (7.0%), Europe (27.9%), and North America (48.8%). The majority of studies were published since 2010 (60.5%). Among those published since 2010, 42.9% were published in journals that endorse the CONSORT statement. Only 17.4% of studies explicitly indicated in the manuscript that the study was a prelude to a definitive trial. The studies were published across a wide range of journals, with 10 studies published in *J Ren Nutr*, 8 in *Am J Kidney Dis*, 5 in *Nephrol Dial Transplant*, 4 in *J Vasc Access*, 3 in each of *Clin J Am Soc Nephrol*, *J Nephrol*, *Nephrology* (*Carlton*), and *Ther Apher Dial*, 2 in each of *Int Urol Nephrol*, *Kidney Int*, *Pharmacotherapy*, and *PLoS One*, with the remaining 39 studies published in different journals.

Evaluation of reporting quality based on CONSORT extension

The mean CONSORT reporting score across all included articles was 18.4 (SD = 4.4, minimum = 8, maximum = 29) out of a possible 34 items (6c, 7b, 11a, 11b, 18, and 19a were excluded as they had a not applicable option). Table 1 shows the level of reporting of individual CONSORT items. The items reported by the largest proportion of articles (top 10%) were “2b. Specific objectives or research questions for pilot trial” (97.7%); “4a. Eligibility criteria for participants” (93.0%); “12. Methods used to address each pilot trial objective whether qualitative or quantitative” (97.7%); and “22. Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence” (97.7%).

The most poorly reported items (bottom 10%) were “3b. Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons” (5.8%); “6b. Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons” (3.5%); “6c. When

applicable, explanation of any interim analyses and stopping guidelines" (7.9%); and "24. Where the pilot trial protocol can be accessed, if available" (8.1%).

Factors related to reporting of CONSORT extension items

Table 3 shows the unadjusted and adjusted IRRs for overall CONSORT reporting by study characteristics. In comparing the total number of reported CONSORT items by the prespecified study characteristics, studies reported in later years (adjusted IRR = 1.026, 95% CI [1.018, 1.034], $p < 0.001$) and an increase of 20 persons in sample size (adjusted IRR = 1.021, 95% CI [1.010, 1.031], $p < 0.001$) had a significantly higher number of CONSORT pilot items reported. After adjusting for other covariates and factors, the remaining study characteristics were not significantly associated with reporting completeness.

DISCUSSION

In this systematic survey, one of the few to examine the completeness of reporting in pilot and feasibility RCTs [14], we found that the mean number of CONSORT extension items for pilot and feasibility studies was 18.4 out of a possible 34 applicable items. We did find, however, that there is a 2.6% increase in the number of CONSORT pilot items reported for each additional year of publication. Larger sample sizes were also associated with higher number of CONSORT pilot items reported; however, the observed effect was relatively small (e.g., there is a 2.1% increase in reporting completeness for an increase in sample size of 20 participants). The number of reported items may continue to improve over time, particularly with the 2016 publication of the CONSORT extension for pilot and feasibility RCTs. Indeed, the completeness of reporting full RCTs in nephrology has improved over time, though reporting quality issues for certain CONSORT (2010) items such as clinical trial design, mode of randomization, and intention-to-treat analysis persist [8, 21,22,23]. Lack of available guidelines prior to the CONSORT extension and lack of its awareness (only recently

published) could be contributing to this suboptimal reporting [13]. These guidelines may help clarify the purpose and reporting of pilot studies in HD patients.

In our sample of pilot studies, we found that the reporting of some items was consistently reported. These items are very similar to those included in the 2010 CONSORT statement, and include specific objectives for the pilot trial, eligibility criteria for participants, methods used to address each pilot trial objective whether qualitative or quantitative, and the interpretation is consistent with pilot trial objectives and findings. However, certain items specific to pilot trials and clinical trial conduct transparency were reported in less than 10% of included studies which, as previously indicated, may be attributable to lack of reporting guidelines for pilot trials until recently. These include changes to methods and assessments or measurements after pilot trial commencement, progression criteria for a future definitive trial, and where the pilot trial protocol can be accessed. These items are critical to the development of a larger, definitive trial that is rigorously designed and well powered, which should be the primary purpose of a pilot study [9]. The low levels of reporting for these items is consistent with our finding that only 17.4% of included studies indicated that they were a prelude to a larger trial, as well as the findings of a previous study on reporting completeness in pilot trials in behavioral interventions (13%) [14]. The manuscripts may not have explicitly stated the pilot study to be a prelude to a definitive study (CONSORT 2a and 22a) as this might be assumed by authors given that it is the purpose of a pilot study; however, this should be explicitly reported for every study as recommended by the guidelines.

Many of the included studies were primarily designed to address questions of clinical efficacy of a wide range of interventions. Given the relatively small sample of the majority of the included trials, these studies were likely underpowered to do so. Though some items were well reported, going forward, it is critical that journals publishing pilot trials in HD patients ensure that these studies adhere

to the pilot trial extension to the CONSORT reporting statement, as well as confirm that the primary objectives of these studies are related to feasibility—not efficacy—objectives. This may be accomplished as part of the peer review process or as a requirement of submission.

There are several limitations of this study that are important to acknowledge. We only included English-language studies due to feasibility purposes, which may limit the generalizability of these findings. As this was a methodological survey and not a systematic review, this study's search was restricted to PubMed. Additionally, there may have been factors important to consider in completeness of reporting that we failed to capture in this study.

CONCLUSIONS

Pilot and feasibility trials of interventions in HD patients can help to inform the design of well-powered clinical trials to address critical challenges in HD today and prevent waste of resources on poorly designed trials [22, 24]. The pilot studies conducted in this patient population over the last two decades examine a wide range of interventions from pharmaceutical to behavioral; however, they were largely not preludes to larger trials. Improving the reporting completeness of these trials through promotion and endorsement of the CONSORT extension specific to pilot and feasibility trials and ensuring that pilot trials focus on feasibility objectives may improve the utility of these pilot trials. Such pilot studies are needed in HD patients to help inform and design interventional trials that are "…sufficiently robust to provide reliable answers and are not constrained by inappropriate complexities in design or conduct" ([24], p., 297).

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Availability of data and materials

The dataset supporting the conclusions of this article is included in its additional file.

Contributions

SDK, AG, CL, and LT designed the study. SDK performed the literature search and conducted the title and abstract screening. AL, SL, SSi, SSz, DS, and SV extracted data from the included published manuscripts. SDK performed the data analyses and SDK, JM, AG, CL, and LT interpreted the data. All authors were involved in the drafting of the manuscript and read and approved the final manuscript.

ETHICS DECLARATIONS

Ethics approval and consent to participate

As this a methodological review and does not involve human subjects, ethics board approval was not sought for this study.

Consent for publication

As this a methodological review and does not involve human subjects, consent for publication was not sought for this study.

Competing interests

The authors declare that they have no competing interests.

TABLE, FIGURES, & SUPPLEMENTARY MATERIALS

Table 1. Reporting of items on the CONSORT Extension for Pilot and Feasibility Trials

CONSORT Items	***n***	**%**	**Lower 95% CI**	**Upper 95% CI**	***N***
Title and Abstract					
1a. Identification as a pilot or feasibility randomized trial in the title	52	60.5%	49.9%	70.3%	86
1b. Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	79	91.9%	84.7%	96.3%	86
Introduction					
2a. Scientific background and explanation of rationale for future definitive trial, and reasons for randomized pilot trial	23	26.7%	18.3%	36.8%	86
2b. Specific objectives or research questions for pilot trial	84	*97.7%*	92.7%	99.5%	86
Methods					
Trial design					
3a. Description of pilot trial design (such as parallel, factorial) including allocation ratio	36	41.9%	31.8%	52.4%	86
3b. Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	5	**5.8%**	2.3%	12.3%	86
Participants					

4a. Eligibility criteria for participants	80	*93.0%*	86.2%	97.0%	86
4b. Settings and locations where the data were collected	57	66.3%	55.9%	75.6%	86
4c. How participants were identified and consented	58	67.4%	57.1%	76.6%	86
Interventions					
5. The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	74	86.0%	77.6%	92.1%	86
Outcome measurement					
6a. Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	79	91.9%	84.7%	96.3%	86
6b. Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	3	**3.5%**	1.0%	9.0%	86
6c. If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial*	7	9.0%	4.1%	16.8%	78
Sample size					
7a. Rationale for numbers in the pilot trial	24	27.9%	19.3%	38.0%	86
7b. When applicable, explanation of any interim analyses and stopping guidelines*	3	**7.9%**	2.3%	19.6%	38
Randomization					
8a. Method used to generate the random allocation sequence	30	34.9%	25.4%	45.3%	86

8b. Type of randomization(s); details of any restriction (such as blocking and block size)	24	27.90%	19.3%	38.0%	86
Allocation concealment mechanism					
9. Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	22	25.60%	17.3%	35.5%	86
Implementation					
10. Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	16	18.60%	11.5%	27.8%	86
Blinding					
11a. If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how*	33	43.40%	32.7%	54.6%	76
11b. If relevant, description of the similarity of interventions*	20	71.40%	53.2%	85.5%	28
Statistical methods					
12. Methods used to address each pilot trial objective whether qualitative or quantitative	84	*97.70%*	92.7%	99.5%	86
Results					
Participant flow					

13a. For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	62	72.10%	62.0%	80.7%	86
13b. For each group, losses and exclusions after randomization, together with reasons	66	76.70%	67.0%	84.7%	86
Recruitment					
14a. Dates defining the periods of recruitment and follow-up	37	43.00%	32.9%	53.6%	86
14b. Why the pilot trial ended or was stopped	8	9.30%	4.5%	16.8%	86
Baseline data					
15. A table showing baseline demographic and clinical characteristics for each group	72	83.70%	74.9%	90.4%	86
Numbers analyzed					
16. For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomized group	39	45.30%	35.1%	55.9%	86
Outcomes and estimation					
17. For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomized group	70	81.40%	72.2%	88.5%	86

Ancillary analyses					
18. Results of any other analyses performed that could be used to inform the future definitive trial*	13	21.30%	12.5%	32.8%	61
Harms					
19. All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	48	55.80%	45.3%	66.0%	86
19a. If relevant, other important unintended consequences*	19	27.90%	18.4%	39.4%	68
Discussion					
Limitations					
20. Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	63	73.30%	63.2%	81.7%	86
Generalisability					
21. Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	38	44.20%	34.0%	54.7%	86
Interpretation					
22. Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	84	*97.70%*	92.7%	99.5%	86
22a. Implications for progression from pilot to future definitive trial, including any proposed amendments	14	16.30%	9.6%	25.1%	86
Other information: Registration					

23. Registration number for pilot trial and name of trial registry	27	31.40%	22.3%	41.7%	86
Protocol					
24. Where the pilot trial protocol can be accessed, if available	7	**8.10%**	3.7%	15.3%	86
Funding					
25. Sources of funding and other support (such as supply of drugs), role of funders	61	70.90%	60.8%	79.7%	86
26. Ethical approval or approval by research review committee, confirmed with reference number	53	61.60%	51.1%	71.4%	86

Note: Italics indicates bottom 10%, and bold indicates top 10%

*Studies for which the item was not applicable were not included in the total *N*

N = total number of studies (i.e., numerator); *n* = count

Table 2. Characteristics of included articles

Characteristics		**Count**	**%**
Intervention type (*N* = 86)	Behavioral/educational	17	19.8%
	Dialysis technology/technique	15	17.4%
	Non-pharmaceutical other	2	2.3%
	Nutritional supplement	12	14.0%
	Pharmaceutical	29	33.7%
	Vascular access technology/technique	11	12.8%
Number of sites (*N* = 86)	Multi center	27	31.4%
	Single center	59	68.6%
Sample size (*N* = 86)	Greater than 50	22	25.6%
	50 or less	64	74.4%
Industry funded (*N* = 86)	Yes	26	30.2%
	No	60	69.8%
Location of study by continent (*N* = 86)	Africa	1	1.2%
	Asia	13	15.1%
	Australia/New Zealand	6	7.0%
	Europe	24	27.9%
	North America	42	48.8%
Year of publication (*N* = 86)	1990–1995	1	1.2%
	1996–2000	8	9.3%

	2001–2005	10	11.6%
	2006–2010	15	17.4%
	2011–2015	38	44.2%
	2016–2018	14	16.3%
Journal endorses CONSORT (only published in 2010 or later)* ($N = 56$)	Yes	24	42.9%
	No	32	57.1%
Journal endorses CONSORT (all years, all published before 2010 set to No)** ($N = 86$)	Yes	24	27.9%
	No	62	72.1%
Prelude to definitive trial ($N = 86$)	Yes	15	17.4%
	No	71	82.6%

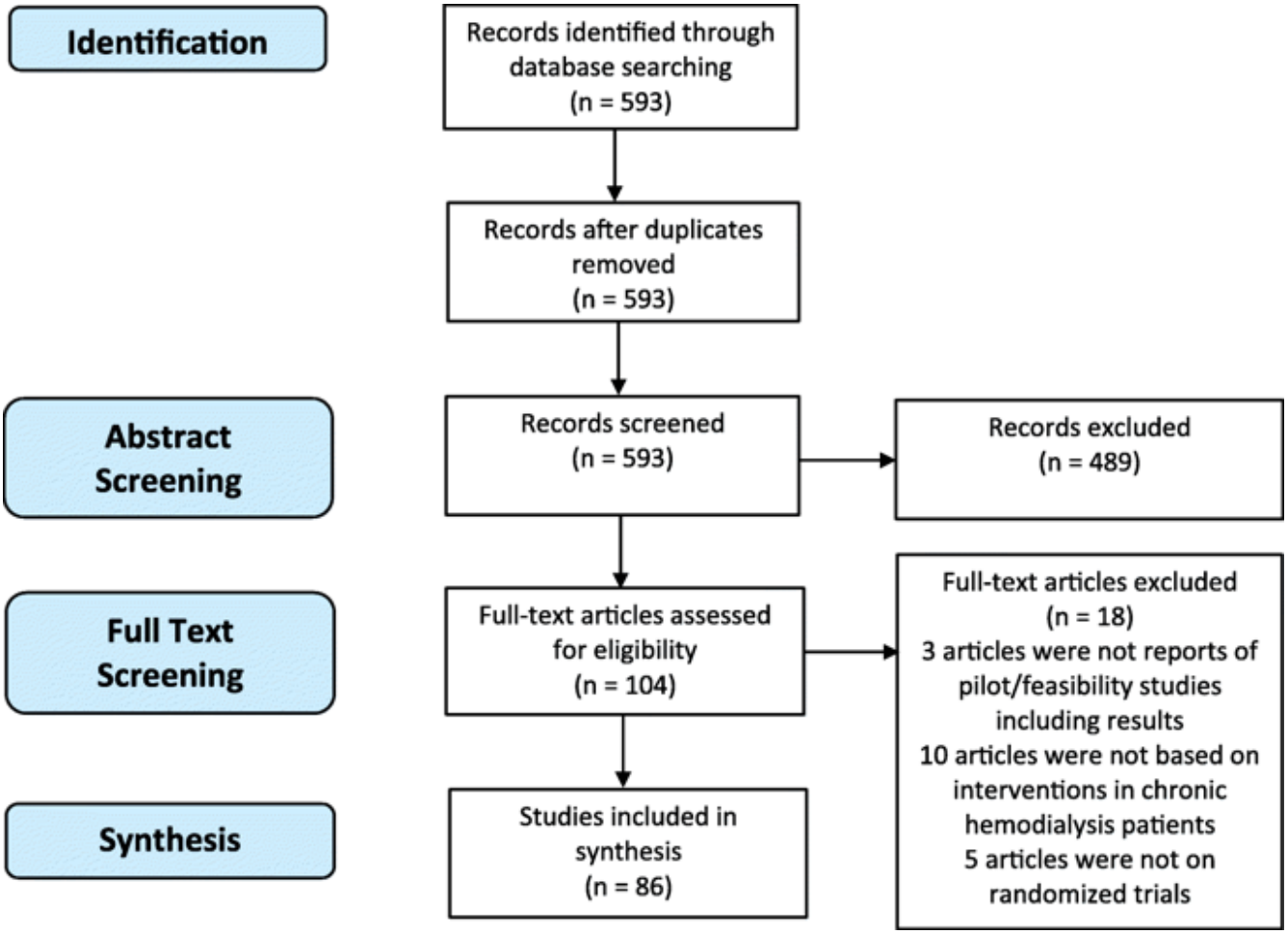
**CONSORT* Consolidated Standards of Reporting Trials; only includes studies published in 2010 or later

**Includes all studies, with all studies published before 2010 set to No

Table 3. Incidence rate ratios for the total number of CONSORT Pilot Trial Extension Items Reported

Variable	**Unadjusted incident rate ratio (95% confidence interval)**	***P*-value**	**Adjusted incident rate ratio (95% confidence interval)**	***P*-value**
Year	1.025 (1.017, 1.032)	< 0.001	1.026 (1.018, 1.034)	< 0.001
Sample size (1 unit increase = 20 participants)	1.019 (1.004, 1.035)	0.011	1.021 (1.010, 1.031)	< 0.001
Multisite study (single center)	0.966 (0.870, 1.073)	0.520	1.030 (0.941, 1.128)	0.517
Industry funding (non-industry funding)	1.026 (0.922, 1.142)	0.639	0.976 (0.880, 1.082)	0.639
Prelude to future definitive trial (not a prelude)	1.070 (0.909, 1.260)	0.416	1.033 (0.900, 1.185)	0.645
Journal endorses CONSORT (does not endorse)	1.122 (1.001, 1.258)	0.049	0.978 (0.870, 1.099)	0.704

Figure 1. PRISMA 2009 Flow Diagram



Additional file 1. Pilot clinical trials in chronic kidney disease patients on hemodialysis.

Accessible at: https://static-content.springer.com/esm/art%3A10.1186%2Fs40814-019-0436-3/MediaObjects/40814_2019_436_MOESM1_ESM.xls

The sample of pilot clinical trials in chronic kidney disease patients on hemodialysis included in the methodological survey. The data dictionary is included in the second tab. (XLS 158 kb)

CHAPTER SIX
CONCLUSION

This thesis focuses on four issues in chronic kidney disease including the need for: (1) technology that can support hemodialysis patients in the management of their nutrition and encourage their adherence to often-complex dietary restrictions; (2) costing data to inform hemodialysis vascular access policy and practice; (3) a hemodialysis central venous catheter (catheter) care protocol that minimizes infection risk and cost while allowing the patient to shower; and (4) well conducted and reported pilot studies to enhance the design of randomized clinical trials. In this concluding chapter, the key results, methodological limitations, and their potential implication for clinical practice and future research are summarized.

The first study presented in this thesis examined chronic kidney disease dietary mobile app interventions including their characteristics, feasibility, user satisfaction, and effectiveness in changing behavior/clinical outcomes. The 13 included studies were almost all single-centre and all had a sample size less than 50. The types of studies include were diverse: 4 were needs assessment/design studies, 2 were case studies, 5 were nonrandomized pilot studies, and 2 were randomized pilot studies. The large majority of apps allowed patients to track their food intake like a food diary, had a calorie-counting function, and provided dietary recommendations regarding minerals. The 4 needs assessment/design studies emphasized the need for such an app,[1-4] particularly one that is accessible on different platforms,[1] has an easy-to-use inferface,[2] is free of malfunctions or errors,[2] has colorful and interactive games/tools/features directed toward pediatric patients,[3] has clear food icons, [4] and is complemented by a nutritional scanner.[4] Of the 7 studies that evaluated usability/feasibility of a mobile app, all found some aspect of the applications feasible/useful.[5-11] Among the 5 studies that measured changes in

dietary behavior, all reported some positive change, including changes in calories,[8, 9] interdialytic weight gain, [5] protein,[8,9] albumin,[12] sodium, [5,9,10] phosphorus,[5, 12] and potassium.[5]

The limitations of this systematic review included restrictions to English-language studies, the lack of full randomized controlled trials in the sample of included studies, the exploratory nature of the included studies, and the relatively short time frame of less than 6 months for outcome evaluations. Due to the variety of study designs a meta-analysis or a quality assessment across the studies could not be conducted. In full consideration of the limitations of the available evidence, there is some suggestion that there is promise for mobile apps to support hemodialysis patients in the management of their often-complex dietary restrictions. In future research, larger, more definitive studies are needed in more diverse samples that evaluate these mobile apps for both user and healthcare provider satisfaction/usability and changes in nutritional markers/clinical outcomes.

The second study examined the total costs of attaining and maintaining patency of arteriovenous access, both fistula and graft, over one, three, and five years among incident hemodialysis patients. The impact of arteriovenous access type and the failure to mature risk score on cost was examined. The failure to mature risk score, is a validated score currently in use in clinical settings based on ethnicity, age, and co-morbidities which predicts the likelihood of a fistula failing to mature, if placed.[13] Increasing failure to mature risk score was associated with increasing present value of total vascular access related costs. Interestingly, while fistulas had higher rates of interventions associated with attaining patency and grafts had higher rates of intervention associated with maintaining patency, as is consistent with previous clinical studies,[14-17] arteriovenous access type was not associated with increasing present value of total vascular access related costs, after adjusting for failure to mature risk score.

This study is limited by our approach of calculating a modeled estimate of the access-related cost, based on the timing and number of events prospectively captured over the access lifetime and unit costs obtained from a provincial costing database, as opposed to the actual costs accrued. Additionally, the generalizability of these findings is limited to the jurisdiction in which the study was conducted. However, the trends observed and methodological approach used may have broader implications in and be adaptable to other settings. In future research, it would be valuable to prospectively capture patient-related costs that were not considered in this study. Despite these limitations this study offers some insight into the issue of the selection of the appropriate arteriovenous access for use on hemodialysis. Policies related to arteriovenous access selection should encourage the consideration of the risk of vascular access maturation failure, as well as the individual patients' circumstances, goals, and preferences.[18]

The third study describes the development of the Hemodialysis Infection Prevention Protocols Ontario—Shower Technique to permit hemodialysis patients with central venous catheters to shower without additional infection risk. The pilot study aimed to determine the feasibility of conducting a parallel randomized controlled trial to evaluate the impact of Hemodialysis Infection Prevention Protocols Ontario- Shower Technique on catheter-related bacteremia in adult hemodialysis patients. The study was positive overall with 4 of the 5 feasibility objectives achieved at 6 months. The first feasibility objective to capture the catheter-related bacteremia rate at a high level of accuracy (success threshold: $\kappa > 0.80$) was achieved, as level of agreement was perfect between the date the catheter-related bacteremia was first suspected and the swabbing of the catheter entry site for microbiology was excellent. The second feasibility objective to screen more than 95% of eligible patients was met, as the large majority (97.8%) of patients were screened for eligibility. The third feasibility objective to have more than 80% of eligible patients consent was not achieved, as less than half (44.2%) of eligible

patients consented to participate in this study. The fourth feasibility objective to have at least 80% of patients in the intervention arm pass the Hemodialysis Infection Prevention Protocols Ontario- Shower Technique test was achieved, as all 33 patients randomized to Hemodialysis Infection Prevention Protocols Ontario- Shower Technique passed at baseline and 3 months, and 88% passed at 6 months. The fifth feasibility objective to have less than 5% of participants in the control arm using aspects of the Hemodialysis Infection Prevention Protocols Ontario- Shower Technique was achieved, as at both 3 and 6 months post baseline, no participants in the control arm were using any aspect of the Hemodialysis Infection Prevention Protocols Ontario- Shower Technique that they were not using at baseline. In exploratory analyses, the preliminary infection rates were similarly low between the Hemodialysis Infection Prevention Protocols Ontario- Shower Technique and standard catheter care and patients were satisfied with the Hemodialysis Infection Prevention Protocols Ontario- Shower Technique, findings that are consistent with other studies of showering with a hemodialysis catheter.[19, 20]

There are several limitations to this study that are important to acknowledge. First and foremost, any examination of clinical outcomes is exploratory and the measurement tool used to capture patient satisfaction is not yet validated. Additionally, as many eligible patients declined to participate, the study may be subject to selection bias, the risk of which we could not fully assess. The most significant limitation was the challenges faced in recruitment, though the availability of pilot data may help patients feel more comfortable to be recruited into the full trial. Despite these limitations, the study does have several important implications for clinical care. While the catheter entry site healing tests were not yet validated, these tests show promise as a systematic approach to assessing healing, instead of the current clinical practice of setting arbitrary time thresholds at which the catheter is potentially considered ‘healed’. In addition, given that the full Hemodialysis Infection Prevention Protocols

Ontario- Shower Technique study was deemed feasible to conduct, the full trial will be well positioned to address some of the key concerns patients, service providers, and healthcare managers have with respect personal hygiene and catheter care practices including the infection risk, cost, and discomfort/inconvenience to the patient.

The fourth study examined the reporting quality of pilot clinical trials in endstage kidney disease patients on hemodialysis. Of 86 included pilot clinical trials, the most commonly examined interventions were pharmaceutical (33%), behavioral/educational (20%), and dialysis technology/technique (17%). Approximately 7 in 10 studies were single center and had a sample size of 50 or less. The reporting across the included articles was not optimal, with an average of approximately 18 of a possible 34 items on the Consolidated Standards of Reporting Trials (CONSORT) extension for pilot trials reported.[21] The most poorly reported item was any changes to assessments or measurements after the study is started, which were reported in less than 5% of pilot studies. More recent years of publication and larger sample sizes were associated with an improvement in the number of items from the CONSORT extension for pilot trials reported.

This study is limited by the inclusion of English-language studies only. Additionally, some factors important to consider in completeness of reporting may not have been captured. However, the study offers some insight into gaps in the reporting of pilot clinical trials in hemodialysis. The lack of guidelines prior to publication of the CONSORT extension for pilot trials may have contributed to the reporting being suboptimal.[21] Reporting may continue to improve with time, as has been observed in other studies examining the reporting of full randomized clinical trials in nephrology.[22-24] Next steps for research and programing in chronic kidney disease include the (further) education of clinical researchers about the CONSORT extension for reporting of pilot trials to improve reporting. There is also need for additional training in the importance of focusing pilot study design on feasibility, rather

than clinical outcomes they are underpowered to address, which may ultimately improve the quality of the pilot studies conducted. Measures to improve the conduct and reporting of pilot studies may in turn inform the design of adequately powered and rigorously conducted randomized clinical trials with appropriately selected outcomes.[25]

In summary, this sandwich thesis four key issues in chronic kidney disease. The methodological approach to each issue was described in detail, as well as its' strengths and limitations. The systematic review shed light on the potential of mobile apps to empower chronic kidney disease patients to better manage their nutrition and complement the work of their supporting team of healthcare professionals. The cost analysis identified that increasing risk of fistula maturation failure was associated with increasing cost. The pilot randomized control trial conducted represented important initial steps in the development and evaluation of a catheter care protocol that balances the need to minimize both infection risk and discomfort to the patient. The methodological review elucidated the key gaps in reporting of pilot trials in hemodialysis, as well as factors associated with more complete reporting. Based on the results of each study, recommendations for future research in chronic disease were made including: conducting larger randomized control trials in more diverse samples to more comprehensively and definitively evaluate nutritional mobile apps, capturing costs related to the patient and their experience to more fully compare the types of arteriovenous access, proceeding with a full randomized trial to evaluate the shower technique protocol, and providing education and training on pilot study conduct and reporting. The work presented in this thesis represents the foundation of a program of research that seeks to improve the quality of life and health outcomes of those living with chronic kidney disease and inform the policies and practices that impact their life and care through the development of innovative health care interventions, the synthesis of knowledge, the promotion of rigorous methodologic approaches, and the analysis of costs.

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