Study Title: A Randomized Pilot Study of Hemodialysis Initiation Comparing Twice-Weekly Hemodialysis Plus Dialysis-Sparing Therapy versus Thrice-Weekly Hemodialysis: The TWOPLUS-HD Trial

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Background, Rationale and Context

Almost all Americans with end-stage kidney disease (ESKD) initiating hemodialysis (HD) are prescribed a dialysis regimen of fixed frequency (thrice-weekly) and fixed dose (dialysis single-pool Kt/V urea [spKt/Vurea] ≥1.2, corresponding to standard Kt/Vurea [stdKt/Vurea] ≥2.1).[1] The target HD treatment dose was validated in trials that involved solely chronic HD patients (i.e., dialysis vintage >2years) with virtually no residual kidney function (RKF); this was then extrapolated as 'optimal' dialysis dose to all patients prescribed intermittent HD.[2,3] In contrast, patients initiating peritoneal dialysis (PD) have the dialysis prescription adjusted according to RKF such that the initial PD regimen consists of shorter dialysis sessions with fewer exchanges; this approach was tested in clinical trials.[4,5] Hitherto, the optimal HD regimen (frequency and dose) for patients with incident ESKD is not known as it has not been studied.

The most common cause of ESKD is progression of chronic kidney disease (CKD), a condition characterized by gradual loss of glomerular filtration over time. More than 90% of incident dialysis patients have an estimated glomerular filtration rate (eGFR) ≥5ml/min/1.73m2 at dialysis initiation;[6] this RKF helps regulate the volume status, maintain phosphate and potassium clearance, and, when pharmacologically enhanced with adjuvant medical therapy, could allow safe and effective introduction of an incremental HD regimen. Chin et al. analyzed the feasibility of incremental HD among incident ESKD patients in the United States by estimating the proportion of patients that could have started maintenance HD with a twice-weekly schedule based on four criteria: RKF; ultrafiltration rate; intradialytic blood pressure; and intradialytic symptoms.[7] Based on their model, the authors concluded that more than half of the patients with

incident ESKD could be treated with incremental HD.[7]Retrospective and observational studies showed that a regimen of twice-weekly HD at dialysis initiation may confer better RKF preservation that thrice-weekly HD treatment.[8,9] Patients with higher levels of RKF generally reported better quality of life[10] and had longer survival on HD than those with lower levels of RKF. [11] In addition, residual glomerular filtration may allow removal of protein-bound uremic solutes that HD does not adequately remove.[12] Thus, an incremental HD regimen could be employed in many patients with ESKD as a result of CKD progression and may have the potential to offer better patient outcomes.

Although beneficial effects of incremental HD on RKF and mortality were noted in previous reports, residual bias lingers even after rigorous adjustment for a variety of important covariates, owing to the nature of study design. A well-designed and executed prospective, randomized trial will offer superior data on the efficacy and safety of incremental HD in order to determine the optimum approach to the initiation of dialysis in patients with incident ESKD.

Objectives

The primary objective of this study is to evaluate the feasibility and safety of incremental HD in incident ESKD patients. The secondary objectives are to evaluate the effects of HD frequency on changes in RKF, clinical and laboratory parameters (i.e., volume management, solute clearance, hospitalization rate), quality of life, and patient survival.

Hypothesis

Patients with ESKD as a result of CKD progression have sufficient RKF such that an initial dialysis regimen of twice-weekly HD plus adjunctive pharmacologic therapy (loop diuretics, potassium-binding agent, and sodium bicarbonate) will afford adequate solute and volume control.

Compared to the conventional HD regimen, a gradual HD regimen with supportive pharmacologic therapy will confer better preservation of RKF.

Methods and Measures

Design

This randomized pilot trial will be parallel-arm in design. We will enroll 50 patients of age ≥18 years, with incident ESKD. Participants will be equally randomized to one of the two regimens: a) twice-weekly HD plus adjunctive pharmacologic therapy (loop diuretic, potassium-binding agent, and sodium bicarbonate) for six consecutive weeks, continued by thrice-weekly HD (intervention group); or b) thrice-weekly HD (comparator group) (Appendix A). Patients will be followed for 12 months after the date of randomization; or until transplant, death, withdrawal of consent, or transfer of care outside Wake Forest healthcare system, whichever occurs sooner. Feedback from the participants will be obtained during the study to (1) evaluate the delivery of study-related information, (2) evaluate coordination of care during the study as it pertained to study-related procedures, (3) evaluate patient perceptions on study-related assessments, (4) elicit patients' motivations for study participation, and (5) obtain participant input regarding future research concerning the study intervention.

Setting

Participant recruitment will occur at Wake Forest Baptist Medical Center (WFBMC) Outpatient Nephrology Clinics, WFBMC Inpatient Nephrology Service, and the Wake Forest Outpatient Dialysis (WFOPD) units.

Subjects selection criteria

The study population will consist of adult patients with incident ESKD who undergo elective initiation of HD.

Inclusion Criteria

1. Age ≥18 years
2. Have CKD (including a failing renal transplant) that advanced to ESKD
3. Have elected HD for renal replacement therapy (RRT)
4. Are deemed to require dialysis initiation by the treating nephrologist or have received ≤ 6 sessions of intermittent hemodialysis within 30 days prior to screening
5. Have a urine output of ≥500ml per 24 hours at the time of screening

Exclusion Criteria

1. Age <18 years
2. Have urine output <500ml per day
3. Have ESKD solely as a result of severe acute kidney injury (AKI) (stage 3 AKI defined by Acute Kidney Injury Network [AKIN]) criteria)
4. Abrupt decline in kidney function preceding HD therapy initiation (i.e., if eGFR was ≥30 ml/min/1.73 m2 within 3 months prior to the initiation of dialysis therapy)
5. Have severe systolic cardiac dysfunction with left ventricular ejection fraction <30%
6. Have an active diagnosis of hepatorenal syndrome
7. Have a significant malignancy that is likely to impact survival
8. Have a medical condition that would jeopardize the safety of the subject.

Sample Size

The primary purpose of this pilot study is to evaluate the feasibility of a randomized intervention between a stepped regimen of HD and a standard regimen of HD. Therefore, for the primary feasibility outcome, we elect a pilot trial sample size of 50 patients total (25 patients per treatment group) which is consistent with recommendations for pilot and feasibility studies where samples of 10 to 20 participants per group have been deemed adequate to assess feasibility outcomes (Stat Methods Med Res 2016, 25(3), pp. 1057-1073). Power calculations for a future multicenter clinical trial will be carried out using the effect size on RKF and variability collected during this pilot study.

Interventions and Interactions

Screening for potential participants will be performed at the outpatient nephrology clinics, outpatient dialysis units, inpatient nephrology service, and inpatient dialysis unit of Wake Forest Baptist Medical Center. The decision to initiate RRT is not part of the study; initiation of RRT will be deemed by patient's nephrologist. After patient's nephrologist decided that initiation of RRT is medically necessary, the overall eligibility for enrollment in this study will be reached as a consensus between the PI and the patient's nephrologist, based on the aforementioned inclusion and exclusion criteria. After written informed consent is obtained, participants will be allocated with equal probability to either incremental HD (intervention) or conventional HD (comparator) strategy. Allocation to incremental or conventional HD will be done using randomly permuted

blocks of varying sizes, stratified by the type of vascular access used at HD initiation, to maintain balance between the groups.

Hemodialysis program. Patients assigned to the intervention arm will receive a gradual HD regimen with twice-weekly HD schedule for six weeks and adjuvant medical treatment during the first six weeks of dialysis treatment, followed by thrice-weekly HD regimen onward. Patients assigned to the comparator arm will receive thrice-weekly HD at the start of dialysis therapy and onward. All participants will receive dialysis against a dialysate (bath) potassium concentration of 3.0mEq/L for their first outpatient HD treatment following randomization. All participants will use a F200 dialyzer following randomization. Beside dialysis frequency, dialyzer type and initial dialysate potassium bath, all other HD prescription parameters (e.g., treatment time, blood flow rate, dialysate flow rate) will be set and adjusted by the treating nephrologist to achieve spKt/Vurea of ≥1.5 with twice-weekly HD schedule and spKt/Vurea of ≥1.2 with thrice-weekly HD schedule. Changes in dialysate (bath) potassium concentration following the first outpatient HD treatment and/or changes in HD frequency can be done at any time during the study, as felt clinically necessary by patient's treating nephrologist. All patients will receive dietary advice and pharmacologic therapy for volume overload, hyperphosphatemia, secondary hyperparathyroidism, anemia and hypertension as guided by patient's nephrologist. According to usual care, phosphate binding agents, active vitamin D analogs, calcium-sensing receptor agonists, erythropoietin stimulating agents and intravenous iron will be used for management of hyperphosphatemia, secondary hyperparathyroidism, anemia and iron deficiency, respectively.

Adjuvant Pharmacologic Treatments/Dialysis-Sparing Therapy. Adjuvant therapy with loop diuretic, potassium-binding agent, and/or bicarbonate-based agent is expected to be necessary during the twice-weekly HD period in the intervention group. All pharmacologic treatments prescribed and administered during the study will be guided and dose-adjusted by patient's treating nephrologist. The treatment schedules described below will be used as guidance. Treatment of hyperkalemia is summarized in Appendix B.

Diuretic therapy. The use of diuretic agents increases sodium and water excretion and improves volume status in dialysis patients with RKF, and has been associated with maintenance of RKF. In an observational study from the Dialysis Outcomes and Practice Pattern Study, loop diuretic use was associated with lower interdialytic weight gain, lower odds of hyperkalemia, twice the odds of retaining RKF, and a 14% lower cardiac-specific mortality (Bragg-Gresham, Am J

Kidney Dis.2007). Start dose, Furosemide, 60-80mg orally/day if uncontrolled hypertension, no discernible peripheral edema, blood pressure stable, no symptoms of congestive heart failure; or Furosemide 80-120mg orally/day if peripheral edema and/or symptoms of congestive heart failure. Dose will be titrated as needed to control hypertension (goal SBP<140mmHg and/or DBP<90mmHg measured on inter-dialytic day or pre-HD) and manage signs and symptoms of volume overload to the best extent possible.

Hyperkalemia treatment. All patients will receive education for low potassium diet. It is expected that 25-30% of the patients in the intervention arm will require treatment for hyperkalemia. Treatment of hyperkalemia will be determined based on baseline serum potassium level available prior to HD initiation. Based on its proven efficacy and safety in clinical trials involving patients with CKD and hyperkalemia, patiromer will be prescribed as the potassium-binding agent of choice.[13-15] Treatment with patiromer will be instituted for serum potassium levels of ≥5.1mEq/L. Patiromer will be administered daily and during the study the dose will be adjusted, as needed, based on pre-HD serum potassium levels (Appendix B). The dose of patiromer will be titrated to maintain pre-HD serum potassium of 4.6 to 5.3 mEq/L.[16] Patiromer will be withheld temporarily or stopped for pre-HD serum potassium levels of ≤4.0mEq/L. Participants randomized to twice-weekly HD arm who were on a potassium binder prior study enrollment and HD initiation will be continued on patiromer (if on treatment with patiromer prior to enrollment) or switched to patiromer (if on a different potassium binder prior to enrollment). Participants randomized to thrice-weekly HD who were on a potassium binder prior study enrollment and HD initiation will have the potassium binder discontinued.

Metabolic acidosis treatment. Treatment with Sodium Bicarbonate will be tailored based on pre-HD serum bicarbonate levels. Start dose, Sodium Bicarbonate 1300-2600mg orally/day if serum bicarbonate ≤18mEq/L, or 650-1300mg orally/day if serum bicarbonate >18mEq/L. Dose will be adjusted as needed for goal pre-HD serum bicarbonate levels between 20-22mEq/L.[17,18]

Participant Feedback. We developed a 24-item Patient Feedback Questionnaire to assess the following domains 5 domains: information and communication, coordination of care, perception on study-related assessments, motivation, and future studies. The answers will be rated on a 5-level scale (**Appendix F**).

Data collection

Sociodemographic (age, sex, race, marital status, educational level, living arrangement) and clinical (ESKD etiology and comorbidities) data will be collected from all participants at enrollment, using direct patient interview and electronic medical records. Assessments of health-related quality of life (using Dialysis Symptom Index questionnaire), depression (using PHQ-9 questionnaire) and anxiety (using GAD-7 questionnaire) will be performed at enrollment and at week 6 and week 12 (month 3).

Laboratory data to include serum sodium, potassium, bicarbonate, phosphorus, calcium, intact PTH, albumin, hemoglobin, ferritin, transferrin saturation and beta-2 microglobulin will be recorded at baseline and then as set intervals according to the schedule of assessments (Appendix C).

A 24-hour urine collection will be performed at baseline (within 1 week prior to initiation of HD or within 1 week after initiation of HD). Inter-dialytic urine collection (starting with the end of one HD session and ending with the beginning of the next successive HD session) will be performed at set intervals during the study (weeks 6, 12 [month 3], 24 [month 6] and 48 [month 12] +/- 7 days). Measurements performed on urine collections will include urine volume, beta-2 microglobulin, urea and creatinine; these measurements will be used to calculate RKF (urea and creatinine clearance) and middle-molecule (beta-2 microglobulin) clearance.

Assessments of dialysis clearance using single poo Kt/V (spKt/V) and standard Kt/V (std Kt/V) will be performed according to standard of care.

Treatment with adjuvant therapy (e.g., Patiromer, Furosemide, Sodium Bicarbonate), intravenous iron, erythropoietin stimulating agent, active vitamin D and calcimimetic will be recorded as average weekly dose during weeks 0 to 6, and average weekly dose during weeks 7 to 12 (month 3) . Prescription of renin-angiotensin inhibitors, beta blockers, antiplatelet therapy and/or lipid lowering medications will be recorded.

Study-specific assessments and measurements will include the Dialysis Symptom Index performed at 12 weeks (month 3), PHQ-9, GAD-7, urine collection and urine-based assays, serum measurement of beta-2 microglobulin, and serum K measurement at week 2 and 4 (Appendix C, Schedule of Assessments). Of note, baseline Dialysis Symptom, serum K measurement at week 1 and week 6, and all other aforementioned blood tests are part of standard of care.

Dialysis prescription (HD treatment time and frequency of administration, achieved blood flow, dialysate flow, potassium and calcium dialysate baths), vascular access used for HD, target weight (TW), inter-dialytic weight gain (IDWG), and ultrafiltration rate (UFR) will be recorded throughout the study. Relative IDWG will be expressed as percentage of TW when divided by the nephrologists' determined target weight. All hospitalizations and deaths (along with the cause) will be recorded from the time of enrollment to study end.

Outcome measures

Primary feasibility outcome

Time point: end of study

Feasibility outcome will be assessed as the ability to recruit participants and protocol adherence. Recruitment will be determined as the proportion of people meeting inclusion criteria who ultimately consent to randomization. Protocol adherence will be determined as the proportion of participants who abide to the HD schedule, including transition from twice-weekly to thrice-weekly HD.

This pilot study will be considered successful based on attaining the following feasibility outcomes assessed at 12 months of study follow-up: (1) ≥70% of eligible patients are recruited, (2) ≥95% of participants randomized in the intervention group will adhere to the HD regimen, (3) ≥80% patients adhere to study-specific timed urine collection, and (4) ≤5% of participants randomized in the control group will cross over to a regimen of less frequent HD.

Primary safety outcomes

Time point: end of month 3

The intervention of stepwise HD schedule will be considered safe, relative to standard HD schedule, if there will be no significant difference in severe adverse events between the two HD treatment groups during the first 3 months of the study.

Severe adverse event(s) will be defined as the requirement of one or more additional HD treatment(s) or hospitalization(s) for: (1) a condition related to poor volume control (i.e., clinically-determined volume overload, decompensated heart failure, or hypertensive urgency/emergency); (2) severe electrolyte imbalance (i.e., serum potassium >6.5mEq/L); (3) severe metabolic acidosis (i.e., serum bicarbonate <15mEq/L); (4) symptomatic uremia (i.e., uremic encephalopathy, uremic pericarditis); or (5) death associated with study intervention.

Secondary outcomes

- Change in RKF.

Time points: weeks 6, 12, 24 & 48

This will be assessed based on timed urine collections at specific time intervals to calculate renal urea and creatinine clearance (baseline, 6 weeks, 2 weeks [month 3], 24 weeks [month 6] and 46 weeks [month 12]).

Residual renal urea clearance (Krt/Vurea) after HD initiation will be calculated as clearance per minute excretion of urea nitrogen using time-averaged serum water urea nitrogen concentration during the collection period.[19]

- Solute clearance

Time points: month 1, month 2, month 3, month 6 and month 12

This will be evaluated using spKt/Vurea and stdKt/Vurea. Single pool Kt/Vurea will be obtained monthly. Standard Kt/Vurea will be calculated monthly, using a method of calculation that includes the contributions of fluid removal.[20] Total stdKt/Vurea will be calculated by adding residual renal urea clearance (Krt/Vurea) (i.e., stdKt/Vurea month 1 will include baseline Krt/Vurea; stdKt/Vurea month 2 will include Krt/Vurea based on inter-dialytic urine collection performed during week 6; stdKt/Vurea month 3 will include Krt/Vurea performed during week 12).[7]

- Incidence rate of hyperkalemia

Time points: month 1, month 2, month 3, month 6 and month 12

Events of hyperkalemia (serum potassium ≥5.5mEq/L on inter-dialytic day or ≥6.0mEq/L pre-HD on dialysis day) will be recorded and incidence rate will be compared between the two groups.

- Incidence rate of metabolic acidosis

Time points: month 1, month 2, month 3, month 6 and month 12

Serum TCO2 will be collected. Events of metabolic acidosis (serum bicarbonate ≤22mEq/L on inter-dialytic day or ≤20mEq/L pre-HD on dialysis day) will be recorded and compared between the two treatment arms.

- Incidence rate of volume overload

Time points: month 1, month 2, month 3, month 6 and month 12

Assessment of volume status will use the following surrogate markers of volume overload: IDWG >2.5kg, relative IDWG >5.7% of the TW, and UFR >10ml/kg/hr. Events of volume overload will be compared between study groups as proportion of markers of volume overload of the total measurements of IDWG and UFR achieved with each HD treatment during the first 3 months, stratified in two periods (week 1 to 6 and week 7 to 12).

- Hospitalization rate

Time point: end of follow-up

Time to first hospitalization, cause of hospitalization and length of stay will be recorded and compared between treatment arms.

- Quality of life, Depression and Anxiety

Time points: weeks 6 & 12

The Dialysis Symptom Index questionnaire will be used to assess participant health-related quality of life. This is a short form that measures the burden of kidney disease, symptoms/problems of kidney disease, and effects of kidney disease scales. The score range is 0-100 with higher scores denoting better outcomes. Depression will be assessed using the PHQ-9 instrument. Anxiety will be assessed using the GAD-7 instrument.

Exploratory outcome

- Patient survival

Timeframe: end of follow-up

The tertiary outcome will consist of exploratory analyses to compare the mortality rate between the two schedules of HD.

Analytical Plan

Feasibility will be assessed using descriptive data regarding eligible patients, enrolled patients, intervention compliance and adherence to study-specific assessments, and drop-out/withdrawal rate among each intervention. The proportion of people meeting each of the feasibility and protocol adherence endpoints with accompanying 95% confidence intervals (CI) will be estimated using skew-corrected score tests with a continuity correction. Progress from pilot to large scale trial will be considered as: i) continue the study without modifications (feasible as is) if all feasibility criteria are met; ii) continue with protocol modifications (feasible with

modifications); or iii) stop the main study (not feasible) if none of the four feasibility criteria was met.

For evaluation of primary safety end points and secondary clinical end points, intention-to-treat principles will be followed. Evaluation of categorical end points will be performed using chi-squared tests. Evaluation of continuous end points will be performed using Student's unpaired t-test for normally distributed variables, or the Wilcoxon rank-sum test for nonparametric data. For comparison of variables measured during the time course of the study, a repeated measures analysis of variance (ANOVA) will be used. The consistency of effects on the primary end point will be explored in a variety of subgroups. Kaplan–Meier methods will be used for time-to-first hospitalization analyses. Missing RKF data for subjects will be replaced (rather than excluding them from the analysis, as missing RKF measurements might not be completely at random) using linear regression to estimate values based on other measurements for each subject (linear trend at point, SPSS). For each group-sequential analysis, the upper bound of the one-sided confidence interval for the hazard ratio (incremental HD to conventional HD) would be calculated with the use of the critical value from the Lan–DeMets–O'Brien–Fleming alpha-spending function, which preserves an overall one-sided alpha of 0.025. No adjustments for multiplicity will be made. An independent Safety Monitoring Committee will review all available data on a quarterly basis. Analyses that signal safety concerns (i.e., higher rates of hospitalization, treatment failure or death in the intervention arm compared to the comparator arm) will be reported to an independent Steering Committee to determine whether the study should be discontinued, be modified and then proceed, or continue with caution.

Descriptive statistics will be used to report the results of Participant Feedback Questionnaire.

Subject Recruitment Methods

Clinical records of Nephrology practices, including WFOPD facilities, WFBMC nephrology outpatient clinics, and WFBMC nephrology inpatient service will be reviewed for eligibility. Study participants will be adults of age ≥18 years with a diagnosis of incident ESKD who meet the following additional inclusion criteria: (1) etiology of ESKD is progression of CKD and (2) need to be initiated on renal replacement therapy and patient elected HD as the modality of choice, or (3) have started dialysis, HD is the intended long-term renal replacement modality,

and have received ≤6 HD sessions. Patients who meet all the eligibility criteria will be approached by the study coordinator, and/or PI for explanation of study participation.

Human Subjects Protection

This study poses **high risks** to the study participants.
The risks associated with receiving HD twice per week include development of fluid overload, uncontrolled hypertension, elevated serum potassium levels, and decreased serum bicarbonate levels. However, given the inclusion criteria (i.e. patients with ESRD due to CKD progression who have residual kidney function at the time of dialysis initiation), planned frequent assessments of the participants in the twice per week HD treatment arm, and administration of medications to prevent these potential complications (diuretics, patiromer and sodium bicarbonate), the risks will be closely mitigated during the study.
The potential participants for this study have already been determined to need renal replacement therapy, elected HD as the dialysis modality of choice, and have indicators of RKF (i.e., eGFR ≥5ml/min/1.73m2, lack of anuria, no indication for urgent HD). Timing of dialysis initiation will be determined by patient's nephrologist according to standard of care. Changes in HD prescription and frequency can be done at any time point according to patient's clinical status, laboratory values, as felt medically indicated by the study PI or patient's nephrologist. Changes to patient's medications can be done during the study, as felt indicated by any of the patient's health care providers, patient's nephrologist, or study PI. Blood collections for this study are being kept to a minimum. There will be no medical visits done exclusively for this study.

Informed Consent

Signed informed consent will be obtained from each subject by the study coordinator, members of the study team, and/or the PI. The participant will have sufficient time to read the Informed consent and to have all questions answered. The personnel involved in this study have knowledge on the medical aspects of HD prescription and complications related to HD. The assessments involved in the study and the chances of being assigned randomly to one of two groups will be explained to each potential participant. We will provide adequate opportunity for the subject to consider all options, and respond to the patient's questions to ensure the

information was comprehended. Informed consent will be obtained in the dialysis centers, outpatient nephrology clinics, or inpatient service. Patients will be made aware of their right to withdraw from the study at any time without adverse effects on their clinical care.

Confidentiality and Privacy

Taking part in this research study may involve collection of information that is considered confidential or private. Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed three years after closure of the study consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

Participants in the intervention arm will have more frequent analysis of their clinical status and lab results. These evaluations will be done at a minimum frequency of once per week in the intervention arms, versus twice per month in the comparator arm according to standard of care. The study team members (principal investigator and co-investigators) will be responsible for the frequent analysis of the participants enrolled in the intervention arm. Participants enrolled in the comparator arm will be evaluated according to the standard of care by their nephrologist.
The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Events related to the type of HD regimen--such as admission for volume overload or hyperkalemia in the incremental HD arm--will be closely tracked. Events will be recorded electronically and reported to the principal investigator monthly. An independent Safety Officer, unblinded to treatment assignments, will review, on a quarterly basis, all events of hospitalizations and cause of hospitalization, within the study cohort. All concerns regarding the frequency of HD will be reported to the Wake Forest IRB. In addition, the principal investigator, Safety Officer, and members of the research group will carefully consider amendments (including halting the trial if necessary).

Reporting of Unanticipated Problems, Adverse Events or Deviations (Appendix D)

The principal investigator along with the research staff will be responsible for periodic evaluation of clinical trial data to ensure continued participant safety, protocol compliance, data collection as well as scientific validity. Adverse events are not anticipated, but any occurring will be documented and reported according to WFSM IRB policies and procedures. Cumulative adverse events and study progress summary will be communicated to the IRB at the time of continuing review.

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB.

Physician Stakeholder Survey

Using the REDCap platform, the PI devised a Survey to identify the nephrologists' opinions and perceived barriers regarding the practice of incremental HD in the US. The Survey is geared to board-certified Nephrologists in the US. No respondent identifying information will be obtained; all responses will be anonymous. The Survey is expected to take less than 5 minutes. The information obtained with this Survey will help the Investigators understand and anticipate barriers to implementing a clinical trial of incremental vs conventional HD in the US. We

provide the emails of the Nephrologists to whom the Survey will be distributed. We provide the link to the REDCap-based Survey.

Appendix

Appendix A. Study Flow Diagram

Appendix B. Treatment of Hyperkalemia

Appendix C. Schedule of Assessments

Appendix D. Protocol Violation, Adverse Events, Cause of Death

Appendix E. Revised Budget

Appendix F. Participant Feedback Questionnaire

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