NYU Langone Health

Official Title:	Radar-A: A Phase 2 Multi-center Study to Evaluate the Safety and Tolerability of Using Point-of-Care-Guided Manipulation of Dialysate Potassium and Dialysate Bicarbonate to Prevent Hemodialysis-Associated Arrhythmias
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RADAR

Reducing Arrhythmia in Dialysis by Adjusting the Rx Electrolytes/Ultrafiltration

Funding Sponsor:	National Institutes of Health National Heart, Lung and Blood Institute R34 NHLBI Clinical Trial Pilot Studies (R34) https://grants.nih.gov/grants/guide/pa-files/PAR-16-037.html
Study Products:	*Dialysis Ultrafiltration Rate* *Potassium and Bicarbonate Dialysis Bath*
Protocol Number:	
Brigham & Women's Initial version dated:	August 9th, 2017
Version:	Version 1.0
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Table of Contents

Study Summary

Title	Reducing Arrhythmia in Dialysis by Adjusting the Rx Electrolytes/Ultrafiltration
Short Title	RADAR
Protocol Number	
Phase	Pilot
Methodology	Randomized, Crossover, Blinded, Multi-arm Interventions: Implanted Loop Recorder Potassium/Bicarbonate Trial (Study A) Ultrafiltration Trial (Study B)
Study Duration	24 months
Study Center(s)	Duke University Medical Center (DUMC) New York University Langone Health (NYU)-coordinating site receiving funding from the NIH with dialysis unit located at Lower Manhattan Dialysis Center (323 E34th St, New York, NY 10016).
Objectives	• To obtain pilot data on adherence, safety and barriers to implementation of proposed interventions. • To obtain pilot data on recruitment feasibility and subject retention. • To obtain pilot data to estimate the potential effect sizes of proposed interventions.
Number of Participants	40 (20 in each of two interventions) (60 participants enrolled with 40 expected to reach randomization. Because patients have the option of enrolling in both study A and B it is possible that the total number of devices required will be less than 40.)
Diagnosis and Main Inclusion Criteria	Dialysis-dependent end-stage renal disease
Study Product/Intervention, Route, Regimen	Study A: Potassium/Bicarbonate Four-Arm Crossover Potassium (K) Removal Maximization strategy, 1 month (lower dialysate K) Potassium (K) Gradient-Minimization Strategy, 1 month (higher dialysate K) Acidosis Avoidance, 1 month (higher dialysate bicarbonate) Alkalosis Avoidance, 1 month (lower dialysate bicarbonate) Study B: Dialysis Ultrafiltration Rate (UFR) Two-Arm Crossover UFR ≤10 ml/kg/hr, 1 month UFR as needed, 1 month
Ancillary Products:	LINQ™ (Medtronic) Implantable Cardiac Loop Recorder (Carelink System) i-STAT (Abbott)- Study A only

Duration of administration	LINQ™: 3-6 months Study A: 4 months Study B: 2 months
Major Outcomes	• Safety: severe Potassium or Bicarbonate abnormalities, or unscheduled hemodialysis (HD) or hospitalization for hyper/hypokalemia or acid/base abnormalities in absence of missed treatment. • Tolerability: treatment adherence • Efficacy: mean and standard deviation of the change in duration of clinically significant arrhythmias per month • Feasibility: recruitment rate, retention
Statistical Methodology	A balanced, uniform crossover design will be used with randomization stratified by site in blocks of 4. **Adherence** will be estimated as % (95% CI) of sessions without protocol deviation. Comparison of adherence percentage pre- vs. post-interim analysis of adherence will be made using linear regression with time period as an independent variable. Exploratory analyses will assess association of adherence with site, dialysis shift (1st-3rd), and dialysis day-of-the-week schedule (Monday/Wednesday/Friday or Tuesday/Thursday/Saturday). **Safety** will be assessed by calculating the incidence rate for serious AEs and intervention-specific complications. Comparisons of incidence rate between interventions will utilize Poisson regression adjusted for randomization scheme and site.
Funding	National Institutes of Health National Heart, Lung and Blood Institute R34 NHLBI Clinical Trial Pilot Studies (R34) https://grants.nih.gov/grants/guide/pa-files/PAR-16-037.html

I. Background and Significance

Trial Rationale—There are more than 466,000 patients on chronic dialysis in the United States, and this population is expanding.[1] Although HD is life-saving, it requires non-physiologic, rapid intra-dialytic removal of fluid and electrolytes 3 times/week, followed by sub-acute post-dialysis re-equilibration, and slow inter-dialytic accumulation of fluids and electrolytes. Cardiovascular (CV) hospitalizations and sudden cardiac arrest (SCA) occur most frequently on HD days, with the greatest frequency on the first HD of the week after the long dialysis-free weekend **(Figure 1**).[2,3] This suggests that rapid electrolyte changes and intravascular shifts trigger CV events: indeed, strong associations between fluid removal rate (ultrafiltration rate [UFR]) and dialysate or serum electrolyte concentration and mortality have been consistently observed in retrospective studies.[4-7] Thus, current paradigms expose patients to high risks of CV morbidity and mortality and clearly require re-evaluation. The growth of this high-risk population[1,8] and failure of standard CV therapies to reduce CV mortality when tested in HD patients[9-12] provide additional motivation to test whether modifying the dialysis prescription can reduce the 1 in 20 annual risk of SCA, lower the incidence of atrial fibrillation (AF), and reduce the high incidence of stroke and CV death in the HD population.[1,13] The overarching hypothesis underlying these trials is that that dialysis induces cardiac arrhythmia and that altering the prescription will lower CV risks.

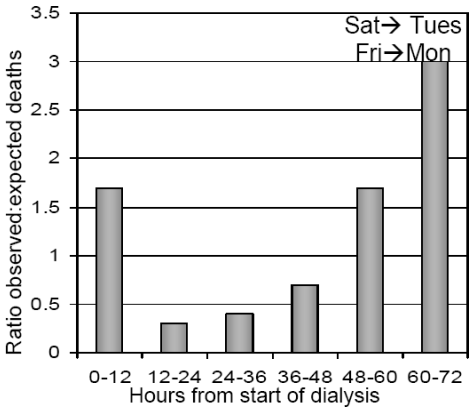


Figure 1: Ratio of observed to expected SCA deaths in relation to timing of dialysis.

Comparing the impact of alternative dialysis protocols on fatal and non-fatal arrhythmia has been hampered by the sample sizes needed to demonstrate an effect on SCA and practical limitations to monitoring arrhythmia for more than a few days. Thus, data linking dialytic parameters to CV death primarily comes from retrospective analyses of large data-sets which provide proof of concept but do not establish causality. Interventional data is limited and comes from short-term studies measuring changes on surrogate measures such as electrocardiogram morphology during a single dialysis session rather than on arrhythmia incidence. Understanding of the most basic aspect of dialysis care is thus inadequate, and whether simple, achievable changes to the dialysis prescription could improve outcomes remains unknown. Recent advances, however, make long-term cardiac monitoring feasible. The investigators propose studies testing whether altering dialysis potassium (K), bicarbonate (HCO3), or UF prescription lowers the incidence of arrhythmia in HD patients. The proposed pilot studies will leverage this technology to perform first-ever randomized trials to test the effects of differential dialysis prescriptions on the occurrence of arrhythmia over more than a few days, thereby advancing understanding of fundamental, but overlooked aspects of dialysis and the study of cost-effective, implementable interventions that improve the health and well-being of a critically underserved, high- risk population. Lastly, they will provide the necessary and sufficient information for the design of definitive trials.

Significance of Sudden Cardiac Arrest (SCA) and pre-SCA arrhythmias in HD patients—SCA risk increases dramatically as eGFR declines and peaks in ESRD[14,15] where it is the most frequent cause of mortality accounting for 28% of deaths.[16] This association is independent of coronary disease severity and traditional CV risk factors,[17,18] and associations between SCA and dialysis timing (**Figure 1**) provide strong evidence that dialysis-specific factors are key triggers of SCA. With 1 in 20 HD patients dying annually from SCA[1], identifying reversible and treatable dialytic SCA triggers is a key strategy for reducing CV mortality.

Because most SCA occur in unmonitored situations, the nature of arrhythmias that precede and predict SCA in HD patients is uncertain. Evidence from a few continuous monitoring studies suggest that a broad spectrum of arrhythmias is responsible. An analysis of 75 SCA survivors on HD who were subsequently prescribed wearable defibrillators found that ventricular fibrillation (VF) or ventricular tachycardia (VT) were the primary arrhythmia in the majority of recurrent SCA events (79%), whereas only 21% were due to asystole.[19] In contrast, another study that used an implantable loop recorder (ILR) to monitor 50 HD patients found that all 6 SCA events that occurred were preceded by bradycardia/asystole. Furthermore, bradyarrhythmias were the most frequent significant arrhythmias (65%), whereas non-sustained VT was infrequent and detected in only 20%, and there were no episodes of sustained VT.[20] This predominance of bradyarrhythmias echoes observations in the Monitoring in Dialysis study (MiD)[21] in which ILR were implanted in 66 HD patients followed for 6-12 months. Two-thirds of all subjects experienced a serious arrhythmia. The majority were bradycardia or asystole whereas sustained VT was detected in only 1 patient. (**Table 1**).

ILM-detected arrhythmias	Number of detected events	Patient Prevalence
Overall detected serious arrhythmia events	1700	66.7% (44/66)
Sustained VT≥30 sec	1	1.5% (1/66)
Bradycardia≤40 BPM x ≥6 seconds	1481	19.7% (13/66)
Asystole≥3 sec	14	9.1% (6/66)
Patient marked event with reviewer confirmed arrhythmia	198	57.6% (38/66)
Atrial Fibrillation	4464	40.9% (27/66)

Table 1: Arrhythmias in MiD

In summary, both non-ventricular arrhythmias (bradycardia /asystole) and ventricular arrhythmias (VT) are potentially important causes of SCA in HD patients. They occur frequently with a sufficiently high incidence to serve as endpoints in interventional trials, and the current trial design leverages ILR technology to comprehensively capture all significant arrhythmias that are reasonable surrogates of SCA risk.

Atrial Fibrillation (AF) is a Major Cause of Morbidity and Mortality in HD Patients— Although SCA is the most frequent cause of mortality in HD patients, AF is also common and is an important cause of morbidity and mortality. Overt AF affects 11.6% of HD patients and its prevalence increased 3-fold between 1992-2006[22,23] Stroke (CVA) is the most feared complication of AF which accounts for >23% of CVA among older adults,[24] and CVA is a particularly critical problem in HD patients. After a CVA, 38% of HD patients die acutely, only 31% of patients are able to function independently, and <46% survive for 2 years.[25-28] The relationship between clinically overt AF and CVA in HD patients is clear. In a Danish study, the risk of AF-associated CVA was 82% higher with ESRD than with preserved kidney function.[29] In the US, CVA incidence in dialysis patients with new onset AF is 9.9/100 patient-years,[30] while the risk of ischemic stroke is 26% higher with chronic AF.[31] In addition to the risk of CVA, AF in HD patients is also

associated with increased risks of mesenteric ischemia, amputation, progressive heart failure,[32-34] and a doubling in risk of death compared to sinus rhythm.[22,23,30]

Clinically overt AF is only the tip of the iceberg. Buitten examined defibrillator recordings from 40 HD patients with implanted defibrillators and found that 34% had subclinical AF which was detected on 20% of patient-days.[35] Similarly, of the 66 HD patients in MiD, there were 4464 episodes of AF detected with 1700 episodes lasting ≥6 minutes. AF was found in 40.9% of subjects (**Table 1**) and 27% of those without known history of AF. The median number of days with AF episodes lasting ≥6 minutes was 7 and daily AF burden was as long as 24 hours. In short, even though the incidence of clinically overt AF is already high, it significantly underestimates true AF incidence in the HD population. Clinically silent AF events also account for a significant proportion of CVA events. In a study of 2580 older patients with pacemakers, pacemaker-detected subclinical AF events >5 minutes were identified in 10.1% and were associated with a 2.5x increased risk of CVA or systemic embolism.[36] Associations of subclinical AF with CVA have not been specifically analyzed in ESRD, but Holter-detected asymptomatic arrhythmias (including AF) are strongly associated with CV death (adjusted HR 4.32). Moreover, most individuals in whom AF is detected (64%) ultimately developed permanent, overt AF.[37]

The high incidence of AF, strong and consistent associations between CVA (as well as other sequela of AF) and overt or subclinical AF suggest that reducing the incidence of AF could be a key strategy to prevent CVA and reduce mortality in HD patients. The proposed studies tackle this critical problem by testing dialysis-specific strategies with a high probability of reducing the incidence and risk of AF.

Dialysis-Related Factors Cause Arrhythmia**—**The dialysis schedule is a clear trigger for CV complications, particularly SCA and AF. In addition to SCA, (**Figure 1**) CV deaths, and CV admissions are most frequent on the first HD day following the weekend, with smaller spikes at the mid and end of week dialysis compared with non-dialysis days.[2] In the MiD study, primary objective arrhythmias (asystole ≥ 3 seconds, bradycardia ≤40 beats per minute (BPM) for ≥6 seconds, and sustained VT≥130 BPM for ≥30 seconds) were most frequent during and shortly after the first weekly HD session and, but were also frequent during the 12 hours prior to the first session. Associations were even more apparent with AF which spiked during each dialysis session and remained high during the 8 hours immediately after dialysis before decreasing over the next 8 hours. (**Figure 3**). These data clearly demonstrate that arrhythmia frequency closely tracks the dialytic cycle, supporting the hypothesis that the arrhythmogenicity of the dialysis procedure is a likely cause and that altering approaches to key components of the dialysis prescription will lower CV risk. **Three key components—dialysate potassium, bicarbonate and ultrafiltration rate will be tested on Study A and Study B respectively. Each is well supported by the literature as a central arrhythmogenic factor in HD patients.**

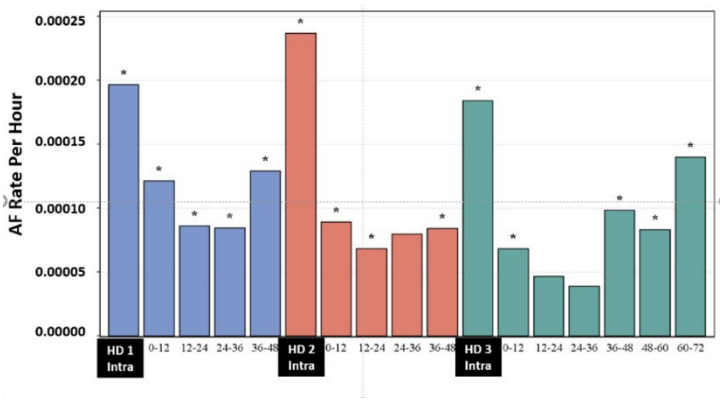


Figure 2. AF rate/hour and dialysis cycle. HD1-3 (blue, red, green)-1st-3rd weekly dialysis session. Numbers below graph=hours after the dialysis session. * P<0.05 vs. HD3 24-36 hours.

Serum and Dialysate Potassium (K) are Associated with Arrhythmia—Both high and low serum K are clear risk factors for all-cause mortality and SCA. Associations of serum K and intradialytic SCA in 43,000 HD patients were U-shaped with risk increased above and below a serum K of 5.1 (**Figure 3**)[5]. Other studies have found elevated pre-dialysis K >6.0 mEq/L to be more strongly associated with all-cause death, arrhythmia-related hospitalization, and SCA.[38,39] In short, these data support the concept that pre-dialysis hyperkalemia is associated with risk while also implying that lower serum K may be dangerous. This points towards the need to prospectively compare the impact of dialysis strategies that focus on maximizing K removal to avoid hyperkalemia with strategies which focus primarily on avoiding hypokalemia.

Removal of sōlutes such as K during HD is governed by the serum-to-dialysate concentration gradient, which can be modified by changing the dialysate concentration. Choosing the ideal dialysate K concentrate is complicated. First, to reduce the risk of nursing errors, most dialysis chains limit the options to two different K concentrates (generally 2 and 3 mEq/L; 2 mEq/L is the most commonly prescribed). Other concentrates (0, 1 or 4 mEq/L) are not readily available. Second, although serum electrolytes levels change during each dialysis session, the dialysate concentration remains fixed; this results in more rapid K removal (flux) during the first hour of treatment when serum-dialysate gradients are maximal, and more gradual reductions later. Thus, lower K dialysates achieve greater K removal with rapid drops in serum K, whereas higher K dialysates remove K more gradually but at a cost of less overall K removal. Each strategy may provoke arrhythmia due to either rapid shifts or inadequate K removal. Third, even though serum K values change throughout the month, the prevailing standard practice is to prescribe dialysate K based on a single, once-monthly pre-dialysis serum measurement; as a result, dialysate K is frequently not appropriate for the prevailing serum K concentration.

Several retrospective studies have examined associations between dialysate K and arrhythmia. In 502 HD patients with witnessed peri-dialytic SCA and 1632 matched controls, low K dialysate ≤1 mEq/L was associated with a doubling in risk (OR 2.06, 95% CI 0.79-0.91). Notably, patients who had a SCA and were prescribed low K dialysate had a mean pre-HD K in the normal range (5.0 mEq/L). This apparent inappropriate prescription of low K dialysate suggests that lack of real time information on prevailing serum K is a major issue and that use of low K dialysates could be safe if point-of-care labs were available to inform prescription choice at the time of dialysis.

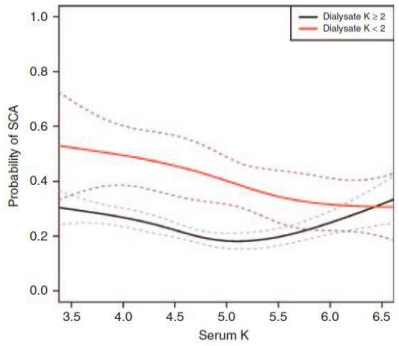


Figure 3. SCA risk according to serum potassium and dialysate K≥2 (black vs. <2.0 mEq/L (red).

Furthermore, the increased risk associated with low K dialysate was not evident when the serum K was >5.5 mEq/L ($P_{interaction}$=0.03, **Figure 3**).[5] These data support the idea that excessive K removal should be avoided, but that aggressive removal is necessary when pre-HD K is high and that POC testing could facilitate safer prescriptions and improve outcomes. Other studies have identified risks with higher K dialysates. In a study of >80,000 HD patients, dialysate K>3 was associated with increased mortality when pre-dialysis K was ≥5.0 mEq/L.[40] Risks associated with intermediate dialysate K concentrations are less clear; in another analysis of a large HD population, all-cause mortality and composite arrhythmia outcomes did not differ between 2 and 3 mEq/L K dialysate. However, these findings were based on single measures of serum and dialysate K and outcomes included events unlikely to be influenced by dialysate potassium such as pacemaker and defibrillator implantation.[38]

The influence of intradialytic K change on arrhythmias was also observed in the MiD study (**Figure 4**). Despite the small sample size (n=66), greater intradialytic K change had a near significant association with post-dialysis arrhythmia (P=0.06). Furthermore, there was a significant interaction with volume removal in adjusted analyses such that the magnitude of risk with greater K removal was maximized at higher UF volumes ($P_{interaction}$=0.02).

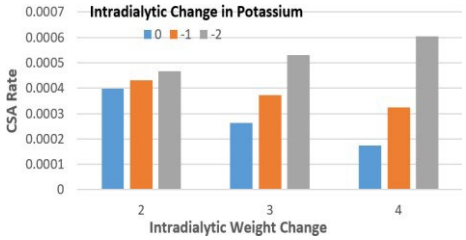


Figure 4. Primary objective arrhythmias (per hour from end of Monday/Tuesday dialysis session to 8 hours post) by intradialytic change in potassium and

<u>Serum and Dialysate Bicarbonate (HCO3) are Associated with Arrhythmia</u>— Unlike potassium, the dialysate HCO3 concentration is finely adjustable; dialysate bicarbonate concentrations can be varied from 20-40 mEq/L in 1 mEq/L increments. U-shaped associations of serum HCO3 and outcomes are also apparent. [41] In large retrospective studies, risks were increased with both high pre-dialysis HCO3 concentrations (>6-fold increase in SCA at HCO3 ≥28 mEq/L)[42] and low HCO3 levels (increased all-cause and CV mortality at levels <20-22 mEq/L[43]). In another analysis, high pre-dialysis HCO3 concentration was associated with increased risk of peri-dialytic SCA (adjusted OR 1.03 per 1 mEq/L increase).[5]

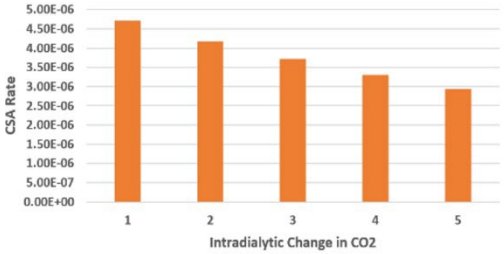


Figure 5. CSA rate according to intradialytic increase in bicarbonate from start of HD to 8 hours after the HD session

Higher dialysate HCO3 was associated with increased mortality (adjusted HR 1.08, 95% CI: 1.01-1.15) in a recent analysis and with trends towards increased SCA and arrhythmia hospitalization, suggesting that intradialytic alkalosis provokes CV events. In contrast, in MiD greater intradialytic increase in serum HCO3 lowered arrhythmia risk and was one of the few factors independently associated with the incidence of implantable monitor detected serious arrhythmia from the start of dialysis until 8 hours later (β=0.89, P<0.001, **Figure 5**). Despite the evidence of risks associated with serum and dialysate HCO3, more than half of US dialysis units do not individualize dialysis HCO3, and approximately 50% of US patients dialyze against HCO3 dialysate ≥38 mEq/L.[7] As with K, there are compelling data suggesting that the standard of care approach to HCO3 exposes HD patients to excessive risks of SCA and arrhythmia.

Summary Dialysate K and HCO3—There is compelling evidence that excursion of both serum potassium and HCO3 outside of a narrow range is associated with SCA and mortality. The proposed trials will test the impact of both dialysate potassium and HCO3 on hard outcomes and long-term arrhythmia risk, which has never been prospectively tested in randomized trials, and will provide crucial data for design of definitive studies that may dramatically impact HD-related morbidity and mortality.

Ultrafiltration (UF) Rate and Arrhythmia Risk—Maintaining normovolemia is a cornerstone of dialysis therapy and is achieved by adjusting fluid removal rates to reach a stable post-dialysis weight. Large interdialytic fluid gains are common and result in high prescribed UF rates. When UF rates exceed the rate of vascular space refilling from the periphery, cardiac filling and myocardial perfusion is impaired leading to adverse outcomes. Multiple studies suggest that high UF rates are associated with mortality. In one study of 22,000 patients, mortality was significantly higher with UF rates ≥10 mL/hr/kg (RR 1.09, P=0.02).[44] A secondary analysis of the HEMO trial similarly found an increase in CV (HR 1.59, 95% CI: 1.29-1.96) or all-cause mortality (HR 1.20, 95% CI: 1.03-1.41) at UF rates >13 ml/hour/kg while mortality rates increased at UF rates >10 mL/hr/kg when analyzed as continuous variable.[6] In the MiD study, an increase in intra- and peri-dialytic clinically significant arrhythmias was also noted with higher UF rates (**Figure 4)**. Although these data underlie recent recommendations to incorporate UF rate as a dialysis quality measure,[45] no randomized data comparing different UF rates on outcomes exist, and multiple factors are likely to cloud associations with UF rates in observational studies. The two trials proposed under this protocol will be the first to provide randomized data on modifications of the UF rate on risk of serious arrhythmias. Furthermore, due to the need to get patients to a dry weight and limited resources to extend dialysis time or add additional sessions, the standard of care remains to dialyze patients with large intradialytic fluid gains using UF rates ≥10 L/kg. In short, despite recent efforts to adopt UF limitation as a quality measure, it has not achieved acceptance as the prevailing standard of care.

Rationale for Implantable Loop Recorder (ILR) Use—The rationale to use ILR devices rather than wearable devices is threefold. First. the duration of monitoring required for adequate data capture (5 months in the dialysate trial, 2 months in the UF trial) mandates use of ILR rather since Holters, wearable patches, or other intermittent monitoring devices can only be practically used for several weeks at most.[46] Second, although an implant procedure is required, ILRs are comfortable once implanted; bulky Holter monitors and wearable patches are uncomfortable, particularly when worn for >1-2 weeks. Finally, Holters and most patch technology require that the device be physically returned and downloaded which creates the high potential for data loss due to patient non-adherence or hospitalization. In contrast, ILR technology can be used with minimal risk, removes issues with comfort and adherence, and ensures full capture of all arrhythmias that occur.

Figure 6
Reveal LINQ

Predicate versions of this technology have been in clinical use since 1998 and are indicated for detecting arrhythmia in patients at risk of or suspected of arrhythmia. Reveal LINQ is 1/3rd the size of a triple-A battery (**Figure 6**) and is placed subcutaneously in the left chest during a brief procedure that can be done in-office under local anesthesia. It continuously records heart rhythm and when programmed alert criteria are met, the event is captured, stored and then uploaded wirelessly to a web-hosted database whenever the LINQ is within 6.5 feet of their transmitter during the programmed daily transmission time. Battery life is approximately 3-years, and devices are conditionally approved for use with MRI.[47,48] The incidence of device related complications is minimal and includes infection (1.2%), device migration, and pain at the implant site (<1%).[47] Since the device is leadless, the vast majority of infections are local and treatable with oral antibiotics or device extraction (an in-office procedure). Bacteremia is an extremely rare complication. To wit, out of 66 HD patients implanted in MiD, there was only 1 definite infection and one possible implantation-related infection. Neither were bacteremic and both were successfully treated with antibiotics without device extraction. Thus, MiD data supports device safety and minimal risk of bacteremia or serious device associated infection in HD patients, regardless of dialysis access type. Out of an abundance of caution patients with history of multiple infections or immune deficiencies will nevertheless be excluded from participation in Study A and B

Figure 7 Abbott i-STAT system and cartridges

Point-of-care Testing (POC)—POC testing will be performed at each dialysis session with dialysate K or HCO3 adjusted accordingly by algorithm. POC testing allows for real-time recognition of extreme excursions in HCO3 and K and immediate dialysate manipulation as needed to maximize safety. It also ensures maximization of differences in serum-dialysate K gradients between tested algorithms while avoiding use of low K dialysate when serum potassium is already low. Further, POC at each session provides the necessary data to evaluate the achieved gradient between serum and dialysate with each strategy, to analyze association of the achieved gradient with arrhythmia, and to specifically asses for interaction between ambient serum and dialysate potassium in terms of CSA risk. Finally, POC testing allows evaluation of the extent to which POC-guided prescription differs from care in which dialysate choice is based on monthly measurement alone as assessed by the % of sessions in which management differs.

Abbott i-STAT Device- POC testing will use the Abbott i-STAT (**Figure 7**), a portable, handheld device that provides lab quality analysis within 2-3 minutes using a few drops of whole blood (≤100uL). Results on the handheld screen can be automatically incorporated into electronic medical records. Results are highly accurate and have been nationally certified by regulatory bodies (CLIA) for clinical analysis of

whole blood samples. For K, the coefficient of variation (CV) is ≤1.3% across all concentrations. Results are tightly correlated with results from high-throughput auto-analyzers with r≥0.98 for all comparison methods.[49] Similar accuracy is obtained for HCO3 with i-STAT—CV ≤3.6% across the measurement range and correlation ≥0.935 against 3 different laboratory standards.[50] In a recent study of critically ill patients, the mean difference between i-STAT and clinical lab chemistries was -0.03 mEq/L for K and -0.34 mEq/L for HCO3.[51] Differences between i-STAT POC and reference dialysis lab results are unlikely to be clinically or systematically meaningful. However, i-STAT results obtained at the same time as standard lab results obtained during routine monthly dialysis lab testing will be compared in an ancillary analysis to confirm accuracy and as a measure of feasibility.

Of note, the BLUE I-STAT CHEM8+ which test both bicarbonate and potassium in a single sample have been marketed in the US for use with venous whole blood specimens in CLIA waived settings. However, in January 2020, Abbott notified customers that Abbott did not pursue FDA clearance or CLIA waived categorization for the BLUE CHEM8+ cartridges after making modifications to a prior version of the cartridges. Thus, the i-STAT BLUE CHEM8+ cartridges are not currently FDA cleared, Abbott has filed a 510(k)-notification seeking FDA approval.

II. Specific Aims

Overview of Trial Design—The overall goal for these trials is to provide the data necessary for the design of definitive clinical trials. Specifically, we aim to test recruitment feasibility, the feasibility of POC electrolyte measurement and POC-directed management of the dialysis prescription, and to provide preliminary estimates of effect size with manipulation of UF rate, dialysate K, and dialysate HCO3. We will perform two related, randomized cross-over trials; Study A- *dialysate interventions trial*, consisting of 2 dialysate potassium interventions and 2 dialysate bicarbonate interventions (4 total cross-over interventions): and Study B-*ultrafiltration rate intervention trial*, consisting of 2 separate ultrafiltration rate strategies.

The central hypothesis underlying Study A and Study B is that the risk of clinically significant arrhythmias in HD patients can be reduced by altering components of the dialysis prescription.

Aim 1—To test the feasibility and safety of POC-guided dialysate prescription adjustment and the feasibility of limiting UF rate in HD patients. The current studies will pilot our educational strategies and the dialysate potassium, dialysate bicarbonate and UF intervention strategies to test their feasibility in a multi-center setting. They will test the hypothesis that ≥80% adherence with proposed interventions is feasible, and that the safety need for unscheduled dialysis or severe abnormalities in potassium and bicarbonate will be minimal.

Aim 2—To assess recruitment feasibility and retention rate for trials combining ILR insertion to monitor arrhythmia and interventions using POC-guided dialysis prescription or UF rate manipulation. Screen failures and retention rates will be captured and analyzed. Whether recruitment rates ≥1 patient per month and retention rate > 90% are achievable in each study will be tested.

Aim 3 —To refine effect estimates of the change in monthly CSA duration during Study A (dialysate potassium intervention to maximize vs. minimize intradialytic potassium removal) and Study B (aggressive vs. conservative ultrafiltration rate). Refining estimates of change in CSA with each pair of interventions will provide key information necessary for design of definitive trials. Whether CSA decreases with minimization of potassium removal, alkalosis limitation and UF rate minimization will be tested.

Substudy Aim**—**To assess the relationship between Reveal LINK EKG morphology and pre-dialysis electrolyte concentrations.

III. Subject Selection

These trials will test the impact of dialysate K/HCO3 and UFR on CSA. Subjects from study-affiliated dialysis units will be screened.

Inclusion Criteria:

a. Maintenance hemodialysis therapy for end-stage renal disease
b. Age 18-85 years
   *To enrich the trial population for arrhythmia events, subjects between 18-40 years old will be required to have at least one of the following: history of congestive failure, diabetes, coronary or peripheral vascular disease, or arrhythmia.
c. > 30 days since dialysis initiation
d. Ability to provide informed consent

Exclusion Criteria:

a. Expected survival <6 months—to allow trial completion
b. Renal transplant, transfer to home or peritoneal dialysis, or to non-study HD facility anticipated within 6 months
c. Prisoners or cognitive disability preventing informed consent
d. Pregnancy. A pregnancy test will be required for women of child bearing potential prior to enrollment. A pregnancy test will not be required for women past the age of child-bearing potential >55 years old, women with a history of surgical sterilization, or for women <55 years of age who have not had a menses within the past 12 months. Women with child bearing potential will be required to use a highly effective method of contraception for the duration of the study. Highly effective methods include hormonal contraception, barrier methods or abstinence.
e. Condition which in the opinion of the investigator increases risk of local infection with ILR placement such as skin conditions, known immune dysfunction or frequent infections suggestive of immune dysfunction.
f. Bleeding disorder that cannot be reversed for ILR placement. For patients on coumadin INR value >2.5 within 72 hours of ILR placement. For patients on novel oral anti-coagulants (NOAC)—inability to hold NOACS for 24 hours before and after the procedure.
g. Existing pacemaker, implantable monitor or defibrillator which precludes device placement
h. Chronic, persistent atrial fibrillation

Additional Inclusion/Exclusion

Criteria: Study A Exclusions:

a. Hemoglobin <8 g/dL—only 100 µL is needed for each POC test, but safety is improved by avoiding serial phlebotomy when anemia is severe.
b. Serum K >6.5 or <3.5 mEq/L within 30 days—severely hyperkalemic or hypokalemic patients are not suitable for testing the proposed algorithms since both algorithms call for similar prescriptions at the extremes of physiologic values.

Study B Inclusion Criteria:

a. It is required that subjects have an interdialytic weight gain necessitating an UF rate of ≥13 mL/kg/hour of dialysis to achieve the target post-dialysis weight in ≥6 dialysis sessions in the month prior to enrollment.

IV. Subject Enrollment

Participant Recruitment and Screening

Participants at dialysis units affiliated with investigators will be pre-screened for eligibility. No one who cannot legally give consent will be approached. In addition to active screening of dialysis unit rosters by study personnel, informational handouts and brochures may be disseminated at affiliated dialysis units in order to allow for interested participants to learn about the study and to contact the study investigator if interested. All study material must be approved by local IRBs before dissemination to potential study participants.

Dialysis unit labs, medical records at the investigator's institution, and treatment or history records at local dialysis units will be reviewed to assess eligibility for enrollment. No study-specific testing is required to confirm eligibility. To introduce the study to potential subjects, a care provider known to the patient will inquire about the subject's interest in learning about research studies and request permission for study staff to approach the patient and present the study. Alternatively, flyers will be posted at dialysis units advertising Study A and B. Flyers will include options for potential subjects to indicate their willingness to be contacted by the study team and will provide contact information so that patients can directly contact the study team to learn about the trials. Each participant's treating nephrologist will be contacted to assess suitability for enrollment prior to consent.

Once preliminary eligibility is confirmed, informed consent will be obtained by a qualified investigator or study site designee during an in-person visit. This visit may take place either at the local dialysis unit or at the investigator's institution, according to investigator and participant preferences. In the event that an in-person consent cannot be obtained, electronic consent through the NYU HIPAA compliant software REDCap will be made available. Study personnel will notify current patients of any changes made to the consent by phone or email including instructions for completing the electronic consent. Currently enrolled subjects may take as long as needed to review these changes, and make a decision to continue on study. For women of childbearing potential, a serum pregnancy test will be performed to determine final eligibility.

Subjects will be compensated for time and expenses for scheduled study visits, up to a total of $300 (6 scheduled study visits). Subjects in both studies (A and B) will be compensated $150 at study visit 4 and study visit 8. He/she and their insurance company will not be charged for the cost of the study related procedures.

Early Withdrawal of Participants

When and How to Withdraw Participants

Early withdrawals will be discouraged and participants who are not willing to continue the intervention will be encouraged to remain in the study and continue study evaluations. However, participants may be withdrawn from the study under the following circumstances that have the potential to compromise patient autonomy or safety:

a. Pregnancy
b. Withdrawal of consent
c. Allergy to or documented intolerance to ancillary study medications for implant procedure (e.g. lidocaine, versed, xylocaine, or other medications used for local anesthetic or conscious sedation)
d. Non-compliance with dialysis schedule compromising ability to follow serum potassium on a monthly basis
e. Organ transplantation
f. Change to a different dialysis modality
g. Prolonged hospitalization
h. Transfer to non-participating dialysis unit
i. Incarceration

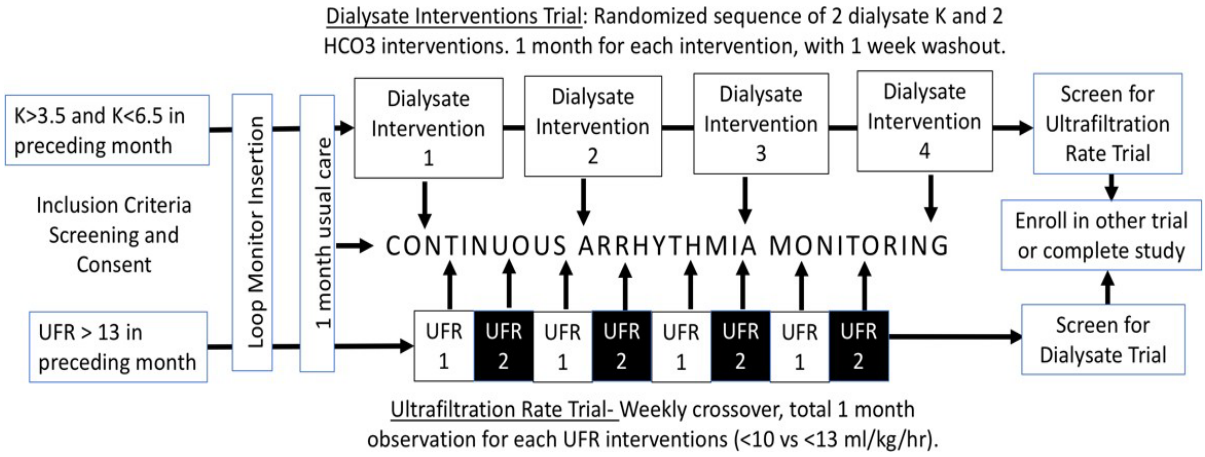
Data Collection and Follow-up for Withdrawn Participants

In the case of withdrawal, every attempt will be made to obtain consent to continue to follow patients for the occurrence of mortality, hospitalizations, and other safety signals via telephone or in-person contact with participants, relatives, and dialysis unit staff and records until scheduled end of follow-up.

Participants will be deemed as lost to follow-up after ≥ 3 attempts have been made to contact the patient via their preferred means of contact (telephone or email), ≥1 attempt has been made to contact the patient via their secondary means of contact, and ≥1 attempt to contact next of kin is unanswered.

V. Description of Study Procedures

Two related, randomized cross-over trials will be performed; Study A-a *dialysate interventions trial*, consisting of 2 dialysate potassium interventions and 2 dialysate bicarbonate interventions (4 total cross-over interventions): and Study B- an *ultrafiltration rate intervention trial*, consisting of 2 separate ultrafiltration rate strategies. A total of 20 patients will be enrolled in each trial. An overview of the study design is illustrated in **Figure 5 below**.



ILR Intervention— Consent and ILR placement at the local site will be followed by a one-month baseline observation period. ILR placement will be followed by wound check visits at 1 week and 1-month post implant. Outpatient insertion of ILR by study cardiologists will occur within 4 weeks of enrollment. Reveal LINQ™ (Medtronic) implantable monitors will be utilized.

Arrhythmia Detection—Detection of clinically significant arrhythmias (CSA) will be achieved using implantable loop monitors (ILR) inserted at the start of each trial. ILR tracings will be batch analyzed by study cardiologists blinded to randomized treatment. Tracings from ILR-detected events meeting automated, validated detection criteria for bradycardia, asystole, AF, sustained or non-sustained ventricular tachycardia (VT) will be manually reviewed at least once every two weeks. Clinically significant arrhythmias will be defined on the basis of arrhythmias likely to lead to sudden cardiac arrest or serious morbidity and mortality and will include atrial fibrillation (AF), asystole lasting ≥ 3 seconds, bradycardia ≤40 beats per minute lasting ≥6 seconds, sustained VT ≥130 beats per minute lasting ≥30 seconds, and any sudden cardiac arrest. Positively adjudicated CSA will be entered into a study database and coded according to arrhythmia type, date and duration.

Dialysate Interventions Trial (Study A)—This trial will test the impact of dialysate K and HCO3 on CSA. After a month of usual care, subjects will cross-over in random order to four month-long periods using alternative approaches to algorithm-specified manipulation of dialysate K or HCO3 guided by POC-obtained laboratory testing prior to each dialysis. There will be a one-week washout with usual care between each intervention period. Randomization sequences will be balanced with respect to treatments to minimize impact of sequence or carryover effects on outcomes. Algorithms tested will compare **a) Minimization of dialysate-serum potassium gradient vs. maximization of potassium removal** (preferential use of high potassium dialysate to minimize gradient vs. low K dialysate to maximize removal); and **b) Alkalosis avoidance vs. acidosis avoidance** (preferential use of lower dialysate HCO3 concentration vs. higher dialysate HCO3). Subjects and investigators will be blinded to the intervention in use. HD nurses and staff will obtain POC chemistry results prior to each HD session and adjust the prescription for dialysate potassium or HCO3 as dictated by the algorithm. Since dialysate prescription changes must be entered manually, dialysis staff cannot be blinded to the algorithms, but they will not assess endpoints or be otherwise involved in interpretation of study data.

Whole blood (100 µL) will be obtained by dialysis staff when the catheter, fistula or graft is accessed prior to each HD session during the K and HCO3 intervention periods. Blood will be drawn into a non-heparinized syringe and added to the i-STAT cartridge for immediate testing—a process similar to routine blood glucose testing during HD. Blood will be immediately tested on the i-STAT according to the manufacturer's protocol. (Alternatively blood may be drawn into heparinized tubes, mixed by inversion, and tested within 10 minutes). Results are saved on the device, printed, and can be entered directly to the study data-base.

Potassium (K) Intervention—This intervention will test whether minimizing intradialytic fall in serum K by using higher K dialysates to minimize serum-dialysate K gradients reduces the incidence of CSAs compared to an approach prioritizing lower K dialysate to reduce the incidence of hyperkalemia. This will be achieved by utilizing an algorithm which couples POC-testing with the choice of one of two dialysate K concentrates (2 or 3 mEq/L potassium, **Table [left]**) that are widely available in dialysis clinics. Although there is potential equipoise regarding use of very low K dialysates (1 mEq/L) in hyperkalemic patients, 1K dialysate is either restricted or not available in the majority of US outpatient HD units.

Dialysate Potassium Intervention Algorithm

POC Serum K (mEq/L)	Dialysate K (mEq/L)	Gradient (mEq/L)
K removal maximization Strategy		
<4	3	0
4-5.0	3	1-2
5.1-6.3	3	2.1-3.3
≥6.4	2	≥4.4
Gradient-Minimization Strategy		
<4	3	0-1
4-5k	2	2-3
5.1-6.3	2	3.1-4.3
≥6.4	2	≥4.4

Substudy—Subjects enrolled in Study A will be offered the opportunity to participate in an optional

substudy. Participants in the substudy will be asked to press the button on the REVEAL patient assistant device to automatically trigger their implanted REVEAL LINQ ILR to record an EKG tracing each time their blood drawn is drawn by the dialysis staff prior to dialysis for POC testing. Patients will also be asked to perform a full transmission upon returning home from dialysis to assure an adequate length of EKG tracing is obtained before and after the patient assistant button is pressed at dialysis.

Bicarbonate (HCO3) Intervention—The bicarbonate intervention is designed to compare an algorithm designed to avoid acidosis (by use of lower dialysate HCO3) with one that avoids alkalosis (by use of higher dialysate HCO3). As shown in the **Table (right)**, POC-HCO3 results will be obtained prior to each HD session and will inform the selection of the dialysate HCO3 concentration. As with potassium, POC-testing allows dialysate HCO3 concentration to be matched according to serum HCO3 and has analogous advantages in terms of safety, achieved gradient, and potential analyses, compared to a design using fixed dialysate concentrations. The algorithm has been designed based on published data on the expected post dialysis increases in serum HCO3 and overall time-averaged serum HCO3 expected from any given combination of pre-dialysis serum and dialysate HCO3 concentrations.[53] As shown in the table, excellent separation of dialysate and serum HCO3 concentrations are expected.

Dialysate Bicarbonate Intervention Algorithm

POC HCO3 (mEq/L)	Dialysate HCO3 (mEq/L)	Gradient (mEq/L)	Expected Change in post HD HCO3	Expected Time Avg HCO3
Acidosis Avoidance				
<20	40	≥20	+12	26
20-24	38	14-18	+6-12	24-26
25-27	33	6-8	negligible rise	26
≥28	26	≤ -2	negligible decrease	26
Alkalosis Avoidance				
<20	36	≥16	+8	24
20-24	31	7-11	+1-3	25
25-27	24	-1-3	negligible rise	24
≥28	20	≤-8	-2	26

Overview of Ultrafiltration (UF) Trial- Study B—The UF rate intervention will use identical inclusion/exclusion criteria as the dialysate Intervention trial with a few exceptions. Subjects are required to have an interdialytic weight gain necessitating an UF rate of ≥13 mL/kg/hour of dialysis to achieve the target post-dialysis weight in ≥6 dialysis sessions in the month prior to enrollment. This criterion is necessary to achieve separation in UF rates between the aggressive and restricted UF rate periods. Conversely, there will be no exclusions on the basis of baseline hemoglobin or serum potassium concentration since point of care testing of electrolytes is not be required and the UF intervention is not expected to impact serum potassium concentration.

After ILR placement, subjects will crossover between two UF rate interventions: 1) UF rate-restricted dialysis, in which UF rates are limited to a maximum of 10 mL/kg/hr for the duration of the session 2) UF rate-unrestricted dialysis. It is anticipated that patients with large interdialytic weight gains in the UF rate-restricted intervention may not achieve their target post-dialysis weight during the prescribed treatment time. In order to prevent progressive volume overload and the need for additional HD sessions to manage volume gains in this scenario, subjects will crossover weekly between the restricted

and unrestricted UF interventions. This weekly crossover accomplishes two important goals: First, it reduces safety concerns by ensure that any volume gained due to limiting the UF are constrained to one week and promptly addressed with unlimited UF the following week. Second, it increases separation between UF rates in the two interventions, since a higher UF-rate will be needed to address any weight and volume gains resulting from UF-rate restriction.

Investigators will be blinded. Subjects will not be blinded as it is not feasible to blind them to the goal UF and post-dialysis weight (typically self-measured); HD staff will have access to the algorithm in order to adjust UF rate accordingly. Following a one-month baseline observation period with usual care, subjects will undergo 4 weeks of each UF intervention administered in alternating weeks as described above, for a total study duration of 12 weeks. Data will be aggregated and results compared using a full month of data for each intervention.

End of Study Procedures—In order to maximize recruitment efficiency and the significant investment in undergoing ILR implantation, patients completing one study will be given the option of continuing to eligibility screening and enrollment for the alternate study. If subjects consent to both Study A and Study B, then the baseline observation period for the second study may be less than 1 month. Those refusing or ineligible will be offered ILR explanation.

Description of Study Visits:
Subjects will meet with a member of the study team for 8-11 study visits, during regular dialysis treatments at their outpatient clinics. Study activities for each of the study visits are described below. In addition to the study visits, subjects will continue their regularly scheduled dialysis treatments and must receive at least half of the treatments at their outpatient clinic (6 out of 12 scheduled) for each treatment period and the 30-day Baseline Observation Period. *Procedures for missed treatments for each period are described below. Adverse events will be collected from the date of consent until study visit #11. For subjects who elect to keep the ILR LINQ device implanted at the end of the last treatment, adverse events and severe adverse events will be collected until a week after study visit #9.

Enrollment and Baseline Study Visits: Study A and Study B

Study visit #1: Screening/Enrollment Visit
Subjects will be consented at the beginning of the screening visit, before any study procedures are performed. This visit will take place at the dialysis unit. If a blood pregnancy test is required, then a sample will be collected at this time and sent to the local lab for processing. Eligibility criteria will be confirmed via review of medical records and medication lists will be reviewed.

Study Visit #2: Reveal LINQ Insertion/Baseline Visit
Within 4 weeks of consent, a physical exam will be performed and subjects will have the ILR device implanted at the local site. If coagulation labs are not clinically available within relevant timeframe (72 hours), then these will also be drawn at this visit. Platelet count must be available within 30 days of the procedure or it will be drawn at this visit. Coagulation parameters and platelet count (as needed) may be drawn up to 72 hours prior to the Reveal LINQ visit to ensure that they are available at the time of the procedure. If the subject is not taking an anticoagulant medication, the coagulation parameters and platelet count may be drawn up to 96 hours prior to the procedure. Concomitant medications will be recorded from this visit until one week after the last study related treatment. As needed for scheduling purposes the procedures needed to complete this visit may take place on more than 1 calendar day.

Procedures will be performed in an outpatient or in an office environment. Due to COVID-19 safety precautions, subjects may be provided with a COVID-19 nasal swab test as part of this visit. Conscious sedation (including alprazolam/midazolam/fentanyl) and prophylactic oral or intravenous antibiotics may be used

at discretion of study cardiologist. Subjects will be given a transmitter/charger and a Patient Care Assistant which they will be required to keep for the duration of their participation in the study. ILR tracings will be uploaded automatically whenever patients are within 6.5 feet of the transmitter during the programmed daily transmission time and reviewed at least once every two weeks via a website on a secure platform by the study team for the occurrence of CSA. The subject may be asked to manually upload data from the transmitter throughout the study if they have a higher number of cardiac related events, are enrolled in the substudy, or at the discretion of the PI. This will take a few minutes and the study team will ensure the patient is aware and capable of completing this task. The Baseline Observation Period begins at this visit and continues for 30 days until Study Visit #4.

Study Visit #3: Week 1 Reveal Visit (+/- 3 days)
Wound check visit at dialysis unit or the local site. Standard of care labs will be reviewed from participants' medical records. If a particular lab is not available from the clinical records, it is not required to draw it for study purposes at this visit. The assays that will be measured include:

Chemistry:

Sodium	Iron
Glucose	Iron Binding Capacity (TIBC)
Urea Nitrogen (BUN)	Ferritin
Serum Creatinine	Albumin
Potassium	Parathyroid Hormone
Chloride	
Calcium	
Phosphate	Single Pool Kt/V (actual)
Bicarbonate	

Hematology:

WBC
Hemoglobin
Platelet Count

Study Visit #4: Week 4 Reveal Visit (+/- 3 days)
This visit will serve to review any adverse events, concomitant medications, and record dialysis treatment data from the baseline month of usual HD care. Subjects will be randomized to a treatment arm of Study A/B and will start study treatment on the next start of their short-interdialytic period (either Monday or Tuesday.) The Baseline Observation Period ends at this visit. Subjects should have completed at least 6 of their 12 scheduled dialysis treatments by this visit.

***Procedure for Missed Dialysis Treatments During Baseline Observation Period:**
At the end of the Baseline Observation Period, subjects who have missed more than half of their treatments (7 or more) during this time will "make up" treatments by extending the observation period for 1 or 2 weeks, beginning on the first Monday or Tuesday upon their return. The treatment intervention schedule will be adjusted accordingly.

Study A Intervention - Dialysate K/HCO_3 Trial: Monthly Visits:

Study treatment to be started on the 1st Monday/Tuesday following the Week 4 Reveal Visit. There will be 4 crossover groups and subjects will rotate monthly through all the treatment groups in a random blinded order. Prior to initiation of all HD sessions, subjects will receive POC testing via the Abbott i-STAT, which requires approximately 100uL of blood. This testing, along with their treatment arm assignment, will drive the dialysate prescription for that specific HD session (see figures/tables further below). The 4 cross-over groups are listed below:

i. Potassium Removal Maximization strategy, 1 month (low dialysate K)
ii. Potassium Gradient-Minimization Strategy, 1 month (high dialysate K)
iii. Acidosis Avoidance, 1 month (low dialysate bicarbonate)
iv. Alkalosis Avoidance, 1 month (high dialysate bicarbonate)

There will be a 1-week washout period between subsequent interventions and during this week, participants' dialysate prescription will be determined by their dialysis physician. Dialysis treatment records will be reviewed at least monthly and standard of care labs will be recorded at visits 5 through 8.

Subjects enrolled in the optional substudy will press the button on the REVEAL patient assistant device to automatically trigger their implanted REVEAL LINQ ILR to record an EKG tracing each time their blood drawn is drawn by the dialysis staff prior to dialysis for POC testing. Subjects will also record a full transmission upon returning home from dialysis with the Carelink Transmitter.

Study Visit #5: **Study A Week 5 Visit** (+/- 5 days)

Visit to take place either at dialysis unit or by phone. Subject will be queried for Adverse Events and any changes in health or medications Dialysis records will be reviewed for standard of care labs and hemodialysis treatment details. Subjects will begin their first treatment period and will receive the treatment intervention assigned for this period with each dialysis session (weeks 5-8.) Subjects who have missed more than half of the treatments (7 or more) during this period will "make up" treatments by extending the first treatment period for 1 or 2 weeks and continue receiving the first assigned intervention. The extension weeks will be referred to as Week 8-1 and Week 8-2 (not week 9 and 10) in order to maintain the schedule of events. The schedule of study visits will be adjusted accordingly. Week 9 will be a washout period.

Study Visit #6: **Study A Week 10 Visit** (+/- 5 days)

Visit to take place either at dialysis unit or by phone. Subject will be queried for Adverse Events and any changes in health or medications. Dialysis records will be reviewed for standard of care labs and hemodialysis treatment details. Subjects will begin their second treatment period and will receive the treatment intervention assigned for this period at each dialysis session (weeks 10-13.) Subjects who miss more than half of the treatments (7 or more) during this period will "make up" treatments by extending this treatment period for 1 or 2 weeks and continue receiving the assigned intervention. The extension weeks will be referred to as Week 13-1 and Week 13-2. Week 14 will be a washout period.

Study Visit #7: **Study A Week 15 Visit** (+/- 5 days)

Visit to take place either at dialysis unit or by phone. Subject will be queried for Adverse Events and any changes in health or medications. Dialysis records will be reviewed for standard of care labs and hemodialysis treatment details. Subjects will begin their third treatment period and will receive the treatment intervention assigned for this period at each dialysis session (weeks 15-18.) Subjects who miss more than half of the treatments (7 or more) during this period will "make up" treatments by extending this treatment period for 1 or 2 weeks and continue receiving the assigned intervention. The extension weeks will be referred to as Week 18-1 and Week 18-2. Week 19 will be a washout period.

Study Visit #8: Study A Week 20 Visit (+/- 5 days)
Visit to take place either at dialysis unit or by phone. Subject will be queried for Adverse Events and any changes in health or medications. Dialysis records will be reviewed for standard of care labs and hemodialysis treatment details. Subjects will begin their fourth and final treatment period for Study A and will receive the treatment intervention assigned for this period at each dialysis session (weeks 20- 23.) Subjects who miss more than half of the treatments (7 or more) during this period will "make up"treatments by extending this treatment period for 1 or 2 weeks and continue receiving the assigned intervention. The extension weeks will be referred to as Week 23-1 and Week 23-2.

***Procedures for Missing Consecutive Dialysis Treatments During Intervention Periods in Study A**: Subjects who have missed less than 6 consecutive weeks, can also "make-up" treatments with a 2-week extension that will begin on the first Monday or Tuesday upon their return to the dialysis clinic. Subjects will receive their last assigned intervention during these make up treatments and the study schedule and dates of their remaining study visits will be adjusted accordingly.
In the event that a subject does not receive outpatient dialysis at his or her usual outpatient dialysis clinic for six consecutive weeks or more, the subject will be reassessed by the site investigator for suitability before continuing in the trial. If deemed appropriate to continue in the study, the rules as described above will be applied so that the subject receives at least 6 dialysis treatments of the assigned intervention.

Although all intervention periods will be scheduled to start on the 1st Monday or 1st Tuesday of a week, no special provision will be made to extend the intervention period if subjects miss their treatment on these days, provided they are able to complete at least 6 dialysis treatments of the assigned intervention. The intervention will simply start on the next scheduled dialysis treatment.

Study B Intervention- Ultrafiltration Rate Trial: Biweekly Visits: Study treatment to be started on the Monday/Tuesday following the Week 4 Reveal Visit. There will be 2 treatments and subjects will rotate back and forth weekly during an 8-week period in a random order. Dialysis unit records will be reviewed at least monthly and standard of care labs will be recorded at visits 5 and 8.

i. **Restricted UFR;** UFR ≤10 ml/kg/hr: 4 alternating weeks
ii. **Standard of Care/ Unrestricted UFR;** UFR as needed: 4 alternating weeks

Study Visit #5: Study B Week 5 Visit (+/- 5 days)
Visit to take place either at dialysis unit or by phone. Subject will be queried for Adverse Events and any changes in health or medications and dialysis treatment records and standard of care labs will be reviewed. Subjects will receive their randomized first UFR based treatment assignment during each dialysis treatment during week 5. Treatment will then switch to the alternate treatment strategy during week 6 at each dialysis session during the week. At the beginning of week 7, treatment will once again alternate back to the first treatment assignment.

Study Visit #6: Study B Week 7 Visit (+/- 5 days)Visit to take place either at dialysis unit or by phone. Subject will be queried for Adverse Events and any changes in health or medications and dialysis treatment records will be reviewed. Treatment assignments will continue alternating weekly between the two treatment options during Week 8 (second assignment) and Week 9 (first assignment.)

Study Visit #7: Study B Week 10 Visit (+/- 5 days)Visit to take place either at dialysis unit or by phone. Subject will be queried for Adverse Events and any changes in health or medications and dialysis treatment records will be reviewed. Treatment assignments will continue alternating weekly between the two treatment options during Week 10 (second assignment) and Week 11 (first assignment.)

Study Visit #8: Study B Week 12 Visit (+/- 5 days)
Visit to take place either at dialysis unit or by phone. Subject will be queried for Adverse Events and any changes in health or medications and dialysis treatment records and standard of care labs will be reviewed Treatment assignment will alternate for the last time and subjects will receive the second assignment during this final intervention treatment (week 12.)

***Procedures for Missed Dialysis Treatments for UFR-based interventions in Study B:**
Subjects in Study B will cross-over between two different, week-long UFR-based interventions, alternating interventions each week for a total of 8 weeks. During this 8-week period, subjects will be scheduled for a total of 24 dialysis treatments at their dialysis clinic; 12 treatments of each of the two UFR-based interventions.

At the end of the 8-week treatment period, subjects who have missed more than half of the treatments (7 or more) for one or both of the two treatment interventions will have the opportunity to "make up" treatments by extending the treatment period for two to four more weeks in order to meet the minimum requirement of 6 treatments received within each treatment intervention.

This "make-up" treatment extension will be scheduled to start on the next Monday or Tuesday following the end of the 8- week treatment period (week 12) and treatment assignment for the first extension week must continue the alternating pattern to avoid a subject receiving the same treatment for two consecutive weeks.

For subjects who have missed less than 6 consecutive weeks, the extension will begin on the first Monday or Tuesday upon their return to the dialysis clinic. In the event a subject does not receive outpatient dialysis at his or her usual outpatient dialysis clinic for six consecutive weeks or more, the subject will be reassessed by the site investigator for suitability before continuing in the trial. If deemed appropriate to continue in the study, the rules as described above will be applied so that the subject receives at least 6 dialysis treatments for both of the assigned interventions.

Study Visit #9: End of Treatment Visit
Upon completion of either Study A or Study B, subjects will be screened and offered the opportunity to consent to participate in the other study. Subjects will be queried for adverse events and dialysis treatment records will be reviewed. If subjects elect to participate in both studies consecutively, then they will not need to redo the Week 1 Reveal insertion follow-up visits, since they will have already received a device. For subjects enrolling in both studies, a 1-week washout period is required (receive SOC hemodialysis treatment) and will then begin another 1-month of baseline monitoring prior to starting the intervention for the second study.

Once a subject has completed Study A and Study B, or a subject is no longer interested or eligible to participate in the second study, he or she will be given the option to come back to New York University Langone Medical Center for device removal. Subjects who choose to keep the device implanted after the last treatment will be followed for adverse events and concomitant medications for one week after this visit. Subjects who choose to have the device removed, will have two more study visits, one to remove the device and another to follow up on the removal procedure.

Study Visit #10: Reveal LINQ Explanation Visit
Following completion of Study A or Study B, subjects will be given the option to come back to the local site for device explanation. Due to the COVID-19 safety precautions, subjects may be provided with a COVID-19 nasal swab test as part of this visit. Subjects will be queried for adverse events, concomitant medications, and Reveal devices will be removed.

If coagulation labs are not clinically available within relevant timeframe (72 hours), then these will also be drawn at this visit. Platelet count must be available within 30 days of the procedure or it will be drawn at this visit. Coagulation parameters and platelet count (as needed) may be drawn up to 72 hours prior to the Reveal LINQ visit to ensure that they are available at the time of the procedure. If the subject is not taking an anticoagulant medication, the coagulation parameters and platelet count may be drawn up to 96 hours prior to the procedure. Concomitant medications will be recorded from this visit until one week after the last study related treatment. As needed for scheduling purposes the procedures needed to complete this visit may take place on more than 1 calendar day.

Study Visit #11: Explant Follow Up Visit

Following explanation, there will be a 1-week wound check visit either at the local site or at the dialysis clinic. Collection of adverse events and concomitant medications will conclude at this visit.

VI. Biostatistical Analysis

Given an overarching aim to assess definitive trial feasibility, analyses will be considered exploratory and conservatively interpreted but no adjustment will be made for multiple comparisons.

Trial Endpoints and Overview of Specific Aims: The long-term goals are to conduct well-powered trials testing the effect of POC testing-guided management of dialysate potassium and bicarbonate or limitation of maximum UF rate on clinically significant arrhythmia (CSA) and hard cardiovascular events. The specific goals of Studies A/B in accordance with the R34 funding mechanism isto provide the key feasibility and effect-size data necessary to plan definitive, subsequent multi-center trials. Towards this end, data on:

- Aim 1: Adherence with Proposed Interventions
- Aim 2: Recruitment Feasibility
- Aim 3: Effect Estimates

Adherence with Proposed Interventions (Aim 1)— In routine practice, the dialysis prescription is adjusted by the physician only once per month in response to monthly laboratory results. Utilizing POC testing and daily adjustment of the dialysate prescription deviates from this standard considerably. Similarly, while a post-dialysis target weight is prescribed by dialysis providers, in routine practice, patients and nurses have daily discretion regarding UF rate. In short, protocolizing the interventions represent a significant change from standard of care that will require active engagement of both patients and HD-unit staff. Estimating the extent of protocol deviation and the safety of proposed interventions in this environment is critical to large-scale implementation of the proposed trials as biologic efficacy is immaterial if interventions cannot be scaled-up.

Adherence Endpoints—Adherence will be assessed for each of the 4 dialysate interventions (K removal minimization vs. maximization, acidosis vs. alkalosis avoidance) as the % of sessions in which POC testing is completed and the dialysate is adjusted according to the algorithm. For the UF trial, it will be assessed as the % of sessions in which the mandated UF rate is delivered. We hypothesize that 90% adherence is achievable. HD staff will be anonymously surveyed once 3 subjects have completed 1 month of each trial and once 6 patients have completed each trial. A questionnaire will identify the impact of time constraints, patient refusal, algorithm complexity, inadequate training on POC devices, clinical concerns, or other factors on protocol adherence. Face-to-face review with HD staff will facilitate identification of other barriers. Where addressable factors are identified, they will be corrected for remainder of the trials. Since the overall goal is to assess implementation feasibility, secondary analyses will compare pre- and post-correction adherence in addition to estimating overall adherence. This adaptive plan will facilitate identification of best practices and ensures that estimates represent the feasibility of subsequent protocols to be implemented after incorporating lessons learned in the pilot experience.

Secondary Feasibility Measures—POC electrolyte measurements will be compared with usual care monthly labs to assess accuracy of POC testing. An additional metric that will be used to determine the impact of POC testing on trial design will be the percent of sessions in which the POC-guided dialysate prescription differs from a hypothetical prescription in which the choice of dialysate is based solely on the once-monthly lab.

Safety Endpoints—The primary safety endpoint will include the incidence of all serious adverse events and intervention-specific complications: a) Potassium Intervention—severe K abnormalities (K ≥6.5 or ≤3.0 mEq/L), or unscheduled HD or hospitalization for hyper/hypokalemia in the absence of a missed treatment; b) Bicarbonate Intervention— severe HCO3 abnormalities (HCO3 <20 or >32 mEq/L) or unscheduled HD or hospitalization for acid base abnormalities in the absence of a missed treatment; c) Ultrafiltration Intervention—Unscheduled HD or hospitalization for volume overload. Secondary safety endpoints include the occurrence of CSAs requiring further management, all-cause mortality, cardiovascular mortality, and hospitalization.

Recruitment Feasibility (Aim 2)—Recruitment feasibility will be analyzed by testing whether an overall recruitment rate of 1 patient/month is achieved in each trial (1-sample test). This is a critical metric, as a large-scale trial cannot be feasibly completed in a practical number of centers if between 0.5-1 patient/month cannot be enrolled. This rate represents a minimum criterion for feasibility.

The percent of screened patients enrolled will be calculated as a secondary feasibility measure to assess the size of the necessary screening pool. Reasons for non-enrollment (vis-a-vis inclusion and exclusion criteria and patient and physician preferences) will be assessed to determine the potential for protocol modification to improve recruitment. Subject retention will be calculated as the percentage of enrolled patients completing the trial. Retention rates of 90% will be considered the benchmark for feasibility.

Effect Estimates (Aim 3) •—Estimating the mean and standard deviation (SD) of the change in duration of clinically significant arrhythmia (CSA) per month is critical for power and sample size calculation and planning definitive studies. The total monthly duration of CSA (in minutes) will be utilized as the primary efficacy endpoint in comparing each pair of interventions (K removal maximization vs. minimization, acidosis vs. alkalosis avoidance, aggressive vs. conservative UF). In the event of incomplete follow-up, CSA duration will be indexed to follow-up time. CSA will be defined on the basis of arrhythmias likely to lead to SCA or serious morbidity and mortality and will include AF, asystole ≥3 seconds, bradycardia ≤40 beats per minute lasting ≥6 seconds, and sustained VT ≥130 beats per minute lasting ≥30 seconds. CSA's will be adjudicated by study electrophysiologists.. Currently, no data exists on the expected impact of the interventions on CSA duration, but given a mean duration of CSA in MiD of 356 ± 1765 minutes, a sample size of 20 subjects provides 80% power for detection of change in CSA duration of 140 minutes/month given within-subject correlation of 0.9, 370 minutes for within-subject correlation of 0.7, and 470 minutes if within-subject correlation is 0.5.

Statistics and Analysis—A balanced, uniform crossover design will be used with randomization stratified by site in blocks of 4.

Adherence will be estimated as % (95% CI) of sessions without protocol deviation. Comparison of adherence percentage pre- vs. post-interim analysis of adherence will be made using linear regression with time period as an independent variable. Exploratory analyses will assess association of adherence with site, dialysis shift (1st-3rd), and day (Monday/Wednesday/Friday or Tuesday/Thursday/Saturday).

Safety will be assessed by calculating the incidence rate (complications per unit follow-up time) for serious adverse events and intervention-specific complications. Comparisons of incidence rate between interventions will utilize Poisson regression adjusted for randomization scheme and site. Exploratory analyses will assess age, sex, race, mean intra-dialytic weight gain, potassium concentration and HCO3 concentration in month prior to randomization on the incidence of adverse events. Given the pilot nature of the trials and major goal of informing feasibility estimates for definitive trials, $P<0.05$ will be considered significant in all safety analyses. No adjustments will be made for multiple comparisons given the pilot nature of the studies.

Efficacy estimates for Aim 3 will utilize the mean duration of CSA as the primary outcome. In the event of incomplete follow-up, this will be indexed to duration of follow-up time (e.g. minutes per day). Change is CSA duration between interventions will be analyzed using mixed effects linear regression with terms for treatment, research site, period, sequence, and random effects for subjects. Primary outcomes for the dialysate trial will compare CSA during potassium maximization vs. minimization, and acidosis vs. alkalosis avoidance. For the UF trial, aggressive vs. conservative UF will be compared. Physiologically, the washout period of 1-week in the dialysate trial and 1 weekend in the UF trial is sufficient to avoid the possibility of carryover effects. Potential for sequence effects is minimized by a design with uniform sequences (all treatments appear once within each sequence). Potential for carryover and randomization sequence effects will be analyzed by including terms for sequence and their interaction with treatment in the models.

Secondary Analysis

Secondary analyses will compare CSA during usual care period and the individual interventions using identical methods:

- effects on AF and potentially lethal arrhythmias (asystole, sustained VT, bradycardia for ≥6 seconds) will be separately assessed as secondary endpoints
- Exploratory analyses will assess association of dialysis day (Monday/Wednesday/Friday or Tuesday/Thursday/Saturday), shift (1st-3rd), and site with CSA

Data for the optional substudy will be analyzed using machine learning algorithms to detect any associations between EKG morphology and baseline electrolyte concentration.

VII. RISKS AND DISCOMFORTS

Risk to Human Subjects

The overall risks of the interventions proposed in this application are minimal. Informed consent will be obtained from all subjects, and regular monitoring will occur in order to prevent or minimize study-associated risks.

While ILR insertion is a pre-requisite that may add minimal risk and POC testing is a research-based measure, all of the randomized interventions to be studied—i.e. the protocol-driven manipulation of the

dialysis prescription—are consistent with standard care of care dialysis practices. Thus, the proposed trials are best considered to be comparisons of standard therapies rather than studies of experimental or novel therapies that might have added risk due to their unstudied or experimental nature.

Inclusions and exclusion criteria have been limited in order to maximize generalizability, and have been designed to ensure that enrolled subjects are suitable for the intervention (e.g. that mean intra-dialytic weight gain is sufficient to justify an UF rate ≥13 mL/hour/kg), to maximize safety (e.g. exclusion of subjects with recent severe hyperkalemia), to ensure that subjects can provide informed consent (e.g. exclusion of potentially vulnerable populations such as prisoners, or mentally incapacitated subjects), and to ensure that subjects are expected to continue dialysis and survive long enough to complete the trials (exclusion of patients with expected survival < 6 months, exclusion of patients with impending transplant). Enrollment will be 5 months in the dialysate interventions trial and 3 months in the UF trial. Data shared between sites from these trials will be de-identified with the code stored locally.

Potential Risks—Potential risks to participants include: (i) risks from phlebotomy; (ii) potential side effects from ILR insertion; (iii) risks from algorithm-based management of dialysate potassium and bicarbonate prescriptions; (iv) risks from algorithm based management of UF rate and (iv) the chance that personal information is lost or confidentiality is breached. Each of these risks is discussed below.

i. Phlebotomy: Momentary discomfort as well as bruising may occur during routine phlebotomy. To eliminate this risk, we will obtain blood through the patients' vascular access while they are receiving dialysis, and there will be no access of the dialysis access or venipuncture purely for study purposes. We plan to use the minimal amount of blood necessary for POC testing, which is <1 mL (100 ul). The total amount of blood required for testing over 5 months will be approximately 52 mL. This is unlikely to cause a significant change in blood counts or symptomatic anemia, and the risks associated with this degree of blood loss can be considered minimal. Risk will be further minimized by putting the protocol on hold for subjects with severe anemia (defined as hemoglobin <8 mg/dL) on the most recent (monthly) standard of care labs and resuming only when anemia resolves.

ii. ILR insertion: ILR insertion requires administration of local anesthesia or conscious sedation and a small subcutaneous puncture for device placement. Risks of local anesthesia are minimal but could include very rare allergic reactions to subcutaneous anesthetic agents (subjects will be screened for anesthetic allergy). Transient bruising and discomfort is expected and will be treated as needed with over the counter agents. Prior investigator experience with ILR devices suggest that more significant complications such as discomfort requiring explanation and bacteremia are very rare. Local infection may occur. Prior experience suggests that even in the dialysis population these are typically mild infections which are treatable with oral antibiotics and do not require device removal. These risks will be disclosed to subjects. Subjects with conditions that place them at high risk of infection (e.g. severe psoriasis, multiple prior infections, immunosuppression) will be excluded to further minimize risks. Finally, subjects will be assessed within 1 week after device implantation and at 1 month to assess for proper wound healing and to allow early identification and treatment of infections.

iii. Side effects of potassium, bicarbonate, and UF interventions: As reviewed in the above plan, each of the algorithms is designed to lower the risk of arrhythmia. Although each is being used within the context of a research study, each algorithm prescribes treatments fully consistent with standard of care dialysis. In theory, the risk of arrhythmia may be increased by mandating a protocol-driven specific choice of therapy from among the available standard of care options. It is uncertain whether this is materially different in nature or degree from the risk patients are routinely exposed to outside of a research environment when physicians in clinical practice currently assign the dialysis prescription at the beginning of each month rather than at each individual session. Therefore, research-associated risks are low and within generally acceptable ranges for research—particularly given the importance of the knowledge to be gained. Potential risks will be further minimized by having the DSMB review all deaths and arrhythmia-related hospitalizations during the study. Events will be reviewed within 1 week in order to assess for potential relatedness, and the DSMB will provide recommendations on the need to halt the study or revise the protocol, or need for ad-hoc review by the DSMB of un- blinded data.

Study A potassium and bicarbonate algorithms may result in significant abnormalities in serum bicarbonate or serum potassium level. Once again this risk, though real, is not materially different than the risk of developing significant electrolyte abnormalities in routine practice in which bicarbonate and potassium may be measured only once a month with dialysis prescription based on that single value.
Study procedures ensure testing of electrolytes at each session (3x/week) in contrast to a frequency of as little as 1x/month in routine practice. Severe electrolyte abnormalities will thus be recognized earlier with study patients than in routine practice. Similarly, POC testing will ensure that the dialysis prescription will be adjusted according to the ambient potassium or bicarbonate at that dialysis session. In routine practice, follow-up testing at outpatient dialysis units typically has a turn-around time of hours (stat testing) or days (routine lab draws) which makes appropriate adjustment of the dialysis prescription unfeasible. Thus, study procedures may actually lower the risk of severe electrolyte abnormities or risk of complications from those abnormalities. However, significant inaccuracy in the point of care testing results could modify the associated risks.

To further mitigate risk, patients with severe abnormalities in potassium (K>6.5 or <3.0) or bicarbonate (<20 or >32) will temporarily come off therapy and be treated off-protocol at the discretion of their clinician.

Study B UF algorithms are designed to either limit UF rates to ≤10 mL/kg/hour or to allow UF rates ≥13mL/kg/hour. As discussed in the research summary, there is significant equipoise regarding the risk/benefit ratio of either strategy, as the use of high UF rates minimizes the risk of volume overload at the expense of rapid fluid shifts, whereas limiting UF rate minimizes the risk of rapid fluid shifts at the expense of increasing the risk of volume overload. Both strategies are routinely employed in clinical care. Thus, it is again unclear whether research-related risks are materially different than those in routine practice. As described in the Research Plan, subjects will cross over weekly between the unlimited and restricted UF treatments, thereby allowing removal of excess fluid accumulated during the restrictive week during the subsequent, unlimited week. This will limit any excessive fluid gains to a maximum of a few liters over the course of the restricted UF week thereby limiting the possibility of volume-related complications in the event patients fail to self-regulate intake of salt and water. Safety, will be further ensured because patients who show signs of significant volume overload will have the

potential to schedule an extra UF session as needed (outside of the protocol) in the event that symptoms of volume overload are intolerable. Lastly, all hospitalizations for myocardial infarction or heart failure will be reviewed by the DSMB. Events will be reviewed within 1 week in order to assess for potential relatedness, need to halt the study or revise the protocol, or need for ad-hoc review by the DSMB of un-blinded data in order to protect research subjects.

iv. Breach of confidentiality: Inadvertent release of information about medical history, laboratory information, or test results poses a psychological/financial risk. To maintain confidentiality and minimize risks to privacy, data will be de-identified and stored using a unique, coded study identifier for each subject. All data will be stored on password-protected servers and will be protected behind medical center fire walls and with contemporary virus software. Only the study staff will have access to the network drive. The only individually identifiable data that will be collected are names, medical record numbers, addresses, and contact phone numbers. These data are required for patient follow-up and for use during registration in the hospital information systems prior to ILR insertion. The file linking the study ID and personally identifiable information will be kept by the PIs in a similarly secure network drive location with access limited to the PIs and study coordinators or staff with responsibility for contacting patients. This file will be accessed only as necessary for patient follow-up or safety concerns. All other recorded data will be identified by study number only, and will be housed separately from data containing patient identifiers. Only the principal investigator (or personnel responsible for contacting patients) will have access to cross-reference the files. Sharing of data between Duke and NYU will involve only de-identified data. REDCAP or other electronic data capture instruments will be used to record study data and create a single, study database.

Adequacy of Protection Against Risks

As reviewed above the risks in this study are either minimal (phlebotomy, privacy) or in other cases (potential cardiovascular adverse events and electrolyte disturbances) are not expected to differ significantly in kind or degree from the risks associated with delivery of non-protocol driven/non-randomized selection of the dialysis prescription according to the routine clinical care. As detailed above, despite the overlapping nature of the standard of care and the experimental therapies, several active steps will be taken to further mitigate risk.

Alternative procedures are not readily available as the risks are chiefly related to alterations in the dialysis prescription. However, there are compelling data implicating the standard of care selection of dialysate potassium, dialysate sodium, and UF rate as important determinants of cardiovascular morbidity and mortality but there is simultaneously an absence of prospective data to guide and optimize dialysis care. Thus, the community of HD patients is currently exposed in an ongoing way to potentially significant and avoidable risks that can only be mitigated if studies such as the one proposed provide data that can inform better choices. Thus any risks inherent to the research plan are proportional to the importance of the knowledge to be gained.

Protections Against Risk

Individuals at increased risk of adverse events from study treatments (such as those with infection, severe hyperkalemia, or anti-coagulation that prevents safe ILR implantation) will be excluded. Patients will be monitored for adverse effects with a follow-up examination of the device incision/pocket 1 and 4

weeks after ILR insertion, and we will have at least monthly review for adverse events thereafter. In addition, due the nature of chronic dialysis, all patients will be seen regularly by other medical personnel approximately 3x/week throughout the course of the study which should allow prompt recognition and response to adverse events. Individuals experiencing significant adverse events (e.g. volume overload requiring or severe electrolyte abnormalities) will have study intervention halted until these conditions can be fully-treated clinically at which point consideration to resumption of protocols can be considered if clinically appropriate (and DSMB review does not suggest modification or termination of the study). In addition, in the event of immediately life-threatening arrhythmias (e.g. ventricular fibrillation, sustained VT, symptomatic asystole, or sustained AF) identified on review of ILR tracings, clinical records will be reviewed and clinical providers contacted in order to institute appropriate therapy

As reviewed above, risks associated with the study procedures are in general not significantly different than risks HD patients are exposed to during routine care and study treatments are within the range of therapies that can be considered standard clinical care and differ mostly by being protocolized, randomized and driven by POC lab results rather than by results of monthly lab testing. Additionally, there are unique, study-specific risks relating to ILR insertion and additional phlebotomy-neither of which is expected to result in significant risk to participants. No vulnerable populations will be enrolled. Pregnant individuals will be excluded given the need for ILR insertion and potential risk of impacting fetal development.

Additionally, subjects will be protected by having all study data reside on limited access network drives, within password protected folders. All systems used for the analysis will be maintainted according to standard data secuirty protocol. Dedicated network drives will be accessible solely by study personnel authorized to use the data with data files protected to restrict access to members of the appropriate research team through file permissions. Access to data will be managed by dedicated information systems and IT professionals. Separate physical hosts and attached disk storage may also be used, as necessary, but no identified data will be stored on portable media. Only members of the project team may log on to those systems. Identifiable data will be also encrypted at the file level as needed.

VIII. POTENTIAL BENEFITS

Although the trial is not designed to provide direct benefit to the patients, it is possible that participants will benefit from participation. Individuals receiving active therapy may benefit due to earlier recognition of electrolyte abnormalities due to POC testing or reduction in arrhythmia risk. Although the duration of the trial is short, it is possible that even a short course of active therapy could produce long- lasting benefits by reducing arrhythmia risk for a few months.

The trials are designed to increase understanding of important mechanisms of CV disease in advanced ESRD, and to facilitate better therapies to prevent and treat CV disease in this population. The ESRD population is large (>350,000 patients), growing, and accounts for nearly 10% of Medicare spending. A primary cause of morbidity, mortality and health care expenditure in this population results from CV disease. Thus, the results of these trials have the potential to profoundly impact public health by reducing CV morbidity from AF and reducing the risk of sudden cardiac death.

IX. MONITORING AND QUALITY ASSURANCE

Investigators will have monthly conference calls to review study progress, assess logistical challenges, address recruitment challenges, and address data.

Data Safety Monitoring Plan

A) The initial form of monitoring will be weekly review by of study progress, blinded listings of adverse events and adverse event logs by both the PI and study coordinators of both sites. Adverse event logs will be kept by the PI and study coordinators, and reported to the IRB in accordance with local and national guidelines. The terminology and severity of adverse events will be categorized according to the most current version of the Common Terminology Criteria for Adverse Events (CTCAE). Relatedness to study interventions will be assigned with one of the following: not related (not related to procedures or interventions), doubtful (an alternative explanation is more likely), possible (might be related to procedures or interventions), probable (might be related, if timing is suggestive, alternative explanation unlikely), very likely (no reasonable alternative explanation, timing is suggestive), related (related to procedures or interventions, and unknown/undetermined. Relatedness to interventions according to standard definitions with unanticipated serious and non-serious adverse events reported to the NYU School of Medicine IRB, DSMB, and NHLBI (sponsor) within 5 working days/7calendar days from the date the investigator first becomes aware of the problem or sooner depending on the standard operating procedures at each institution. Unanticipated problems that are not adverse events will be reported to the IRB and the NHLBI within 14 calendar days of the investigator becoming aware of the problem.

B) A formal DSMB will include 3 individuals including 2 nephrologists and a cardiologist experienced with ESRD-related care and research and will be aided by an independent statistician. DSMB members will be charged with regular review with 5 working-days of potentially-related serious adverse events—specifically the occurrence of volume-related hospitalizations, deaths and arrhythmia related hospitalizations. At the DSMB's discretion, such reviews may be used to trigger a request for un-blinded information, a request for a formal, full-DSMB meeting and review of study data, or halting or modifying the study. Please see the DSMB appendix for additional information. The PIs will be responsible for providing a copy of the DSMB reports to the NHLBI for both regularly scheduled DSMB meetings and DSMB review of unanticipated serious adverse events.

Data to be Reviewed:

The investigators safety committee (blinded) and DSMB (un-blinded) will review data pertaining to study progress and quality, to side effects, adverse events and any CV events or fatal events with a focus on fluid overload, myocardial infarction, and arrhythmia related hospitalization, and severe electrolyte disturbances.

Frequency of Meetings:

Investigators will review safety data monthly and as needed in the event of serious adverse events and the committee of PIs from each site will review accumulated events monthly. Given the small size of the study 2 formal DSMB analyses are planned. The first after 10 subjects complete 1 month and the 2nd after 10 subjects complete the study. It is expected that approximately 2/3rds of enrollment will have been completed at the latter point, and that drug exposures will have been sufficient to provide adequate power to detect important safety signals. In no case, will these meetings occur less than annually. Nevertheless, this point is early enough to significantly limit the total patient-exposure in the even that safety signals are serious enough to warrant early termination of the trial.

Regardless of study progress, the DSMB will meet no less than annually to review external data, study progress including feasibility, recruitment/enrollment, data quality and adverse events using un-blinded data prepared by an independent statistician.

Stopping Rules:

After each meeting the DSMB will be asked to recommend whether the study should be continued unchanged, modified, or continued unchanged. Given the small sample size of the trial and low likelihood of significant events, there will be no formal stopping rules for efficacy or safety, and it is not anticipated that the trials will be terminated on the basis of efficacy. Ad hoc meetings of the DSMB may be convened at an earlier or later time point, in the event that safety signals identified by the study team merit an earlier or later review.

ClinicalTrials.gov Requirements: The principal investigator of this proposal, as the responsible party, will comply with Public Law 110-85 (FDAAA), and will register this clinical trial on ClinicalTrials.gov. Data will be made available within 1 year of completion.

X. Study Procedures Study A

	SCREENING/ENROLLMENT		LINQ INSERTION / BASELINE			DIALYSATE INTERVENTIONS							END OF STUDY	
Procedure	**Pre screening**	**Screening/ Enroll (Day -30 to Day -1)**	**ILR/Baseline (Day 0)**	**Week 1 Reveal**	**Week 4 Reveal**	**Week 5 Crossover 1**	**Week 9 Washout 1**	**Week 10 Crossover 2**	**Week 14 Washout 2**	**Week 15 Crossover 3**	**Week 19 Washout 3**	**Week 20 Crossover 4**	**ILR Explant Visit**	**Explant Follow-up Visit**
OVERALL STUDY VISIT NUMBER		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5		Visit 6		Visit 7		Visit 8	Visit 9 (if needed)	Visit 10 (if needed)
Preliminary eligibility assessment	X													
Informed consent		X												
Confirm eligibility		X	X											
Demographics & medical history		X												
Physical Exam, Vital Signs Assessment			X										-	-
Serum pregnancy (WOCBP)[1]		X												
Concomitant medications		X	X		X	X		X		X		X		
Review of Dialysis Treatment Records					X	X		X		X		X		
Record SOC labs				X		X		X		X		X		
Adverse events			X	X	X	X		X		X		X	X	X
ILR Placement			X											
Wound Check				X	X									X
ILR Explantation													X	
Coagulation Labs		X*	X*											

*Coagulation parameters (INR) will be drawn as needed to ensure that values ≤72 hours old are available at the time of LINQ insertions.

Study Procedures Study B

	SCREENING/ ENROLLMENT		LINQ INSERTION / BASELINE			UF INTERVENTIONS				END OF STUDY	
Procedure	**Pre screening**	**Screening/Enroll Visit (Day -30 to Day -1)**	**ILR/Baseline Visit (Day 0)**	**Week 1 Reveal**	**Week 4 Reveal**	**Week 5 Crossover 1**	**Week 7 Crossover 2**	**Week 10 Crossover 3**	**Week 12 Crossover 4**	**ILR Explant Visit**	**Explant Follow-up Visit**
OVERALL STUDY VISIT NUMBER		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 (if needed)	Visit 10 (if needed)
Preliminary eligibility assessment	X										
Informed consent		X									
Confirm eligibility		X	X								
Demographics & medical history		X									
Physical Exam, Vital Signs Assessment			X								
Serum pregnancy (WOCBP)[1]		X									
Concomitant medications		X	X		X	X	X	X	X		
Review of Dialysis Records					X	X	X	X	X		
Record SOC labs				X		X			X		
Adverse events			X	X	X	X	X	X	X	X	X
ILR Placement			X								
Wound Check				X	X						X
ILR Explantation										X	
Coagulation Labs		X*	X*								

*Coagulation parameters (INR) will be drawn as needed to ensure that values ≤72 hours old are available at the time of LINQ insertions. If necessary, these may be drawn up to 72 hours prior to the LINQ insertion visit.

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RADAR

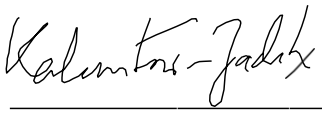
Reducing Arrhythmia in Dialysis by Adjusting the Rx Electrolytes/Ultrafiltration

Funding Sponsor: National Institutes of Health
National Heart, Lung and Blood Institute R34 NHLBI Clinical Trial Pilot Studies (R34) https://grants.nih.gov/grants/guide/pa-files/PAR-16-037.html

I have reviewed and approve the attached Data Safety Monitoring Board Charter

Kamyar Kalantar-Zadeh, MD, MPH, PhD

DSMB Member Printed Name



Signature

Date

Version 2018-7-12

Data and Safety Monitoring Board Chart

RADAR Study A & B

The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the principle investigators and sponsor to monitor patient safety and evaluate the efficacy of the interventions. The RADAR Study A and RADAR Study B are funded by the National Heart Lung and Blood Institute (NHLBI)

DSMB RESPONSIBILITIES

The initial responsibility of the DSMB will be to review the study protocols, consent documents and plans for data safety monitoring, and approve the initiation of these clinical trials. After this approval, and at periodic intervals during the course of the trials, the DSMB responsibilities are to:

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- evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial sites, and other factors that may affect study outcome;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- protect the safety of the study participants;
- report on the safety and progress of the trial;
- make recommendations to the Principal Investigator and Co-Investigator and Sponsor and, if required, to the Food and Drug Administration (FDA) and the Institution Review Boards (IRBs) concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- ensure the confidentiality of the trial data and the results of monitoring;
- assist the investigators and sponsor in maintaining scientific integrity by commenting on any problems related to study conduct, enrollment, sample size, and/or data collection.

MEMBERSHIP

The DSMB will consist of at least 3 members all of whom will be required to constitute a quorum. Members of the DSMB shall have no financial, scientific, or other conflict of interest with the studies. Written documentation attesting to absence of conflict of interest is required. A DSMB chair will be selected by the DSMB members at the first meeting

BOARD PROCESS

The DSMB will meet a minimum of once a year at the call of the Chair, with advance approval of the sponsor and investigators. In addition, meetings will be scheduled after 10 subjects complete 1 month in each protocol and after 10 subjects complete each study. In no case, will these meetings occur less than annually. A representative of the investigative team will be present at the open portion of each meeting, but only the DSMB members will attend the closed portions of the meetings.

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In addition, to regular meetings DSMB members will be charged with regular review with 5 working-days/7 calendar days of unanticipated serious and non-serious adverse events as well as potentially-related serious adverse events—specifically the occurrence of volume-related hospitalizations, deaths and arrhythmia related hospitalizations. At the DSMB's discretion, such reviews may be used to trigger a request for un-blinded information, a request for a formal, full-DSMB meeting and review of study data, or halting or modifying the study.

MEETING FORMAT

An appropriate format for DSMB meetings consists of open and closed sessions. This format may be modified as needed. A brief open and/or an executive session will usually be held before the closed session.

Open Session:

The members of the DSMB, and the investigators including the study biostatistician will attend the open session. Issues discussed will include the conduct and progress of the study, including patient recruitment, data quality, general adherence and toxicity issues, compliance with protocol, and any other logistical matters that may affect either the conduct or outcome of the study. Major protocol amendments may also be presented in this session.

Closed Session:

The closed session will be attended by voting DSMB members, and DSMB biostatistician. **The discussion at the closed session is completely confidential.**

Analyses of blinded outcome data are reviewed by masked intervention groups, including baseline characteristics, primary and secondary outcomes, adverse events, adherence and dropouts, and examination of any relevant subgroups. However, the DSMB may request that the DSMB biostatistician unmask the data for either safety or efficacy concerns.
The DSMB will discuss information presented to it during the closed and open sessions and decide whether to recommend continuation or termination, protocol modification or other changes to the conduct of the study in the Executive Session. The DSMB can become unblinded if trends develop either for benefit or harm to the participants.

Should the DSMB decide to issue a termination recommendation, a full vote of the DSMB will be required. In the event of a split vote, majority vote will rule and a minority report should be appended. Reasons for early termination may include:

1 Serious adverse effects in the entire intervention group or in a dominating subgroup;

1 Greater than expected beneficial effects;

1 Logistical or data quality problems so severe that correction is not feasible.

Final Open Session (optional):

The final session may be attended by voting DSMB members, investigators, and the sponsor.

The Chairperson of the DSMB shall report on the recommendations of the DSMB regarding study continuation and concerns regarding the conduct of the study. Requests regarding data presentation for subsequent meetings will be made. Scheduling of the next DSMB meeting may be discussed.

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REPORTS

Interim Reports: Interim reports will be prepared by the Data Coordinating Center, located at the NYU Langone. The reports will be distributed to the DSMB and the sponsor at least 7 days prior to a scheduled meeting. These interim reports are numbered and provided in sealed envelopes or by secure email as the DSMB prefers. The contents of the report are determined by the DSMB. Additions and other modifications to these reports may be directed by the DSMB on a one- time or continuing basis. Interim data reports generally consist of two parts:

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Part 1 (**Open Session Report**) provides blinded information on study aspects such as accrual, baseline characteristics, and other general information on study status. This report is generally shared with all investigators involved with the clinical trial. The reports contained in this section may include:

- Comparison of Target Enrollment to Actual Enrollment by Month
- Comparison of Target Enrollment to Actual Enrollment by Site
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- Treatment Duration for Subjects who Discontinue Therapy
- Adverse Events/Serious Adverse Events by Site and Subject

Part 2 (**Closed Session Report**) may contain unblinded data on study outcomes, including safety data, including serious adverse events or termination. Data will be presented by blinded treatment groups; however, the DSMB may request that the treatment groups be unblinded to ensure that there are no untoward treatment effects. This report should not be viewed by any members of the clinical trial. A designated DSMB statistician from the NYU Langone will be provided with the key to un-blind the data and will prepare the reports as needed. This statistician will not have other rolls in the trial aside from preparation of the DSMB reports. The primary (blinded) study statistician will not review the unblinded reports.

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Appendix 1-RADAR Study A & B Proposed DSMB Members

1. Dr. Peter McCullough, MD, MPH (Chair)—Baylor Heart and Vascular Hospital, Dallas TX, (Cardiology),
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Peter A. McCullough, MD, MPH

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Glenn M. Chertow, MD, MPH

DSMB Member Printed Name

Signature

July 14, 2018

Date

Version 2018-7-12

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