PROTOCOL TITLE:

DIDIT: Diuretic/Cool Dialysate Trial

PRINCIPAL INVESTIGATOR:

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Internal Medicine; Nephrology

VERSION NUMBER:

V7.0

DATE:

July 12th, 2019

REGULATORY FRAMEWORK:

Please indicate all that apply:

☐	DOD (Department of Defense)
☐	DOE (Department of Energy)
☐	DOJ (Department of Justice)
☐	ED (Department of Education)
☐	EPA (Environmental Protection Agency)
☐	FDA (Food and Drug Administration)
☒	HHS (Department of Health and Human Services)
☐	Other:

Is this a clinical trial under ICH-GCP E6? ☒ Yes ☐ No

If yes, please confirm that the research team is familiar with and agrees to comply with the investigator requirements cited in ICH-GCP E6. ☒ Yes ☐ No

ICH-GCP E6 can be accessed by copying and pasting this URL into your browser:
http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf

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1. Objectives

Each year in the United States, approximately 100,000 people start maintenance dialysis therapy suffering high mortality rates, frequent hospitalizations, and marked decline in quality of life. The overarching aim of the "**Di**uretic/Cool **Di**alysate **T**rial" (DIDIT) is to improve outcomes of incident hemodialysis (HD) patients by recognizing the importance of residual renal function (RRF). This pilot study will demonstrate the feasibility of loop diuretic (bumetanide) use and/or cool dialysate, and will obtain preliminary information that will inform future examination into whether these interventions will slow the rate of RRF decline in HD, improve quality of life, and reduce overall mortality.

The proposed pilot study challenges the current widespread paradigm of discontinuing loop diuretics when initiating chronic HD and/or maintaining the dialysate at a constant temperature of 37 °C for all patients.

Specific Aim: We aim to conduct a pilot randomized controlled trial (RCT) to assess feasibility and safety, and to inform the design of a full-scale trial of bumetanide and/or cool dialysate using a two-by-two factorial design, compared to usual care.

The long-term goals of this proposed work are to optimize survival, health-related quality of life (HRQOL) and other outcomes of HD patients by providing them a low dose of a loop diuretic and by lowering the dialysate temperature at the start of their transition to dialysis therapy. The design will permit a rapid scaling-up of the interventions to a larger clinical trial since the incremental dialysis prescription takes advantage of resources and personnel that are readily available. This pilot study will substantially accelerate our ability to address fundamental issues in the care of this population, which is burdened by low HRQOL and can change the current paradigm and practice pattern.

Hypothesis: Use of bumetanide and/or cool dialysate during the first six months of HD will slow the rate of RRF decline, decrease inflammation and oxidative stress, improve HRQOL and decrease mortality. To explore this hypothesis we propose to conduct a pilot RCT.

2. Background

Many clinical trials have examined the extent to which outcomes could be improved in the prevalent dialysis population. However, incident HD patients have been largely overlooked despite their high mortality, morbidity and marked decrements in HRQOL. This proposal addresses the gap of care in incident HD patients by focusing on maintaining RRF, one of the strongest predictors of survival and HRQOL in the first year of dialysis therapy.

Many different factors have been implicated in the decline of RRF in HD, and therefore many different therapeutic strategies have been suggested for the preservation of RRF in these patients. In this study, we intend to evaluate two different therapeutic approaches: the use of a loop diuretic (bumetanide) and/or the use of cool dialysate during the HD session.

Diuretic therapy remains the cornerstone of managing fluid overload. The role of diuretics in managing HD patients is not yet clearly defined (1). Diuretics can be used to minimize RRF loss in chronic HD patients (1). More specific loop diuretics are not nephrotoxic, confer better fluid balance, maximize urine production, allow less aggressive ultrafiltration and are associated with decreased cardiac mortality (1, 2). The DOPPS study verified that loop diuretics are the most often prescribed diuretics to chronic HD patients (2). In clinical practice, many patients begin HD chronically using small doses of a loop diuretic, but since there is little evidence that these are beneficial, their use is suspended when the volume of residual diuresis is reduced to minimum values.

While currently not the standard of care in the US, cool dialysate may confer significant survival benefits. Cool dialysate has been associated with decreased intradialytic hypotension which may minimize kidney injury and slow RRF decline. The current US paradigm is to maintain dialysate temperature according to physician's discretion, usually at 37 °C. Cool dialysate may decrease inflammatory and oxidative stress from HD therapy, and thus minimize kidney injury, slow the decline of RRF, and decrease morbidity and mortality. This important strategy of preserving RRF is not routinely applied to HD patients.

The use of bumetanide is also not currently the standard of care, but additionally may provide survival benefits by minimizing RRF loss. Specifically, bumetanide is not nephrotoxic, confers better fluid balance, maximizes urine production, may allow less aggressive ultrafiltration and is associated with decreased cardiac mortality.

Each year in the US approximately 100,000 people begin chronic dialysis and 80,000 die resulting in the growth of the prevalent population which now exceeds 400,000 patients on chronic dialysis. Prevalent HD patients have a mortality rate of 20% per year. Even more disconcerting is that during the first six months of therapy the annualized mortality is 35-40%. Although many clinical trials have examined the extent to which outcomes could be improved in the prevalent dialysis population, incident HD patients have been largely overlooked despite their high mortality, morbidity and marked decrements in HRQOL. This proposal addresses the crisis of care in incident HD patients by focusing on maintaining RRF, one of the strongest predictors of survival and HRQOL in the first year of dialysis therapy.

3. Study Design

This pilot RCT will demonstrate the feasibility and safety of performing a large scale study of diuretic use and/or cool dialysate by examining recruitment, retention, and key outcomes. This study will further assess whether the use of a diuretic compared to non-use of a diuretic (placebo) and/or the use of cool dialysate (35.5 ºC) compared to 37 ºC for up to 6 months will improve RRF, improve HRQOL and reduce hospitalizations. by randomizing 20 chronic hemodialysis patients from DCI centers in the greater Albuquerque area, to either bumetanide and cool dialysate randomized in a two-by-two factorial distribution.

No Diuretic (placebo) and 37°C dialysate	**No Diuretic (placebo) and 35.5°C dialysate**
Diuretic and 37°C dialysate	**Diuretic and 35.5°C dialysate**

The study sample will be selected using an approach to limit drop-out while enhancing generalizability and the main analysis will be intention-to-treat. ***Considering the intervention cannot be double-blinded, we have made efforts to reduce bias by using objective outcomes and blinding the assessment of patient-reported outcomes.*** Subjects will be recruited for 18 months. An additional 6 month period will be used to complete the intervention in the last subjects and they will be re-assessed at month 8 for an end of study evaluation. The recruitment and participation parameters for development of this formal RCT will assess whether the large scale study can meet enrollment criteria and target timelines, and whether patients can be maintained on the study protocol without safety concerns.

In this pilot study we will assess as primary patient outcomes:

- The change in RRF over 6 months
- The association of cool dialysis and/or diuretic with inflammation
- The association of cool dialysis and/or diuretic use with acute kidney injury (AKI) biomarkers.

The secondary patient outcomes will be:

- Change in HRQOL
- Time to first-hospitalization.

Being a pilot study, our focus is on assessing whether changes in RRF can be detected with the proposed technique (urinary creatinine and urea clearance). Biomarkers of inflammation and AKI will be collected to supplement the functional measurement of renal filtration and as surrogate biomarkers of benefit or safety (e.g. nephrotoxicity) that can be monitored in the large scale study.

4. Inclusion and Exclusion Criteria

Hemodialysis patients required for this pilot project will be identified from the patient population treated at DCI centers in the greater Albuquerque area. The average age of patients at the study sites is approximately 58 years, and the population is roughly split between genders and is racially diverse. Approximately 95% of the dialysis clinic population speak or understand English. The study site population demographics are similar to those in the Southwestern region and include more Hispanic patients than nationally. NIH standards for collecting data will be maintained, and when providing informed consent the investigators will rely on two separate questions for patients to self-identify ethnicity and race (in that order).

The study is open to all volunteers, irrespective of gender, race, ethnicity, or sexual preference. Women will constitute nearly half of the expected sample, and minorities are well represented. This is not an NIH-defined Phase III Clinical Trial, but analyses will be conducted at the conclusion of the study to determine whether the intervention affected women or men or members of minority groups and their subpopulations differently.

Consented participants must have adequate RRF (See second exclusion bullet below) to complete this study. Adequate RRF is determined by the result of the first 24-hour urine collection. The participant's RRF will either allow them to continue or exclude them from the study.

- Participants with adequate RRF will be randomized to one of the four study arms listed above.
- The randomization process may take up to 7 days.
- Randomized participants will have any ordered diuretics discontinued before they begin taking the "study drug"
- There is no "taper" or "time delay for stopping their diuretic and starting the "study drug"

Inclusion Criteria:

- Age ≥18 years
- Primary speaking language is English or Spanish.
- Patient is on chronic in-center HD prior to randomization
- HD takes place at one of the participating Dialysis Clinic Inc. (DCI) sites during the data collection period.
- Subject urinates more than 200 ml of urine a day (self-reported).
- Patients must be willing and able to sign the consent form.

Exclusion Criteria:

- Age <18 years of age.
- RRF <2 mL/min/1.73 m^2 as determined by 24-hour urine collection.
- Allergy or contraindication to bumetanide.
- Expectation that native kidneys will recover.
- History of poor adherence to treatment.
- Unable to verbally communicate.
- Requires more than 3 HD treatments per week due to medical co-morbidity (such as, but not limited to: severe volume overload requiring frequent HD e.g. in systemic oxalosis, or requiring total parenteral nutrition).
- Scheduled for living donor kidney transplant in the next 6 months.
- Intention to change to peritoneal dialysis, or home HD in the next 6 months.
- Plan to relocate to another center within the next 7-8 months.
- Expected geographic unavailability at a participating HD unit for >2 consecutive weeks or >4 weeks total during the next 6 months (excluding unavailability due to hospitalizations)
- Post kidney transplantation

- Currently in an acute or chronic care hospital
- Life expectancy <6 months or intention to withdraw dialysis therapy within 6 months.
- Current pregnancy, nursing mother or actively planning to become pregnant in the next 8 months
- Current use of investigational drugs
- Participation in another non-observational clinical trial that contradicts or interferes with the therapies or measured outcomes in this trial
- Unable or unwilling to follow the study protocol for any reason (including mental incompetence)
- Unable or unwilling to provide informed consent or sign IRB-approved consent form.

The following special populations will not be included in this study:

- Patients who are too infirm or lack the capacity to meaningfully participate in medical decisions and to sign the informed consent form.
- Children and adolescents constitute <2% of the dialysis population, and our preliminary survey of the study sites found no children and adolescents were active patients. In any case, the renal and other physical factors of children and adolescents with ESRD are not directly comparable to those of adults.
- Prisoners.

The study is open to all volunteers, regardless of gender, race, ethnicity, or sexual preference. All study consents and documents will be in English or Spanish, except for the PROMIS-57, which is currently unavailable in Spanish. Patients who are Spanish speaking only will not complete this questionnaire. If the questionnaire becomes available, we will add it with IRB approval.

5. Number of Subjects

Up to 50 patients may be recruited/consented for this study.

It is unknown, at this time, how many eligible subjects will need to be approached in order to attain the desired number of study participants. We will continue to recruit until 20 patients have been followed to completion post protocol modification.

6. Study Timelines

- The duration of an individual subject's participation in this research is 8 months.
- Subject recruitment will occur over 18 months.
- See table 1 *"Schedule of study tests/assessments/intervention"*, Study Procedures section 12, for procedure timeline.
- Anticipated data collection is to be completed by the end of year 2. Once all data has been collected and verified, data analysis and report preparation will take place over a 6 month period.

7. Study Endpoints

- Recruit and randomize 25 incident chronic in-center HD patients with urine output >200 mL/day and to 3 mg of oral bumetanide once daily and/or to cool dialysate (35.5 ºC).
- Estimate recruitment and retention rates anticipated in a full-scale study.
- Compare changes in RRF markers between groups.
- Collect preliminary data on adverse events (AE) and serious adverse events (SAE), biomarkers of inflammation and injury to native kidneys, HRQOL, health care utilization and other potential outcomes of a full-scale trial.

8. Research Setting

Potential subjects will be recruited at Dialysis Clinic Inc. (DCI) centers located in Albuquerque and Rio Rancho.

Pre-dialysis and 24 hour urine collections will take place at the participant's home. As appropriate to the study timeline, lab values will be collected from the participant's DCI records.

Study blood samples collected at DCI will have their initial spin done at DCI by study personnel using DCI's centrifuge. These samples and any collected urine samples will be transported to a UNM study lab or to a Tricore® lab for final processing. No collected specimens will be sent to DCI laboratory.

9. Resources Available

Dr. Mark Unruh, MD is the UNM Nephrologist overseeing this study. This site has been granted approval to recruit and complete study visits at the Albuquerque, New Mexico Dialysis Clinics Inc. and the Rio Rancho clinic. The PI, sub-investigators, biostatistician, micro-RNA specialist, lab staff and study coordinators and research assistants make up the study team. This team has broad expertise to successfully complete the proposed aim and efficiently deliver findings for immediate clinical and public health application.

Study physicians will be responsible for medical decision-making, and for ordering and the evaluation of necessary diagnostics and therapeutics for this study.

The 20 recruited/consented subjects that will complete this study will be recruited at the four DCI clinics in Albuquerque and at the Rio Rancho DCI clinic. The four DCI study sites should be able to supply the research subjects needed to be recruited for this study.

Recruitment will last 18 months. An additional 6 month period will be used to complete the intervention in the last subjects.

The study investigators recognize that recruitment is the major factor for a successful RCT and will use a multi-faceted approach to enhance recruitment. First, the

nephrologists and staff of the dialysis units will be informed of the study and will provide materials to help explain the importance of study participation. The physicians and dialysis staff will also be educated on the study rationale and the scientific importance of study participation. The dialysis clinics and nurse educators will be provided with brochures and posters that will be conspicuously displayed in the dialysis clinic waiting areas. Special attention will be placed on the recruitment of minority participants.

10. Prior Approvals

The following approvals have been obtained for this study:

- Bumetanide drug form attachment
- Departmental Scientific Review Form

11. Multi-Site Research

This is not a multi-site study

12. Study Procedures

Table 1: *Schedule of the study tests/assessments/intervention during the pre-trial (4 wks), intervention (24 wks or 6 months) and post-trial periods (4 wks).*

		Study Phases →	pre	intervention						post	Time to do
	Measurements/Tests	Month →	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Intervention	Randomization Intervention: (to one of the following arms) • Cool dialysate and placebo • Cool Dialysate and Bumetanide (3mg/day) • Isothermic dialysate and placebo • Isothermic dialysate and Bumetanide (3mg/day)		X								
	Issue (Bumetanide or placebo): For participants whose pre-intervention 24-hour urinary Creatinine and Urea clearance results allow them to complete the study, any current diuretic will be discontinued prior to taking the "study drug".			X			X				During Dialysis
	Bumetanide/placebo compliance check						X			X	
Blood tests & HD Rx	Routine: (Obtain from DCI monthly labs) • Albumin (g/dL) • Hemoglobin (g/L) • Intact parathyroid hormone (pg/ml) • Kt/V • Potassium (mEq/L) • Calcium (mg/dL) • Sodium (mEq/L) • BUN (mg/dL) • Creatinine (mg/dL)		X	X	X	X	X	X	X	X	Collect with DCI monthly labs if values are older than 30 days
	Additional blood tests: **[Total blood: 11ml: 10ml collected; 1ml waste]** • B2-microglobulin (drawn pre- and post-HD) • Cystatin • NGAL • KIM-1 • CRP (mg/L)		X			X			X		Collected with DCI monthly labs

	• IL-6 • TNF-α • IL-1β										
	microRNA (drawn pre- and post-HD) **[Total blood: 8mls; no waste]**	X						X			
	Pregnancy testing (blood serum testing) **[1ml]**	X								Prior to randomization	
	HD treatment data collected: (From DCI pt. Chairside flow sheet) • HD Run time • Membrane type • Dialysate bath • QB (Blood flow rate: BFR ml/min) • QD (Dialysis fluid flow rate: DFR ml/min) • UF (Ultrafiltration) time • BP (Every 30 minutes and min & max) • Pre & Post dialysis weight • Height (one time only)	X	X	X	X	X	X	X	X		
	•										
Questionnaire	• Dialysis Symptom Index • PROMIS-57	X			X			X			phone or in person (30 minutes)
Comorbidity & Clinical data	Charlson comorbidity index (CCI) and underlying kidney disease	X			X			X	X	3-5 min	Study Staff
	Medications: • In-center o EPO o Iron o Vitamin D • Outpatient medications	X	X	X	X	X	X	X	X		
	Demographics: • Age • Gender • Race • Ethnicity • Marital status	X									
	Adverse Events: • Emergency room visits • Hospitalization(s) • Outpatient visits • Mortality • Transplantation • PD (Peritoneal dialysis) • Transfer to other unit • Relocation • Hypotensive episode • Dialysis access event o Clotting o Stenosis o Revision o New graft or catheter	X	X	X	X	X	X	X	X		
	History and physical exam by MD (PI, sub-I or their designees)	X									
Urine	24 hour urine collection: RRF • Start collecting urine day before midweek dialysis session (Note date/time) • Stop collecting urine 24 hours later (Note date/time) o Creatinine o Urea o	X			X			X		Collected before a midweek dialysis session	
	*Urine fresh void: **[20mls]** • Urinary cystatin C • Urine creatinine • uNGAL	X			X			X		Collected before dialysis session	

	• uKIM-1 • uHGF									
	• *Urinary microRNA (taken from fresh void)	X					X			

13. Data Analysis

For both studies, patient characteristics and outcomes will be summarized by study arm. Primary outcomes include 6-month change in RRF. Differences between baseline and 6 months will be calculated and analyzed with a mixed model that incorporates potentially important covariates, such as age, gender and ethnicity. For measurements that will be taken monthly, such as albumin, a repeated measures analysis of variance also will be conducted on the measurements rather than the differences. If needed, transformations or analyses based on ranks will be utilized. This approach will also be used for other outcomes that can be treated as continuous variables, such as HRQOL, inflammatory markers and the number of days of hospitalization. For discrete variables, such as the number of hospitalizations, either logistic regression or Poisson regression will be used. The time to first hospitalization will be examined using Kaplan-Meier plots. To adjust for study site and baseline covariates, the proportional hazards model will be used. All analyses will be intent-to-treat, in that patients will be included in analyses regardless of whether the intervention was applied as intended. Estimates of mean change will be obtained along with 95% confidence intervals. All analyses will be conducted in SAS.

This pilot study will inform the design of a larger clinical trial. For Specific Aim 2, the proportions recruited and retained will be estimated. With a recruitment and randomization of 20 patients, the proportion retained can be estimated to within ± 0.18 with a 95% confidence interval. Estimates of mean changes, along with estimates of variability, will be obtained and used in designing the larger clinical trial.

14. Provisions to Monitor the Data to Ensure the Safety of Subjects

An independent Investigator Monitor will review all data captured for the study including unanticipated events. This will allow us to assess whether more frequent monitoring will need to take place and how it will affect others currently enrolled. The Investigator Monitor will have the authority to recommend stopping the study early or modifying the study design for safety concerns. He/she will review source documents and compare them for accuracy against data currently collected. The Investigator Monitor will meet with the Principal Investigator to discuss the progress of the patients enrolled in the study. The Investigator Monitor will review the progress of the study within 2 weeks after the first patient is randomized into the study. The Investigator Monitor and the Principal Investigator will conduct monitoring visit approximately every 3 months thereafter. The Investigator Monitor will terminate the study if the safety, welfare and health of patients is jeapordized due to conducting the study according to protocol. Unanticipated events will be reported by the research team to the Investigator Monitor

and the IRB within 24 hours of becoming aware of the event. The investigators must assess the adverse event (AE)/serious adverse event (SAE) relationship to the hemodialysis frequency, the diuretic and/or iohexol. The research team will also be responsible for preparing and submitting the reports. Every effort will be made to protect subject confidentiality throughout the study. In order to preserve privacy of study data, a series of security procedures will be undertaken which are routinely used by UNM. All information will be kept confidential, and paper patient data will be maintained in a secure location under lock and key. Data collected from study evaluations will be identified by study identification codes, and only numeric identifiers will be stored in the databases. No data element that alone or in combination can identify specific individuals will be entered. Identifying features including names, Social Security Numbers, and address may be provided to the PI or research assistant (RA), but will not be available to the database or the analyst. Any identifying data will be kept in a secure locked file by the PI and RA separate from the study database. Through the use of the security measures available with our hardware and software, access to information will be restricted on a 'need-to-know' basis.

15. Withdrawal of Subjects

Subjects may withdraw from this study at any time. Subjects should notify the study PI or staff member of their intent to withdraw in writing. Information collected prior to withdrawal will remain part of the study.

Active treatment with the study interventions will be terminated if the patient:

- Withdraws their informed consent
- Is unable to follow/comply with study procedures
- Undergoes kidney transplantation
- Transfers to home dialysis
- Transfers care to a dialysis facility outside of the Albuquerque DCI clinics or Rio Rancho.
- Becomes pregnant while on study drug.

16. Data Management/Confidentiality

For this study, pre-screened eligible patients will be tracked using an ACCESS® database which is stored on a secured UNM HSC network drive. The following PHI is included in this database: subject's name and contact number; patient's emergency contact name and phone number; HD start date; age. This database will be used for study visit scheduling only. Participant name and other identifying information will be linked to a unique study ID once consented. This study ID will not display any information that can identify the participant. All of the data collected from the participant will be coded using participant study ID and kept in a locked cabinet, and/or password protected

computer files. The master list linking participant identifying information to participant study data will be kept in a separate, secure location at UNM. Only the UNM study team will have access to the master list. We will keep the link between participant identifying information and study data until the end of the research study. This link will only be available to UNM, and will not be accessed by researchers at other institutions.

Participant responses to questionnaires will be kept strictly confidential, and dialysis clinic staff members will not have any knowledge of the patients' answers to these questionnaires.

Data Management: The study team will store all study related data and the database secure network servers are sitting behind firewalls and are monitored by network personnel on a 24 h/day, 7 days/week basis. Secure access and training of our data entry staff will be provided by the study team, and confidentiality of data will be carefully maintained. Only study personnel will have access to the secured data.

The investigators will oversee the development of the primary data collection forms. Where applicable, data entry screens in the Web-based program will be constructed in the same format as printed materials. Data entry will be done directly into the REDCap system or similar system at each of the clinical sites. The study staff will coordinate online training on the use of the data entry system, data collection procedures, and patient confidentiality.

Once a patient is recruited and deemed eligible for the study, to initiate inclusion in the web-based tracking system, the University of New Mexico (UNM) will obtain the patient profile (name, participant ID, randomization status and contact information). The tracking system will monitor enrollment, track follow-up rates, and data entry process, and provide up to date status reports. Site coordinators at the clinics will manually enter recruit data into a "firewalled" database via the internet.

Documents will be maintained in a locked area and only necessary research personnel will have access to this information. Only the participant ID number will be entered into the main study database. All research reports, articles, and presentations will present only aggregate study findings, and participants will never be identified by name or any other personal identifier.

Data will be kept for a minimum of 6 years after study completion in line with federal guidelines. PHI and identifiable information will be destroyed 6 years after study closure with UNM HSC HRRC. Non-identifiable information will be destroyed after data analysis is complete.

17.Data and Specimen Banking

Neither data nor specimens will be banked for this study.

18. Risks to Subjects

Hemodialysis: may be associated with complications. Hemodialysis can lead to low blood pressure (25% of all dialysis sessions) which may result in abdominal discomfort, nausea, vomiting, muscle cramps, dizziness and anxiety. In addition, hemodialysis can lead to bleeding, tachycardia and other abnormal heart rhythms, electrolyte imbalances, clotting or infection of the vascular access, and rarely, death. ***However, the risks associated with HD would be present <u>whether or not</u> the patient chooses to participate in this study.*** It is unknown whether use of diuretic and cool dialysate will increase or decrease the risk of these complications.

Cool dialysate (35.5°): The most common complication for patients dialyzed with cool dialysate is feeling colder, and if severe, they may develop shivering.

> Patients will be monitored for patient comfort during dialysis to assess cold intolerance that may occur with cool dialysate. If these symptoms are observed, then the PI will determine whether this is a safety endpoint.

Bumetanide: Muscle cramps, severe dizziness, and hearing changes, like ringing in the ears, are the most common side effects of bumetanide (1.1%). A very serious allergic reaction to this drug is also rare.

> Patients will be monitored for hypersensitivity reaction or musculoskeletal symptoms to determine tolerability of patients to the diuretic.

Psychological: Participants may be asked some questions of a personal nature. They are free to decline to answer any question at any time.

Loss of Privacy: Participation in research may involve a loss of privacy. Steps will be taken to mitigate the risk related to confidentiality of study data.

Pregnancy: The risk(s) of cool dialysate and/or Bumetanide on a developing fetus are unknown; therefore, subjects who are pregnant or actively planning to become pregnant in the next 8 months will not be allowed to participate in this study.
Subjects of child-bearing potential will have a pregnancy blood test done prior to study randomization. Subjects that refuse pregnancy testing will not be allowed to participate in this study.

Nursing Mothers: It is not known whether Bumetanide is excreted in human milk. Breast feeding should not be undertaken while the participant is on this drug. Breast feeding females will not be allowed to participate in this study.

Hemodialysis Access Site Blood Draws: Infection, bleeding, and damaging the HD access site.

19. Potential Benefits to Subjects

The benefits of this study outweigh the risks. The physical risks and the confidentiality risk are low, particularly given the awareness of the study team and the availability of supportive staff at the dialysis clinics. The investigators are experienced and the study is designed to address feasibility and safety issues. The research burden on all subjects is also modest. Participants will have the altruistic satisfaction of helping shape an intervention and influence a policy that may be of great value to the more than 300,000 people in the United States whose lives are prolonged with hemodialysis.

20. Recruitment Methods

The study coordinator will conduct a pre-screening query of the DCI database to identify potential study subjects. These subjects will then be approached during their routine scheduled HD sessions by a study coordinator to determine their interest in the study.

21. Provisions to Protect the Privacy Interests of Subjects

Hemodialysis is performed in a common open area with several dialysis stations. Face-to-face visits will take place at one of the Albuquerque or the Rio Rancho DCI clinic. Every effort will be made to incorporate privacy protections during these visits (private room, partitioned area), while DCI eMR will provide any required de-identified study information.

22. Economic Burden to Subjects

Research Procedures	Number of Samples/Procedures	Responsible Party	
		Study	3rd Party Payer or Participant
Urine Collections	All	☒	☐
Bumetanide or Placebo Administrations	Study Arm Dependent	☒	☐
Dialysate at 35.5° C	Study Arm Dependent	☒	☐
Physical Examination	1	☒	☐
_____	_____	☐	☐
_____	_____	☐	☐
Standard of Care Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**
Dialysate at 37°	Study Arm Dependent	☐	☒
_____	_____	☐	☐
_____	_____	☐	☐

_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐

Enrolled subjects will not be charged for any study drugs or study procedures.

23. Compensation

All participants will receive compensation for their time, effort, and involvement in this study. If they complete all parts of the study, they will receive a minimum of $250 via a re-loadable payment card. Study payment(s) will be uploaded to their card within 24 hours of completion of a scheduled study event with the exception of weekends and holidays. Subjects will receive payment for their study participation per the DIDIT Compensation Table:

DIDIT Compensation Table ($250)			
Event	Compensation Amount	Number of Events	Total Compensation
24 hour urine collection	$50	3	$150
Phone session 1** (Questionnaires)	$30	1	$30
Phone session 2** (Questionnaires)	$30	1	$30
Phone session final** (Questionnaires)	$40	1	$40
Additional study visits*	$10	Unknown	Unknown

*If a study participant is required to return to the clinic for research specimen collection, they will be compensated in accordance with the DIDIT Compensation Table above.

** Questionnaires may be completed in person or over the phone.

24. Compensation for Research-Related Injury

If the enrolled subject is injured or becomes sick as a result of their participation in this study, UNMHSC will provide the subject with emergency treatment, **at their cost.**

No commitment is made by the University of New Mexico Health Sciences Center (UNMHSC) to provide free medical care or money for injuries to participants in this study.

In the event an enrolled subject has an injury or illness that is caused by their participation in this study, reimbursement for all related costs of care will be sought from their insurer, managed care plan, or other benefits program. If the enrolled subject does not have insurance, they may be responsible for these costs. Enrolled subjects will also be responsible for any associated co-payments or deductibles required by their insurance.

It is important for an enrolled subject to tell the investigator immediately if they have been injured or become sick because of taking part in this study.

25. Consent Process

The consent process will take place at Albuquerque DCI Clinics and the Rio Rancho DCI clinic. [Hemodialysis is performed in a common open area with several dialysis stations]. Potential participants will be approached by DCI staff and asked if they would like to hear about a research project that they may be eligible for. If the subject verbalizes interest, the DCI staff will then introduce the study coordinator. The potential participant will be asked if they agree to discuss the study in an open environment, or if they would prefer to discuss the study privately. Study information and the acquisition of informed consent will then take place in their environment of choice. Potential subjects may not be consented if they choose a private environment and that environment is not available.

An informed consent form will be used following the guidelines of the Study protocol and Institutional Review Board (IRB) and applicable regulations for informed consent. Study coordinators will obtain informed consent for the proposed study. Study coordinators will contact potential study subjects at the dialysis clinic to describe the study and, if they are interested, the subject will be given an unsigned consent form, which will include details regarding the voluntary nature of the study, its purpose, potential risks and benefits, issues of compensation and expense, and methods to confidentiality. At this time or at the next dialysis session, the study coordinator will review the consent form with the participant and address any questions or concerns. All potential participants will be given as much time as they need for consent review prior to signing an ICF. Prior to signing the consent, potential participants will be asked to verbalize the purpose of the study as a check for understanding. The consent form will then be signed and dated by the participant before initiation of any study activity. The

original signed consent form will be stored in the study file at UNM HSC. A copy of the signed consent form will be given to the participant. An additional copy of the consent form will be placed in the participant's DCI medical record.

For potential participants that are identified as Spanish speaking, the same consent process described above will be utilized. The process will be completed by one of the three Spanish speaking team members approved by the IRB.

Consented subjects who successfully meet all pre-trial criteria will be encouraged, in an ongoing basis, to complete the research project.

26. Documentation of Consent

A document of informed consent will be used for this study. A copy of the signed/dated consent will be given to the subject. A copy of the signed/dated consent will be placed in the subject's DCI medical record.

27. Study Test Results/Incidental Findings

Participants that complete the study will have a residual renal function review letter sent to their Nephrologist. Incidental study findings will not be shared with study participants.

28. Sharing Study Progress or Results with Subjects

Consented subjects will not be provided with a summary of the trial progress while the study remains underway nor will they be provided with study results.

29. Inclusion of Vulnerable Populations

No vulnerable populations will be recruited for this study.

30. Community-Based Participatory Research

NA

31. Research Involving American Indian/Native Populations

NA

32. Transnational Research

NA

33. Drugs or Devices

Neither an IND nor an FDA "IND exemption letter" is needed for this study. Bumetanide is an FDA approved loop diuretic. Bumetanide is already being used as a loop diuretic in the Chronic Kidney Disease/End Stage Renal Disease population.

If the participant is randomized to Bumetanide [3mg], bottled (labeled with subject's name, study ID, instructions) drug will be dispensed from the *UNMH investigational pharmacy* to the research study coordinator monthly. If the participant is not randomized to Bumetanide they will be given an equivalent placebo, bottled (labeled with subject's name, study ID, instructions) placebo will be dispensed from the *UNMH investigational pharmacy* to the research study coordinator monthly. The study coordinator will instruct the participant on how to take the self-administered study "drug". The study coordinator will be responsible for tracking participant "drug" compliance monthly.

Checklist Section

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

I. Waivers or Alterations of Consent, Assent, and HIPAA Authorization

A. Partial Waiver of Consent for Screening/Recruitment

Complete this checklist if you are requesting a partial waiver of consent so that you can review private information to identify potential subjects and/or determine eligibility prior to approaching potential subjects for consent or parental permission.

1. Describe the data source that you need to review (e.g., medical records):

   Electronic medical records will be accessed at DCI to query for patients that meet the study pre-screening criteria: age, date HD was started in order to improve chances of a successful study.

2. Describe the purpose for the review (e.g., screening):

   Pre-screening: We will need to access and remove the following PHI from DCI: patient's name, age and HD start date. This information will allow us to approach eligible participants for their interest in this study. There will be minimal risk to the patient as their information will be stored securely off-site at UNM and will only be accessible by approved research staff. Records will be retained for seven years after study closure, and then destroyed. Study information will be kept confidential and will not be reused or shared with other entities.

3. Describe who will conducting the reviews (e.g., investigators, research staff):

   UNM research staff will access the DCI database and conduct pre-screening reviews.

   Do all persons who will be conducting the reviews already have permitted access to the data source?

☒ Yes

☐ No. Explain:

4. Verify that each of the following are true or provide an alternate justification for the underlined regulatory criteria:

   a) The activity involves no more than minimal risk to the subjects because the records review itself is non-invasive and the results of the records review will not be used for any purposes other than those described above.

      ☒ True

      ☐ Other justification:

   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects because eligible subjects will be approached for consent to participate in the research and are free to decline. Further, the information accessed during the records review will not be disclosed to anyone without a legitimate purpose (e.g., verification of eligibility).

      ☒ True

      ☐ Other justification:

   c) The research could not practicably be carried out without the waiver or alteration because there is no other reasonably efficient and effective way to identify who to approach for possible participation in the research.

      ☒ True

      ☐ Other justification:

   d) Whenever appropriate, potentially eligible subjects will be presented with information about the research and asked to consider participation. *(Regulatory criteria: Whenever appropriate, the subjects will be provided with additional pertinent information after participation.)*

      ☒ True

      ☐ Other justification:

Partial Waiver of HIPAA Authorization for Screening/Recruitment
Complete the following additional questions/attestations if the records you will review to identify potential subjects and/or determine eligibility include Protected Health Information (PHI).

5. Will you be recording any PHI when conducting the records review to identify potential subjects and/or determine eligibility?

   ☒ Yes. Describe: We will be recording patient name, age and hemodialysis start date.

   ☐ No

6. If you answered "Yes" to question 6 above, please describe when you will destroy identifiers (must be the earliest opportunity consistent with the conduct of the research) or provide justification for why they must be retained:

   Patients who are being pre-screened through the DCI eMR (DARWIN®) database will have the above information collected and stored. If the patient is deemed eligible, but declines to consent, this pre-screen information will be kept by the research team for seven years after study closure and then destroyed.

7. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   ☒ True

   ☐ False

B. Waiver of Documentation of Consent

Complete this checklist if you intend to obtain consent verbally but will not be obtaining signatures from subjects on a consent form to document consent. Waivers of documentation of consent are commonly requested when using scripts, information sheets, or email or survey introductions to present the elements of consent instead of using a traditional consent form.

1. Are you requesting a waiver of documentation of consent for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Provide justification for <u>one</u> of the following:

   a) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked

whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.

b) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

3. Do you intend to provide subjects with a written statement regarding the research in lieu of a traditional consent form?

☐ Yes. Please attach a copy to your submission in Click.

☐ No

C. Alteration of Consent

Complete this checklist if you intend to obtain consent but will be eliminating or altering one or more of the required elements of consent. Alterations of consent are commonly requested for research involving deception or for minimal risk research when an abbreviated consent is desired and one or more of the required element are not relevant to the research.

Note: FDA-regulated research is not eligible for an alteration of consent.

1. Which element(s) of consent do you wish to eliminate and why?

2. Which element(s) of consent do you wish to alter and why?

3. Provide justification for each of the following regulatory criteria:
   a) The research involves no more than minimal risk to the subjects:

   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

   c) The research could not practicably be carried out without the waiver or alteration:

d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

D. Full Waiver of Consent/Parental Permission

Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort). Full waivers of consent are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

Note: FDA-regulated research is not eligible for a full waiver of consent using these criteria. If you believe that your FDA-regulated research may be eligible for a waiver under another mechanism, such as planned emergency research, contact the HRPO for assistance in determining what information to provide to the HRRC.

1. Are you requesting a waiver for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Provide justification for each of the following regulatory criteria:

   a) The research involves no more than minimal risk to the subjects:

   b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:

   c) The research could not practicably be carried out without the waiver or alteration:

   d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:

E. Full Waiver of Consent/Parental Permission (Public Benefit or Service Programs)

Complete this checklist if you are requesting a full waiver of consent for all subjects or certain subject groups (e.g., retrospective cohort) and the research involves the evaluation of a public benefit or service program.

1. Are you requesting a waiver for some or all subjects?

☐ All

☐ Some. Explain:

2. Provide justification for each of the following regulatory criteria:

   a) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs:

   b) The research could not practicably be carried out without the waiver or alteration.

F. Full Waiver of HIPAA Authorization

Complete this checklist if you are requesting a full waiver of the requirement to obtain HIPAA authorization for all subjects or certain subject groups (e.g., retrospective cohort). Full waivers of HIPAA authorization are commonly requested when the research does not include any opportunity for interaction with subjects (e.g., chart review).

1. Are you requesting a waiver of authorization for some or all subjects?

   ☐ All

   ☐ Some. Explain:

2. Describe your plan to protect health information identifiers from improper use and disclosure:

3. Describe your plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so):

4. Describe why the research could not practicably be conducted without the waiver or alteration:

5. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

   ☐ True

   ☐ False

G. Other Waiver Types

If you are seeking another waiver type (e.g., Planned Emergency Research, Waiver of Parental Permission to Protect Child Participants, Enforcement Discretion for In Vitro Diagnostics, etc. contact the HRPO office for assistance in determining what information to submit for the HRRC's consideration.

II. Vulnerable Populations

A. Adults with Cognitive Impairments

Complete this checklist if the subject population will include adults with cognitive impairments.

This checklist does not need to be completed if the research doesn't involve interactions or interventions with subjects and will be conducted under a waiver of consent.

1. Describe why the objectives of the study cannot be met without inclusion of adults with cognitive impairments.

2. Describe how capacity to consent will be evaluated.

3. If subjects may regain capacity to consent, or if subjects may have fluctuating capacity to consent, describe your plans to evaluate capacity to consent throughout the research and to obtain consent to continue participation if capacity is regained.

4. Describe your plans, if any, to provide information about the research to subjects and the steps you will take to assess understanding.

5. Describe your plans to obtain assent, including whether assent will be obtained from none, some, or all subjects.

6. Describe why risks to subjects are reasonable in relation to anticipated benefits to the subjects.

7. If this study involves a health or behavioral intervention, describe why the relation of the anticipated benefit to the risk of the research is at least as favorable to the subjects as that presented by alternative procedures.

8. Describe your plans for monitoring the well-being of subjects including any plans to withdraw subjects from the research if they appear to be unduly distressed.

B. Children

Complete this checklist if the subject population will include children.

1. Select the category of research that you believe this research falls within and provide justification for any associated criteria. If there are different assessments for different groups of children or arms (e.g., placebo vs. drug), include a memo to provide an assessment for each group.

   ☐ Research not involving greater than minimal risk. *(Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.)*

   ☐ Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

   Provide justification for each of the following criteria:

   (1) The risk is justified by the anticipated benefit to the subjects:

   (2) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches:

☐ Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

Provide justification for each of the following criteria:

(1) The risk represents a minor increase over minimal risk:

(2) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations:

(3) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition

C. Pregnant Women and Fetuses

Complete this checklist if the subject population will include pregnant women and fetuses.

This checklist does not need to be completed if the research is both minimal risk and is not conducted, funded, or otherwise subject to regulation by DHHS, DOD, or EPA.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.

2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; ***or***, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

3. Any risk is the least possible for achieving the objectives of the research.

D. Neonates of Uncertain Viability or Nonviable Neonates
Complete this checklist if the subject population will include neonates of uncertain viability.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, ***or***, the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research

E. Nonviable Neonates
Complete this checklist if the subject population will include nonviable neonates.

Provide justification for each of the following:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

3. Individuals engaged in the research will have no part in determining the viability of a neonate.

4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means.

   Verify each of the following:

5. Vital functions of the neonate will not be artificially maintained
   - ☐ True
   - ☐ False

6. The research will not terminate the heartbeat or respiration of the neonate
   - ☐ True
   - ☐ False

7. There will be no added risk to the neonate resulting from the research
   - ☐ True
   - ☐ False

F. Biomedical and Behavioral Research Involving Prisoners

Complete this checklist if the subject population will include prisoners.

Note: Minimal risk for research involving prisoners is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

1. Select and justify which allowable category of research involving prisoners this research falls within:

   ☐ Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects

   ☐ Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects

   ☐ Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults)

☐ Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject

☐ Epidemiologic studies in which the sole purpose is to describe the prevalence or incidence of a disease by identifying all cases or to study potential risk factor associations for a disease, the research presents no more than Minimal Risk and no more than inconvenience to the subjects, and Prisoners are not a particular focus of the research.

2. Provide justification for each of the following regulatory criteria:

   a) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired

   b) The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers

   c) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless justification is provided, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project

   d) The information is presented in language which is understandable to the subject population

   e) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole

f) When appropriate, adequate provision has been made for follow up examination or care after research participation, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact

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III. Medical Devices

Complete this checklist if the research evaluates the safety or effectiveness of a medical device. If more than one medical device is being evaluated, provide the requested information for each.

A. Device Name:

B. Manufacturer:

C. Does the research involve a Significant Risk Device under an IDE?

☐ Yes. Include documentation of the FDA approval of the IDE with your submission. *Acceptable methods of documentation include: (1) FDA letter noting IDE number and approval status; (2) Industry sponsor letter noting IDE number and FDA approval status; or (3) FDA-approved industry sponsor protocol with IDE number noted*

☐ No

D. Is the research IDE-exempt?

☐ Yes. Include a FDA letter with your submission noting the determination that the research is IDE-exempt or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is IDE-exempt*.

☐ No

E. Does the research involve a Non-Significant Risk (NSR) Device?

☐ Yes. Include a FDA letter with your submission noting the determination that the research is NSR or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is NSR**.

☐ No

* This FDA guidance includes a description for when a device study is exempt from the IDE requirements:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf

**This FDA guidance includes information on how to differentiate between Significant Risk and Non-Significant Risk device studies:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf