HiLo: Pragmatic trial of higher vs lower serum phosphate targets in patients undergoing hemodialysis

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Principal Investigator	Myles Wolf, MD, MMSc
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PROTOCOL APPROVAL PAGE

Study Title: HiLo: Pragmatic trial of higher vs lower serum phosphate targets in patients undergoing hemodialysis

Version: 5.0

Date of Issue: September 24 2021

Study Funding Source: National Institute of Digestive, Diabetes and Kidney Disease (NIDDK)

We, the undersigned, have read and approve this protocol and agree on its content.

_____
NIDDK Representative

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Date

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Principal investigator

_____
Date

PROTOCOL VERSION AND AMENDMENT TRACKING

Version Number/Amendment	Approval Date	Summary of Changes
1.0	November 19, 2018	Initial Submission
2.0	August 16, 2019	Added protocol number; removed DCI as recruiting center; updated primary outcome / analytical approach to a hierarchical composite of all-cause mortality and all-cause hospitalizations; adjusted randomization stratification to above and below provider's median facility census; updated sample size language; added interim analysis and stopping rules
3.0	November 1, 2019	Added pregnancy exclusion
4.0	February 02,2021	Clarified inclusion as at least 3 months of dialysis treatment, not specific to in-center hemodialysis; added Calciphylaxis and Nocturnal in-center dialysis as exclusion criteria
5.0	September 21 2021	Changed randomization and analysis to individual level randomization from cluster-randomized design

PROTOCOL SYNOPSIS

Protocol Title	HiLo: Pragmatic trial of higher vs lower serum phosphate targets in patients undergoing hemodialysis
Short Title	HiLo
Protocol Number	Pro00100325
Funding Source	National Institutes of Diabetes and Digestive and Kidney Diseases
Study Design	Pragmatic, open-label, clinical outcomes trial with individual-level randomization
Principal Investigator	Myles Wolf, MD, MMSc
Study Objectives	1. To determine whether less stringent control of serum phosphate to target levels of ≥6.5 mg/dl versus the current standard approach of targeting serum phosphate levels of <5.5 mg/dl will result in lower rates of the hierarchical composite outcome of all-cause mortality and all-cause hospitalization among patients with ESRD undergoing hemodialysis. 2. To demonstrate the capacity to conduct a second-generation, large-scale, randomized pragmatic clinical trial that requires individual-level informed consent in partnership with two dialysis provider organizations.
Intervention / Comparator Arms	High protocol: Target a serum phosphate range of ≥6.5 mg/dl Low protocol: Target serum phosphate of <5.5 mg/dl
Enrollment Period	24 months
Duration	45 months
Dialysis Provider(s)	Outpatient hemodialysis facilities operated by: 1. DaVita, Inc. 2. University of Utah
Data Coordinating Center	Duke Clinical Research Institute (DCRI)
Number of Facilities, Patients	100-150 facilities, ~4400 patients
Main Eligibility Criteria	<u>Dialysis Facility Eligibility</u> • Willingness of the medical director, treating nephrologists and dietitians to adopt either the high or low phosphate target ranges for participating patients • Willingness of the facility manager to allow dietitians to participate in training and regularly scheduled teleconferences throughout the duration of HiLo • Facility dietitian comfort with the phosphate targets and willingness to implement the trial procedures and attend training and teleconferences throughout the duration of HiLo <u>Patient Eligibility</u> Inclusion criteria: • Adults ≥18 years

	• Undergoing 3 times weekly in-center hemodialysis and having received dialysis treatment for at least 3 months • Able to provide informed consent Exclusion criteria: • Females who are pregnant or who plan to become pregnant while in the study • Calciphylaxis • Nocturnal in-center dialysis
Outcomes	Primary: hierarchical composite outcome of all-cause mortality and all-cause hospitalization rate Main Secondary Outcomes: all-cause mortality; all-cause hospitalization rate Additional Secondary Outcomes: total inpatient hospital days PPY of follow-up; serum albumin and protein catabolic rate (PCR), as markers of diet and nutrition.
Duration of Intervention	45 months
Analytic Approach	Primary efficacy analysis will use the intention to treat (ITT) sample that includes all randomized patients. Primary outcome: The primary analysis of HiLo is the comparison of the Finkelstein-Schoenfeld scores across the two serum phosphate arms on the hierarchical composite endpoint of time to all-cause mortality and hospitalization rate. Main secondary outcomes: Cox regression will be used to estimate the effect of phosphate target arm on time-to-all-cause mortality; per person year hospitalization rate ratios will be compared between the two serum phosphate arms. Additional secondary outcomes: Use mixed effect models to examine individual participants' total number of days spent in the hospital per total length of follow-up according to two serum phosphate arms.
Study Oversight	An independent Data and Safety Monitoring Board (DSMB) appointed by NIDDK will review trial progress, data quality, and safety throughout the course of the trial in accordance with a Data and Safety Monitoring Board Charter.

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ABBREVIATIONS

CVD	Cardiovascular disease
DCRI	Duke Clinical Research Institute
DSMB	Data and Safety Monitoring Board
EHR	Electronic health record
ESRD	End-stage renal disease
ICD-10	International Classification of Disease (ICD)-10 codes
IRB	Institutional Review Board
KDIGO	Kidney disease improving global outcomes
MOP	Manual of Procedures
PCR	Protein catabolic rate
PID	Participant identifier
PPY	Per-patient year
TSAT	Transferrin saturation

1. BACKGROUND AND RATIONALE

1.1 Background and Rationale for the HiLo Trial Question

For patients with end-stage renal disease (ESRD) undergoing dialysis, clinical outcomes have improved modestly in recent years, but rates of hospitalization (~2 per patient-year) and mortality (15–20%) remain unacceptably high.[1] Poor outcomes are driven primarily by increased risk of cardiovascular disease (CVD),[1] but interventions that are proven to improve clinical outcomes in the general population by targeting traditional CVD risk factors have mostly failed in patients with ESRD.[2-4] The lack of efficacy of traditional interventions has led the nephrology community to invoke and target putative ESRD-specific risk factors for CVD and death.

Hyperphosphatemia is a ubiquitous complication of ESRD that is independently associated with increased risks of CVD and death.[5-9] Experimental data suggest that hyperphosphatemia may contribute to arterial calcification, and left ventricular hypertrophy which are associated with increased risk of CVD events and death in ESRD.[10-15] Hyperphosphatemia also exacerbates increases in parathyroid hormone and fibroblast growth factor 23 levels, each of which are associated with CVD and mortality in ESRD.[6,16-22] Based on this body of observational human and preclinical data, the nephrology community has advanced hyperphosphatemia as a putative – but unproven by randomized controlled trial – contributor to adverse outcomes in ESRD.

Starved for therapeutic advances to improve outcomes in ESRD, opinion-based clinical practice guidelines suggest that phosphate levels be maintained at ~5.0 mg/dl in ESRD using phosphate binders and low phosphate diet. However, there have been no randomized outcomes trials to evaluate the optimal serum phosphate target and no placebo-controlled trials tested the effects of FDA-approved phosphate binders on clinical outcomes.[23,24] Thus, major questions in the field that affect daily clinical practice in every dialysis facility across the US remain unanswered: “Do phosphate binders, as currently deployed, improve clinical outcomes in ESRD?” More fundamentally, “Does lowering of serum phosphate towards the normal range improve outcomes in ESRD?”

While patients who adhere to burdensome binder and dietary regimens may realize theoretical benefits of strict phosphate control, excessive treatment to achieve an unnecessarily low serum phosphate may actually worsen outcomes by: 1) paradoxically increasing risk by inducing calcium, lanthanum or iron overload;[25-28] 2) promoting gastrointestinal side effects that exacerbate malnutrition, which is a potent risk factor for death in ESRD;[29] and 3) eroding patients’ quality of life by adding phosphate-related demands to an already high pill burden.[30,31] All of these potential risks may have escaped detection precisely because of the lack of randomized outcomes trials. Thus, clinical equipoise is the scientific premise for conducting the HiLo trial.

1.2 Rationale for Pragmatic Trial Design

There is increasing interest in pragmatic, or real-world, trials because of their potential for efficient, yet rigorous, evidence generation, and the relevance of the findings to broad populations of individuals with the condition of interest rather than highly selected subgroups. Several aspects of ESRD care are ideally suited to conducting large-scale pragmatic clinical trials based in dialysis facilities. Patients are treated in their facilities thrice weekly for 3–4 hours per session during which study education, informed consent

and trial activities can occur. Laboratory tests are performed in a regimented fashion at central laboratories and all results are integrated into dialysis providers' electronic health records (EHR) that can serve as databases for interventional studies. Dialysis provider organizations use protocols to standardize care across their facilities; for example, protocols to manage bone and mineral metabolism and anemia are the norm. This enables standardized integration of protocol-driven randomized interventions into the fabric of daily clinical practice while also providing a natural mechanism for rapid translation of trial results into future clinical practice. These attributes supported execution of the pragmatic "TiME" trial in >250 dialysis facilities across the US as one of the initial NIH Collaboratory Demonstration Projects.[32] Our team will leverage best practices and many lessons learned from TiME to execute HiLo, which will answer a critical clinical question while simultaneously advancing the fertile field of pragmatic trials in ESRD.

The design and implementation approach of HiLo will incorporate the following pragmatic features:

1. **Liberal eligibility criteria:** This will accelerate enrollment and promote generalizability of the results.

2. **Use of an internet-based, centralized informed consent process administered at dialysis units:** A historical obstacle to executing HiLo pragmatically is the need for individual-level patient consent. Requiring numerous study personnel in scores of dialysis units across the country would be too costly for a pragmatic budget. However, new pragmatic trial advances that are being pioneered by PCORNet and the Duke Clinical Research Institute (DCRI) enable an approach to obtaining informed consent via tablets and associated web-based communications applications, such as Skype, that require a small centralized team of study personnel. The DCRI is successfully using this approach for the ADAPTABLE trial,[33] which will serve as a precedent and model for HiLo.

3. **Leveraging clinical practice to implement the intervention:** Dietitians employed by dialysis organizations are present in all dialysis units and routinely use protocols to manage bone and mineral metabolism parameters. Phosphate management protocols will be tailored specifically to HiLo that have the same "look and feel" as those used in clinical practice by the dietitians, who will implement the protocols.

4. **Flexible implementation of the intervention using already approved medications:** Consistent with current practice, the HiLo protocol will dictate the target serum phosphate, but specific binder choices will remain at the discretion of local providers. Since HiLo participants will be treated with standard or lower doses of phosphate binders already used in clinical practice, they will not incur increased costs of study medications.

5. **Use of clinical laboratory data to implement and continuously monitor the intervention:** To titrate phosphate treatment and support centralized monitoring, the trial will use serum phosphate levels that are already measured at least monthly in routine care. DCRI Bioinformatics will build automated algorithms to monitor achievement of serum phosphate targets at the levels of randomization group and individual participant. Reliance on clinically acquired rather than trial-

driven phosphate levels will reduce cost and enhance the generalizability of HiLo's results to the non-trial setting.

6. **Use of EHRs to extract clinical data and ascertain endpoints:** HiLo will derive all trial data from the rich clinical and laboratory databases that are maintained and updated daily by the dialysis providers. Monthly secure data transfers from the dialysis provider organizations to DCRI will be orchestrated by DCRI Bioinformatics and will include demographic and clinical data, repeated measures data on serum phosphate and many other lab tests, and clinical data, including all hospitalizations and deaths. Since hospitalization and mortality data are captured with high precision in real time in the dialysis organizations' databases, this will eliminate costs related to outcomes adjudication. Using a similar approach to data acquisition, the TiME trial found a high degree of completeness for most data elements.

7. **Collection of Patient Reported Outcomes:** In support of an ancillary study awarded to Northwestern University the HiLo study team will collect patient responses to 6 surveys (Kidney Disease and Quality of Life (KDQOL™-36), PROMIS Gastrointestinal Belly Pain 5a, PROMIS Gastrointestinal Constipation 9a, PROMIS Gastrointestinal Diarrhea 6a, PROMIS Gastrointestinal Gas and Bloating 13a, and PROMIS Gastrointestinal Nausea and Vomiting 4a) and transmist de-identified responses to Northwestern University via secure file transfer platform requiring multi-factor authentication. The goal of the ancillary study is to determine the impact of change in care on patients' perceived quality of life. Survey responses will be collected at baseline (time of consent), six months from consent, and one year from consent. Surveys will be sent from the Duke REDCap system for patients who chose to complete surveys online. Duke will provide the contact phone number to Northwestern University for patients who chose to complete the surveys over the phone. Northwestern University will collect phone responses and conduct all analyses regarding PRO data.

8. **Ability to merge HiLo data with Medicare claims data:** Treatment of the majority of patients with ESRD is supported by Medicare, regardless of age. Since virtually all HiLo participants will be Medicare beneficiaries, it will be possible to merge the HiLo database with Medicare claims data to obtain International Classification of Disease (ICD)-10 codes from all hospitalizations experienced by HiLo participants. This will enable us efficient conduct of secondary analyses of cause-specific hospitalization to determine whether HiLo trial effects are primarily driven by specific events, for example, cardiovascular or infectious hospitalizations.

2. OBJECTIVES, OUTCOMES, AND GOALS

HiLo will be a pragmatic, open-label, multicenter, individual-randomized trial of ~4400 patients with ESRD undergoing in-center maintenance hemodialysis at 100-150 units maintained by two dialysis organizations that care for a substantial proportion of the US dialysis population.

2.1 Primary Objectives

The 1st objective of HiLo is to test the following primary and secondary hypotheses of HiLo:

Primary hypothesis: Compared to the current standard approach of targeting serum phosphate levels of <5.5 mg/dl, less stringent control of serum phosphate to target levels of ≥6.5 mg/dl will yield a reduction in the hierarchical composite outcome of time to all-cause mortality and all-cause hospitalization among patients with ESRD undergoing hemodialysis.

Secondary hypothesis: The main secondary hypotheses are that less stringent control of serum phosphate will reduce risk of all-cause mortality as well as the risk of all-cause hospitalization (individually) compared to the current standard approach of strict phosphate control (superiority analysis). In addition, the trial will test the secondary hypotheses that less stringent control of serum phosphate will result in increased serum albumin and protein catabolic rate (PCR), as markers of diet and nutrition.

2.2 Secondary Objectives

The 2nd objective of HiLo is to conduct a second-generation pragmatic clinical trial in dialysis.

In partnership with two dialysis provider organizations, demonstrate the following for a trial embedded in clinical care delivery:

1. Feasibility of obtaining informed consent using electronic devices (e-consent)
2. Use of a single IRB of record for hundreds of dialysis facilities
3. Successful implementation of a trial-driven treatment algorithm by dietitians at the participating dialysis units
4. Harmonization of data from a large for-profit dialysis provider and an academically-owned small dialysis provider
5. Effective monitoring of trial implementation using a centralized approach

2.3 Primary Outcome

Hierarchical composite of time to all-cause mortality and all-cause hospitalization rate (total counts per person-years of follow-up).

2.4 Secondary Outcomes

Time to all-cause mortality; and all-cause hospitalization rate, expressed as total counts per person-years of follow-up.

Additional secondary outcomes: total inpatient hospital days per person-years of follow-up; serum albumin and protein catabolic rate (PCR), as markers of diet and nutrition.

2.4.1 Pragmatic Trial Demonstration Goals

The HiLo Trial is one of the pragmatic trial demonstration projects of the NIH Health Care Systems (HCS) Research Collaboratory. These demonstration projects are intended to be large clinical trials that are conducted within the clinical care environment and evaluate interventions implemented by care providers and relying as much as possible on data obtained as part of routine clinical care. HiLo has the following demonstration project goals:

1. To implement an electronic consent process;
2. To use of a single IRB of record to oversee hundreds of dialysis facilities;
3. To implement a trial-driven treatment algorithm by dietitians at the participating dialysis units
4. To harmonize across 2 different dialysis providers' data elements obtained through clinical care;
5. To monitor safety without using individual adverse event reporting.

3. STUDY ORGANIZATION

3.1 Study Leadership

Principal Investigator: Myles Wolf, MD, MMSc
Co-Investigators: Tamara Isakova, MD, MMSc, Geoffrey Block, MD, Laura Dember, MD, Matthew Roe, MD, Hrishikesh Chakraborty, DrPH

3.2 Dialysis Provider Organizations

HiLo will be conducted in partnership with 2 dialysis provider organizations and represented by:

- DaVita, Inc.: Steven Brunelli, MD, MSCE
- Dialysis Program at University of Utah Health: Srinivasan Beddhu, MD

3.3 Data Coordinating Center: The Duke Clinical Research Institute (DCRI)

DCRI will serve as the Data Coordinating Center for HiLo and it will support trial design, operations, site management, IRB reporting, bioinformatics, biostatistics, data safety monitoring board meeting preparation, and dissemination of HiLo's results.

3.4 Subcommittees

The following subcommittees will be established to address specific aspects of trial conduct and analysis.

Table 1: HiLo Subcommittees

Subcommittee	Operational Support from DCRI
Protocol & Manual of Operations	Protocol & MOP development Regulatory documentation for Central IRB
Informed Consent and Recruitment & Retention	Informed consent development Piloting informed consent Creation of participant tracking algorithms Creation of materials to promote engagement
Phosphate Intervention & Monitoring	Algorithms development Piloting algorithms
Communications, Education & Training	Creation of education materials and toolkits Creation of communication platforms
Design & Analysis	Data extraction & synchronization Data quality monitoring

Resource Sharing & Publications	Assist with dissemination of information Support for resource sharing

4. STUDY DESIGN

This study will be conducted in accordance with current U.S. Food and Drug Administration regulations and guidelines, International Conference on Harmonisation guidelines on Good Clinical Practice (ICH E6, the principles of which have their origin in the Declaration of Helsinki), and all other applicable national and local laws and regulations.

4.1 Overview of Study

HiLo is a pragmatic, multicenter, open-label, clinical outcomes trial with individual-level randomization. HiLo will compare the effects on hospitalization, mortality, diet, and nutrition of two different phosphate management strategies in ~4400 patients being treated with maintenance hemodialysis at 100-150 facilities operated by (1) a large national for-profit dialysis corporation (DaVita, Inc.) and (2) a smaller regional academic program (University of Utah). HiLo will randomize individuals to either liberal control of serum phosphate, targeting ≥6.5 mg/dl, or strict control of serum phosphate, targeting <5.5 mg/dl.

4.2 Study Setting

The trial will be conducted in ~100-150 facilities operated by 2 dialysis provider organizations. The dialysis facilities will be distributed throughout the United States.

4.3 Facility and Participant Selection

4.3.1 Facility Eligibility

Dialysis facilities will be eligible for participation if they meet the following criteria:

- Willingness of the medical director, treating nephrologists and dietitians to adopt either the high or low phosphate target range for participating patients;
- Willingness of the facility manager to allow dietitians to participate in training and regularly scheduled teleconferences throughout the duration of HiLo; and
- Facility dietitian comfort with the phosphate targets and willingness to implement the trial procedures and attend training and teleconferences throughout the duration of HiLo.

4.3.2 Participant Eligibility

The eligibility criteria are broad in order to maximize the generalizability of the trial findings.

- Inclusion criterion:
  - Adults ≥18 years
  - Undergoing 3 times weekly in-center hemodialysis and having received dialysis treatment for at least 3 months
  - Able to provide informed consent

- Exclusion criteria:
  - Females who are pregnant or who plan to become pregnant while in the study
  - Calciphylaxis
  - Nocturnal in-center dialysis

4.4 Participant Timeline

Participants will be followed for up to 27 (enter at enrollment end) – 45 (enter at enrollment start) months.

4.5 Randomization

Following consent, patients will be randomized in a 1:1 ratio to the two treatment arms. The randomization will be stratified by site in random sized blocks.

4.6 Intervention

Two phosphate titration protocols will be used that have the same "look and feel" as those used in practice in an effort to sustain a mean time-averaged difference in serum phosphate between the two arms of ≥1 mg/dl:

1. **Low serum phosphate target** that is consistent with **current standard of care**: The goal is to titrate and maintain serum phosphate to <5.5 mg/dl.
2. **Higher serum phosphate** target that is the **intervention strategy:** The goal is to titrate and maintain serum phosphate to ≥6.5 mg/dl by setting a serum phosphate threshold >7.0 mg/dl when binders will be initiated, as has been done previously.[34]

A mean serum phosphate of 4.8–5.2 is anticipated in the low arm and 6.5–6.8 in the high arm, as observed in two pilot clinical trials.[34,35] Since serum phosphate is 4–7 mg/dl in most patients with ESRD, ≥1 mg/dl difference equates with a ≥33% difference within the modifiable range of time-averaged phosphate exposure. Specific binder choices will be relegated to the discretion of local providers based on local practice.

4.6.1 Frequency of Serum Phosphate Measurements

Dialysis clinics measure serum phosphate monthly and typically repeat levels biweekly during active binder titration, per their standard of care. No additional dedicated laboratory testing will be conducted for HiLo.

4.6.2 Phosphate Binder Choices

All classes of FDA-approved phosphate binders that are used in routine dialysis practice will be available for use in HiLo with the choices of specific binders left to the patients' provider teams.

4.6.3 Titrations Strategies

Below are example initial phosphate titration algorithms. DCRI will work with the dialysis providers to optimize the algorithms, within the framework of the dialysis providers' current procedures, during the first 6 months of the UG3 phase of the trial:

Figure 1: Example Treatment Algorithm for Low Phosphate Group

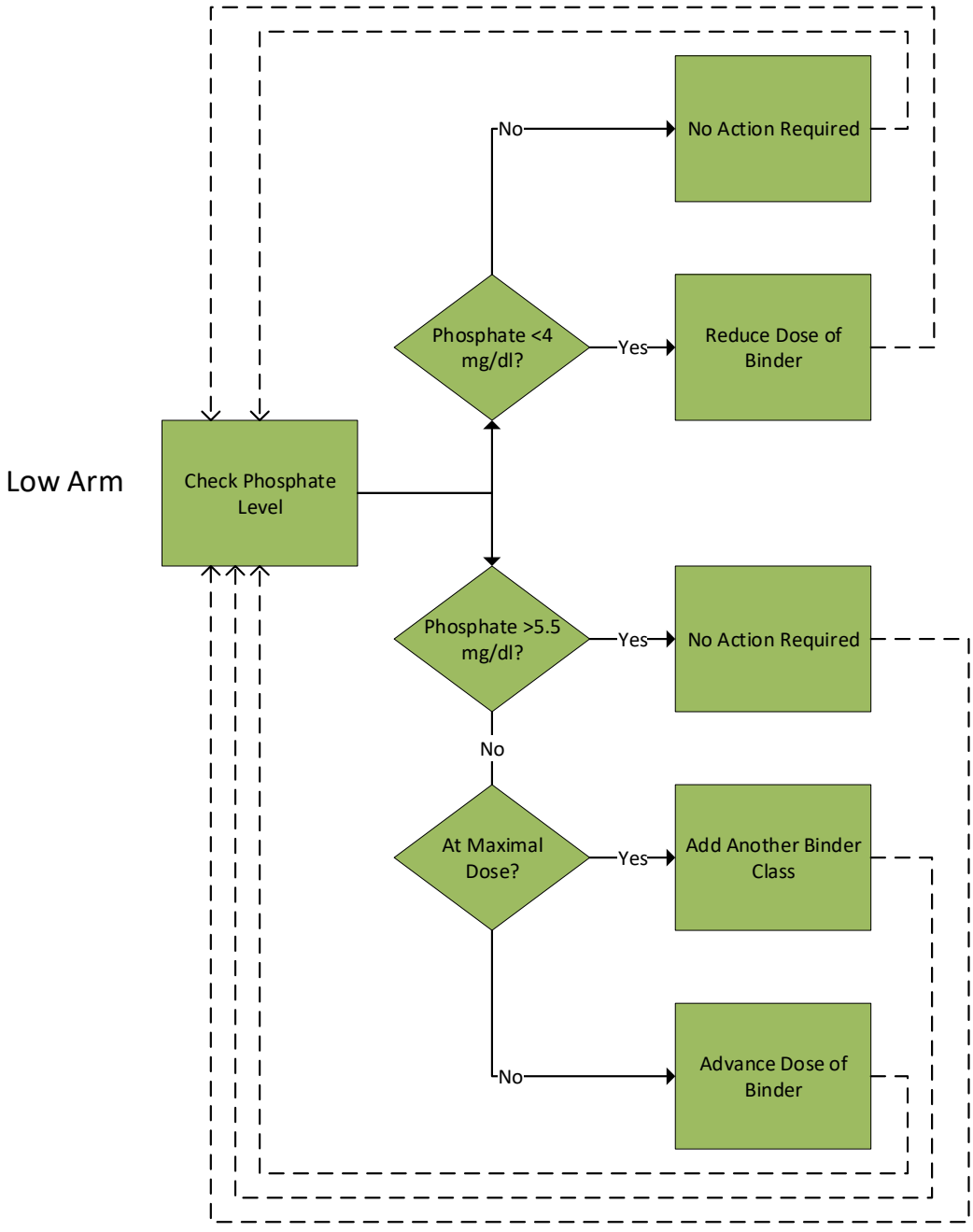
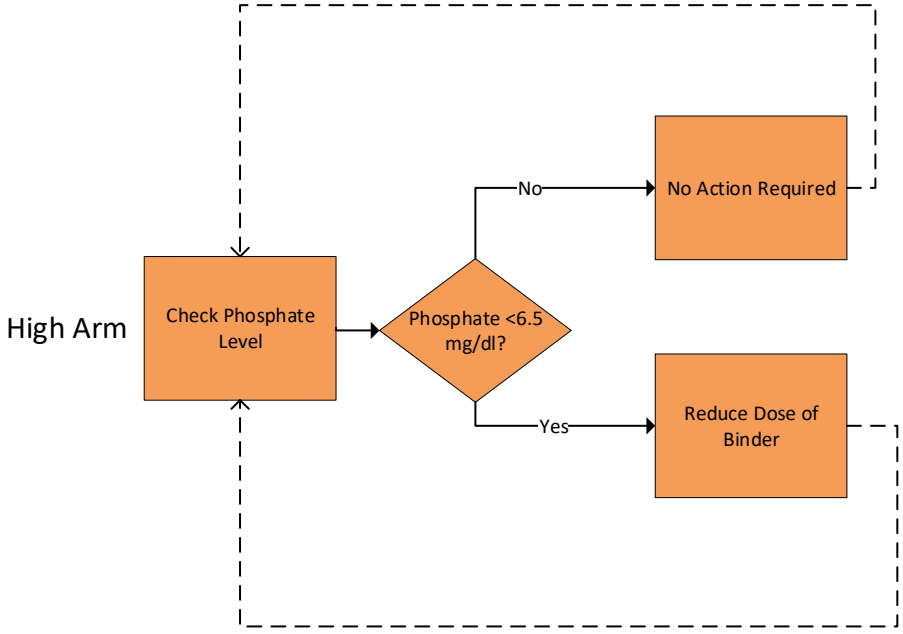


Figure 2: Example Treatment Algorithm for High Phosphate Group



4.6.4 Thresholds of Phosphate Control

The 2 arms will have different thresholds of serum phosphate at which therapeutic changes will be considered.

Table 2: Serum Phosphate Thresholds

Arm	Phosphate Target	Action Threshold	Action, Upper Threshold	Action, Lower Threshold
Low	<5.5 mg/dl	≥5.5 mg/dl	Binder therapy increased	Binder therapy decreased
High	≥6.5 mg/dl	<6.5 mg/dl		

4.6.5 Approach to Phosphate Binders

To achieve desired serum phosphate targets, dialysis facilities randomized to the low arm will manage serum phosphate levels in accordance with current standard of care. Dialysis facilities randomized to the high arm will manage serum phosphate levels in accordance with the intervention strategy that allows for less intensive serum phosphate control and more liberalized serum phosphate targets. DCRI will work with the dialysis providers to on their approach to these titrations, based on the current procedures being implemented at their dialysis units. Further details will be available in the study Manual of Procedures.

4.6.6 Approach to Diet

Throughout the duration of the study, in-center dietitians will provide feedback and recommendations about diet during in-person meetings using the same general approaches and frequency that they use in clinical care. During these meetings, participants' dietary intake will be reviewed and standard recommendations for healthy nutrition for dialysis patients will be conveyed. Dietitians at dialysis facilities will provide all participants with identical dietary phosphate recommendations but the frequency of their delivery will vary, tailored to the facility's randomized phosphate arm (high vs. low) and the current serum phosphate level of the participant relative to the facility's randomized target (within, above or below range). For example, participants at the units randomized to the low arm whose serum phosphate is above target may receive more frequent and intensive dietary counseling to reduce phosphate intake, for example, by minimizing intake of high phosphate processed foods. Conversely, participants in the units randomized to the high phosphate arm who are below target may be advised to liberalize their diet to increase phosphate intake, for example, by increasing intake of dairy products. DCRI will work with the dialysis providers on their approach to dietary recommendations, based on the current procedures being implemented at their dialysis units.

4.6.7 Approach to Management of Hypercalcemia and Secondary Hyperparathyroidism

Clinicians will manage hypercalcemia and secondary hyperparathyroidism as they do in usual clinical care, for example, by altering the binder regimen to reduce calcium intake, or using calcimimetics or vitamin D analogs to lower PTH.

4.7 Dialysis Provider Staff Roles

4.7.1 Role of Dietitians in Implementing HiLo Interventions in Facilities

Dietitians at dialysis units will be the on-the-ground personnel who will implement the HiLo protocols for phosphate management. The decision to have dietitians implement the protocols is based on multiple considerations:

1. Dietitians are employed by dialysis organizations, are present in all dialysis units, and usually serve as the primary decision makers for titration of phosphate-related treatments. Relying on clinical personnel to implement the trial intervention is consistent with the goals of pragmatic trials.

2. The HiLo phosphate algorithms will feel "natural" to both dietitians and patients. Dietitians have well established relationships with the patients who will participate in HiLo, they see them in the dialysis unit at least monthly, and are comfortable discussing phosphate management with them. The existing rapport between dietitians and patients will facilitate adherence to the interventions.

3. Dietitians are among the most motivated caregivers on dialysis teams. Anecdotally, they are often the most committed and scientifically inquisitive members of care teams, constantly seeking better approaches to enhance patient care in general, and diet and nutrition in particular, including phosphate management. To fully engage dietitians in the design and conduct of HiLo, DCRI will: (1) recruit 2 dietitian representatives to the HiLo Steering Committee to provide input into design and implementation; (2) identify a group of dietitians who will serve as local champions for HiLo and interact directly with dietitians at the units within their respective regions; and (3) drive interest among dietitians by having a HiLo presence at the DaVita and DCI national meetings and distributing HiLo newsletters throughout the conduct of the trial. DCRI will hold regular conference calls during the planning and conduct of the trial with participating dietitians for training updates and to review protocol adherence using a strategy of friendly competition across centers to maximize intervention fidelity. DCRI has initiated discussions with our dialysis partners about methods for recognizing and incentivizing participating dietitians.

4.7.2 Role of Treating Nephrologists

Although dialysis facilities will be randomized to high or low serum phosphate targets, the specific phosphate binding medications will be prescribed by the treating nephrologist(s) thus allowing for individualization of the prescription based on other considerations. Also consistent with standard practice, patients can have input into the prescribed medications through discussions with the treating nephrologist(s).

Participants may be discontinued from their study arm at the discretion of the dialysis provider physician. These participants will continue to be followed and will be included in the intent-to-treat analyses.

4.8 Adherence

In accordance with the clinical monitoring plan the DCRI will continuously monitor serum phosphate and remediate deviations from targets using webinars first and then in-person training visits, if needed. Sites will be notified by the DCRI whenever point-of-care serum phosphate measurements are repeatedly in the “action required” range; such notifications will be linked to a reminder of the facility’s treatment group assignment and the facility’s serum phosphate goals.

5. STUDY PROCEDURES

All of the HiLo Trial processes will be described in detail in the Manual of Procedures (MOP). The MOP will include trial activities occurring at the dialysis facilities, dialysis provider organization data warehouses, and the DCC at DCRI. The DCC is responsible for maintaining the manual and any associated documents, and will ensure that all relevant collaborators are informed about study procedures.

5.1 Facility Selection

In aggregate, our partnering dialysis provider organizations offer >3000 individual freestanding dialysis facilities to choose from in order to assemble a final roster of participating sites in HiLo. DCRI will work with our partners from the dialysis provider organizations to develop a strategy to select a suitable roster of dialysis facilities for HiLo; general considerations will include:

- Regional diversity across the US to maximize generalizability;
- Stability of candidate facilities, e.g. to exclude those with a dwindling census that could close;
- Willingness of medical directors, facility managers and dietitians to endorse the clinical equipoise that justifies HiLo and adopt either serum phosphate target for their patients;
- While provider organizations will support HiLo, facility managers should endorse the suitability of their dietitians to participate in training and regularly scheduled teleconferences throughout the duration of HiLo;
- Facility dietitian comfort with the different phosphate targets and willingness to implement the trial procedures and attend training and teleconferences throughout the duration of HiLo.

5.2 Participant Identification

Patients receiving care at participating dialysis facilities who meet the eligibility criteria will be identified through the electronic data systems of the dialysis provider organizations by the HiLo Trial Information Technology (IT) teams at the provider organizations. A unique research participant identifier (PID) for each participant will be generated. The PID will not be related to the patient's medical record number or any other identifier. Each dialysis provider organization will maintain the key to the unique identifiers for participants enrolled from their organizations. The keys to the unique identifiers will not be transmitted to the DCRI. During the data extraction process, all personal identifiers will be replaced by the PID.

5.3 Participant Enrollment

Since HiLo includes a phosphate target that differs from current practice guidelines,[24] the greater-than-minimal-risk research requires individual-level consent. HiLo initially used a cluster-randomized design in which participating dialysis centers were randomized to either the intervention or control arm. After completing enrollment in 30 dialysis units (14 Hi and 16 Lo sites), there was concern for biased enrollment. Therefore, the remainder of the trial will utilize individual-level randomization to ensure that arm assignment does not influence patients' willingness to participate. Patients enrolled in the cluster-randomized design will remain in the study through completion. For the individual randomized phase, the HiLo study will randomize approximately 3,800 additional participants (1,900 per arm).

5.3.1 Informed Consent

The trial will require that participants provide informed consent because the research poses greater than minimal risk. Electronic consent (eConsent) is rapidly becoming a new standard to improve efficiency, effectiveness and compliance of the informed consent process. Leveraging DCRI experience in other pragmatic trials, the study team will create an eConsent form and study educational materials that will be available at all participating dialysis facilities and also contain links to centralized clinical experts at DCRI that will be available to engage potential participants and answer their questions.

5.3.2 HIPAA Authorization

HIPAA Authorization forms will be obtained with informed consent.

5.4 Data Collection and Tracking

The electronic data systems of the dialysis provider organizations contain detailed clinical information from every dialysis treatment and the results of laboratory tests and hospitalization dates. These data are maintained in central electronic data warehouses. For HiLo, a pre-specified subset of data elements will be extracted from the central data warehouses and securely (encrypted) transferred to the DCRI database at regular intervals. No laboratory studies will be performed specifically for the trial. The following data elements will be obtained from clinical care data for all trial participants at the indicated frequency:

Demographic and comorbidity data at study entry:

- Dialysis facility zip code
- Age
- Sex
- Race
- Ethnicity
- Height
- Weight
- Dialysis vintage
- Co-morbid illnesses noted on admission to the dialysis facility (ICD-9/10 codes)
- Cause of end-stage renal disease

For patients who decide not to participate in the trial, de-identified demographic and comorbidity data will be transmitted to the DCRI to allow comparison of characteristics of participating and non-participating patients.

Dialysis treatment data:
- Dialysis adequacy, single pool Kt/V, modality change: all available data
- Pre-dialysis and post-dialysis weights: every session
- Vascular access type (presence or absence of catheter): once per month

Laboratory data: monthly
In alignment with usual practice, all values available for the following laboratory test results will be made available to the DCRI by electronic data transfer on a monthly basis.
- Hemoglobin
- Albumin
- Calcium
- Phosphate
- Protein catabolic rate
- Serum ferritin
- Transferrin saturation

Laboratory data: once every 3 months
- Intact parathyroid hormone

Hospitalizations data: all

Medications: all
All available data on medications will be made available to DCRI by electronic data transfer on a monthly basis, including but not limited to:
- Phosphate binders
- Activated vitamin D
- Home medications
- Calcium
- Calcimimmetics (oral and IV)

Status change: all
- Date of transfer to another dialysis facility
- Date of kidney transplantation
- Date of transfer to peritoneal dialysis
- Date of withdrawal from dialysis
- Date of death

The study team will also be collecting and transmitting patient reported outcomes (as well as name and phone number for patients that wish to complete the surveys via telephone) to Northwestern University.

- Kidney Disease and Quality of Life (KDQOL™-36)
- PROMIS Gastrointestinal Belly Pain 5a
- PROMIS Gastrointestinal Constipation 9a
- PROMIS Gastrointestinal Diarrhea 6a
- PROMIS Gastrointestinal Gas and Bloating 13a

- PROMIS Gastrointestinal Nausea and Vomiting 4a
- Name
- Phone Number

5.5 Participant Withdrawal

Participants may decide to withdraw from the study at any time. Patients who initially participate but later elect to withdraw from the trial will have no data transmitted to the DCRI after the date of withdrawal. Additionally, participants who increase dialysis frequency to more than three times weekly, including participants in the high arm who become pregnant, will be withdrawn from the study by the dialysis provider.

Data transmitted to the DCRI prior to withdrawal will remain in the trial database. Contact information for the research personnel from the relevant dialysis provider organization will be available at participating dialysis facilities throughout the duration of the trial to facilitate communication such as a decision to withdraw from the trial. Participants who elect to discontinue phosphate binder medications or protocol-based treatment algorithms will remain as trial participants and continue to have data transmitted to the DCRI unless they withdraw from the trial.

6. POTENTIAL RISKS

6.1.1 Breach to Participant Confidentiality

Due to necessity of data merges from with data systems outside the enrolling site, breach to confidentiality is a potential risk. To minimize this risk, primary identifiers will be retained only within the data systems where required to conduct the study; these will be omitted as data travel downstream and only study IDs will be in the analysis datasets. Further de-identification and anonymization methods will be used when making data available for outside investigators. DCRI is part of the Duke HIPAA covered entity and has experience working with PHI in the research context; DCRI is extremely prudent in keeping patient data secure and confidential.

6.1.2 Risks Related to Hyperphosphatemia Management

Observational studies have linked hyperphosphatemia in patients with ESRD to increased risks of CVD and death.[5-9] Phosphate binders are the mainstay of management of hyperphosphatemia in patients undergoing dialysis treatment. Use of these medications can lead to gastrointestinal side effects, including nausea, vomiting, abdominal pain, bloating, dyspepsia, diarrhea, and constipation.[37] Use of calcium-based phosphate binders can also lead to hypercalcemia.[37] It is anticipated that gastrointestinal side effects will be reduced in the high phosphate target arm and they will remain similar to pre-intervention levels in the low phosphate target arm. Risks related to hyperphosphatemia management in both arms will be managed according to usual clinical care, which typically entails adjustment of phosphate binder dose and/or substitution of drug class.

7. SAFETY ASSESSMENTS

7.1 Adverse Event Reporting and Follow-up

Among patients undergoing hemodialysis, adverse events of moderate or higher severity are extremely common and usually result in hospitalization (or death). Based on this information, and given that hospitalization is the primary outcome of HiLo, additional information on adverse events will not be collected. Periodically reports will be generated related to laboratory-based events and allow the DSMB to review in a blinded manner the rates of these events in high versus low target groups. All laboratory parameters are measured either monthly or quarterly for all patients as part of routine clinical care:

- Hypophosphatemia, defined as serum phosphate <2.0 mg/dL;
- Hyperphosphatemia, defined as serum phosphate >7.5 mg/dl;
- Hypercalcemia, defined as total uncorrected serum calcium >10.5 mg/dL;
- Excessive iron supplementation, defined as serum ferritin >1000 ng/ml and transferrin saturation (TSAT) >50% (to assess for the potential effects of excess iron-based binder use); and
- Secondary hyperparathyroidism, defined as parathyroid hormone (PTH) levels 9 times the upper limit of normal for the assay, based on the threshold articulated in the international KDIGO guidelines.

8. STATISTICAL ANALYSIS PLAN AND DETERMINATION OF SAMPLE SIZE

8.1 Sample Size

The primary analysis of HiLo is the comparison of rank sum scores on the hierarchical composite endpoint of time to all-cause mortality and hospitalization rate. Simulations were employed to estimate the power of the planned analysis. The assumptions for the simulation include:

- 48-month study with a 24-month enrollment period
- Annual loss to follow-up rate of 5%
- 15% annual mortality rate in the standard of care arm and a hazard ratio of 0.85 comparing the intervention arm to the standard of care arm
- 35% of participants are “non-susceptible” to hospitalizations (will not have any hospitalizations during the course of the study).
- In the susceptible population, an average of 1.8 hospitalizations per year in the standard of care arm and 1.53 hospitalizations per year in the intervention arm (15% difference).

1000 different study populations with 3800 participants were simulated under the above assumptions and analyzed using the planned analysis method. The power was estimated as the percentage of significant results out of the 1000. The results of the simulation provided an estimated power above 95%. Under these same assumptions, there would be at least 80% power to detect a treatment difference for both mortality and hospitalization when analyzed as separate endpoints. These results indicate that the trial will have sufficient power to detect a treatment effect with a population size of 3800 participants.

8.2 Statistical Design

In the primary analysis of efficacy, the intention to treat (ITT) sample will be used that includes all randomized patients.

8.3 Primary Outcome Analysis

The primary outcome for HiLo is the hierarchical composite endpoint of time to all-cause mortality and the all-cause hospitalization rate in that order. Participants will have a rank score calculated using all pairwise comparisons and subsequently tested by the method proposed by Finkelstein and Schoenfeld.[38] Participants will be hierarchically compared first on time to all-cause mortality, and compared on hospitalization rate only if the mortality comparison is not possible (e.g., both participants in an individual comparison survive throughout the follow-up period).

8.4 Major Secondary Analyses

The other main secondary outcome for HiLo is time-to-all-cause death, which will be compared between the serum phosphate treatment arms. Standard Cox regression methods will be employed to estimate the effect of phosphate treatment arm on time-to-all-cause death.

8.5 Other Planned Secondary Analyses

As an alternative approach to analyzing the secondary outcome of hospitalization, the analysis will be repeated after substituting individual participants' total number of days spent in the hospital per total length of follow-up in HiLo. Additional secondary outcomes related to nutrition are change from baseline in serum albumin, and PCR. Mixed effect models will be used for all available longitudinal observations in the ITT population to compare change from baseline in these secondary continuous variables between the two arms. Supplemental analyses will consider the "as treated" sample.

8.5.1 Interim Analyses

One interim analysis will be completed when 50% of patients have been enrolled and have at least 24 months of median follow-up time accrued to assess efficacy on the primary outcome. Throughout the trial, the mean separation in serum phosphate between the treatment groups will be continuously monitored, targeting a mean separation of at least 0.75 mg/dL and ideally, a mean separation of at least 1.0 mg/dL.

9. DATA AND SAFETY MONITORING

9.1 Data and Safety Monitoring Board

The NIDDK will convene a Data and Safety Monitoring Board (DSMB) to oversee the HiLo Trial. The DSMB will include individuals with expertise in dialysis, nutrition, clinical trials, and biostatistics. Members of the DSMB will not be involved in the conduct of the trial. The DSMB will review trial progress, data quality, blinded reports of rates of laboratory-based events in the high versus low target groups, and safety throughout the course of the trial in accordance with a Data and Safety Monitoring Board Charter. The DSMB will meet regularly and make recommendations to NIDDK about study progress, safety and trial continuation. DSMB reports will be submitted to the central Institutional Review Board (IRB).

9.2 Stopping Rules

The DSMB can make recommendations to stop the trial based on safety or other concerns. There will be no pre-specified stopping rules for efficacy or futility, however the DSMB will review the results of the interim analysis (see Section 8.5.1) with the following being considered:

- Futility of serum phosphate separation
- Futility of enrollment

10. DATA MANAGEMENT AND QUALITY CONTROL

10.1 Data Extraction and Transfer

The dialysis provider organization data warehouse teams already have processes in place to ensure that data are captured appropriately from the various originating units. DCRI will develop a module to ensure that records transmitted from the central warehouse are accurately incorporated in the study database. Pre-specified data elements will be transmitted to DCRI from the 2 dialysis provider organizations on a monthly basis. The transferred data will be cumulative – each month the information technology groups at the provider organization will generate and transfer a complete data set for overwriting the previous one. The dialysis provider IT groups will notify DCRI when each data transfer is occurring so the DCRI IT team can confirm that the transfer was successful. Standardized file formats for transmitted data will be defined during the UG3 phase in order to enable automation of extraction, transfer, and loading processes.

10.2 Data Quality Procedures

Primary responsibility for data quality will reside with the dialysis provider organization data warehouse teams. Data from individual dialysis units are regularly transmitted for inclusion into central data warehouses for each of the participating dialysis organizations. The data being extracted and transmitted from these central warehouses is expected to be an accurate representation of the source data collected at each dialysis unit.

10.3 Data Security

DCRI will use a web-based validated, electronic reporting platform. All data files being exchanged will be transferred using secure servers. During the data extraction by the dialysis providers, all personal identifiers other than dates of service and date of birth (IDs; such as medical record number, hospital account number, names) will be replaced by a unique study participant identifier. The provider organizations will manage the individual study IDs and ensure they are unique across all participants. This will be accomplished by establishing mutually exclusive ranges of values for study IDs between the two providers. In the case of relevant dates of services or procedures or dates of birth, one of the standard methods for de-identifying dates will be used, such as elapsed time from starting event versus actual starting and ending dates or age versus birth date.

For security reasons, and in compliance with regulatory guidelines, it is imperative that only the persons who own the user IDs and passwords access the system using their own unique access codes. Access codes are nontransferable. Study personnel who have not undergone training may not use the system and will not be issued user ID and password until appropriate training is completed.

11. STUDY RESPONSIBILITIES

11.1 Investigator Responsibility/Performance

By signing this protocol, DCRI and the study PI agree to be responsible for implementing and maintaining quality control and quality assurance systems to ensure that all work incidental to this protocol is conducted and data are generated, documented, and reported in compliance with the protocol; accepted standards of Good Clinical Practice (GCP); and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The principal investigator (PI) ensure that all personnel responsible for study conduct are provided current copies of the study protocol.

The PI will ensure that NIDDK is provided with copies of all institutional review board (IRB) actions regarding the study.

11.2 Training

The training of appropriate dialysis provider personnel will be the responsibility of DCRI. To ensure protocol understanding and compliance, DCRI will present a formal training session to dialysis provider personnel, to include instructions for study procedures, informed consent, and regulatory requirements.

The dialysis provider leadership are responsible for ensuring that his or her staff conduct the study according to the protocol.

11.3 Clinical Monitoring

DCRI will employ a “risk-based monitoring” (RBM) strategy that ensures human subject protection and data quality are held in the utmost regard. Data-Driven Trial Management (DDTM) is a targeted analysis–based surveillance effort designed to proactively minimize risk and improve quality.

DCRI focuses on a simple and pragmatic project management strategy based on the following quality by design principles with human subject protection and data quality and integrity as the foundation of project planning and execution: 1) the correct participants are consented and enrolled, 2) acceptable protocol adherence is met, 3) complete data is obtained, and 4) good clinical practices (GCP) are followed.

Integrated DCRI systems support our RBM strategies allowing us to closely monitor and track agreed upon key risk indicators and follow-up quickly with necessary interventions. Based on our significant data quality experience, the DCRI has established strategies and supporting tools to deliver high quality data that is critical for all trials including long term, event driven trials. By integrating the varied data sources and providing seamless reporting of trial data status, the study team is enabled to proactively manage trials.

As part of a concerted effort to follow the study in a detailed and orderly manner in accordance with established principles of GCP and applicable regulations, a DCRI team member will maintain frequent contact with point persons from the dialysis providers.

11.4 Study Documentation

Study documentation includes all electronic medical record data, the study database, sponsor-investigator correspondence, and regulatory documents (e.g., signed protocol and amendments, IRB or EC correspondence and approval, approved and signed participant consent forms, etc.).

The DCRI will prepare and maintain complete and accurate study documentation in compliance with GCP standards and applicable federal, state, and local laws, rules and regulations.

By signing the protocol, the PI acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, study documentation will be promptly and fully disclosed to NIDDK by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review, and audit at reasonable times by representatives of NIDDK or responsible government agencies as required by law.

The PI agrees to promptly take any reasonable steps that are requested by NIDDK as a result of an audit to cure deficiencies in the study documentation and the study database.

11.5 Source Documentation

For this study, the source documentation is the electronic health record (EHR) at the dialysis providers.

11.6 Protocol Deviations

Because this is a pragmatic trial intended to evaluate effectiveness of the phosphate targets under real-world conditions, protocol deviations will be limited to: 1) enrollment of individuals who do not meet eligibility criteria or provide informed consent, and 2) breach of participant confidentiality. Deviations will be reported to DCRI and to the IRB.

11.7 Protocol Changes

All modifications to the protocol will be approved by the Steering Committee and submitted to the IRB for approval prior to implementation. Changes will be incorporated into the protocol as amendments. Protocol amendments and new versions of the protocol will be distributed to all HiLo personnel and partners.

11.8 Data Transmittal and Record Retention

The clinical data generated at the dialysis facility is retained at the data warehouse of the dialysis provider organization in accordance with each organizations standard operating procedures.

The trial database at the DCRI will be maintained for a period of 2 years following completion of the study, after which it will be archived. A copy of the data will be transferred to the NIDDK Repository in accordance with NIDDK policy. Data elements that are unique to one of the dialysis provider organizations, infrequent values, or any other elements that have potential for identifying a provider organization, dialysis facility, or participant will not be included in the repository data.

The DCRI will maintain the electronic trial master file and all other study-specific documentation for at least 2 years after the formal discontinuation of this study. The DCRI will notify NIDDK prior to the destruction of any study documentation. Such documentation is subject to inspection by NIDDK as well as other regulatory agencies, as provided by law.

11.9 Study Closeout

Upon completion of the study (defined as all participants have completed all follow-up visits, and all data transfer are complete), DCRI will notify the site of closeout. The DCRI monitor will ensure that the electronic trial master files are up-to-date and complete. DCRI will then notify the IRB of the site closures. Following the analysis of the study data and writing of the final study report/manuscript, DCRI will notify the IRB of study closure.

11.10 Data Sharing

A data sharing policy will be developed by the HiLo Steering Committee. The policy will be consistent with the data sharing policy of the NIDDK. Data that can potentially be linked to a specific participating dialysis provider organization will not be transmitted to NIH data repositories. This includes all data elements that are collected by only one of the two dialysis provider organizations and data categories with counts below a specified threshold. All PHI will be removed from any shared data sets including dates, ages >89 years and any other sparsely represented values that could potentially be identifying.

12. ETHICAL CONSIDERATIONS

By signing this protocol, the principal investigator (PI) agrees to conduct the study in compliance with the protocol, DCRI standard operating procedures and/or guidelines, International Conference on Harmonisation guidelines on Good Clinical Practice (ICH E6, the principles of which have their origin in the Declaration of Helsinki), and all other applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

12.1 Role of DCRI

As the study sponsor, DCRI has overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the FDA. DCRI will ensure adherence to the sponsor's general responsibilities as listed in21 Code of Federal Regulations [CFR] 312.50 and other responsibilities including monitoring (21 CFR 312.56), and protocol amendments (21 CFR 312.30).

12.2 Informed Consent

The PI and dialysis providers have both ethical and legal responsibility to ensure that each participant being considered for inclusion in this study is given a full explanation of the study. Informed consent will be obtained from all participants before any study-related procedures are performed.

Informed consent will be documented through an electronic consent process approved by the same IRB/EC responsible for approval of this protocol. The ICF will conform to FDA regulations in 21 CFR Part 50 and to the institutional requirements for informed consent and applicable regulations.

The study details and consent process will be reviewed with the prospective study participants, and study staff will be available to answer questions regarding procedures, risks, and alternatives.

Once the appropriate essential information has been provided to the participant, and it is felt that the participant understands the implications of participating, the participant will sign and date and IRB-approved electronic consent. The participant will receive a copy of the signed ICF. The signed and dated consent will be maintained electronically as a part of the study documentation.

The participant will be informed in a timely manner through their dialysis provider if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial.

12.3 Confidentiality of Participants

Participant confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique participant identification (ID) code (ID number and participant name code) will be used that allows identification of all data reported for each participant.

Participant information collected in this study will comply with the standards for protection of privacy of individually identifiable health information as promulgated by HIPAA (Health Insurance Portability and Accountability Act) and as mandated in Title 45 CFR Parts 160 and 164. All records will be kept confidential, and the participant's name will not be

released at any time. Participant records will not be released to anyone other than DCRI or its designees and responsible regulatory authorities when requested. In all cases, caution will be exercised to assure the data are treated confidentially and that the participant's privacy is guaranteed.

12.4 Authorization for Use and Disclosure of Protected Health Information (HIPAA)

An authorization for use and disclosure of protected health information (PHI) under the HIPAA Privacy Rule (45 CFR § 164.102 *et seq*) will be obtained from every trial participant before or at the time of enrollment. It will be presented to, and signed by, the participant at the same time or prior to the electronic consent form. The dialysis provider is responsible for obtaining participants' authorizations and signatures and for explaining the elements of the HIPAA authorization form, if necessary.

HIPAA authorization will be a separate form from the electronic consent. A signed copy of the HIPAA document will be filed in the participant's medical records. Participants will be given the other signed duplicate for their personal records.

The HIPAA authorization form will contain all elements required under the HIPAA Privacy Rule. By law, IRB approval of the HIPAA authorization form for use in this study is not required, and no such approval will be sought or requested.

The dialysis provider will promptly inform DCRI of any restrictions on the use or disclosure of PHI of any participant to which the dialysis provider has agreed under the Privacy Rule. The dialysis provider will also promptly inform DCRI of any written revocation of any participant's HIPAA authorization.

12.5 Institutional Review Board Review

The appropriate IRB/EC must approve the protocol and informed consent documents, agree to monitor the conduct of the study, and agree to review study progress periodically, at intervals not to exceed 1 year. DCRI will ensure that the IRB/EC has approved the study *before* the study may begin.

In addition, the investigator must provide the following documentation to NIDDK:

1. IRB/EC annual re-approval of the protocol, per current Title 21 CFR 312.66 regulations and 1997 International Conference on Harmonisation guidelines.

2. IRB/EC approval of revisions to the informed consent documents or any amendments to the protocol. Any revisions to the protocol that may increase participant risk exposure must be approved before implementation. Administrative changes (such as a change in address or phone number) must be sent to IRBs/ECs but do not require their approval.

The Duke University Institutional Review Board will serve as the IRB of record for the HiLo Trial and provide regulatory oversight for the trial activities at the dialysis facilities and DCRI. Authorization agreements between the Duke IRB and the dialysis provider organizations will be established.

12.6 Financial Disclosure/ Conflict of Interest

Financial and other competing interests for the investigators are documented, provided to the IRB, updated annually, and maintained at DCRI.

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