

# The HiLo Trial: Progress

NIH Health Care Systems Research Collaboratory  
Steering Committee Meeting  
May 1, 2019

# Study Background: Building an evidence-based phosphate (P) target

## End Stage Renal Disease (ESRD)

- Affects ~500,000 patients in the U.S. alone
- Hospitalization: Average ~2 per patients per year
- Mortality: 15–20% per year
- Driven primarily by high risk of cardiovascular disease (CVD)
- Established CVD treatments don't work well in ESRD

## Hyperphosphatemia

- Very common complication in ESRD
- Lab studies suggest that high P might cause CVD – arterial calcification & cardiac hypertrophy
- In patients, high P is associated with CVD & death

Our current opinion-based approach tells us to lower P to <5.5 mg/dl using P binders and a low P diet.

**But...there is no proof in patients that lowering high phosphate helps!**

# We may (or may not) be managing hyperP correctly



## We have no randomized trials to inform the best way to treat hyperP

- No trials tested how low or close to normal we should try to push P levels.
- We know from trials that P binders can lower serum P levels – that we can “treat the numbers.”
- But no trials have tested if treating the numbers improves outcomes and what matters most to patients, such as hospitalizations, death, and quality of life.

## Without randomized trials, we don't know:

- The ideal serum phosphate target: should it be 4, 5, 6, or 7 mg/dl?
- If the way we currently manage P levels helps improve only “the numbers” or does it help improve outcomes and what matters most to patients.
- If our current opinion-based approach might actually make things worse...

# Despite our best intentions to help patients, might we be doing things wrong?

**By trying to achieve unnecessarily low P targets, we might be increasing risks by:**

- Giving too much calcium, lanthanum or iron in P binders.
- Worsening GI side effects and nutritional status by increased use of P binders.
- Worsening quality of life by adding large doses of P binders to an already high pill usage.
- Subconsciously worsening other aspects of care by labeling individual patients as “non-compliant.”

**We may be introducing these potential harmful risks because we have no evidence from trials**

**We need to learn from the past:**

- Correcting anemia in ESRD was thought to be beneficial.
- When the trials were finally done, we learned that treating anemia was not helpful!
- Use of aluminum based P binders was thought to be effective and safe until we learned about their toxicity.

# Goals of HiLo: To determine how to best manage hyperphosphatemia in patients receiving hemodialysis



**Primary:** HiLo will test which of two P management strategies will confer lower rates of all-cause mortality and hospitalization in patients with ESRD undergoing hemodialysis:

- Lo: Usual target P of <5.5 mg/dl; or
- Hi: Less strict target P of 6–7 mg/dl

**Secondary:** HiLo will test which P management strategy will enhance markers of diet and nutrition, and improve quality of life.

# Dietitians will lead the HiLo treatment strategies



## Low serum phosphate target

- No change from current treatment
- Goal: titrate serum phosphate to 5.0 mg/dl
- Aim for and anticipate 4.8–5.2 mg/dl

## Higher serum phosphate

- This is the new approach to be tested in comparison to the current standard
- Goal: titrate serum phosphate to 6–7 mg/dl
- Anticipate 6.5–6.8 mg/dl

**Specific binder choices, diet recommendations? Local care teams will treat based on their preferences & practice.**

# Do We Need Informed Consent?

## Regulatory Criteria for Waiving Consent

- 1. The research involves no more than minimal risk to the subjects**
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects
3. The research could not practicably be carried out without the waiver or alteration
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation

# Informed Consent Approach



- Electronic consent form on tablets at the dialysis facilities
- Informed consent video on tablets – covers same information as the electronic consent form, but in a conversational style
- Helpline to connect participants with nephrologists at Duke who can answer questions about the study

## Benefits of electronic consent approach:

- Reduce the burden on dialysis facility staff
- Empower patients
- Innovate in ESRD trial design



# Original primary outcome

## All-cause hospitalization

- Critical to all stakeholders: patients, providers, payers
- For many patients, avoiding hospitalization is more important than prolonging survival
- Hyperphosphatemia contributes to complications → hospitalization
- Accepted endpoint in other areas (e.g., heart failure)
- Dialysis providers: near 100% complete data about hospitalizations
- Collecting real-time hospitalization data eliminates adjudication
- Continuous variable desirable statistically

## Limitations:

- Zero-inflated distribution of hospitalization: effect on sample size calculation and ICC
- Death before hospitalization: worst outcome not “counted”

# Revised Primary Outcome

- Hierarchical composite outcome of all-cause mortality (time-to-event) and all-cause hospitalization rate (# events per person-years)
- We will compare two serum phosphate arms using the Generalization of the Gehan Wilcoxon (GGW) test proposed by Finkelstein and Schoenfeld
- Enables simultaneous testing of mortality, hospitalizations
- Prioritizes mortality
- Based on 5000 trial simulations: Original sample size of 4400 enables HiLo to retain >80% power even if the within-cluster intra-class correlation (ICC) is 5-fold higher than initially estimated.

# Communication and Training Materials



- Talking points for dietitians and facility staff
- Training videos for dietitians
  - Will also be hosting webinars and recording talks w/ dialysis centers
- eConsent
  - Video consent with patient ambassador
  - Information videos about phosphate and the importance of research
- Public website in validation testing
  - Areas for community partners, kidney professionals, study participants and their families
  - Videos, educational materials, links to resources and other community materials

# Phosphate monitoring tool

- Goal: maintain  $\geq 1.0$  mg/dl separation in serum P between arms
- Plan: monthly phosphate monitoring:
  - Overall in each treatment arm
  - Overall within each randomized dialysis facility, which corresponds to each individual participating dietitian; and
  - Within each individual study participant
- Can readily calculate separation in the serum phosphate curves by dialysis organization, facility size, and geographic region

# Phosphate Monitoring

Target phosphate	Hi >6.5	Lo <5.5	Points
In range	>6.5	<5.5	2
Near range	6.0 – 6.5	5.5 – 5.9	1
Out of range	<6.0	>5.9	0

Patients can score 0 (all out of range) to 6 (all in range) over previous 3 months.

Individual patient scoring:

- **Scores of 4-6: sufficiently in range**
- **Scores of 3: near range**
- **Scores of 0-2: out of range**

Facility level scoring:

- **≥75% of patients scores 4-6**
- 50-74.9% of patients scores 4-6
- **<50% of patients score 4-6**

# Patient Advisory Group



- Enlisted the help of the American Association of Kidney Patients (AAKP) to invite 7 patients to participate as ambassadors
- Ambassadors have provided feedback on the protocol/design, and the informed consent.
- Will review all other patient-facing materials
- Patients may be concerned with health outcomes for participating in the Hi arm

# Status Updates

- Received IRB approval
- Submitting amendment for changes to outcomes
- DSMB requests
  - Statistical Analysis Plan
  - Reporting on separation and facility performance
  - Strategy for managing under-enrollment
  - Strategy for minimizing impact of hospitalizations on phosphorus levels
- Transition Report: June 1, 2019

# Data Sharing

- NIDDK Repository – private archive managed by the NIDDK
- Patient level: de-identified
- Facility level: de-identified
- Provider level: de-identified