The HiLo Pragmatic Clinical Trial

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HILO: PRAGMATIC TRIAL OF HIGHER VS LOWER SERUM PHOSPHATE TARGETS IN PATIENTS UNDERGOING HEMODIALYSIS

Funded under RFA-RM-16-019: NIH Health Care Systems Research Collaboratory - Demonstration Projects for Pragmatic Clinical Trials (UG3/UH3DK118748)
Building an evidence-based phosphate 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
- Ubiquitous 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

Based on preclinical & observational data, opinion-based guidelines: keep P <5.5 mg/dl using binders, diet

But…there is no proof in patients that lowering high phosphate helps!
We may (or may not) be managing phosphate correctly

No RCTs inform the best way to treat hyperphosphatemia
  • Phosphate binders can lower serum phosphate – we can “treat the numbers.”
  • But no trials tested if reducing serum phosphate improves outcomes: hospitalizations & death

Without randomized trials, we don’t know:
  • The ideal serum phosphate target: should it be 4, 5, 6, or 7 mg/dl?
  • If current approach to phosphate phosphate management improves outcomes

Might we actually be making things worse?
  • Giving too much calcium, lanthanum or iron binders
  • Worsening GI side effects and nutritional status
  • Worsening quality of life: pill burden, costs
  • Subconsciously worsening other aspects of care: labeling patients as “non-compliant”

We may be introducing potential risks because we have no evidence from trials!
Equipoise to conduct HiLo

Hyperphosphatemia associates with CVD and mortality in observational studies

Hyperphosphatemia associates with arterial calcification and stiffness

Hyperphosphatemia worsens secondary hyperparathyroidism

Hyperphosphatemia worsens secondary excess of fibroblast growth factor 23

Many of these factors are linked to left ventricular hypertrophy, heart failure, & death

HiLo

Association of hyperphosphatemia with poor outcomes does not prove causality

Some phosphate binders may increase arterial calcification

Binders are cumbersome, costly, have many side effects, and may reduce quality of life

Onerous dietary restrictions, binder side effects may exacerbate malnutrition, which is a risk factor for death

Patients that do not reach phosphate goals may be stigmatized as "non-compliant"

We owe it to our patients to finally perform a randomized clinical trial that tests which phosphate treatment target provides the best clinical outcomes for patients.

HiLo Trial
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 ≥6.5 mg/dl

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

**Design:** Pragmatic, multicenter, n=4400, clinical outcomes trial

**Pragmatic features:** Cluster randomization; broad entry criteria; eConsent; no traditional on-site study staff; remote site monitoring; reliance on EHR with no CRFs; no AE reporting; outcomes based on EHR with no adjudication;
HiLo is a new kind of trial: A pragmatic trial

- Based in “real world” practice, collects “real world” data
- “Real world” answers to important “real world” questions
- Liberal eligibility criteria: Aim to be all-inclusive
- Minimal on-site study staff
- Clinical caregivers implement interventions that are woven into their day-to-day practice
- Tests standard treatments already used in practice
- Leverage EHRs to eliminate case report forms
- Leverage EHRs to collect adverse event data
- Leverage EHRs to collect outcomes data
- Eliminate outcome adjudication
- Ensure that trial results:
  - Generalize to all patients who undergo hemodialysis
  - Can be easily integrated into practice when the trial ends
  - Provide benefits of the new knowledge to all patients!


**HD is ideal setting for pragmatic trials:** accessible study population, frequent clinical encounters, granular & uniform data collection via EHR, many unanswered questions about major aspects of dialysis care
Cluster randomization

- Dialysis facilities are randomized instead of individual patients
- All patients in a unit who consent are assigned to one treatment or the other
- Individual patients provide informed consent
- Individual patient results are analyzed while accounting for the “clusters”
- Why cluster randomize?
  - Simplify operational logistics
  - Easier for patients, care teams
  - Prevent “blending” of Hi and Lo arms
Eligibility criteria

Dialysis Facility:
• Director, facility manager, dietitians willing to adopt either Hi or Lo target.
• Facility managers willing to allow dietitians to participate.
• Facility dietitians willing to discuss the trial with potential participants, implement the trial, and attend start-up teleconference(s).

Individual Patient Criteria: All welcome!
• Facilitate enrollment & maximize relevance of results to future patients.
• Adults >18 years of age treated with standard in-center, 3x weekly HD.
• Willing & able to provide written informed consent.
Informed consent

Informed consent needed: “Research involves more than minimal risk”

- We use “eConsent:"
  - Relatively new pragmatic approach to clinical trial design
  - Informed consent obtained electronically by smart phone, tablet or computer
  - HiLo website will offer both written and video-based consent materials
  - Dialysis facility staff will be asked to refer patients to the HiLo website
  - DCC also maintains a study pager/hotline through which patients can ask questions, seek more information from study nephrologists

45 CFR Part 46 (“The Common Rule”)
Patients are asked to:

- Learn about the study through the website’s patient videos
- View the electronic informed consent video
- Provide consent if they wish to participate
- Share their medical information with the research team
- Follow their care team’s guidance to achieve, maintain P target
- Continue their usual dialysis care without change
Patients are **NOT** asked to:

- Undergo any extra study visits
- Undergo any extra blood tests
- Undergo any other new tests
- Fill out any other paperwork besides the consent & HIPPA forms
- Change any other aspect of their treatment other than phosphate management
Dietitians are critical to success

• “On-the-ground” caregivers who implement HiLo interventions
• Employed by dialysis organizations & present in all dialysis units
• See all patients at least monthly
• Existing rapport with patients will facilitate adherence
• Among the most motivated caregivers on dialysis teams
• Part of primary decision making team for titration of P-related Rx
• Working with caregivers in the clinic to implement trial = pragmatic, “real-world” data
Dietitians are asked to:

- Commit to adhere to the phosphate target
- Offer patients participation in the study
- Contact study team with any questions or concerns
- Deliver care in the same manner you otherwise would
- Watch 2 short training videos: ~20 minutes total
- Review study materials and attend a virtual site activation meeting to ensure understanding of how the study will be conducted at their unit
  - Protocol Summary
  - Informed Consent Document
  - Dietitian Talking Points
  - Frequently Asked Questions guide
- Review monthly site monitoring reports
- Attend office hours when feasible
Dietitians are **NOT** asked to:

- Change how they deliver care
- Fill out any additional paperwork beyond the screening tracker
Recruitment process & targets

- Activating sites in phases:
  - 8 sites initially to gain initial experience, learn best practices
  - 20-30 at a time as study progresses and workflows are refined
- Enrollment period will be brief: 2 – 6 months per facility
  - Facilities are asked to approach ~10 eligible patients per week until all eligible patients have been approached
- All recruitment materials are preloaded on iPads shipped to facilities
- To approach eligible patients, dietitians present the iPad
- Once patients consent, EHR data transfers are activated
Effects of COVID

- 1st site activated, 1st patient enrolled March 11th
  - Enrolled five patients in first week
- All units paused activation/enrollment activities March 18th
- Dietitians were charged with executing COVID safety protocols
  - “All hands on deck”
  - Entrance screenings, temperature checks, increased sanitation, sterilization practices, etc.
  - Safety protocols accounted for 50-80% of a dietitians daily effort
- Two units became COVID Cohorts
  - Vance County (Lo): COVID Negative Unit
  - Kerr Lake (Lo): COVID Positive Unit
Other potential effects of COVID

• Recruitment challenges as HD staff is diverted
• Fear of outbreaks in ESRD units
• Effects on ICC in a cluster-randomized setting
• Effects of “cohorting” patients in COVID+ and COVID- units
• Solutions:
  – More time to activate sites and recruit
  – More facilities with smaller n per facility
  – Ascertainment of COVID status, hospitalizations, deaths for 2’ analyses
# Current enrollment – as of 10/02/2020

## Hi Arm

<table>
<thead>
<tr>
<th>Site</th>
<th>Total N</th>
<th>Ineligible (%)</th>
<th>Approached (%)</th>
<th>Consented (%)</th>
<th>Declined (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5034-Southpoint</td>
<td>80</td>
<td>24 (30)</td>
<td>56 (100)</td>
<td>28 (50)</td>
<td>25 (44.6)</td>
</tr>
<tr>
<td>3503-Durham W.</td>
<td>83</td>
<td>20 (24.1)</td>
<td>63 (100)</td>
<td>41 (65.1)</td>
<td>21 (33.3)</td>
</tr>
<tr>
<td>5540-Bull City</td>
<td>63</td>
<td>15 (23.8)</td>
<td>20 (41.7)</td>
<td>7 (35)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>3024-Durham</td>
<td>95</td>
<td>22 (23.2)</td>
<td>29 (39.7)</td>
<td>22 (75.9)</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>321</strong></td>
<td><strong>81 (25.2)</strong></td>
<td><strong>168 (70)</strong></td>
<td><strong>98 (58.3)</strong></td>
<td><strong>58 (34.5)</strong></td>
</tr>
</tbody>
</table>

## Lo Arm

<table>
<thead>
<tr>
<th>Site</th>
<th>Total N</th>
<th>Ineligible (%)</th>
<th>Approached (%)</th>
<th>Consented (%)</th>
<th>Declined (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*3906-Vance Co.</td>
<td>105</td>
<td>22 (20.9)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>994-Burlington</td>
<td>70</td>
<td>12 (17.1)</td>
<td>23 (39.7)</td>
<td>20 (87)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>*11186-Kerr Lake</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5144-N. Burlington</td>
<td>58</td>
<td>16 (27.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>263</strong></td>
<td><strong>50 (19)</strong></td>
<td><strong>23 (10.8)</strong></td>
<td><strong>20 (87)</strong></td>
<td><strong>3 (13)</strong></td>
</tr>
</tbody>
</table>

* - Enrollment currently paused due to COVID

Overall consent rate for units that have completed enrollment (consented/total census): 42.3%
Based on this rate, to recruit n=4400, would need to recruit sites with total census ~ 10,500
Data collection: All captured from EHR

- Demographic and comorbidity data (age, sex, race, etc.)
- Dialysis treatment data (Kt/V, PCR, etc.)
- Laboratory Data (phosphate, calcium, PTH, iron, anemia, etc.)
- Hospitalizations data (component of primary outcome)
- Medications (phosphate binders, vitamin D, sensipar, etc.)
- Status Changes:
  - Transfers, transplant, withdrawal
  - Death (component of primary outcome)

Data is collected automatically via IT “bridge” built by DCRI
DCRI continuously monitors serum phosphate and provides monthly site monitoring reports to all sites
Intervention fidelity: Phosphate monitoring

- **HiLo goal:** achieve a mean difference in serum P between arms of \( \geq 1 \) mg/dl
- Monthly electronic health record data transfers to remotely monitor serum phosphate:
  1. Overall
  2. By facility
  3. By individual patient
- Educational tools for dieticians & patients
  - Co-developed with Patient Advisory Group
  - FAQs, Dietician Strategies for Patient Engagement

Site Monitoring Report – Enrollment

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Southpoint Dialysis Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis Provider</td>
<td>DAVITA</td>
</tr>
<tr>
<td>Phosphate Target</td>
<td>&gt;=6.5 mg/dl</td>
</tr>
<tr>
<td>Site Size</td>
<td>75</td>
</tr>
<tr>
<td>Approachable Patients</td>
<td>53</td>
</tr>
<tr>
<td>Weeks from Site Start</td>
<td>24</td>
</tr>
</tbody>
</table>

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**Average Weekly Patients Approached Target Rating**

- 7.0
- 10.0
- 0.0
- 2.2
- 15.0

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**Percentage of Expected**

- 70.7% of Expected Approached
- 56.3% of Expected Enrolled
- 52.8% of Expected Continuing
- 54.1% of Expected Continuing
- 100.0% of Expected Continuing
- 100.0% of Expected Continuing

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**Metric**

- **Expected Patients Approached**: 75 (Site) 247 (Study-wide)
- **Actual Patients Approached**: 53 (Site) 135 (Study-wide)
- **Patients Consented and Eligible**: 28 (Site) 73 (Study-wide)
- **Patients Consented but not Eligible**: 0 (Site) 0 (Study-wide)
- **Patients Declined**: 25 (Site) 62 (Study-wide)
- **Patients in Progress**: 0 (Site) 0 (Study-wide)
- **Patients Active on Study**: 28 (Site) 73 (Study-wide)
Site Monitoring Report – Phosphate

Mean Phosphate by Month

Baseline Average: 6.5 mg/dl

Proportion of Patients in Range

In Range >=6.5 mg/dl

Near Range 5.5 - <6.5 mg/dl

Out of Range <5.5 mg/dl

Subject number

5034-006
5034-010
5034-012
5034-013
5034-014
5034-019
5034-021
5034-027
5034-032
5034-038
5034-040

Subject number

5034-060
5034-062
5034-075
5034-015
5034-026
5034-023
5034-037
5034-055
5034-064
5034-072
5034-079
5034-080
Preliminary data: Treatment arm separation

The mean and standard error of participant’s mean phosphate level using all phosphate levels collected within each study month are presented, e.g. all phosphate levels collected from day 1 (enrollment date) to day 30 from a participant were used to get the participant’s mean phosphate level for study month 1, and then the mean phosphate levels from all participants from one treatment arm were used to calculate the mean phosphate level and standard error for the arm.

Data as of August 31, 2020

\(^a\)The mean and standard error of participant’s mean phosphate level using all phosphate levels collected within each study month are presented, e.g. all phosphate levels collected from day 1 (enrollment date) to day 30 from a participant were used to get the participant’s mean phosphate level for study month 1, and then the mean phosphate levels from all participants from one treatment arm were used to calculate the mean phosphate level and standard error for the arm.
Proportion of patients in/near/out of range – Hi Arm

By calendar month

Data as of August 31, 2020
Primary outcome: Hierarchical composite of all-cause mortality & all-cause hospitalization

- Important to all stakeholders: patients, families, clinicians, dialysis providers, payers/Medicare
- For many patients, avoiding hospitalization/enhancing QOL is main goal
- Hyperphosphatemia thought to contribute to multiple complications that result in hospitalization and death
- Hospitalization: accepted endpoint in other areas
- Dialysis EHR: Complete data on dates of hospitalizations, deaths
- Collecting real-time EHR data: no event adjudication = pragmatic
Analytic strategy

- We will use Finkelstein & Schoenfeld method to calculate hierarchical composite score for individual patients by:
  - 1st: Compare time-to-death: Winner assigned ‘+1’ and loser assigned ‘−1’
  - 2nd: If tied on time-to-death, then compare hospitalization rate: Winner assigned ‘+1’, loser assigned ‘−1’, and tie assigned ‘0’
- After all pairwise comparisons, calculate each patient’s score: net number of wins minus losses
- To account for cluster design, we will use Wilcoxon Rank Sum Test for cluster data (Rosner 2003) to compare overall scores between Hi vs Lo arms
- For clinical interpretation, we will also report time-to-death and hospitalization rates separately using cluster-adjusted methods
Power analysis using simulation

- Synthetic study populations based on assumptions for all-cause mortality and zero-inflated hospitalizations
- Create hierarchical composite scores using Finkelstein and Schoenfeld method and compare Hi vs Lo treatment arms using Wilcoxon Rank Sum Test for cluster data and Mixed model to estimate power
- Completed 5,000 iterations for each set of simulations

### Model Assumptions

<table>
<thead>
<tr>
<th>Assumption</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time of 2-4 years to simulate time to administrative censoring</td>
<td></td>
</tr>
<tr>
<td>Annual loss to follow-up rate of 5%</td>
<td></td>
</tr>
<tr>
<td>Annual mortality rates of 15% ('Hi' arm) and 12.8% ('Lo' arm); equivalent to a clinically relevant mortality HR of 0.85</td>
<td></td>
</tr>
<tr>
<td>Annual hospitalization rate of 2.0 ('Hi' arm) and 1.89 ('Lo' arm) per patient; equivalent to a conservative 5.5% difference</td>
<td></td>
</tr>
<tr>
<td>35% of study population without a single hospitalization</td>
<td></td>
</tr>
<tr>
<td>Assume an ICC of 0.001 for mortality and 0.003 for hospitalization</td>
<td></td>
</tr>
</tbody>
</table>

### Simulation Results

| Simulation 1: 80 clusters with 55 patients each for 5000 iterations         | Mixed Model 86.3% Power | Wilcoxon Rank Sum 87.0% Power |
| Simulation 2: 120 clusters with 36 patients each for 5000 iterations        | Mixed Model 85.0% Power  | Wilcoxon Rank Sum 85.8% Power |

Safety

- An independent Data Safety Monitoring Board (DSMB) monitors the trial
- Given pragmatic design and primary outcome, we do not collect information on AEs as in traditional RCTs
- We monitor routine serum phosphate, calcium, PTH
- Since individual patients’ care is ultimate responsibility of primary teams, they may, at their discretion, reduce or temporarily discontinue phosphate binders as needed for:
  - Hypercalcemia
  - GI symptoms
  - Hypophosphatemia
  - Patient preference
Patient Advisory Group: HiLo Ambassadors

- Coordinated with the AAKP: 6 members of Patient Advisory Group
- We sought input on:
  - Informed consent document and process
  - Educational materials that help people better understand the study
  - Potentials barriers & how to overcome
  - Strategies to help patients participate and stay in trial
- Materials reviewed: Protocol, Informed consent form, eConsent script, informational videos, FAQs, flyer, website content
- How to overcome challenges to make study participation and visits easier
- Strategies or motivations to help patients successfully participate and stay in trial
What is the best blood level of phosphate for people with kidney failure on dialysis?

What is HILO?

HiLo is a clinical research study on how best to manage blood phosphate levels in patients on dialysis. Researchers will compare how participants feel, how often they are hospitalized, and how long they live based on the level of phosphate in their blood.

Why HILO?
What does success look like?

Any **clear, proven** answer to the question!

If we **prove** that the higher target is better = success

If we **prove** that the lower target is better = success

If we can’t prove which target is better = **failure**
Questions