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

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But...there is no proof that lowering high phosphate in individual patients helps improve their outcomes!

Based on preclinical & observational data, opinion-based guidelines: Maintain P <5.5 mg/dl using binders, diet
Goal of HiLo: Generate clinical trial-grade evidence for management of hyperphosphatemia in hemodialysis

**Goal:** Compare two phosphate targets in patients with ESRD on hemodialysis:
- Lo: Usual target phosphate/standard of care of <5.5 mg/dl; or
- Hi: Less strict target phosphate of ≥6.5 mg/dl

**Primary outcome:** Hierarchical composite of:
1. All-cause mortality followed by
2. All-cause hospitalization

**Initial design:** Pragmatic, multicenter, cluster randomized, n=4400

**Informed consent:** Required – more than minimal risk

**Other pragmatic features:** eConsent; no traditional on-site study staff – clinical dietitians support recruitment; all baseline, phosphate monitoring, outcome and safety data via collected EHR
PICOTS Considerations

• Population: ESRD; unique, available, frequent interactions
• Intervention: 2 therapeutic targets on biochemical parameter; how to get to target → individual/local choice
• Comparison: defined comparison of outcomes between 2 groups
• Outcomes: Hierarchical of (1) all-cause mortality, (2) all-cause hospitalization
• Timing: Prevalent dialysis, at least 3 months vintage
• Setting: Dialysis units across the country
HD: Ideal Setting for Pragmatic Trials

- Highly accessible study population
- Frequent & regular clinical encounters
- Highly granular & uniform data collection as part of routine clinical care
- Infrastructure of dialysis provider organizations allows for:
  - Centralized implementation
  - Inclusion of large number of facilities with broad geographic distribution
- Many unanswered questions about fundamental aspects of dialysis care
Dietitians are critical to HiLo’s success

Dietitians: “On-the-ground” caregivers who will work with other care providers to implement HiLo interventions.

- Present in all dialysis units
- See all patients at least monthly
- Among the most motivated caregivers on dialysis teams
- Are part of a primary decision making team for titration of P-related management.
Informed Consent

Informed Consent needed: the “research involves more than minimal risk”

• We will use “eConsent:”
  • A 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

For additional questions from facility staff or patients, the Data Coordinating Center will maintain a study pager/hotline through which more information can be obtained from nephrologists helping to lead the study

45 CFR Part 46 (“The Common Rule”)
Data Collection: All captured from EHR

- Demographic and comorbidity data at study entry and start of HD
- Dialysis treatment data
- Health-Related Quality of Life
- Routine laboratory Data
- Hospitalizations
- Medications
- Status Changes: transfer, transplant, switch to PD, withdrawal, death

Duke Clinical Research Institute continuously monitors serum phosphate and provides monthly feedback to facilities on how their patients are doing adhering to their assigned P targets.
Primary outcome: All-cause mortality & hospitalization

- All-cause mortality is a gold standard outcome in clinical trials.
- Hospitalization is also extremely important to all stakeholders: patients, families, clinicians, dialysis providers, payers/Medicare.
- HyperP contributes to multiple complications that result in hospitalization.
- Hospitalization is an accepted endpoint in other therapeutic areas.
- Will be collecting real-time outcomes using EHR data.
Wins, losses and ties:

1. Red wins for later death
2. Red wins for later death despite more hospitalizations
3. Tie on death, hospitalizations despite subsequent death
4. Red wins for fewer hospitalizations after tie on death
5. Tie on death, hospitalizations
6. Blue wins for fewer hospitalizations after tie on death
7. Tie on death, hospitalizations despite more later hospitalizations
8. Red wins for fewer hospitalizations after tie on death
9. Blue wins for fewer hospitalizations after tie on death

Longitudinal follow-up time
At 10% enrollment...

- Imbalance in baseline characteristics between Hi and Lo arms

<table>
<thead>
<tr>
<th></th>
<th>Hi N=255</th>
<th>Lo N=179</th>
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<tbody>
<tr>
<td>Mean age, years</td>
<td>57.5 ± 13.8</td>
<td>61.6 ± 13.9</td>
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<tr>
<td>Mean phosphate, mg/dl</td>
<td>6.6 ± 2.2</td>
<td>5.8 ± 1.7</td>
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</tbody>
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- Imbalance in enrollment rates between arms

<table>
<thead>
<tr>
<th>Arm</th>
<th>% Ineligible</th>
<th>Approached</th>
<th>Consented</th>
<th>Consent Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hi</td>
<td>31.2%</td>
<td>625</td>
<td>237</td>
<td>37.9%</td>
</tr>
<tr>
<td>Lo</td>
<td>21.2%</td>
<td>502</td>
<td>318</td>
<td>63.3%</td>
</tr>
</tbody>
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- Pivot to individual level randomization