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

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State of the art in ESRD

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

But...there is no proof that lowering high phosphate in individual patients helps improve their outcomes!
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
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>
</tr>
</thead>
<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>
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Potential Sources of Imbalances at the 10% Point

1. Cluster effect
   - Result of small number of clusters included to date
   - Differential population demographics within active clusters

2. Subgroup of severe outliers driving differences

3. Post randomization consent for non-blinded intervention:
   - Introducing biased enrollment
   - Based on treatment assignment and/or prior phosphate control
   - Could occur at the levels of patients and/or dietitians
   - Could occur subconsciously and/or actively
Considerations to Promote Balance

• Maintain course:
  – Leverage EHR for root cause analysis to compare enrolled to all eligible
  – Activate more sites
  – Develop additional dietitian- and patient-facing education strategies

• Add upper phosphate entry point to exclude severe upper outliers

• Consent entire units before randomizing them
  – Would risk substantial attrition between enrollment and randomization
  – Could shift from biased enrollment $\rightarrow$ biased withdrawal

• Pivot to individual level randomization
QUESTIONS AND DISCUSSION