HiLo

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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)

Duke Clinical Research Institute

DaVita Clinical Research

NIH National Institute of Diabetes and Digestive and Kidney Diseases

HEALTH UNIVERSITY OF UTAH

State of the art in ESRD

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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

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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…

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- Imbalance in baseline characteristics between Hi and Lo arms

	Hi N=255	Lo N=179
Mean age, years	57.5 ± 13.8	61.6 ± 13.9
Mean phosphate, mg/dl	6.6 ± 2.2	5.8 ± 1.7

- Imbalance in enrollment rates between arms

Arm	% Ineligible	Approached	Consented	Consent Rate
Hi	31.2%	625	237	37.9%
Lo	21.2%	502	318	63.3%

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 → biased withdrawal
- Pivot to individual level randomization

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QUESTIONS AND DISCUSSION