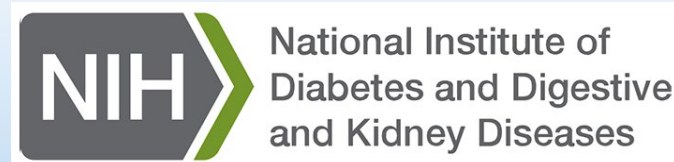


HILO: PRAGMATIC TRIAL OF HIGHER VS LOWER SERUM PHOSPHATE TARGETS IN PATIENTS UNDERGOING HEMODIALYSIS

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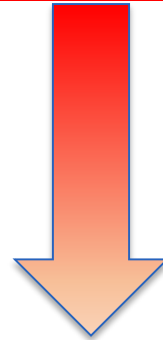


Duke Clinical Research Institute



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

	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

QUESTIONS AND DISCUSSION