HiLo
A Pragmatic Trial Sponsored by the National Institutes of Health

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

Myles Wolf, MD, MMSc
Charles Johnson, MD, Professor of Medicine
Chief, Division of Nephrology
Professor, Population Health Sciences
Duke University School of Medicine

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

HiLo
A Pragmatic Trial Sponsored by the National Institutes of Health

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

HiLo
A Pragmatic Trial Sponsored by the National Institutes of Health

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

A Pragmatic Trial Sponsored by the National Institutes of Health

- 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

HiLo
A Pragmatic Trial Sponsored by the National Institutes of Health

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

A Pragmatic Trial Sponsored by the National Institutes of Health

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.

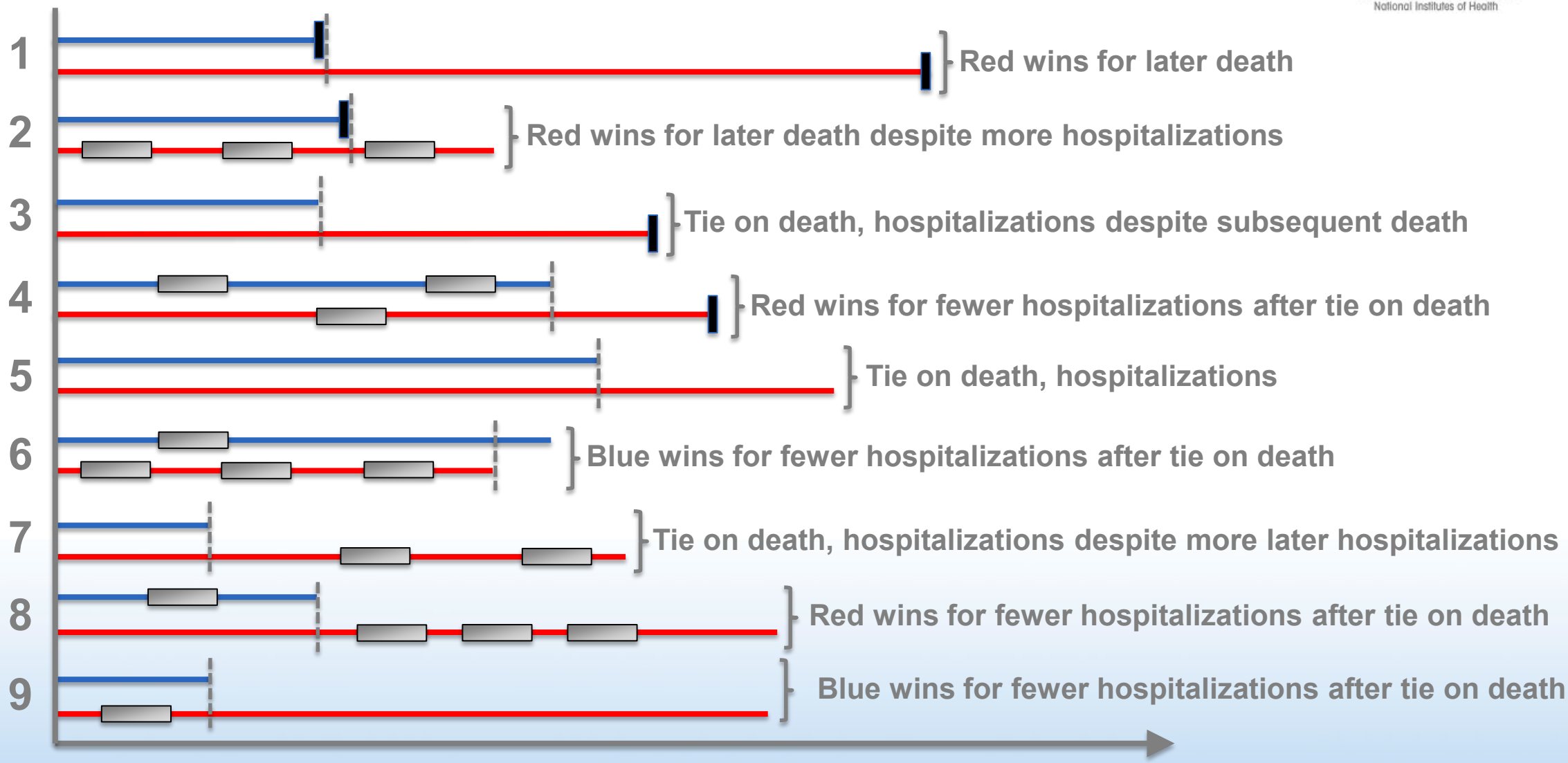
Primary outcome: All-cause mortality & hospitalization

HiLo
A Pragmatic Trial Sponsored by the National Institutes of Health

- 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: Death Hospitalization

HiLo
A Pragmatic Trial Sponsored by the National Institutes of Health



At 10% enrollment…

HiLo
A Pragmatic Trial Sponsored by the National Institutes of Health

- 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%

- Pivot to individual level randomization