The HiLo Trial
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ESRD: Trials needed & an ideal setting for pragmatism

• ESRD population is desperately in need of clinical innovation
  • High event rates
  • Few, if any therapies proven by RCT

• Highly accessible study population with 3 x weekly clinical encounters

• Highly granular, regular, uniform data collected in routine clinical care → EHR
  • Remote biochemical monitoring
  • Pragmatic ascertainment of outcomes, covariates

• Centralized infrastructure of dialysis provider organizations allows for
  • Centralized implementation
  • Inclusion of large number of facilities with broad geographic distribution
  • Facility-level randomization
Hypotheses

1. **Primary:** Compared to the current standard approach of targeting serum phosphate levels of $<5.0 \text{ mg/dl}$, less stringent control of serum phosphate to target levels of $6–7 \text{ mg/dl}$ will yield non-inferior rates of all-cause hospitalization among patients with ESRD undergoing hemodialysis.

2. **Main secondary:** Compared to strict phosphate control, less stringent control will reduce risk of all-cause mortality, enhance markers of diet and nutrition, and improve quality of life.
Overview of study design: An ‘A’ vs. ‘B’ trial in dialysis

Pragmatic, multicenter, cluster-randomized, open-label, non-inferiority, outcomes trial

• Compare effects of two different phosphate management strategies
  • Liberal P control, targeting 6–7 mg/dl, or
  • Strict P control, targeting <5.0 mg/dl
  • Facility-level cluster randomization: simplify trial execution, prevent within-facility “bleeding” of intervention arms, support remote study monitoring

• N = ~4400 patients being treated with hemodialysis at >100 facilities

• Partners
  1. Large national for-profit dialysis corporation: DaVita, Inc.
  3. Small regional academic program: University of Utah

• Build on lessons learned from the TIME trial
Outcomes

1. Primary
   - All-cause hospitalization rate: total counts per person-years of follow-up (continuous)

2. Secondary
   - All-cause mortality, time-to-event
   - Total inpatient hospital days per person-years of follow-up
   - Cause-specific hospitalizations in Medicare beneficiaries based on merging clinical data from HiLo with claims data from the CMS Virtual Research Data Center as in PROVEN
   - Diet & nutrition: serum albumin, protein catabolic rate (PCR)
   - Quality of life: F36-SF
   - Customized dialysis-phosphate Patient-reported outcomes (PROs) TBD during UG3 phase
Pragmatic features

- Liberal eligibility criteria
- Internet/tablet-based eConsent for individual patient-level informed consent
- In-center dietitians implement the intervention
- Develop P management protocols with “look and feel” as in clinical practice
- Implementation of intervention using approved medications
- Use of EHR data to remotely & continuously monitor fidelity of interventions
- Use of EHRs to extract clinical data, outcomes
- Merge with Medicare claims for 2’ analyses
Possible HiLo results: Would rapidly influence ESRD practice

1. **Higher P target non-inferior:**
   - Contradicts guidelines
   - Relax P target, dietary restrictions
   - Reallocate dialysis resources
   - Reduce burden on patients

2. **Higher P target superior:**
   - Contradicts guidelines
   - Relax P target, dietary restrictions

3. **Higher P target inferior = low P target superior:**
   - Fail to reject null hypothesis
   - First definitive clinical trial-grade evidence for opinion-based guidelines for P management
   - For CMS: justify P as a validated dialysis quality-of-care measure
   - Support additional trials of P control in earlier stages of CKD