Department of Medicine
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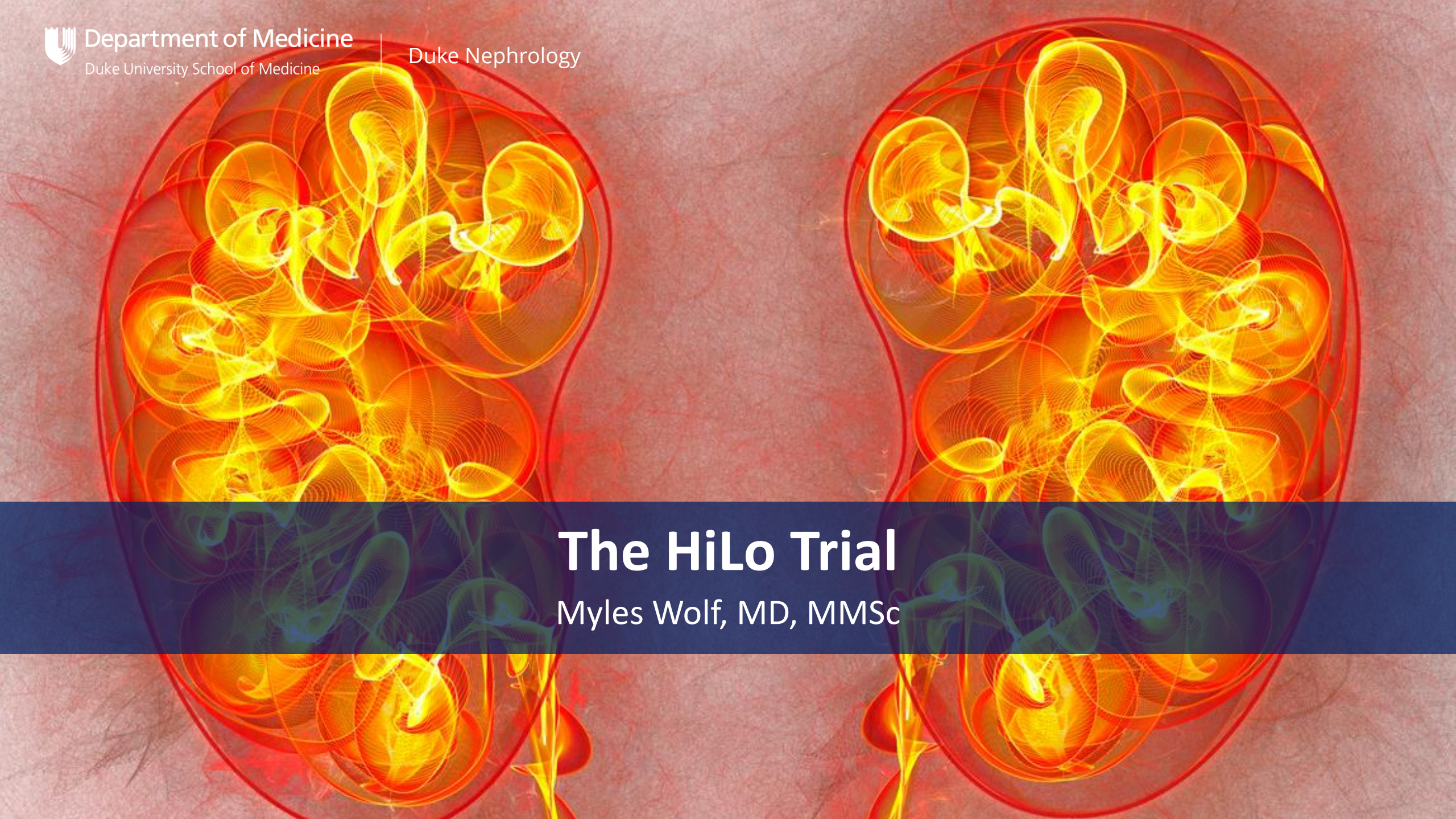


The HiLo Trial

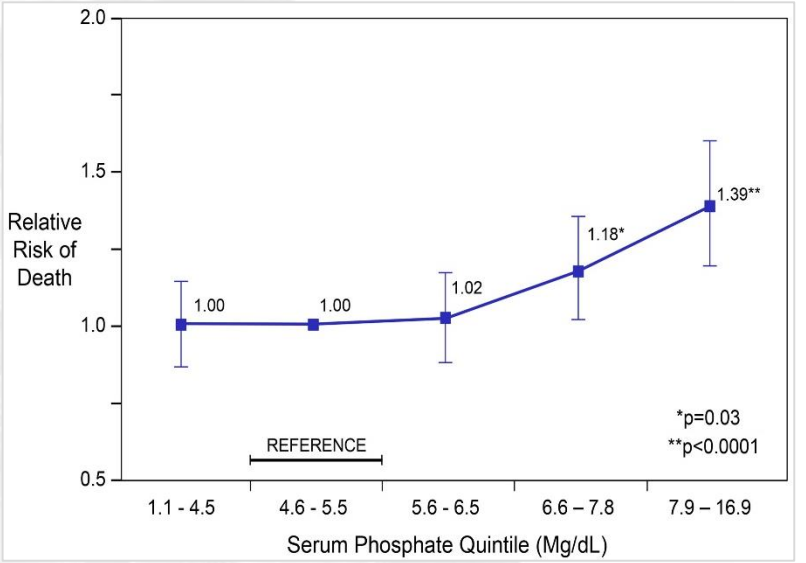
Myles Wolf, MD, MMSc

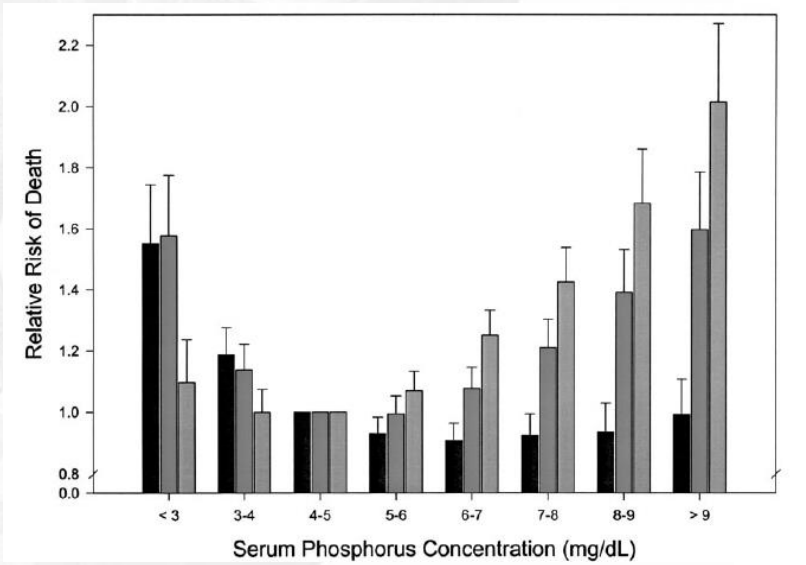
ESRD: Trials needed & an ideal setting for pragmatism

- 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

Scientific basis of HiLo

- End-stage renal disease (ESRD): ~500,000 in US alone
- Unacceptably high rates of:
  - Hospitalization: ~2 per patient-year
  - Mortality: 15–20%
  - Driven primarily by CVD, but CVD interventions failed in ESRD trials
- Focus on ESRD-specific risk factors: Hyperphosphatemia
  - Ubiquitous complication of ESRD
  - Experimental data: causal effects on arterial calcification, LVH, high PTH, FGF23
  - Hyperphosphatemia & all of above *associated* with CVD, death
- Based on *preclinical* & *observational* human data, *opinion-based* guidelines suggest P <5.0 mg/dl using P binders, low P diet





Block GA, AJKD 1998; Block GA, JASN 2004

Clinical equipoise

- Lack of RCTs…for anything
  - Target P unproven by RCT
  - No RCT tested the effects of FDA-approved phosphate binders on clinical outcomes
- Major unanswered questions:
  1. Do phosphate binders, as currently deployed, improve outcomes in ESRD?
  2. Does lowering serum P towards normal improve outcomes in ESRD?
- Hidden risks – excessive treatment to unnecessarily low target may worsen outcomes:
  - Paradoxically increasing risk by inducing calcium, lanthanum or iron overload
  - Causing GI side effects that exacerbate malnutrition
  - Eroding patients' QOL: adding P-related demands to high pill burdens
- These potential risks may have escaped detection precisely because of the lack of RCTs

Hypotheses

1. **Primary:** Compared to the current standard approach of targeting serum phosphate levels of <5.0 mg/dl, less stringent control of serum phosphate to target levels of 6–7 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.
  2. Mid-sized national non-profit dialysis corporation: DCI, Inc.
  3. Small regional academic program: University of Utah
- Build on lessons learned from the TIME trial

DaVita®
DCI® Dialysis Clinic, Inc. A Non-Profit Corporation
U HEALTH UNIVERSITY OF UTAH

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

Justification of all-cause hospitalization as primary outcome

- Important to all ESRD stakeholders: patients, families, clinicians, dialysis providers, payers
- For many patients, avoiding hospitalization/enhance QOL >>> prolong survival
- HyperP contributes to multiple complications → hospitalization
- Somewhat "noisy":
  - Includes events unlikely to be influenced by P control
  - But… more frequent hospitalization: marker of poor health, correlates with mortality in ESRD
  - All-cause mortality: subject to the same noisiness.
  - To address noise, HiLo powered to detect a small effect size
- Hospitalization: accepted endpoint in other areas
- Dialysis providers: near 100% complete data about dates/duration of hospitalizations; not causes
- Collecting real-time data on all-cause hospitalization eliminates events adjudication
- Continuous variable: more desirable statistically than time-to-event outcomes

Eligibility Criteria

Dialysis Facility:

- Willingness of MD director, nephrologists, dietitians to adopt either P target
- Willingness of facility managers to allow dietitian participation
- Facility dietitian willingness to implement trial, attend training teleconferences

Individual Participant Criteria:

- Liberal to simplify study, facilitate enrollment, maximize generalizability
- Adults >18 years of age treated with standard in-center maintenance HD
- Willing/able to provide written informed consent
- All vintages; pre-specified secondary analysis stratified by vintage < versus >3 years

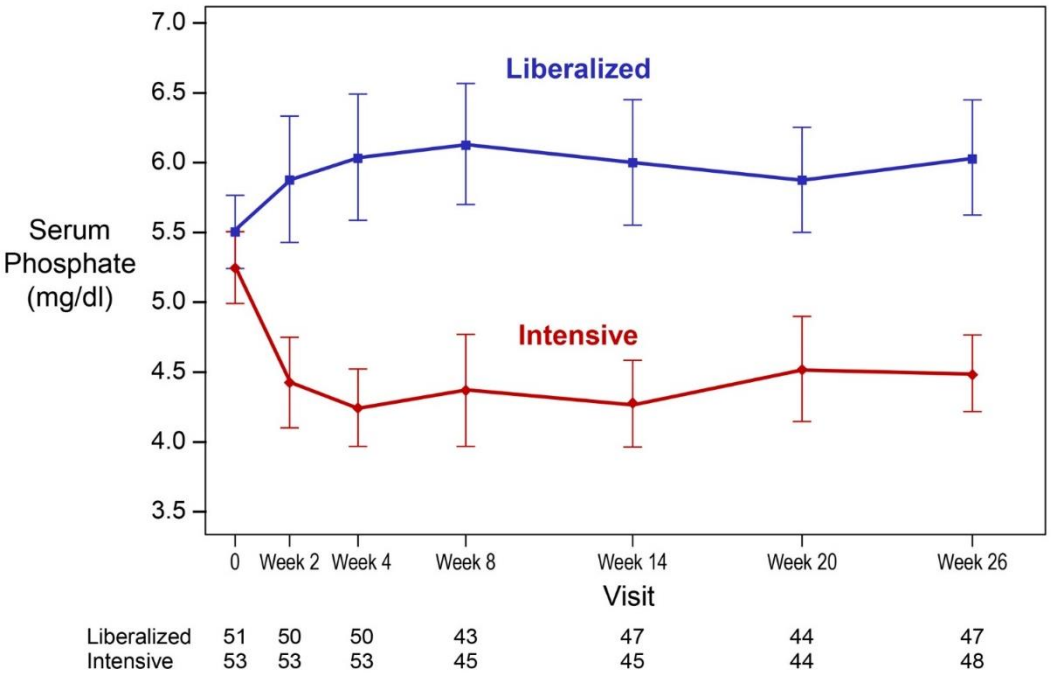
Intervention arms: Phosphate titration

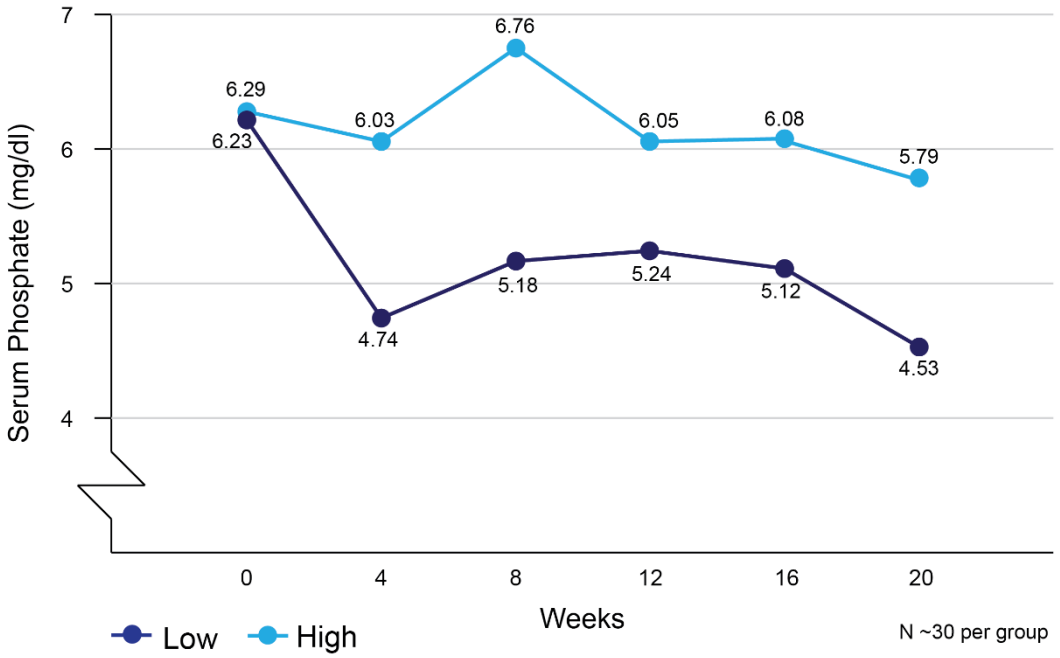
HiLo will develop two phosphate titration protocols with same "look and feel" as in practice

1. **Low serum phosphate target**
   - Current standard of care
   - Goal: titrate serum phosphate <5 mg/dl
   - Anticipate 4.8–5.2 mg/dl
2. **Higher serum phosphate**
   - Intervention strategy
   - Goal: titrate serum phosphate to 6–7 mg/dl
   - Anticipate 6.5–6.8 mg/dl

- Since serum P = 4–7 mg/dl in most patients with ESRD, ≥1 mg/dl difference = ≥33% difference within modifiable range of time-averaged P exposure
- Specific binder choices: discretion of local providers based on local practice

Preliminary pilot trials





Wald R, et al. *Clin J Am Soc Nephrol.* 2017. Bhargava R, et al; Abstract: *J Am Soc Nephrol 2014*

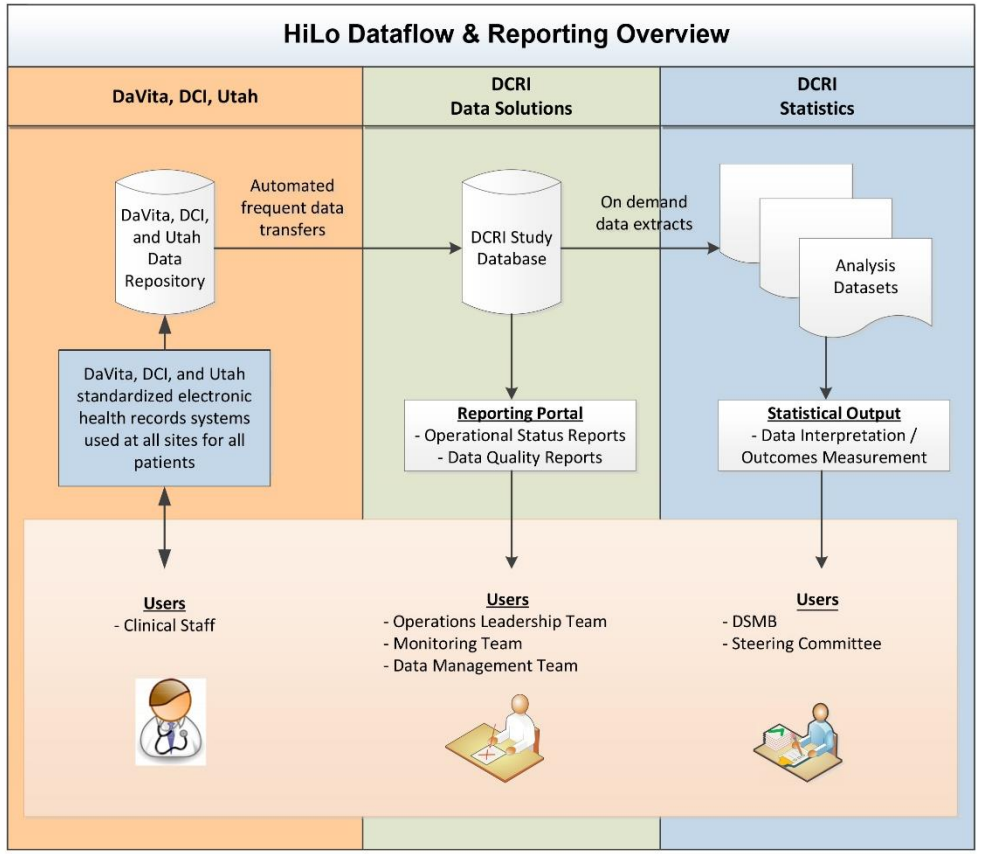
Pivotal role of dietitians

- Dietitians: on-the-ground personnel who implement HiLo
  - Employed by dialysis organizations
  - Present in all dialysis units
  - Among the most motivated caregivers on dialysis teams
  - See all patients at least monthly
  - Serve as primary decision makers for titration of P-related Rx
  - Existing rapport with patients will facilitate adherence
  - Relying on clinical personnel to implement trial: consistent with pragmatism
- To engage dietitians in HiLo:
  - Recruit dietitian representatives to Steering Committee: input into design & implementation
  - Identify regional dietitian champions for HiLo
  - Drive interest via presentations at national meetings: nephrology, dialysis company, dietitians

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

Bioinformatics platform



Sample size, primary analysis

- **Primary analysis:** comparison of per-person year (PPY) hospitalization rates between P target arms
  - Null hypothesis: low P target is superior (lower hospitalization rate)
  - Alternative hypothesis: high P target is non-inferior
- **Sample size assumptions**
  - 45-month study
  - 18-month enrollment period
  - 2.0 PPY mean hospitalization rate
  - Non-inferiority delta of 0.114 = 5% of 2.0 PPY mean hospitalization rate
  - SD of the hospitalization rate of 1.0, 1.2, or 1.4 for both groups
  - Annual loss to follow-up: 5%
  - Two-sided α: 0.05
  - Power: 80% or 90%
  - Mean enrollment of 30–35 patients per facility with SD of 0 and 9.5
  - Intra-class correlation coefficient between two patients from the same facility of 0.003
- Randomizing 120–150 facilities (65−75/P target arm), 4400 patients will provide >80% power to detect non-inferiority of the high P target

Sample size, secondary analysis

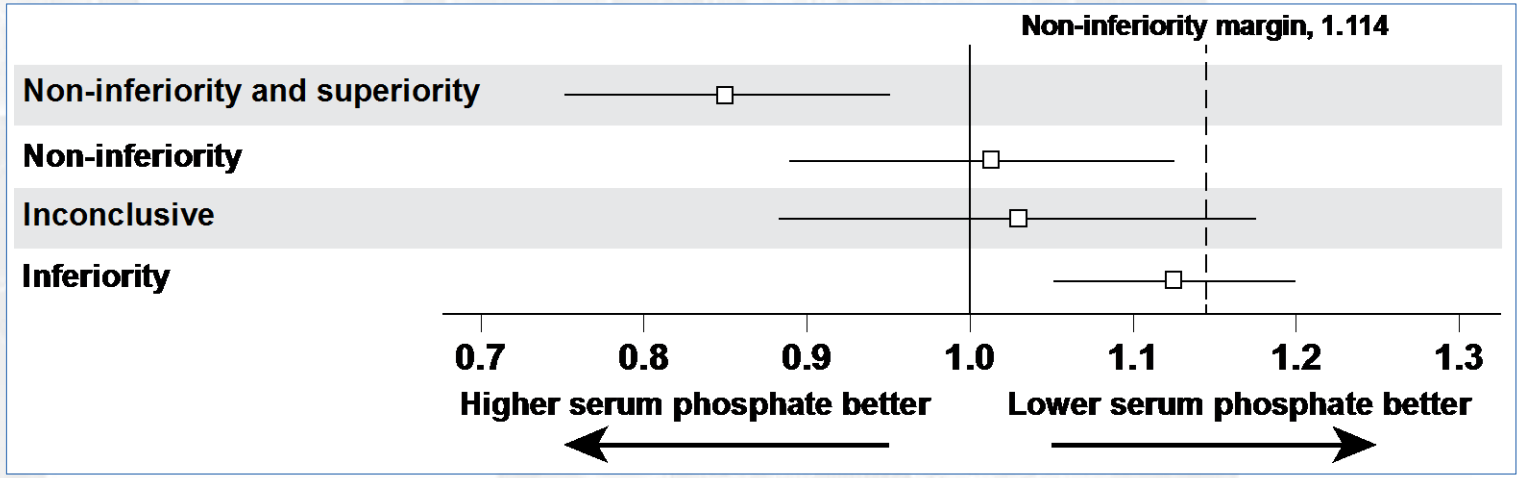
- **Main secondary analysis:** comparison of mortality rates between P target arms
  - Null hypothesis: survival curves are the same
  - Alternative hypothesis: higher mortality in one arm or the other
- **Sample size assumptions**
  - 45-month study
  - 18-month enrollment period
  - Annual mortality rate of 15%
  - Hazards ratio of mortality comparing P target arms: 0.8 and 0.85
  - Annual loss to follow-up: 5%
  - Two-sided α: 0.05
  - Power: 80% or 90%
  - Mean enrollment of 30–35 patients per facility with SD of 0 and 9.5
  - Intra-class correlation coefficient between two patients from the same facility of 0.0012
- Randomizing 120–150 facilities (65−75/P target arm), 4400 patients, will provide >80% power to detect a HR of 0.85 for all-cause death between P target arms, >90% power to detect a HR of 0.80.
- Change from baseline in serum albumin, PCR, QOL, PROs: continuous variables; ample power

Safety

- Independent DSMB to be convened by NIDDK
- Given pragmatic design, we will not collect information on AEs as in traditional RCTs
- Will monitor relevant, already collected laboratory parameters:
  - Monthly serum phosphate, calcium, PTH.
- Will monitor for primary, secondary outcomes:
  - Will capture clinically important AEs through all-cause hospitalizations, all-cause death
- Since individual patients' medical care is ultimate responsibility of primary providers, they may, at their discretion, reduce or temporarily discontinue P binders as in non-RCT setting, e.g.:
  - Hypercalcemia
  - GI symptoms
  - Hypophosphatemia
  - Participant preference

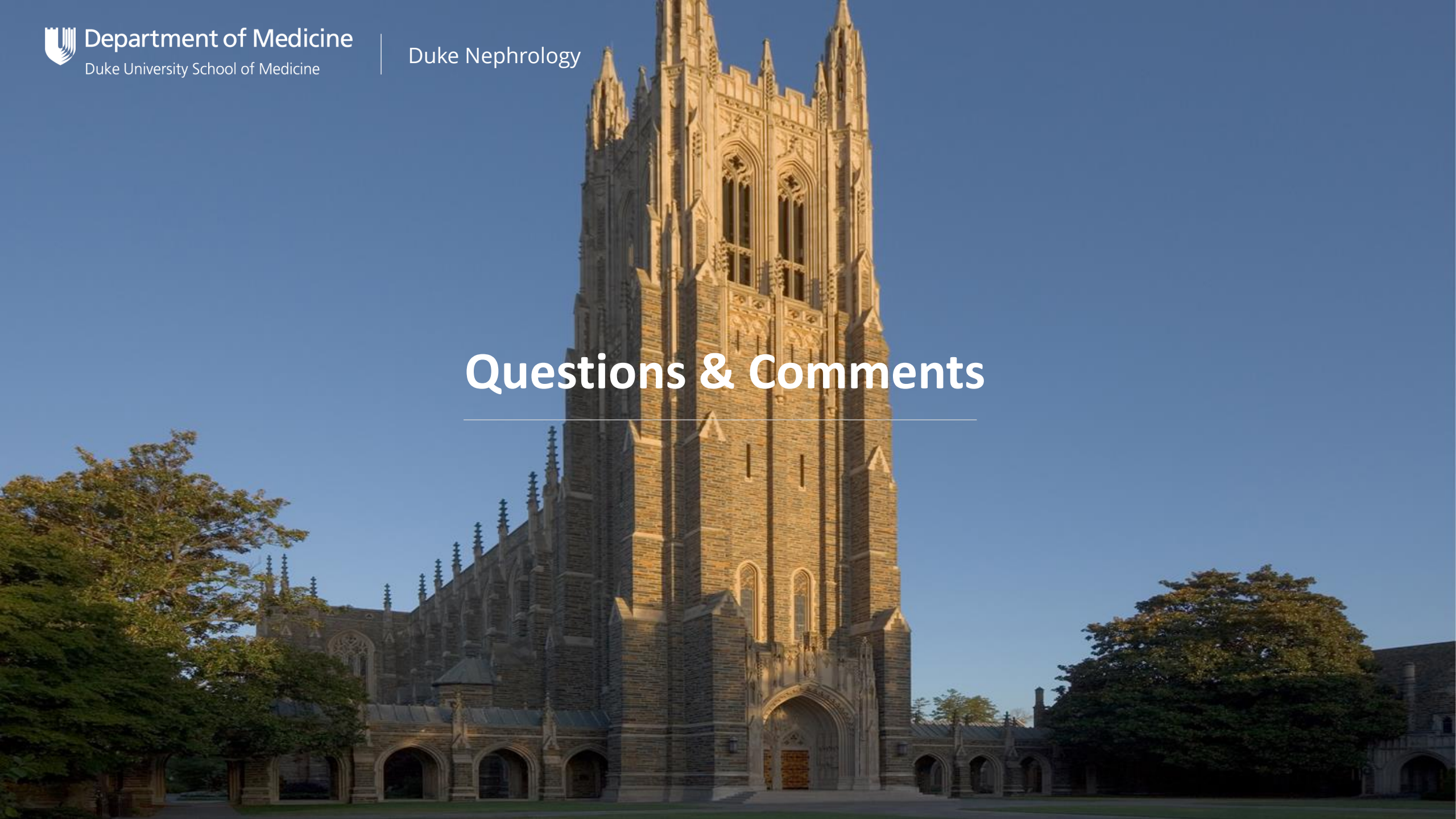
Possible HiLo results: Would rapidly influence ESRD practice

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



Leadership team

Name	Affiliation	Role
Myles Wolf, MD, MMSc	Duke University, Duke Clinical Research Institute	Principal Investigator, Steering Committee Chair
Srinivasan Beddhu, MD	University of Utah Health	Steering Committee, Utah liaison
Geoffrey Block, MD	Denver Nephrology Associates	Steering Committee
Steven Brunelli, MD, MSCE	DaVita Clinical Research	Steering Committee, DaVita liaison
Hrishikesh Chakraborty, DrPH	Duke Clinical Research Institute	Steering Committee, Statistical lead
Laura Dember, MD	University of Pennsylvania	Steering Committee
Tamara Isakova, MD, MMSc	Northwestern University	Steering Committee
Matthew Roe, MD	Duke Clinical Research Institute	Steering Committee
Daniel Weiner, MD, MS	Dialysis Clinic, Inc.	Steering Committee, Dialysis Clinic, Inc. liaison
Dietitian, TBD	DaVita	Steering Committee, Dietitian Co-lead
Dietitian, TBD	Dialysis Clinic, Inc.	Steering Committee, Dietitian Co-lead
Dietitian, TBD	University of Utah Health	Steering Committee, Dietitian Co-lead
Laura Johnson, MHA	Duke Clinical Research Institute	Project Leader
Brian McCourt	Duke Clinical Research Institute	Bioinformatics lead



Questions & Comments

DCRI Data Driven Trial Management (DDTM)