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Design and Rationale of HiLo: A Pragmatic, Randomized Trial of Phosphate Management for Patients Receiving Maintenance Hemodialysis

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Abstract

Rationale & Objective: Hyperphosphatemia is a risk factor for poor clinical outcomes in patients with kidney failure receiving maintenance dialysis. Opinion-based clinical practice guidelines recommend the use of phosphate binders and dietary phosphate restriction to lower serum phosphate levels toward the normal range in patients receiving maintenance dialysis, but the benefits of these approaches and the optimal serum phosphate target have not been tested in randomized trials. It is also unknown if aggressive treatment that achieves unnecessarily low serum phosphate levels worsens outcomes.

Study Design: Multicenter, pragmatic, cluster-randomized clinical trial.

Setting & Participants: HiLo will randomize 80–120 dialysis facilities operated by DaVita Inc and the University of Utah to enroll 4,400 patients undergoing 3-times-weekly, in-center hemodialysis.

Intervention: Phosphate binder prescriptions and dietary recommendations to achieve the “Hi” serum phosphate target (≥6.5 mg/dL) or the “Lo” serum phosphate target (<5.5 mg/dL).

Outcomes: Primary outcome: Hierarchical composite outcome of all-cause mortality and all-cause hospitalization. Main secondary outcomes: Individual components of the primary outcome.

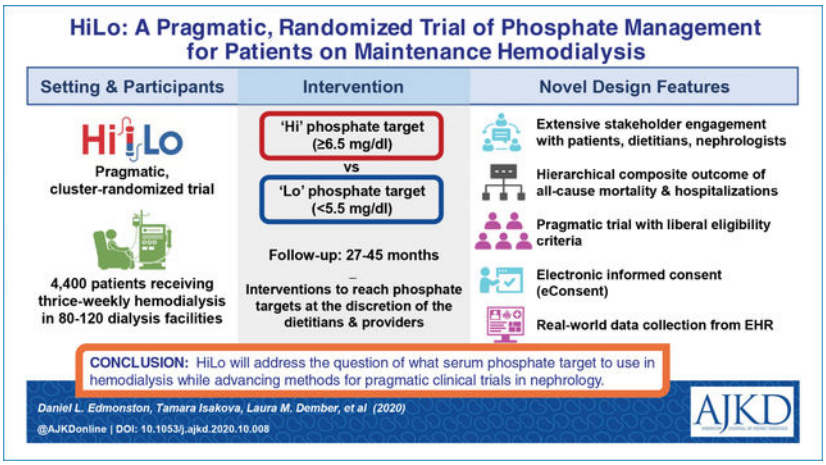
Results: The trial is currently enrolling.

Limitations: HiLo will not adjudicate causes of hospitalizations or mortality and does not protocolize use of specific phosphate binder classes.

Conclusions: HiLo aims to address an important clinical question while more generally advancing methods for pragmatic clinical trials in nephrology by introducing multiple innovative features including stakeholder engagement in the study design, liberal eligibility criteria, use of electronic informed consent, engagement of dietitians to implement the interventions in real-world practice, leveraging electronic health records to eliminate dedicated study visits, remote monitoring of serum phosphate separation between trial arms, and use of a novel hierarchical composite outcome.

Trial Registration: Registered at ClinicalTrials.gov with study number NCT04095039.

Graphical Abstract:



Scientific Basis of the HiLo Study

Dialysis outcomes have improved somewhat in recent years, but hospitalizations and mortality rates are still unacceptably elevated.[1] These poor outcomes mainly arise from an increased risk of cardiovascular disease, but most interventions targeting traditional cardiovascular risk factors that improve clinical outcomes in the general population have not been found to be effective when evaluated in randomized trials of patients with kidney failure.[2–4] The lack of benefit of traditional cardiovascular interventions has led the nephrology community to invoke and target putative kidney failure–specific risk factors for cardiovascular disease and death.

Hyperphosphatemia

Hyperphosphatemia is a ubiquitous complication of kidney failure that is associated with increased risks of cardiovascular disease and death in observational studies.[5–9] Experimental data suggest that hyperphosphatemia contributes to arterial calcification, which itself is associated with increased risk of cardiovascular events and death.[10–13] Arterial stiffness due to calcification promotes left ventricular hypertrophy, which is associated with heart failure, arrhythmia, and death.[14,15] Hyperphosphatemia also exacerbates kidney failure–associated increases in circulating levels of parathyroid hormone and fibroblast growth factor 23, each of which are associated with left ventricular hypertrophy, heart failure, arrhythmias, and infectious mortality in patients with kidney failure.[6,16–22]

The Contemporary Standard of Care

Based on these data, the nephrology community has embraced opinion-based practice guidelines that recommend aggressive treatment of hyperphosphatemia to less than 5.5 mg/dL or “toward the normal range” in patients with kidney failure undergoing hemodialysis.[23–25] Because standard hemodialysis removes an insufficient amount of phosphate, most patients must restrict their dietary phosphate intake, and more than 80% require treatment with phosphate binders to achieve recommended serum phosphate targets.[26,27]

Phosphate binders have been the cornerstone of hyperphosphatemia management for patients undergoing maintenance hemodialysis for decades, but all contemporary binders received approval from the US Food and Drug Administration on the basis of lowering serum phosphate levels in patients with hyperphosphatemia and kidney failure; no placebo-controlled randomized trial of any phosphate binder demonstrated beneficial effects on hard clinical outcomes. The single outcomes trial that compared calcium-based versus polymer-based binders yielded equivocal results.[28] Thus, major questions in the field that affect daily clinical practice remain unanswered. Do phosphate binders, as currently deployed, improve survival or other clinical outcomes in patients with kidney failure undergoing hemodialysis? More fundamentally, does aggressive lowering of serum phosphate levels toward the normal range improve clinical outcomes in such patients?

Equipoise

Clinical practice guidelines are predicated on the assumption that tight phosphate control will improve clinical outcomes by attenuating adverse effects of hyperphosphatemia,[23,24] but it is also possible that patients who are prescribed strict phosphate control may incur significant risks that have eluded detection precisely because of the lack of randomized outcomes trials (Fig 1).[29–40] The uncertainty of whether strict phosphate control improves, worsens, or has no effect on clinical outcomes in patients with kidney failure undergoing hemodialysis provides clinical equipoise to perform a randomized outcomes trial to compare different strategies to manage hyperphosphatemia.

Design of the HiLo Study

Overview of HiLo

HiLo is a pragmatic, multicenter, open-label, cluster-randomized trial that will compare the effects of 2 phosphate management strategies on the hierarchical composite outcome of all-cause mortality and all-cause hospitalization. HiLo will enroll 4,400 adults with kidney failure undergoing standard 3-times-weekly maintenance hemodialysis in facilities managed by DaVita Inc and the University of Utah, each of which contributed to the design of HiLo. Acting as the central institutional review board, the Duke University Institutional Review Board approved the study.

HiLo: A Pragmatic Clinical Trial

In contrast to explanatory trials, pragmatic trials are based in real-world practice and rely on real-world data to answer real-world clinical questions. Many aspects of hemodialysis care are ideally suited to large-scale pragmatic clinical trials.[41] Patients are treated 3 times weekly for several hours during which research activities can occur. Results of standardized laboratory testing and incident deaths and hospitalizations are reported in robust electronic health records that can be the source of trial data. Routine use of clinical protocols by dialysis personnel facilitates the weaving of research protocols into the fabric of daily clinical practice while also providing a mechanism for rapid translation of trial results into future clinical practice. These attributes supported execution of the pragmatic Time to Reduce Mortality in ESRD (TiME) trial in more than 7,000 patients treated at 266 dialysis

facilities across the United States.[42] Like the TiME trial, HiLo incorporates many pragmatic features (Fig 2). Unlike a traditional explanatory trial that might incur $50-$100 million in costs to compare the effects of 2 different phosphate management strategies on clinical outcomes, HiLo will be executed for 5%–10% of the cost.

Cluster Randomization

HiLo randomizes dialysis facilities to simplify trial operations and to ensure that only a single study-specific phosphate target is implemented in each facility. To minimize imbalances between the "Hi" and "Lo" arms, the cluster randomization is stratified by dialysis provider organization and facility size (Fig 3).

Liberal Eligibility Criteria

For a specific dialysis facility to be eligible to participate in HiLo, its medical director, dietitian, and lead administrator must be willing to have their facility randomized to either the Hi or Lo arm. All adult patients aged 18 years or older are eligible if they have received maintenance, in-center hemodialysis 3 times weekly for at least 3 months.

Intervention

HiLo is randomizing dialysis facilities to one of 2 arms. The Lo arm will have a serum phosphate target of <5.5 mg/dL, which is the current standard of care. Patients in the Lo arm should experience no change in their management. The Hi arm will have a serum phosphate target of ≥6.5 mg/dL, which is the novel intervention to be tested. Patients in the Hi arm should experience liberalized diets and less intensive phosphate-binder regimens.

The target serum phosphate level in the Hi arm was chosen based on results of epidemiologic studies of phosphate and clinical outcomes, preliminary data from previous pilot clinical trials, and consideration of what degree of hyperphosphatemia would be accepted by patients, practitioners, and regulatory bodies.[5,43–48] HiLo expects the mean serum phosphate levels to range between 5.0 and 5.4 mg/dL in the Lo arm and 6.5 and 6.9 mg/dL in the Hi arm. This will result in achieving HiLo's goal of a time-averaged separation of at least 1 mg/dL between arms. Because the vast majority of patients undergoing hemodialysis exhibit maintained serum phosphate levels of 4–7 mg/dL,[49] sustaining ≥1 mg/dL separation between randomized treatment arms would represent a time-averaged difference in serum phosphate exposure of at least 33% of the modifiable range.

To mirror usual clinical practice, phosphate-binder prescriptions and dietary recommendations are left to the discretion of local care teams. Any phosphate binder may be used, and there are no HiLo-specific titration protocols. Likewise, local care teams manage all other aspects of dialysis independently of guidance from HiLo.

Outcomes

The primary outcome of HiLo is a hierarchical composite outcome that prioritizes time to all-cause mortality and secondarily considers all-cause hospitalization rate when patients cannot be compared in terms of mortality (details described in the following). The main

prespecified secondary outcomes are the individual components of the composite outcome: time to all-cause mortality and total hospitalization events per total follow-up time.

Limitations and Potential Challenges

HiLo will not account for use of calcium- versus non-calcium-based phosphate binders, which may influence clinical outcomes.[50] Because hospitalizations are reported by dialysis facilities when patients miss sessions, short hospitalizations that do not result in a missed outpatient dialysis session may escape detection. Further, HiLo will not adjudicate causes of hospitalizations. Because of the cluster-randomized design, outbreaks of coronavirus disease 2019 (COVID-19) within specific dialysis facilities could reduce power by increasing within-cluster correlations of mortality and hospitalizations. Although the pragmatic, multicenter design of HiLo will enhance generalizability, the results may not generalize to maintenance dialysis populations outside the United States. Also, the trial may fail to achieve ≥1 mg/dL phosphate separation in the intervention groups.

Novel Aspects of HiLo

Electronic Consent

Informed consent is often waived in pragmatic trials that test strategies to enhance implementation of proven therapies.[51] Because HiLo will test a “more than minimal risk” intervention that differs from the current opinion–based standard of care, HiLo must obtain individual-level informed consent.[25] To obtain consent from 4,400 patients without on-site study staff, HiLo distributes tablet devices that connect to secure web-based electronic consent (eConsent) modules, one each for the Hi and Lo arms, on the HiLo web site (hilostudy.org). The eConsent videos are co-narrated by a nephrologist and a patient with kidney failure and are accompanied by a suite of concise educational videos about clinical research participation, phosphate and its management in kidney failure, and the “nuts and bolts” of HiLo. As critical stakeholders, patients participated in the HiLo Patient Advisory Group, which was convened by the American Association of Kidney Patients and provided input on all videos and the design of HiLo. To backstop the eConsent, a central team of HiLo nephrologists is available to answer potential participants’ questions by telephone.

Rolling Recruitment Strategy

HiLo is performing brief, time-limited enrollment of prevalent patients; for a given facility, 1 week of enrollment will be allotted per 10 eligible patients. This “get-in, get-out” approach will speed enrollment by ensuring that more enrollment time is spent in facilities with large numbers of eligible patients rather than maintaining active enrollment in previously enrolled facilities that slowly accrue smaller numbers of new patients (typically, less than 10%–20% of the facility’s census per year). Reducing the time until facilities can return to usual clinical practice, free from enrollment, should ease their operational burdens. Rolling recruitment will also enable an ongoing assessment of the enrollment rate overall and in each arm, which HiLo will use to guide the number of facilities that ultimately need to be activated.

Engaging Dietitians

Dialysis dietitians helped design HiLo and are represented on its steering committee. Dietitians are highly motivated, scientifically inquisitive caregivers who are ideally positioned to be the on-the-ground personnel who support execution of HiLo. Dietitians are employed by dialysis organizations, are present in all facilities, establish long-term relationships with their patients through at least monthly contacts, and often serve as primary decision makers for titration of phosphate-related treatments. The strong rapport between dietitians and patients may also facilitate adherence. Operationally, dietitians approach patients with the HiLo tablets that are preloaded with all study materials, including the eConsent modules. The dietitians keep a master list that contains the names, eligibility status, approach status, and consent status of each patient. The Duke Clinical Research Institute site-management team runs weekly reports with REDCap software and reconciles with a deidentified version of the master list to ensure that dietitians are approaching patients and using the consent module properly. Although dietitians facilitate the consent process, they do not obtain consent and thus are not considered “engaged” in research from a regulatory standpoint.[52] Dietitians help enrolled patients achieve their serum phosphate targets by using a combination of phosphate binder and dietary recommendations. Dietitians are not asked to alter any other aspect of their care, nor are they asked to engage in study-specific data collection.

Eliminating Case-Report Forms and Traditional Adverse Event Reporting

The HiLo bioinformatics team created information-technology portals to receive monthly data transfers from DaVita Inc and the University of Utah and collate them into a single HiLo-specific database that contains demographic data; laboratory test results; dates of hospitalizations, transfers to other facilities, or other kidney-replacement modalities; and death. This bioinformatic solution eliminated the need for case-report forms.

Because most clinically important, serious adverse events in patients with kidney failure treated by maintenance hemodialysis culminate in hospitalizations, which are captured in the primary outcome, HiLo is not performing traditional adverse event reporting. Instead, HiLo monitors laboratory parameters, including serum phosphate, calcium, and parathyroid hormone levels. Just as in usual practice, local care teams are empowered to reduce or discontinue phosphate binders, for example, in the event of hypercalcemia, gastrointestinal symptoms, hypophosphatemia, or patient preference.

Remote Monitoring to Maintain Phosphate Separation

The success of HiLo hinges on maintaining sufficient separation of serum phosphate concentrations between arms over time. This is especially challenging in a pragmatic trial that lacks on-site study personnel or monitors. To meet this challenge, HiLo delivers monthly reports to participating dietitians that provide details on achieved serum phosphate levels in the overall facility and within each individual study participant, along with local and study-wide enrollment data. This pragmatic approach will significantly reduce monitoring costs by directing remediation strategies only to specific facilities and patients that deviate excessively from targets.

Some patients assigned to the Lo arm will be unable to maintain their serum phosphate concentration less than 5.5 mg/dL, and, in some patients assigned to the Hi arm, serum phosphate level will decrease to less than 6.5 mg/dL. This potential limitation, which is analogous to incomplete adherence in other trials, will tend to reduce the overall separation in serum phosphate level between treatment arms. Like drug intervention trials, HiLo is targeting an average of at least 75% "adherence" with targets in each arm throughout the study and will conduct secondary "as-treated" analyses in patients in whom the target serum phosphate level is achieved in at least 75% of months in the study.[53,54] In addition, the sample size for HiLo offers 85% rather than 80% power (discussed further below). This cushion will help offset some loss of power due to failure to reach serum phosphate level targets in a proportion of patients in each arm.

Primary End Point and Analysis

Conundrum—All-cause mortality and all-cause hospitalization are plausibly related to and potentially modified by phosphate control. Avoiding hospitalization is of paramount importance to all stakeholders in care of patients receiving maintenance hemodialysis, including payers, dialysis provider organizations, clinicians, and, most importantly, patients and their families. Indeed, for many patients with kidney failure, it is more important to enhance quality of life by avoiding hospitalizations than to prolong survival.[55]

Despite its clinical importance, constructing a primary outcome incorporating hospitalization presents several challenges. If all-cause hospitalization alone was the primary outcome, death would be a censoring and competing event. Because some patients with kidney failure die without prior hospitalizations, censoring deaths in a trial of phosphate management could distort the results. Alternatively, hospitalization and mortality could be combined in a time-to-event composite. However, given the high rates of hospitalization, often for reasons unrelated to phosphate, this approach would yield a trial with seemingly high power on account of a high event rate, but, in actuality, power would be decreased by many noninformative events. A different approach was needed to address the challenge of combining into a single primary endpoint time to all-cause mortality and all-cause hospitalization rate.

Solution: Hierarchical Composite Outcome—Finkelstein and Schoenfeld developed a method to accommodate analyses of composite outcomes that include individual components that are measured on different scales and can be prioritized differently.[56] For HiLo, the hierarchical endpoint prioritizes all-cause mortality as the most important endpoint; all-cause hospitalization will be considered only when patients cannot be compared in terms of mortality. This method was employed to secure Food and Drug Administration approval for a treatment for a rare cardiovascular disease,[57] but, to our knowledge, few, if any, nephrology trials have used this novel approach.

Figure 4 conceptualizes the analysis of the hierarchical composite outcome of HiLo, which is based on the concept of the "win ratio."[57] Each patient in the Hi arm is compared with each patient in the Lo arm. Follow-up time for each pairwise comparison is restricted to the amount of time shared by both patients, which is equivalent to the shorter follow-up

time between the pair. In each pair, the patients are compared first in terms of mortality. Those who survive longer are assigned a "win," and their score is increased by 1; a "loss" is attributed to the comparators who died sooner, and their score is reduced by 1. If neither patient in a pair died during their shared follow-up time, the comparison shifts to hospitalizations during the shared follow-up period. In each paired comparison, patients with more hospitalizations are assigned a loss; the comparator patients are assigned a win. If the frequency of hospitalizations is equal, a "tie" results and the matched pair's scores remain unchanged. This process is continued until all permutations of all possible comparisons between all patients in the Hi and Lo arms are concluded. (Of note, individual patients' outcomes vary across different paired comparisons because of variable follow-up time in their comparators [Fig 4].)

After all comparisons are complete, patients' final scores describe their overall outcomes compared with the complete population in the other arm of the trial; higher positive scores indicate better outcomes, and more negative scores indicate worse outcomes.[58] A statistical test is used to test the null hypothesis that there is no difference in the distributions of the scores between treatment groups.

Sample Size Determination—Because standard power calculation methods cannot be used for hierarchical composite endpoints, HiLo performed data simulations to determine power and sample size. We generated the simulated trial data by using the Moran algorithm[59] based on internal data from DaVita Inc and the TiME trial.[42] We generated the time-to-event data assuming proportional hazards. We also assumed uniform accrual to simulate administrative censoring. Other assumptions and parameters are shown in Fig 5. The HiLo biostatistical team generated 5,000 independently simulated datasets for each of 2 different enrollment patterns: 80 clusters of 55 patients each and 120 clusters of 36 patients each. After calculating the scores for the hierarchical composite endpoint using the Finkelstein and Schoenfeld method, 2 methods were used to analyze the scores: a parametric method based on repeated-measures mixed modeling[60] and a nonparametric adaptation of the Wilcoxon rank-sum method for clustering.[61] To estimate power, the number of iterations that had a significant result ($P < 0.05$) was divided by the total of 5,000 iterations. As shown in Figure 5, the parametric and nonparametric methods each yielded ≥85% power.

Statistical Analysis—We will use the clustered Wilcoxon test to analyze the primary hierarchical outcome in the intention-to-treat population.[61] For the secondary analysis of all-cause mortality, we will use a Cox proportional-hazards model with censoring at study withdrawal, loss to follow-up, and end of follow-up; we will account for clustering by using the sandwich estimator. For the secondary analysis of all-cause hospitalization, we will reject the null hypothesis of no difference between groups if the 95% confidence interval around the estimated mean difference in hospitalization rates between the arms excludes zero; to account for clustering, we will inflate the variance by using the analysis of variance method.[62]

Limitations of the Hierarchical Composite Outcome—Potential limitations of the hierarchical endpoint include how to interpret the results of the analysis of rank scores in clinical terms. However, the primary analysis of the scores should be viewed as the test of

whether one arm was superior to the other, whereas the prespecified secondary analyses will quantify the clinically meaningful magnitude of effect on each component of the primary outcome. Indeed, HiLo will have more than 80% power to detect a hazard ratio of 0.85 for mortality between the Hi and Lo arms and more than 90% power to detect a hazard ratio of 0.80. Power will be even greater for the secondary analysis of all-cause hospitalization rate.

Although it would be desirable to capture causes of hospitalization and death, this would require extensive, non-pragmatic ascertainment and adjudication of data not currently collected by dialysis facilities. This could be addressed in the future by merging HiLo data with Medicare claims data, which are available for the majority of the dialysis population.

Conclusion

Although considered dogma, the currently recommended serum phosphate target level in patients with kidney failure treated by maintenance hemodialysis is built on a shaky foundation. HiLo is using a pragmatic yet rigorous design that was vetted by key stakeholders—patients, dietitians, nephrologists, and large dialysis organizations—to compare clinical outcomes in response to titrating to higher versus lower serum phosphate target levels. Enrollment began in 2020, and follow-up will extend to 2024. For the study's primary objective, HiLo will be a success if it yields evidence that the Hi or Lo target is superior to the other. What must be avoided is a noninformative result caused by insufficient enrollment or insufficient separation of the serum phosphate curves. Beyond phosphate management, HiLo will also be a success if it enhances the clinical trial culture in nephrology by ushering in wider use of stakeholder engagement, eConsent, electronic health record data, remote study monitoring, and innovations in primary outcomes. By retaining rigor at reduced cost, these advances could help the nephrology community answer many open questions with clinical trial–grade evidence.

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PLAIN-LANGUAGE SUMMARY

Citing observational and preclinical studies that link hyperphosphatemia to adverse clinical outcomes, current clinical practice guidelines recommend reduction of serum phosphate “toward the normal range” in patients with kidney failure undergoing hemodialysis. However, no randomized clinical trials have tested whether lowering serum phosphate levels improves clinical outcomes. HiLo is a pragmatic cluster-randomized clinical trial that will test the effects of targeting a “Hi” or a “Lo” serum phosphate level (≥6.5 vs <5.5 mg/dL) on the hierarchical composite outcome of all-cause mortality and all-cause hospitalization. HiLo incorporates multiple pragmatic features including liberal eligibility criteria, cluster randomization, electronic informed consent, dietitian-implemented interventions, remote study monitoring, real-world data collection from existing electronic health records, and a novel hierarchical composite outcome.

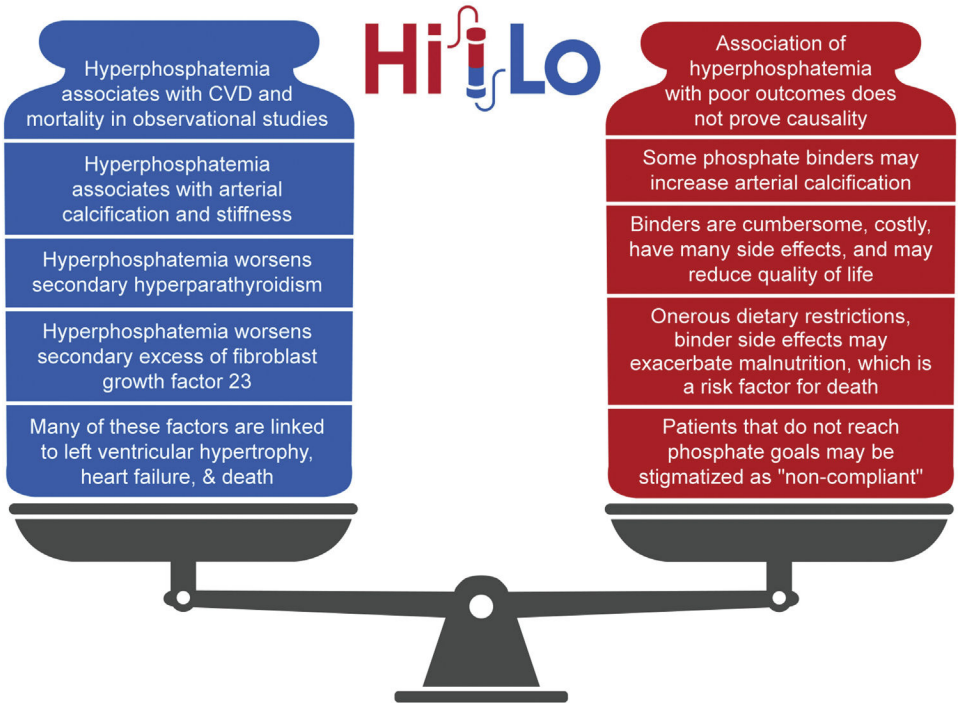

Figure 1.

Equipoise for HiLo. With multiple factors in favor of and against more aggressive reduction of serum phosphate levels, there is clinical equipoise to conduct a randomized trial of strict versus liberal management of hyperphosphatemia in patients with kidney failure undergoing hemodialysis. Abbreviation: CVD, cardiovascular disease. Created with BioRender.com.

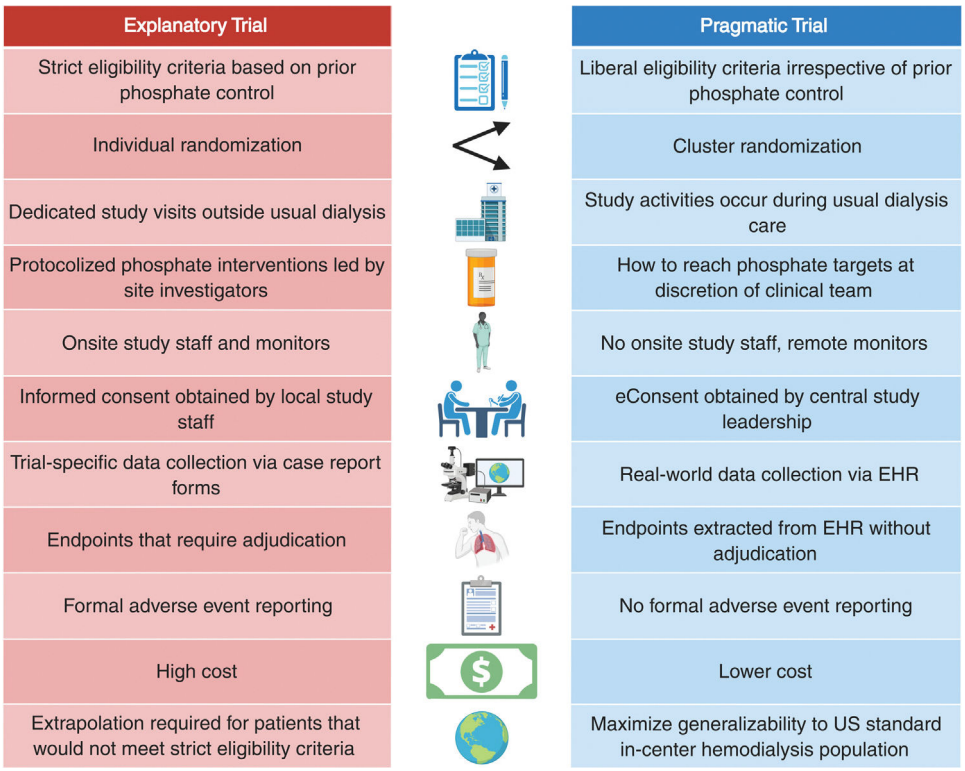

Figure 2.

Differences between pragmatic and traditional explanatory clinical trials. Pragmatic clinical trials differ from traditional explanatory trials across multiple domains. Here, we demonstrate how the current pragmatic design of HiLo would differ if it were conducted as a traditional explanatory trial. Created with BioRender.com.

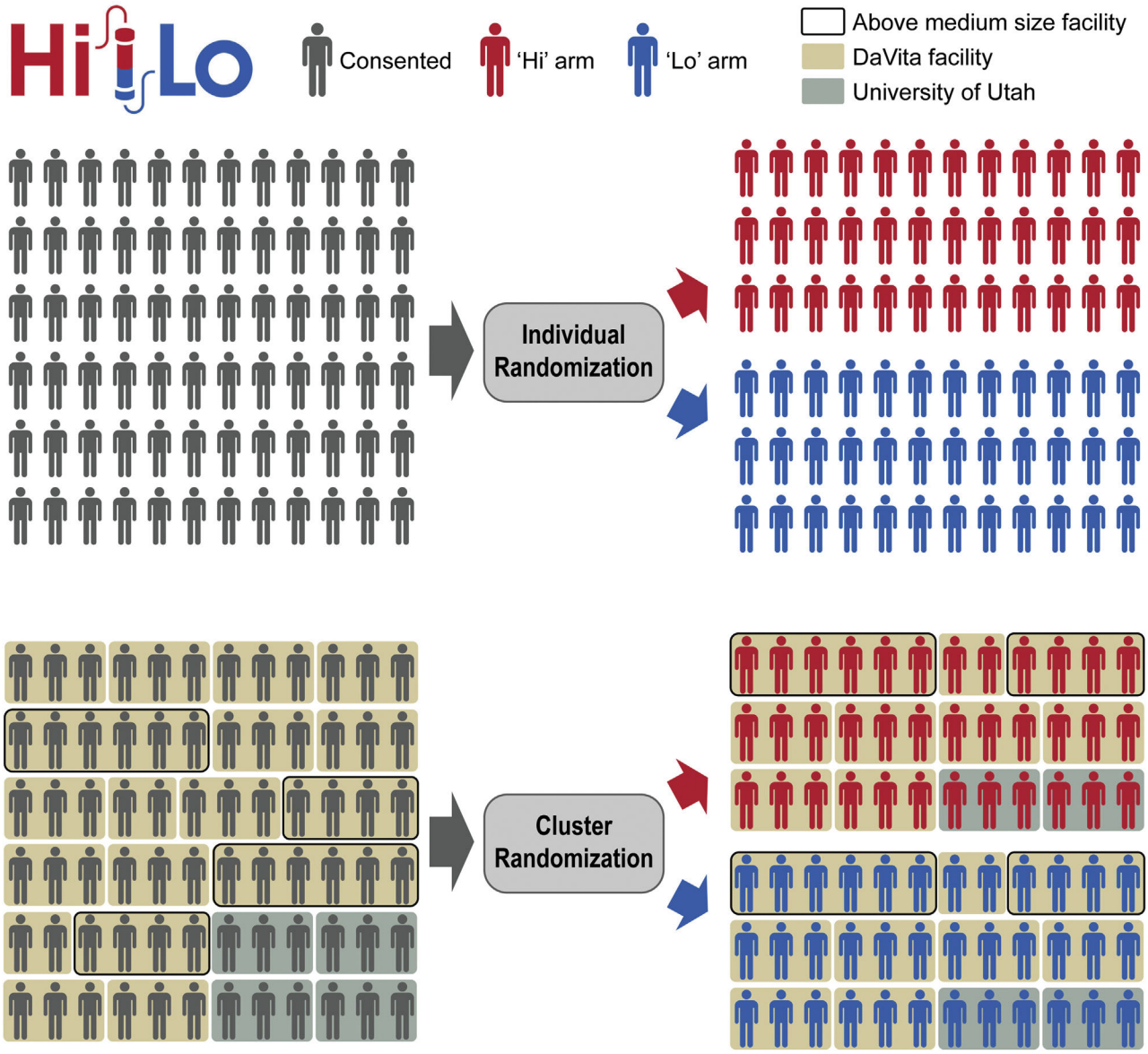

Figure 3.

Cluster versus individual randomization in HiLo. To maintain the fidelity of the intervention using a pragmatic approach, HiLo employs cluster randomization in which entire dialysis facilities are randomized instead of randomizing patients individually. To balance the sizes of the Hi and Lo arms, HiLo will stratify the cluster randomization by facility type (Davita Inc or University of Utah) and by facility size (less or more than the median; latter represented as outlined groups). Created with BioRender.com.

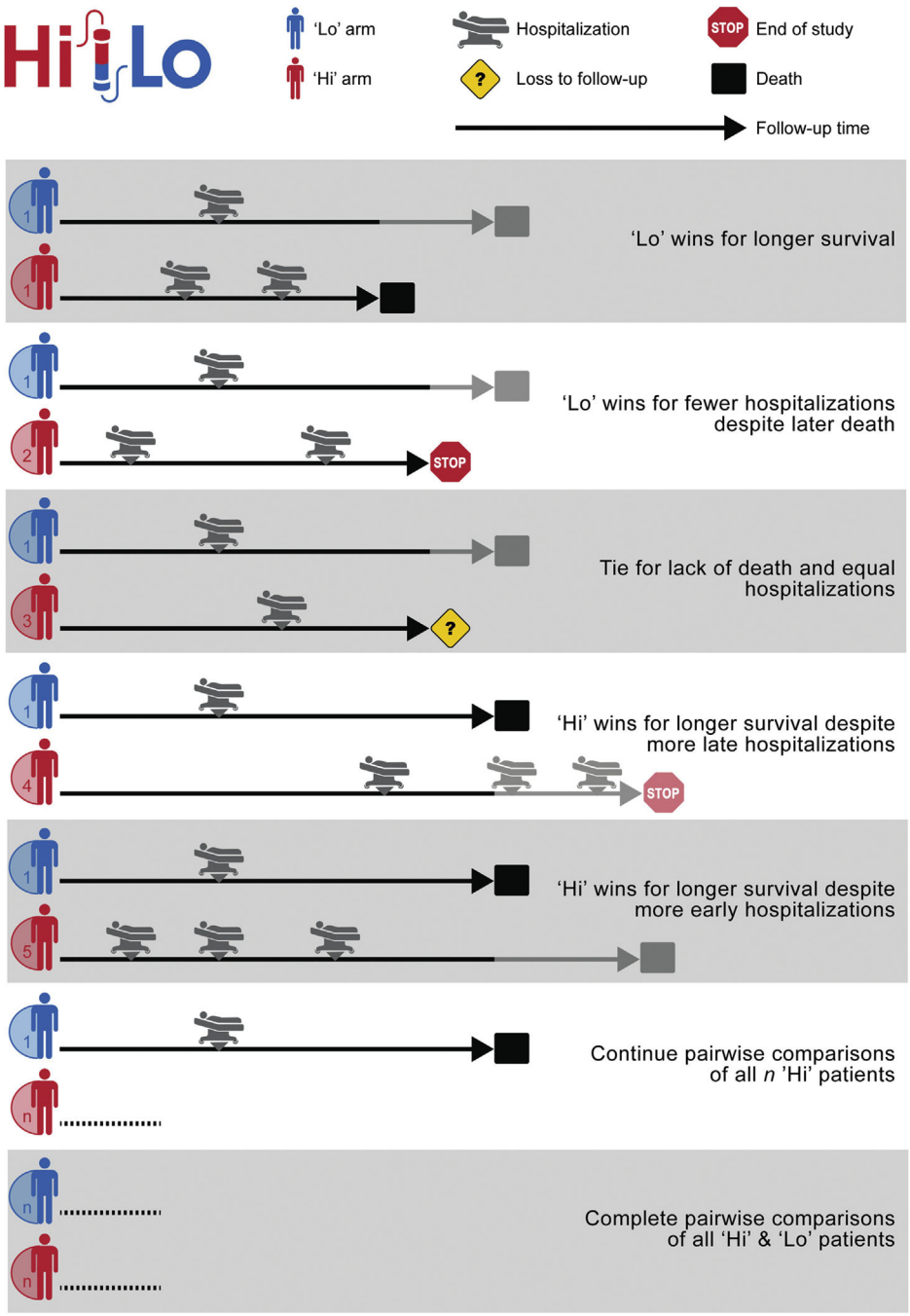

Figure 4.

Analysis of the primary hierarchical composite outcome of HiLo. The primary outcome of the HiLo trial is a hierarchical composite outcome of time to all-cause mortality and number of hospitalizations. In a pairwise manner, the outcomes for each patient randomized to the Lo and Hi groups are compared. Follow-up duration for each pairwise comparison is defined by the earliest occurrence of death or a censoring event (eg, loss to follow-up or end of study) in either comparator patient. The pairs are first compared on the basis of survival to determine the "winner" who survived longer. If both patients in a pairwise

comparison survive throughout the duration of the shared follow-up period, the winner is the patient who had fewer hospitalizations during follow-up. Note that the shared follow-up period is the only time relevant to a given pairwise comparison. As a corollary, an individual patient's follow-up time will vary across pairwise comparisons depending on the duration of follow-up in their comparators. The final 2 scenarios denote the continuation of pairwise comparisons for Lo patient 1 with all *n* remaining Hi patients (second from bottom) and all *n* remaining Lo patients with all *n* Hi patients (bottom) until all comparisons of all Hi versus all Lo patients are complete. After all pairwise comparisons are complete, the total scores in the 2 arms are tallied and tested for significant differences. Created with BioRender.com.

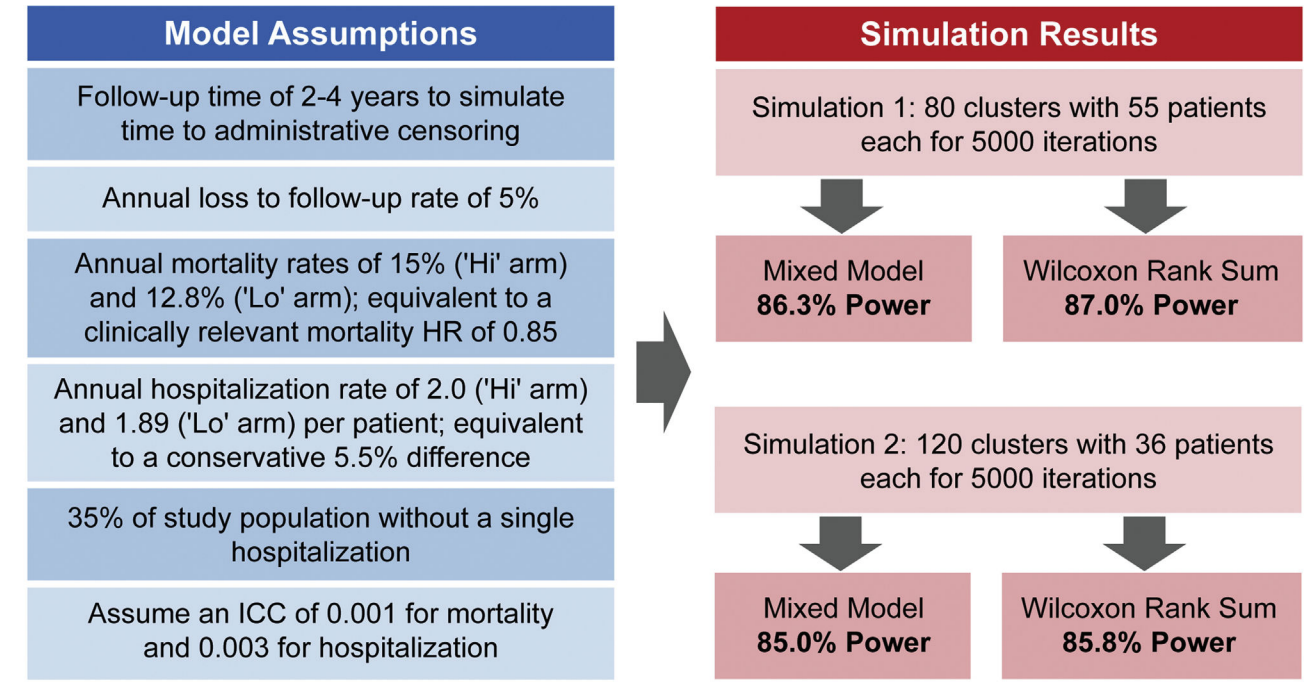

Figure 5.

Sample size and power simulations for HiLo. Because conventional power calculation methods cannot be applied to hierarchical composite outcomes, HiLo used simulated datasets based on data from DaVita Inc and the TiME trial to determine power and sample size. The figure lists the key assumptions that were used to randomly generate 5,000 iterations of simulated study databases for each of 2 different study compositions: 80 clusters of 55 patients each and 120 clusters of 36 patients each. Then, 2 analytic approaches were used to analyze the simulated datasets: one parametric (mixed model) and one nonparametric (Wilcoxon rank-sum method). All 4 approaches yielded power of 85% or higher. Abbreviation: ICC, intraclass correlation coefficient. Created with BioRender.com.