NIH Collaboratory Rethinking Clinical Trials®

Health Care Systems Research Collaboratory

Regulatory/Ethics Consultation Call:

Pragmatic Trial of Higher vs. Lower Serum Phosphate Targets in Patients Undergoing Hemodialysis (HiLo)

Thursday, August 16, 2018
Meeting Participants

Davy Andersen (Duke), Judith Carrithers (Advarra), Lesley Curtis (Duke), Laura Dember (University of Pennsylvania), Tamara Isakova (Northwestern University), Laura Johnson (Duke), MariJo Mencini (Duke), Cathy Meyers (NIH), Tammy Reece (Duke), Jeremy Sugarman (Johns Hopkins), Wendy Weber (NIH), Kevin Weinfurt (Duke), Liz Wing (Duke), Myles Wolf (Principal Investigator, Duke)

AGENDA ITEMS	DISCUSSION	ACTION ITEMS
Review of Demonstration Project	• Myles Wolf, Principal Investigator (Duke University), gave an overview of the HiLo demonstration project. The trial will compare 2 different strategies for treating hyperphosphatemia in patients with end-stage renal disease (ESRD). Hyperphosphatemia (high serum phosphate level) is a ubiquitous complication of ESRD that is associated with increased risks of cardiovascular disease and death. The opinion-based practice guidelines on which the nephrology community currently relies recommend aggressive treatment of hyperphosphatemia to near normal levels (<5.0 mg/dl) in patients with ESRD; however, the optimal serum phosphate target has not been tested in a randomized clinical outcomes trial. HiLo will address this state of clinical equipoise by testing whether liberal control of serum phosphate targeting 6-7 mg/dl ("Hi") will yield non-inferior rates of all-cause hospitalization compared with the current standard approach of strict control of serum phosphate ("Lo"). • **Collaborative network partners:** o DaVita, Inc. o Dialysis Clinic, Inc. (DCI) o Dialysis Program, University of Utah Health o Duke University • **NIH Institute:** National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	

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	• **Trial design:** HiLo is designed as a pragmatic, open-label, cluster-randomized clinical outcomes trial of ~4400 patients with ESRD undergoing hemodialysis at >100 facilities operated by 3 dialysis provider organizations. In the UG3 phase, the study will engage stakeholders, finalize the protocol and obtain IRB approval, pilot a centralized electronic informed consent process, and develop the bioinformatics platforms for recruitment, data capture, and intervention monitoring. The UH3 phase will involve the evaluation of the 2 different serum phosphate targets for patients with dialysis-dependent ESRD and plan for dissemination and broad implementation of study findings. o **Primary outcome:** Rate of total all-cause hospitalization between the 2 study arms. o **Secondary outcomes:** Rate of all-cause mortality and change in serum albumin as an indicator of protein malnutrition. • Those on the call agreed that there seems to be clinical equipoise on this research question. • The study team intends to educate and engage clinicians, dieticians, and facility managers around the uncertainty related to phosphate control in this setting and the trial's aims to generate real-world evidence concerning it in a pragmatic, randomized A vs. B trial. • The study will use patient-reported outcomes specifically designed for this research. • The EHR systems of the 3 partnering dialysis organizations will contain all the data the study needs. No case report forms will be needed.	
Status of IRB approval	• The Duke IRB is serving as the central IRB for the study. An early protocol was submitted July 30, 2018. The study team plans to submit an amendment after the protocol is final for the UG3 phase. The Duke IRB recognizes the preliminary status of the current protocol.	
Risk classification	• Risks to participants include risk of elevated serum phosphate levels, calciphylaxis, and potential loss of confidentiality. • Those on the call agreed that the study poses greater than minimal risk to participants in the "Hi" arm, while those in the usual care arm ("Lo") will not face a greater risk than current standard of care.	

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	• However, based on observational data, achieving low serum phosphate levels, requires that patients take lots of phosphate binders, which can add risk. Other studies suggest that excessive calcium loading itself can cause harms similar to those attributed to phosphate.	
Consent	• Because the trial is greater than minimal risk for those in the Hi arm, consent cannot be altered or waived for participants in this arm. • The dialysis facilities will be cluster-randomized, but consent from individuals will be obtained. • The study team plans to obtain Informed consent from patients in both study arms (Hi and Lo clusters). This will also enhance the ability to do patient-reported outcomes (PRO) data collection. • It was believed that the study should be transparent with all participants about their assignment and what risks and options they have. This should include information such as which approach the clinic is taking to serum phosphate control (eg, a more liberal approach vs. a more standard approach). This might require 2 different types of consent documents that include information tailored to cluster assignment. • In this regard the implications of using a Zelen or pre-randomization type of design in a cluster randomized trial were discussed.[1] • The study team plans to use a video to provide study information to participants. • A web portal will be used to capture electronic consent. • There was a question about whether there would be enrollment bias based on the pre-randomized patient assignment. In a setting where consent is being obtained, the consent process could be designed so that researchers can ask why participants decline to participate. This could be informative about differences between those who agree and those who refuse. • It was suggested that the study team conduct a pilot study of the consent process to see how it affects decision making and enrollment rates in the different arms of the trial since	Completed: The Collaboratory coordinating center sent the study team 2 articles: (1) "Ethical and regulatory issues of pragmatic cluster randomized trials in contemporary health systems" (Anderson et al. 2015, *Clinical Trials*) and (2) "Gatekeepers for pragmatic clinical trials" (Whicher et al. 2015, *Clinical Trials*).

[1] See the NIH Collaboratory Demonstration Project SPOT (Suicide Prevention Outreach Trial: Greg Simon, PI).

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	it might be permissible to use a different approach to disclosure and authorization in the "Lo" arm, which might minimize burden without affecting patients' rights or welfare. • The study team can look at the provisions of FDA guidance and the revised Common Rule about the equivalence of electronic informed consent to actual written consent (as is being employed in the ADAPTABLE aspirin study[2]).	
Privacy/HIPAA	• The dialysis organizations manage their own HIPAA authorizations. • Data will be sent to the Duke Clinical Research Institute (DCRI) from DaVita, DCI, and University of Utah. DCRI will work with DaVita, DCI, Utah to determine best approach for transfer of data. • There were no additional privacy concerns.	
Monitoring and oversight	• The study will not use site monitors/onsite visits. • There will not be designated study coordinators at the recruiting locations. Instead, local dieticians will coordinate/communicate with the clinical research associate (CRA)/Lead CRA. • NIDDK requires a data and safety monitoring board (DSMB) and will convene it on their own separate from the study team.	
Issues beyond the study	• A certificate of confidentiality will be automatically provided per new NIH policy. This certificate adds provisions for future research uses and confidentiality obligations for future data sharing. • The question about potential enrollment bias related to pre-randomization is of relevance across other PCTs, and it would be interesting to gather information from other trials to help understand this possibility.	

[2] See http://theaspirinstudy.org/.

SPECIFIC AIMS

As the population ages and therapeutic advances improve life expectancies of chronic diseases, the prevalence of end-stage renal disease (ESRD) inexorably increases. Kidney transplantation is the preferred treatment for ESRD, but an insufficient supply of healthy organs renders dialysis the only life-saving treatment option for most patients. Although dialysis outcomes have improved modestly in recent years, rates of hospitalization (~2 per patient-year) and mortality (15–20%) remain unacceptably high, driven primarily by increased cardiovascular risk. Multiple interventions that are proven to prevent cardiovascular disease and death in the general population failed to significantly improve outcomes in clinical trials of patients with ESRD. These disappointing results stimulated the nephrology community to reach for new but unproven approaches to improve outcomes in ESRD.

Hyperphosphatemia is a ubiquitous complication of ESRD that is *associated* with increased risks of cardio-vascular disease and death in observational studies. Based on these data, and starved for therapeutic advances to improve outcomes in ESRD, the nephrology community advanced *opinion-based* practice guidelines that recommend aggressive treatment of hyperphosphatemia to near normal levels (<5.0 mg/dl) in patients with ESRD, but the optimal serum phosphate target has never been tested in a randomized outcomes trial. The cornerstone of phosphate control is the combination of thrice-daily phosphate binders, which reduce serum phosphate by limiting dietary phosphate absorption, and strict adherence to low phosphate diets. More than 80% of patients with ESRD are treated with metal- or polymer-based phosphate binders, but none of these were tested in placebo-controlled randomized clinical outcomes trials. While patients who adhere to burdensome, life-long binder and dietary regimens may realize theoretical benefits of strict phosphate control, excessive treatment to achieve an unnecessarily low serum phosphate may actually *worsen* outcomes by: 1) inducing metal overload; 2) promoting early satiety that exacerbates ESRD-associated malnutrition; and 3) eroding patients' quality of life by adding phosphate-related demands to an already high pill burden. Similarly, restricting dietary phosphate intake may contribute to protein malnutrition and reduced quality of life. All of these potential risks may have escaped detection precisely because of the lack of any randomized outcomes trials.

Clinical equipoise is the **scientific premise** for conducting "HiLo", which is a pragmatic, open-label, cluster-randomized clinical outcomes trial of ~4400 patients with ESRD undergoing hemodialysis at >100 facilities operated by 3 dialysis provider organizations. HiLo will test the hypothesis that liberal control of serum phosphate, targeting 6–7 mg/dl, will yield non-inferior rates of all-cause hospitalization compared to the current standard approach of strictly targeting serum phosphate levels <5.0 mg/dl. The main secondary endpoints will be all-cause mortality and change in serum albumin as an indicator of protein malnutrition.

During the 12-month milestone-driven UG3 phase, we will execute following four Specific Aims:

Aim 1: Establish the framework for a successful HiLo trial and energize support from its key stakeholders.
Aim 2: Finalize the HiLo protocol and secure regulatory approval using a central IRB.
Aim 3: With input from providers and patients, develop, pilot, and optimize HiLo's centralized electronic informed consent process.
Aim 4: Create, pilot and optimize HiLo's bioinformatics platforms for recruitment, data capture, and intervention monitoring.

During the 48-month UH3 phase, we will execute the following three Specific Aims:

Aim 1: Conduct the HiLo cluster-randomized pragmatic trial evaluating two different serum phosphate targets for dialysis-dependent ESRD.
Aim 2: Prepare for post-trial dissemination of the findings and broad implementation in accordance with the results.
Aim 3: Advance the field of pragmatic trials through active participation in Collaboratory-wide initiatives.

Throughout the UG3 and UH3 phases, members of the HiLo Steering Committee will actively contribute to Collaboratory Working Groups and will engage the Collaboratory's expertise to: 1) develop strategies to address any unanticipated operational, ethical, regulatory, design, and technological challenges; and 2) ensure that HiLo implements best practices for quality control and electronic data extraction and sharing.

HiLo will answer a critical clinical question using a pragmatic design that is rigorous, efficient, and generalizable beyond the research setting. Fully responsive to RFA-RM-16-09, HiLo will use non-restrictive eligibility criteria, a "real-world" intervention implemented by clinicians, a primary endpoint that is highly relevant to all stakeholders, and data acquired entirely through clinical care. Importantly, HiLo will advance the field of pragmatic trials by delivering a "greater than minimal risk" intervention that requires individual-level informed consent. Nephrologists and trial experts will lead the HiLo Steering Committee which will be supported by a sophisticated team of clinical trials professionals at the Duke Clinical Research Institute (DCRI), which is also the Coordinating Center for the NIH Health Care Systems Research Collaboratory. By providing critical new data in response to longstanding calls to define the optimal serum phosphate target in ESRD, HiLo will efficiently generate actionable results that will be rapidly translated into ESRD care through the well-established networks of US dialysis units.