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** August 16, 2018	**PROPOSED ACTIONS** August 16, 2018	**CURRENT STATUS** As of October 18, 2019
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;		• The trial remains largely unchanged. • Dialysis Clinic, Inc., is no longer participating in the trial because they were not willing to commit to the study design. A strategy for phased enrollment has been developed. This involves selecting a certain number of sites (10-20 depending on size) and having dietitians approach 10 patients per week until all eligible patients in the dialysis unit have been approached (anticipated time is 3-5 months). Enrollment will then cease at that site. This allows us to focus closely on the status of enrollments and be able to act quickly if concerns at a unit are identified. In addition, this will also decrease the financial burden by not having to purchase 150 iPads that will

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	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) • **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		be used during the consent process that would be necessary if simultaneous enrollment at all sites was used.

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	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. ○ **Primary outcome:** Rate of total all-cause hospitalization between the 2 study arms. ○ **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,		• The pilot of the centralized electronic informed consent has not yet taken place. The research team is still building the consent module, getting the necessary IRB approvals, and performing user acceptance testing with some DaVita dietitians. The pilot should begin within the next 2 months.

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	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.		• Plans to collect PROs have been abandoned due to resource constraints.
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.		• Awaiting IRB review of final materials (updated protocol, informed consent form, patient materials, etc.) in which Duke is requesting to be the IRB of record for the study and Dr. Wolf is designated as the site investigator for all the sites. • Awaiting IRB confirmation that DaVita and the University of Utah are considered to not be engaged in research.
Risk classification	• Risks to participants include risk of elevated serum phosphate		

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	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. • 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	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	• No change. We plan to obtain consent from all participants in both Hi and Lo arms using an electronic consent module loaded on iPads that will be provided to the dialysis units. • A video for both versions of the consent will be filmed on October 7, 2019. • The team will pilot the process in 10 local DaVita dialysis units next month. • We have incorporated questions regarding a patient's decision to not

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	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.	trials" (Whicher et al. 2015, *Clinical Trials*)	consent in order to monitor trends in responses and take appropriate actions to mitigate risks to enrollment.

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

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	• 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 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		• As described above, the pilot for the consent process has not yet taken place. Following the pilot for the basic process, consent for both arms will be initiated using 10 dialysis centers in the Raleigh/Durham and surrounding area. The team will consider lessons learned and implement any necessary changes to the consent process prior to future enrollment.

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	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.		A clinical monitoring plan is being finalized. Based on input from the DSMB, we have developed a report for monitoring phosphorus and enrollment targets. In lieu of having study coordinators performing on-site visits to the dialysis units the Duke Clinical Research Institute's site management & monitoring team will review enrollment reports weekly during the enrollment phase. Any concerns will be communicated with the unit staff and members of the steering committee. The reports should assist in identifying enrollment issues and participants who are

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

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			not reaching their targets, and therefore would need to have the dietitians work with those patients to reach their target.
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.		