Ethics/Regulatory Call with Dr. Dember's Demonstration Project – TiME
MINUTES
Date: May 28, 2013

Participants:

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These minutes were circulated to all participants on the call for two rounds of review and they reflect all corrections that were received.

AGENDA ITEMS	DISCUSSION	ACTION ITEM
Review of Demonstration Project	• Dr. Dember gave an overview of The Time to Reduce Mortality in End-Stage Renal Disease (TiME) trial, a large pragmatic clinical trial designed to determine whether dialysis facility implementation of a minimum hemodialysis session duration of 4.25 hrs for persons receiving thrice-weekly maintenance hemodialysis increases survival, reduces hospitalizations, and improves health-related quality of life (QOL) compared with usual care. • Approximately 400 outpatient dialysis facilities throughout the United States operated by two large dialysis provider organizations will be randomized 1:1 to the intervention or to usual care. Dialysis provider organizations have given written agreement to participate. • A total of 6432 patients will be enrolled over 1 year and followed for up to 3 years.	

	• The primary study outcome is mortality; secondary outcomes are hospitalization rate and health-related QOL.	
Minimal risk	• Some call participants felt that FDA might view the trial as more than minimal risk, although it was also noted that FDA does not formally comment on trials unless they have jurisdiction over them (and the trials call for an IDE or IND). NIH and FDA/CDRH are having discussions about dialysis products that would be used in the trial (dialysis products are not regulated as significant-risk devices). Per NIH representatives on the call, CDRH staff agrees that the dialysis schedule proposed in the TiME trial is consistent with approved product labeling for these devices. Therefore, IDE regulations should not apply in this instance, and FDA would not have jurisdiction over the TiME trial. • OHRP related that they had previous informal communications with staff at FDA about the trial, before the protocol had been finalized, and that issues of FDA jurisdiction and minimal risk were raised. OHRP encouraged NIH staff to follow up with FDA on these issues. • Determination that the risk of the research to participants is minimal is based on the following: 1) For patients in the usual-care group, there is no intervention (medical care is not affected by trial participation) and the risk of loss of confidentiality is minimal. 2) For patients in the intervention group, dialysis session duration will be longer than it would have been otherwise for some patients, and no different for some patients (because a duration of 4.25 hrs is within the range of typical dialysis treatments). There are no known or anticipated medical risks of dialysis treatments of 4.25 hrs compared with shorter treatments. Because the duration of sessions will be prescribed by the treating nephrologist and is not mandated by the treatment protocol to be at least 4.25 hrs, the treatment duration will not be affected by trial participation if the treating nephrologist feels that session durations of 4.25 hrs or longer are not appropriate for the patient. As occurs routinely in dialysis, patients in intervention facilities will have ongoing	• NIH staff will follow up with FDA/CDRH staff, and will formally submit the final protocol document and device information to FDA/CDRH to address issues of jurisdiction, and to inquire whether FDA has further concerns regarding the trial.

	opportunities to influence the prescribed treatment session duration through frequent clinical interactions with the treating nephrologists and with other members of the dialysis facility staff. • The rationale as presented by the study team is included in the appended document. • If FDA does not have authority and does not have additional concerns about the trial, OHRP representatives indicated that they did not have other concerns.	
Consent (patient and physician)	• All trial participants will have end-stage renal disease and will receive treatment with maintenance hemodialysis due to their underlying disease and not because of trial participation. • Assuming FDA confirms that they do not have jurisdiction as described above, and IRB determines that the research is minimal risk, a waiver of consent feasible under 45 CFR 46.116. • All patients starting treatment in participating dialysis facilities will be provided with written information about the trial and a toll-free telephone number to contact research staff who can answer questions (a separate information sheet for patients will be available in the usual-care and intervention facilities). Additionally, there will be informational posters in the dialysis units throughout the duration of the trial (information sheet content appears in an appended document). • The research cannot practicably be conducted without a waiver of consent, as detailed in the appended document.	• Need to revise patient information sheet to further clarify that a patient's treatment time might differ as a result of the trial.
HIPAA	• Dr. Dember felt that criteria for 45 CFR 164.512 are satisfied and a waiver of HIPAA is acceptable. No objections or concerns were raised.	
Monitoring and oversight	• The NIH requires a data and safety monitoring plan to be submitted and approved by the primary NIH IC (NIDDK). • In accordance with NIDDK policy, they have determined that a formally-appointed, external DSMB is required. • The DSMB identified/supported by NIH/NIDDK will have the authority to make formal recommendations to the NIH about early	

	termination of the trial for futility, efficacy, or safety. • No objections or concerns were raised.	
Issues beyond the TiME trial	• FDA role in pragmatic clinical trials such as this remains unclear.	• Further follow-up can be arranged to report back to this group if needed.
Conclusion of meeting	• Follow-up needed, as noted in action items.	• A case study will provide guidance for others on the process and value of open dialogue with regulators.

SUPPLEMENTARY MATERIAL FOR TiME TRIAL

TiME Trial

Regulatory Considerations

May 28, 2013

1. Participating Institutions and Organizations
2. Trial Synopsis
3. Risk Determination
4. Information Provided to Patients, Opt-Out Mechanism, and Waiver of Consent
5. Approach to Consent for Dialysis Facility Personnel and Physicians
6. Waiver of HIPAA Authorization
7. Study Oversight
8. Specific Aims of Grant Application

1. Participating Institutions and Organizations

Prime Grant Awardee
University of Pennsylvania, Philadelphia, PA
Principal Investigator: Laura M. Dember, M.D.

Data Coordinating Center
Clinical Research Computing Unit / Center for Clinical Epidemiology and Biostatistics
Perelman School of Medicine at the University of Pennsylvania

Dialysis Provider Organizations
DaVita, Inc
Fresenius Medical Care North America

Steering Committee
Steven Brunelli, M.D., M.S.C.E., DaVita Inc.
Alfred Cheung, M.D., University of Utah
John Daugirdas, M.D., University of Illinois-Chicago
Michael Flessner, M.D., Ph.D., NIDDK/NIH
Tom Green, Ph.D., University of Utah
Paul Kimmel, M.D., NIDDK/NIH
Csaba Kovesdy, M.D., University of Tennessee
Eduardo Lacson, Jr. M.D., M.P.H., Fresenius Medical Care
Dana Miskulin, M.D., M.S., Tufts University
Ravi Thadhani, M.D., M.P.H., Massachusetts General Hospital
Wolfgang Winkelmayer, M.D., DSc, Stanford University

Study Sites
Approximately 400 outpatient dialysis facilities throughout the United States

2. TiME Trial Synopsis

Objective
The TiME to Reduce Mortality in End-Stage Renal Disease (TiME) trial is a large, pragmatic clinical trial designed to determine whether dialysis facility implementation of a minimum hemodialysis session duration of 4.25 hours for individuals receiving thrice-weekly maintenance hemodialysis increases survival, reduces hospitalizations and improves health-related quality of life compared with usual care.

Participating facilities
Four hundred and two dialysis facilities operated by two large dialysis provider organizations will be randomized (1:1) to either the Intervention or Usual Care. The dialysis facilities will be distributed throughout the United States. Facility eligibility criteria include 1) willingness of the facility's medical director, nephrologists and clinical leadership to adopt a facility approach of

recommending dialysis sessions of at least 4.25 hours for patients initiating treatment with maintenance hemodialysis, 2) ability of the facility to accommodate session durations of at least 4.25 hours for eligible participants, and 3) use of the electronic data systems of the dialysis provider organization.

Participating patients

6432 patients will be enrolled over one year and followed for up to 3 years. Eligibility criteria include initiation of maintenance dialysis within the previous 120 days, age of at least 18 years, and competency for providing consent for dialysis treatment.

Intervention and Usual Care

The Intervention facilities will adopt the approach of recommending that patients who are new to dialysis have treatment sessions of at least 4.25 hours. This approach will be formally approved by the Governing Body of the dialysis facility prior to implementing the trial intervention. In the Usual Care facilities, there will be no trial-driven recommendation about dialysis session duration. In both Intervention and Usual Care facilities, dialysis session duration will be prescribed by the treating nephrologists. Although the dialysis facilities in the Intervention arm will adopt an approach of recommending that dialysis session duration is at least 4.25 hours, the specific treatment times will be prescribed by the treating nephrologists allowing for individualization of the prescription based on other considerations including patient characteristics and patient preferences.

Primary Outcome: mortality

Major Secondary Outcomes: hospitalization rate, health-related quality of life

Data Collection

The electronic data systems of both of the dialysis provider organizations contain highly detailed clinical and treatment-related information from every dialysis treatment as well as the results of laboratory tests and hospitalization dates. Both provider organizations maintain these data in central data warehouses. For the TiME Trial, a pre-specified subset of data elements will be extracted from the central data warehouses and transferred to the Data Coordinating Center database at scheduled intervals. No laboratory studies will be performed specifically for the trial. The health-related quality of life assessment will be made using the KDQOL™36, a kidney disease-specific instrument that is administered by both dialysis provider organizations to all patients as part of routine practice and in accordance with a CMS requirement that quality of life be assessed at least once per year. Data elements for the trial include demographic and baseline comorbidity information, dialysis treatment data from all dialysis sessions (prescribed duration, delivered duration, pre- and post-treatment weights, pre- and post-treatment blood pressures), laboratory data, KDQOL™36 component summary scores and dates of hospitalizations, renal replacement modality changes, and death.

Analysis

The primary analysis will be an intention to treat comparison of time to death between intervention and usual care facilities. Secondary analyses will incorporate adjustment for co-variables that are not balanced between randomization groups. With the planned number of patients and clusters (dialysis units) there will be 80% power to detect a HR for mortality of 0.85 comparing the Intervention facilities to the Usual Care facilities assuming a mortality rate of 18% per year in the Usual Care group, an intra-class correlation coefficient for mortality of 0.03, a two-sided p value of 0.05, and a loss to follow-up rate of 5% per year.

Study Oversight

An independent Data and Safety Monitoring Board (DSMB) has been appointed by the National Institutes of Diabetes and Digestive and Kidney Diseases. The DSMB has reviewed the protocol and will monitor trial progress, data quality, dialysis treatment and clinical/laboratory data, outcome event rates, and interim analyses during the conduct of the study in accordance with a Data and Safety Monitoring Plan. The DSMB will have the authority to make formal recommendations to the NIH about early termination of the trial for futility, efficacy, or safety.

3. Risk Determination

Our determination that the risk of the research to participants is minimal is based on the considerations that follow. It is important to recognize that all trial participants will have end-stage renal disease and will be receiving treatment with maintenance hemodialysis because of their underlying disease and not because of trial participation.

3.1 Risks for Participants in the Usual Care facilities

There is no intervention for participants in Usual Care facilities and medical care for these participants is not affected by trial participation. Dialysis session duration is not altered based on trial participation for individual patients or the dialysis facility overall. A potential concern for "usual care" control groups in any trial is that an intervention that is potentially beneficial will be withheld because of trial participation. This is not a concern for the TiME trial as there will be no trial-based restrictions on care provided at the Usual Care facilities throughout the duration of the trial.

The only risk for patients in Usual Care facilities is loss of confidentiality resulting from the access by TiME Trial research personnel at the two dialysis provider organizations to electronic medical record data in order to confirm participant eligibility and abstract data for transmission to the Data Coordinating Center at the University of Pennsylvania. The research teams for the two participating organizations will have access only to health data for patients receiving care at their own organization (i.e., DaVita research team will not have access to Fresenius Medical Care patient data, and vice versa). All electronic medical record data used by research personnel at the provider organizations will be maintained in password protected computer files and or locked offices to ensure that access is limited to the research team. Each participant will have a unique research participant identifier (PID) that will be generated by the dialysis provider organization. The PID will not be related to the patient's medical record

number or any other identifier. The structure of the PID will be identical between the dialysis provider organizations. The provider organizations will manage the individual PIDs and will ensure that the individual identifiers are unique across all study subjects by establishing mutually exclusive ranges of values for PIDs between the two providers. Each of the dialysis provider organizations will maintain the key to the PIDs for participants enrolled from their organizations in password protected computers. The keys to the unique identifiers will not be transmitted to the Data Coordinating Center. During the data extraction process, all personal identifiers will be replaced by the PID. No direct identifiers will be transmitted to the Data Coordinating Center. The only protected health information that will be transmitted to the Data Coordinating Center are dates. It is extremely unlikely that patients will be identifiable by these dates because of the tremendous overlap in dates of care across participants (and non-participants) since patients at all dialysis facilities receive thrice-weekly on either Monday, Wednesday and Friday, or Tuesday, Thursday and Saturday. The identity of dialysis facilities or clinicians will not be transmitted to the Data Coordinating Center. Within the dialysis provider organizations data extraction from the clinical data warehouses will be performed by highly trained information technologists with extensive experience protecting electronic health information. The data will be transmitted to the Data Coordinating Center using secure ftp sites and maintained in password-protected files on secure servers. Because of the processes in place to protect identifiers from improper use or disclosure, the plan to destroy links to identifiers after data analysis and manuscript publication are complete, and the written assurances that PHI will not be reused or disclosed to other individuals as described in Section 6.1, the access to PHI involves no more than a minimal risk to the privacy of individuals.

3.2 Risks for Participants in Intervention Facilities

The risk of loss of confidentiality for patients in Intervention facilities is the same as for patients in Usual Care facilities and involves no more than a minimal risk to the privacy of individuals as described in Sections 3.1 and 6.1.

For some of the patients receiving care in Intervention facilities, the dialysis session duration will be longer than it would have been if the facility were not participating in the trial, and for some patients in Intervention facilities the duration will be no different than it would have been if the facility were not participating in the trial. Because dialysis session duration of 4.25 hours is within the range of typical dialysis treatments, there will be patients for whom implementing a facility approach of recommending a minimum treatment of 4.25 hours will not alter care (i.e., those patients who otherwise would have had treatments 4.25 hours or longer). Because the duration of dialysis sessions will be prescribed by the treating nephrologist and is not mandated by the treatment protocol to be at least 4.25 hours, the treatment duration will not be affected by trial participation if the treating nephrologist feels that a session duration of 4.25 hours or longer is not appropriate for the patient. As occurs routinely in dialysis clinical care, patients in Intervention facilities will have ongoing opportunities to influence the prescribed treatment session duration through frequent clinical interactions with the treating nephrologists and with other members of the dialysis facility staff. In routine clinical dialysis care, patient preferences are incorporated into dialysis session prescriptions, and allowance for incorporation of patient preferences into the prescription will be maintained in the Intervention facilities (and in the Usual Care facilities).

Risks of increasing the duration of dialysis sessions to 4.25 hours

Typical dialysis sessions in the United States have durations of 3 to 5 hours. There is a substantial body of observational data and some data from small clinical trials demonstrating better clinical outcomes among patients who receive dialysis treatments that are longer than 4 hours. In addition to survival advantages, these benefits include greater hemodynamic stability, better blood pressure control, less hyperphosphatemia, less myocardial stunning, less progression of left ventricular hypertrophy, decreased fatigue, improvement in measures of quality of life and improvement in 6-minute walk score. Longer dialysis sessions are associated with less hemodynamic stress because of slower removal of fluid (fluid removal goals during dialysis are based on inter-dialytic fluid gains and not the dialysis session duration). While not all studies found benefits associated with longer dialysis sessions, studies have not identified harms (including studies of dialysis session durations of 6-10 hours). Dialysis session durations of 6-10 hours are increasingly being used in the United States and have been used for decades in other countries. Currently, there are approximately 1400 patients undergoing in-center nocturnal hemodialysis (6-8 hours) in dialysis facilities operated by Fresenius Medical Care, one of the dialysis provider organizations participating in the TiME trial.

There are risks related to end-stage renal disease and the hemodialysis procedure; however, these risks should not increase as a result of performing dialysis sessions that are 4.25 hours in duration. Serious complications of hemodialysis related to technical aspects of the dialysis procedure such as air embolism and hemolysis are extremely rare, typically occur within the first 10-60 minutes of a dialysis session, and are not related to dialysis session duration. It is anticipated that some participants will find it burdensome to spend more time at the dialysis facility than they would otherwise. However, because patient input into his/her session duration is permitted throughout trial participation (as it is in clinical care), this potential burden can be readily eliminated.

3.3 Summary of Risks of the TiME Trial

3.3.1 Usual Care group: The research involves a risk of loss of confidentiality that is no greater than a minimal risk to privacy. There are no other risks associated with the research for participants in the Usual Care group.

3.3.2 Intervention group: In addition to loss of confidentiality of protected health information that is no greater than a minimal risk to privacy, participants in the Intervention facilities may experience burdens associated with spending more time having dialysis treatments. These risks are minimal because patient input into session duration is maintained such that any actual or anticipated burdens can be eliminated. The additional dialysis time resulting from the trial intervention does not have medical risks, and because treating nephrologists will prescribe the dialysis session durations, the opportunity for individualized care is maintained.

4. Information Provided to Patients, Opt-Out Mechanism, and Waiver of Consent

4.1 Information Provided to Patients and Opt-Out Mechanism

All patients starting treatment in participating dialysis facilities will be provided with written information about the trial. Additionally, there will be informational posters in the clinical care areas of the dialysis units throughout the duration of the trial. The information sheet for the Usual Care facilities will include: 1) the trial sponsor, 2) the purpose of the trial, 3) the approach to dialysis session duration at the facility (no change as a result of the trial), 4) the treating physician's role in prescribing the duration of the dialysis sessions, 5) a description of the transmission of de-identified patient data to the University of Pennsylvania, 6) a statement that no additional testing will be performed for the trial, and 7) a toll-free telephone number to speak with the research teams at the dialysis provider organizations to obtain information about the trial, have questions answered, or to opt-out of trial participation. The information sheet for the Intervention facilities will include: 1) the trial sponsor, 2) the purpose of the trial, 3) the approach to dialysis session duration at the facility (4.25 hours or longer as long as the treating nephrologist thinks that is medically appropriate for the patient, 4) the treating physician's role in prescribing the duration of the dialysis sessions, 5) a description of the transmission of de-identified patient data to the University of Pennsylvania, 6) a statement that no additional testing will be performed for the trial, 7) a statement that patients can participate in the trial (i.e., have data transmitted to the University of Pennsylvania) even if treatment sessions are shorter than 4.25 hours, and 8) a toll-free telephone number to speak with the research teams at the dialysis provider organizations to obtain information about the trial, have questions answered, or to opt-out of trial participation.

4.2 Rationale for Waiver of Consent

We have requested a waiver of the requirement for informed consent based on the following criteria set forth by the Federal Policy for the Protection of Human Subjects (HHS 45 CFR part 46):

4.2.1 The research involves no more than minimal risk to subjects.

See Section 3 above for the anticipated risks of the research. For both the Usual Care and Intervention groups the probability and magnitude of harm or discomfort anticipated to result from the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

4.2.2 The waiver will not adversely affect the rights and welfare of the subjects.

4.2.2.1 Patients initiating dialysis treatment at a participating facility will be provided with written information about the trial at the time they initiate dialysis and information about the trial will be posted in the dialysis facilities throughout the duration of the trial.

4.2.2.2 Throughout the duration of the trial, patients will have the opportunity to contact research personnel via a toll-free telephone number in order to obtain more information about the trial and have questions answered.

4.2.2.3 Patients will have the opportunity to opt out of trial participation.

4.2.2.4 Although Intervention facilities will have a trial-driven approach to dialysis session duration, opportunity for individualizing treatment durations will be maintained since the dialysis session duration will be prescribed by the treating nephrologist who will be able to incorporate other considerations including preferences of participating patients into the session length determinations.

4.2.2.5 Participant confidentiality will be protected through the mechanisms described in Section 3.1.

4.2.3 Whenever appropriate, the subjects will be provided with pertinent information after participating in the trial.

After the trial is over, the researchers will prepare a summary of the major findings for distribution by the participating facilities to patients receiving care at the facilities.

4.2.4 The research cannot practicably be conducted without the waiver.

The major objective of this trial is to determine whether clinical outcomes are improved for patients treated with maintenance hemodialysis if dialysis session durations are at least 4.25 hours. Several factors are relevant to the assessment of practicability of obtaining consent:

4.2.4.1 The trial is designed to evaluate effectiveness rather than efficacy and therefore aims to enroll as broad a group of patients as possible in a large number of dialysis facilities rather than in a highly selected subset. Previous clinical trials evaluating dialysis dose or frequency have enrolled patients that are not representative of the overall U.S. patient population. Without the waiver of the requirement for consent, it is anticipated that there will be bias that will undermine the scientific objective of evaluating effectiveness of the intervention.

4.2.4.2 Cluster randomization by dialysis facility is necessary in order to implement the intervention without contamination of the "usual care" arm in which the intention is to not influence the duration of dialysis session. Because the randomized treatment assignment for the dialysis facility will be determined before patients are enrolled, a requirement for patient-level informed consent will likely result in important differences in the characteristics of participants in the two treatment groups. These differences in baseline characteristics will undermine the scientific validity of the research.

4.2.4.3 An important objective of this research is to implement the trial using the routine clinical care delivery model of the health care setting in which participants are receiving care. The trial is being conducted at approximately 400 dialysis facilities throughout the United States with routine dialysis care delivered by physicians, nurses and dialysis technicians and no active data collection. Because the clinical care

providers at the dialysis facilities do not conduct research and do not have training in the protection of human subjects, relying on these individuals to obtain consent for research is not appropriate and is not consistent with NIH requirements for NIH-sponsored research.

4.2.4.4 Standard infection control practices in dialysis facilities limit some of the more innovative approaches to consenting that can be implemented in non-dialysis settings (e.g., electronic consent using facility computers or tablets shared across patients).

4.2.5 The research involves the use of devices (dialysis equipment) in accordance with current product labeling and therefore an IDE submission is not required.

5. Approach to Consent for Dialysis Facility Personnel and Physicians

During the process of enrolling dialysis facilities, the medical directors, facility managers, and nephrologists will be provided with information about the trial and the research team will confirm willingness to have the dialysis facility participate in the trial. For facilities randomized to the Intervention group, a formal adoption by the facility's Governing Body of the approach to recommend a minimum dialysis session duration of 4.25 hours will be required. Dialysis unit personnel and physicians will not be asked to sign an informed consent document as they will not be research participants. The data set will not include any information about treating physicians or dialysis facility staff and there will be no opportunity to link clinician practices or behavior with patient outcomes. Additionally, there will be no identifying information about dialysis facilities included in the data set.

6. Waiver of HIPAA Authorization

The trial will be conducted with a waiver of HIPAA authorization. Justification for waiving HIPAA authorization is based on the following criteria provided in the HHS Regulation 45 CFR 164.512:

6.1 The use of disclosure of protected health information (PHI) involves no more than a minimal risk to the privacy of individuals because a) processes will be in place to protect PHI from improper use or disclosure; b) PHI will be destroyed at the earliest possible time; and c) there will be no improper use or disclosure of PHI.

Processes to protect PHI from improper use or disclosure include i) limiting access to medical records to trained research personnel who have knowledge about protecting patient confidentiality, ii) maintaining links to direct identifiers in secure, role-based password-protected files stored within the data warehouses of the dialysis provider organizations with no transmission to the Data Coordinating Center, iii) transmitting to the Data Coordinating Center only a limited dataset that contains no direct identifiers and has dates as the only PHI), and iv) extracting from the clinical data warehouses and transmitting to the Data Coordinating Center only the specific data elements required for the research. The link between identifiers and the

data set will be destroyed after data analyses and publication of manuscripts is complete, and all PHI (dates) will be stripped from the data set prior to any transmission of data from the Data Coordinating Center to investigators or to the NIH data repository. Assurances that the PHI will not be reused or disclosed will be provided through written statements by the researchers with access to the PHI.

6.2 The research could not practicably be conducted without the waiver.

The aim of the trial is to evaluate effectiveness of the intervention for the broad population of patients treated with maintenance hemodialysis rather than to assess efficacy of the intervention for a selected subset of patients. The trial is being conducted within a health care delivery setting at approximately 400 dialysis facilities throughout the United States with routine dialysis care delivered by physicians, nurses and dialysis technicians. Dialysis treatment information and clinical data will be collected through large-scale data extractions. The health care providers at the dialysis facilities who will be generating trial data through routine clinical care are not research personnel and thus are not able to administer research documents such as a HIPAA waiver of authorization. Under this implementation model, obtaining authorization from participants for use and disclosure of PHI is not practicable.

6.3 The research could not practicably be conducted without access to and use of the PHI.

The researchers at the dialysis provider organizations (employees of the covered entities) require access to PHI in order to establish eligibility for trial participation and to extract data generated through routine clinical care from the clinical data warehouses for transmission to the Data Coordinating Center. The only PHI that will be transmitted to the Data Coordinating Center is a limited dataset comprised of dates of dialysis sessions, death, and hospitalizations. There will be no direct identifiers transmitted to the Data Coordinating Center. Dates of dialysis sessions are needed to evaluate adherence to the intervention, to determine whether adherence is maintained over time, and to evaluate separation in treatment duration between treatment groups throughout the duration of the trial. Dates of death and dates of hospitalizations are needed these events are outcomes for the trial.

7. Study Oversight

The trial is being conducted under a cooperative agreement between the National Institutes of Health and the University of Pennsylvania with subcontracts from the University of Pennsylvania to the two participating dialysis provider organizations and to the six academic institutions with which the members of the Steering Committee are affiliated. The Institutional Review Board of the University of Pennsylvania is serving as the IRB of record for the trial. The dialysis provider organizations have provided written authorization for this approach.

An independent Data and Safety Monitoring Board (DSMB) has been appointed by the National Institutes of Health. The DSMB has reviewed the protocol and will monitor trial progress, data quality, dialysis treatment and clinical/laboratory data, outcome event rates, and interim analyses during the conduct of the study in accordance with a Data and Safety Monitoring Plan. The DSMB will have the authority to make formal recommendations to the NIH about early termination of the trial for futility, efficacy, or safety.