Time to Reduce Mortality in End-Stage Renal Disease (TiME)

Laura Dember, MD

Meeting Participants (May 28, 2013):

☒	Jeremy Sugarman (Johns Hopkins)	☒	Emma Meagher (Univ Penn)	☒	Julie Kaneshiro (OHRP)	☒	Paul Kimmel (NIH)
☒	Rob Califf (Duke)	☒	Susan Ellenberg (Univ Penn)	☒	Robert Star (NIDDK)	☒	Josephine Briggs (NIH)
☒	Laura Dember (Univ Penn)	☒	Megan Singleton (Univ Penn)	☒	Catherine Meyers (NIH)	☒	Cheri Janning (Coord Center)
☒	Denise Cifelli (Univ Penn)	☒	Jerry Menikoff (OHRP)	☒	Wendy Weber (NIH)	☒	Tammy Reece (Coord Center)
☒	Rosemary Madigan (Univ Penn)	☒	Irene Stith-Coleman (OHRP)	☒	Sarah Carr (NIH)	☒	Monique Anderson (Duke)
☒	Tracy Ziolek (Univ Penn)	☒	Ivor Pritchard (OHRP)	☒	Michael Flessner (NIDDK)	☐	

The minutes from the May 28, 2013 meeting were circulated to all participants on the call for two rounds of review and they reflect all corrections that were received.

AGENDA ITEMS	DISCUSSION May 28, 2013	PROPOSED ACTION May 28, 2013	CURRENT STATUS as of May 25, 2015
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		The project is using a single IRB of record. The plan is unchanged.

	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.	• 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.	A formal request to the FDA for a determination regarding the need for an IDE (Investigational Device Exemption) was submitted by the NIDDK. The determination by the FDA was that the TiME trial is exempt from the IDE regulations because it meets the conditions for an exempt investigation as provided by 21 CFR 812.2 (c)(2): a marketed postamendment device that is used or investigated in accordance with the indications in the labeling.

	• 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 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.	The project is using waiver of informed consent with an opt-out mechanism. Information documents describing the research are provided to all potential participants and are posted in dialysis facilities for the duration of the trial. The documents provide a toll-free telephone number that can be used by patients to obtain additional information, ask questions, and/or opt out of trial participation. The approach to consent did not change other than a modification to the information document that clarifies for patients in intervention facilities that the treatment time might be longer as a result of the trial. The plan did not change.
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.		The plan did not change.
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 project is using an external Data and Safety Monitoring Board. The plan did not change.

	• 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.	As described above, the team obtained a formal determination from the FDA that the trial does not require an IDE.
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.	
Additional regulatory or ethics issue(s) that arose after the meeting			None noted.
Additional follow-up information			None noted.