

# TiME Trial

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

A large, cluster-randomized, pragmatic trial to evaluate the effects on mortality, hospitalizations, and quality of life of increasing the dialysis session duration for thrice weekly maintenance hemodialysis

<b>Sponsor</b>	<b>National Institute of Digestive, Diabetes and Kidney Disease (NIDDK)</b>
<b>NIH Grant Number</b>	<b>1UH2AT007797-01, UH3DK102384</b>
<b>University of Pennsylvania Protocol Number</b>	<b>817911</b>
<b>Principal Investigator</b>	<b>Laura M. Dember, MD</b>
<b>Clinical Trials.gov Number</b>	<b>NCT02019225</b>
<b>Date: September 20, 2013</b>	<b>Version Number: 1.1</b>
<b>Amendment #1: June 26, 2015</b>	<b>Version Number: 1.2</b>
<b>Amendment #2: June 7, 2016</b>	<b>Version Number: 2.0</b>

**TiME Trial  
Approved Protocol Amendments**

<b>Amendment 1 to Protocol Version 1.1: June 26, 2015</b>		<b>Section</b>
1.	Protocol date and version Date changed from September 20, 2013 to June 26, 2015 Version changed from 1.1 to 1.2	Cover Page
2.	Enrollment period Changed to 3 years	Protocol Summary Table
3.	Duration of trial Changed to 4.5 years	Protocol Summary Table
4.	Analytic approach wording changed to more clearly describe primary and secondary analysis populations: Changed from “Primary treatment analysis population” To “Primary analysis population” Change from “Secondary treatment analysis population” To “Secondary analysis population”	Protocol Summary Table
5.	Analytic Approach Correction of anthropometric volume cutoff for inclusion in primary analysis population from <4.25 liters to ≤ 4.25 liters	Protocol Summary Table
6.	Current approach to prescribing hemodialysis session duration: Changed from: “The TiME Trial will evaluate the effects on outcomes of dialysis session durations of at least 4.25 hours prescribed...” To: “The TiME Trial will evaluate the effects on outcomes of prescribing dialysis session durations of at least 4.25 hours...”	Section 1.1
7.	Potential physiological benefits of longer dialysis treatment time Changed from: “Longer dialysis session lengths increase the removal of solutes that are...” To: “Longer dialysis sessions increase the removal of solutes that are...”  Changed from: “...rapid removal of fluid has been linked to mortality presumably because of deleterious hemodynamic alterations” To: “...rapid removal of fluid has been linked to mortality presumably because of hemodynamic alterations”  Changed from: “The occurrence of such “stunning” episodes has been associated with increased risk of mortality, as a result of transient coronary under-perfusion.” To: “The occurrence of such “stunning” episodes has been associated with increased mortality.”	Section 1.1
8.	Treatment time and body size Correction of anthropometric volume cutoff for inclusion in primary analysis population: Changed from: “...less than 42.5 Liters” To: “...less than or equal to 42.5 Liters”	Section 1.1

## TiME Trial: Approved Protocol Amendments

Amendment 1 to Protocol Version 1.1: June 26, 2015		Section
9.	<p>Why women and smaller patients often have shorter treatment times</p> <p>Deleted an unnecessary word (but) from the following sentence:            Changed from: “....do not take into account removal of fluid and uremic toxins with larger molecular weights and but may be suboptimal in terms of survival and quality of life.”            To: “....do not take into account removal of fluid and uremic toxins with larger molecular weights and may be suboptimal in terms of survival and quality of life.”</p>	Section 1.1
10.	<p>Randomization</p> <p>Changed from: “The allocation sequence will be based on a permuted randomization procedure with a block size of four stratified by 1) dialysis provider organization, 2) proportion of prevalent patients receiving dialysis via a central venous catheter...”            To: “The allocation sequence will be based on a permuted randomization procedure stratified by 1) dialysis provider organization, 2) proportion of prevalent patients at a dialysis facility receiving dialysis via a central venous catheter...”</p>	Section 4.4
11.	<p>Other Secondary Effectiveness Outcomes</p> <p>Wording correction            Changed from: “intra-dialytic weight gain”            To: “inter-dialytic weight gain”</p>	Section 4.7.2.3
12.	<p>Participant Timeline</p> <p>Changed from: “Participants will be followed until the administrative end of the trial which will be 3 years after the trial begins”            To: “Participants will be followed for 3 years”</p>	Section 4.9
13.	<p>Waiver of Informed Consent</p> <p>Added the following detail about how participants will get information at the end of the trial:            “Dissemination of pertinent information can be accomplished by distributing information documents at participating facilities after the trial is over.”</p> <p>Changed formatting such that underlined statements are headings rather than embedded in a paragraph</p> <p>Added the heading: “<u>The research question cannot be practicably answered without a waiver of informed consent</u>” just prior to “A major objective of the trial is to evaluate effectiveness of the intervention for the overall population of patients receiving maintenance hemodialysis rather than to evaluate efficacy of the intervention for a selected, non-representative subset”</p> <p>Removed the following sentence (last sentence of the section) because of redundancy due to new heading:            “<u>Thus, answering the research question is not practicable without a waiver of informed consent</u>”.</p>	Section 5.3.1

**TiME Trial: Approved Protocol Amendments**

<b>Amendment 1 to Protocol Version 1.1: June 26, 2015</b>		<b>Section</b>
14.	<p>Waiver of HIPAA Authorization</p> <p>Removed the following redundant text from the end of item #2 because the same sentence is also at the beginning of the paragraph:</p> <p>“The TiME Trial is designed 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.”</p>	Section 5.3.2

<b>Amendment 2 to Protocol Version 1.2: June 7, 2016</b>		<b>Section</b>
1.	<p>Protocol date and version</p> <p>Date changed from September 20, 2013 to June 26, 2015</p> <p>Version changed from 1.1 to 1.2</p>	Cover page
2.	<p>Number of Facilities &amp; Patients</p> <p>Sample size increased from 6432 to 6880 participants</p>	Protocol Summary Table
3.	<p>TiME Trial Study Group</p> <p>Changed affiliation of Eduardo Lacson, Jr, M.D. from Fresenius Medical Care to Tufts University</p>	Section 3.2
4.	<p>Participant and Facility Incentive Program (new section)</p> <p>Added the following new text:</p> <p>“A Participant Incentive Program will be implemented at Intervention facilities to encourage patient adherence to longer treatment times. Participants will receive a monetary incentive if they achieve a specified increase in their session duration. The criteria for receiving the incentive payments will be provided to participants in writing.</p> <p>A Facility Incentive Program will also be implemented. Intervention facilities will receive a monetary award if the facility meets specified session durations for their participants.</p> <p>The DCC will determine on a monthly basis which patients and facilities meet the incentive criteria. The payments will be distributed by the research teams at the dialysis provider organizations. Incentive programs will be piloted at 10 Intervention facilities to assess the impact and optimize the implementation before initiating a study-wide roll-out of the program.”</p>	Section 4.6.2
	<p>Revised Sample Size (new section)</p> <p>Added the following new text and table:</p> <p>“Sample size calculations were repeated after the trial was underway to incorporate the following changes to assumptions that affect study power. These changes include the following:</p> <p>1) Facility enrollment did not begin until just prior to participant enrollment rather than being carried out and completed during the 12 months prior to participant enrollment. As a result the duration of participant enrollment</p>	Section 6.2.1

<b>Amendment 2 to Protocol Version 1.2: June 7, 2016</b>								<b>Section</b>																																																																																										
<p>increased from 1 year to 3 years. The duration of the trial was increased to 4.5 years to maintain a median follow-up of 2.5 years.</p> <p>2) A total of 266 rather than 402 facilities agreed to participate and 10 facilities withdrew from the trial after randomization resulting in a smaller number of clusters and larger size of clusters.</p> <p>3) The percentage of participants who were lost to follow-up because of transplantation or facility transfer was higher than anticipated.</p> <p>4) The observed intra-cluster correlation coefficient (ICC) for mortality determined during the trial after approximately 5000 participants were enrolled was lower than anticipated with observed ICC of approximately 0.01 rather than 0.03.</p> <p>Table 2R shows sample size requirements under scenarios that incorporate the modifications described above including enrollment period of 36 months and a total study duration of 54 months, a cluster number of 256 and cluster size standard deviation (SD) of 10 or 16, a loss to follow-up rate of 10%, and an ICC for mortality of 0.012 or 0.015. For the primary analysis, the desired detectable hazard ratio for mortality risk is 0.85 comparing the Intervention arm to the Usual Care arm in the primary treatment assessment population. A sample size of 6,880 (4250 in primary analysis population) provides 77 – 82% power to detect a HR of 0.85 with a two-sided alpha of 0.05.</p> <table border="1"> <thead> <tr> <th>Enrollment Time/Total Study Time (mos)</th><th># Clusters</th><th>SD for Cluster Size (1° Analysis Population)</th><th>Annual Loss to F/U</th><th>Annual Mortality Rate</th><th>ICC for Mortality</th><th>Sample Size for 1° Analysis Population</th><th>Total Sample Size</th><th>Power to detect HR 0.85</th></tr> </thead> <tbody> <tr> <td>12/36</td><td>402</td><td>0</td><td>5%</td><td>18%</td><td>0.03</td><td>4020</td><td>6432</td><td>80%</td></tr> <tr> <td>36/54</td><td>256</td><td>10</td><td>10%</td><td>18%</td><td>0.015</td><td>4020</td><td>6432</td><td>78%</td></tr> <tr> <td>36/54</td><td>256</td><td>16</td><td>10%</td><td>18%</td><td>0.015</td><td>4020</td><td>6432</td><td>76%</td></tr> <tr> <td>36/54</td><td>256</td><td>10</td><td>10%</td><td>18%</td><td>0.012</td><td>4020</td><td>6432</td><td>80%</td></tr> <tr> <td>36/54</td><td>256</td><td>16</td><td>10%</td><td>18%</td><td>0.012</td><td>4020</td><td>6432</td><td>78%</td></tr> <tr> <td>36/54</td><td>256</td><td>10</td><td>10%</td><td>18%</td><td>0.015</td><td>4250</td><td>6800</td><td>80%</td></tr> <tr> <td>36/54</td><td>256</td><td>16</td><td>10%</td><td>18%</td><td>0.015</td><td>4250</td><td>6800</td><td>77%</td></tr> <tr> <td>36/54</td><td>256</td><td>10</td><td>10%</td><td>18%</td><td>0.012</td><td>4250</td><td>6800</td><td>82%</td></tr> <tr> <td>36/54</td><td>256</td><td>16</td><td>10%</td><td>18%</td><td>0.012</td><td>4250</td><td>6800</td><td>80%</td></tr> </tbody> </table>								Enrollment Time/Total Study Time (mos)	# Clusters	SD for Cluster Size (1° Analysis Population)	Annual Loss to F/U	Annual Mortality Rate	ICC for Mortality	Sample Size for 1° Analysis Population	Total Sample Size	Power to detect HR 0.85	12/36	402	0	5%	18%	0.03	4020	6432	80%	36/54	256	10	10%	18%	0.015	4020	6432	78%	36/54	256	16	10%	18%	0.015	4020	6432	76%	36/54	256	10	10%	18%	0.012	4020	6432	80%	36/54	256	16	10%	18%	0.012	4020	6432	78%	36/54	256	10	10%	18%	0.015	4250	6800	80%	36/54	256	16	10%	18%	0.015	4250	6800	77%	36/54	256	10	10%	18%	0.012	4250	6800	82%	36/54	256	16	10%	18%	0.012	4250	6800	80%	
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5.	<p><b>Reports and Interim Analyses</b></p> <p>Corrected patient enrollment completion to 3 years</p> <p>Modified interim analysis plan:            Changed from: “Two interim analyses comparing treatment effectiveness between the treatment and control arms at 12 and 24 months are proposed.”            To: “An interim analysis will be performed when participants reach 50% information-time.”</p>							Section 7.3																																																																																										

<b>Protocol Summary</b>	
<b>Title</b>	Time to Reduce Mortality in End-Stage Renal Disease (TiME) Trial
<b>Short Title</b>	TiME Trial
<b>Protocol Number</b>	817911
<b>Sponsor</b>	National Institutes of Health: NIDDK, Office of the Director
<b>Design</b>	Cluster-randomized, open label, pragmatic clinical trial
<b>Principal Investigator</b>	Laura M. Dember, M. D.
<b>Objectives</b>	<ol style="list-style-type: none"> <li>1. To determine whether dialysis facility implementation of a minimum hemodialysis session duration of 4.25 hours (versus usual care) for patients with end-stage renal disease initiating treatment with thrice weekly maintenance hemodialysis has benefits on mortality, hospitalizations and health-related quality of life.</li> <li>2. To demonstrate the capacity to conduct a large, pragmatic clinical trial in partnership with two large dialysis provider organizations.</li> </ol>
<b>Intervention</b>	Intervention facilities will recommend a minimum hemodialysis session duration of 4.25 hours. Control facilities (“Usual Care”) will not implement a trial-driven recommendation about dialysis session duration.
<b>Enrollment Period</b>	3 years
<b>Duration</b>	4.5 years
<b>Study Center(s)</b>	Dialysis facilities operated by DaVita and Fresenius Medical Care, two large dialysis provider organizations
<b>Data Coordinating Center</b>	Clinical Research Computing Unit, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine
<b>Number of Facilities &amp; Patients</b>	<p>402 dialysis units</p> <p>6880 patients</p>
<b>Main Eligibility Criteria</b>	<p><b>Dialysis Facility Eligibility</b></p> <ol style="list-style-type: none"> <li>1. Willingness of the facility’s Medical Director, nephrologists and clinical leadership to adopt a facility approach of prescribing dialysis sessions of at least 4.25 hours for patients initiating treatment with maintenance hemodialysis (incident patients).</li> </ol>

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	<ol style="list-style-type: none"> <li>Capacity to accommodate treatment session durations of at least 4.25 hours for incident patients.</li> <li>Facility use of the electronic data systems of the dialysis provider organization.</li> </ol> <p><b>Patient Eligibility</b></p> <p><b><u>Inclusion Criteria</u></b></p> <ol style="list-style-type: none"> <li>Initiation of maintenance dialysis within the past 120 days.</li> <li>Treatment with maintenance dialysis in a participating facility.</li> <li>Age <math>\geq 18</math> years.</li> </ol> <p><b><u>Exclusion Criteria</u></b></p> <ol style="list-style-type: none"> <li>Unwillingness to participate. Patients receiving dialysis in facilities in the Intervention arm can participate without agreeing to a minimum dialysis session duration of 4.25 hours. Data collection for such participants will be identical to those who receive the session duration of <math>\geq 4.25</math> hours.</li> <li>Patients who are unable to provide consent for dialysis care will be excluded from trial participation.</li> </ol>
<b>Outcomes</b>	<p><b>Primary Outcome:</b> death</p> <p><b>Major Secondary Outcomes:</b> hospitalizations, health-related quality of life</p>
<b>Duration of intervention</b>	Up to 3 years
<b>Analytic Approach</b>	<ol style="list-style-type: none"> <li><b>Primary outcome:</b> intention to treat comparison of time to death between Intervention and Usual Care groups.</li> </ol> <p>Analysis will include generation of the hazard ratio and 95% confidence interval for the intervention. Significance testing will be performed with two-tailed p values of <math>\leq 0.05</math> considered significant. Survival curves with 95% confidence intervals will be generated using the Kaplan-Meier method. Secondary analyses will incorporate adjustment for co-variables that are not balanced between randomization groups.</p>

Protocol Summary	
	<ol style="list-style-type: none"> <li>2. <b>Secondary outcomes:</b> <ol style="list-style-type: none"> <li>a) comparison of hospitalization rates between Intervention and Usual Care groups</li> <li>b) comparison of change over time in KDQOL™36 domains between Intervention and Usual Care groups</li> </ol> </li> <li>3. <b>Primary analysis population:</b> patients with anthropometric volume ≤ 42.5 liters. Referred to as “Primary Treatment Assessment Population.”</li> <li>4. <b>Secondary analysis population:</b> all patients. Referred to as “Extended Analysis Population.”</li> </ol>
<b>Study Oversight</b>	An independent Data and Safety Monitoring Board (DSMB) appointed by NIH will review trial progress, data quality, and interim analyses throughout the course of the trial in accordance with a Data and Safety Monitoring Plan.



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# **1. Background and Rationale**

## **1.1. Background and Rationale for the TiME Trial Intervention**

### **Outcomes for patients receiving maintenance hemodialysis treatment**

Approximately 400,000 individuals in the United States require maintenance dialysis treatments because of end-stage renal disease (ESRD). The number of patients undergoing treatment with maintenance dialysis has grown substantially over the past decade and is expected to steadily increase due to the lack of therapies to prevent progression of chronic kidney disease, the growing prevalence of diabetes mellitus and hypertension, and the shortage of donors for kidney transplantation. Despite improvements in dialysis technology over the past 40 years, as well as the development of new pharmacological treatments for complications of ESRD, the morbidity and mortality for patients treated with maintenance dialysis remains exceptionally high. Data from the United States Renal Data Systems indicate that only 50% of patients are still living 3 years after starting maintenance dialysis. In the first year of dialysis, a period of particular vulnerability, patients have an average of 2.2 hospitalizations and a mortality rate of 21%. Implementation of quality improvement programs by dialysis provider organizations that incorporate multiple interventions for patients starting dialysis (e.g., the IMPACT and RightStart programs) has been associated with improvements in outcomes<sup>2,3</sup>. However, establishing best practices for patients treated with maintenance dialysis has been hampered by limited data from clinical trials<sup>4</sup>.

### **Current approach to prescribing hemodialysis session duration**

Hemodialysis performed three times per week has been the standard regimen for maintenance hemodialysis for the last four decades. Clinical practice guidelines and regulatory agency standards have focused on urea removal from the body as the metric for determining dialysis “dose”. The index of “urea reduction ratio” (URR), calculated as the percentage reduction in serum blood urea nitrogen during the hemodialysis session, or of Kt/V, which incorporates the total body water into the urea clearance determination, are universally used to monitor dialysis adequacy. These indices can be readily obtained for all patients on a regular basis, and although they statistically explain less than 5% of the mortality risk in the multivariable analysis of maintenance hemodialysis cohorts<sup>6</sup>, because of convenience for patients and staff, the duration of dialysis sessions has been predominantly driven by the achieved URR or Kt/V. With increases in the efficiency of dialyzer membranes, the accepted goal URR of at least 65%, or Kt/V of 1.2, can be met for many patients with treatment durations of 3-3.5 hours. As detailed in the sections that follow, there are several potential benefits of treatment sessions that are longer than 3-3.5 hours. The TiME Trial will evaluate the effects on outcomes of prescribing dialysis session durations of at least 4.25 hours, even if urea clearance-based targets can be achieved with shorter sessions.

### **Potential physiological benefits of longer dialysis treatment times**

Longer dialysis sessions increase the removal of solutes that are larger than urea and thus have a slower rate of transfer from the plasma across the dialyzer membrane into the dialysate compartment. Longer treatment times also facilitate complete removal of fluid that has accumulated during the 2-3 day periods between dialysis sessions<sup>8</sup> which is of presumed benefit given the known deleterious effects of excess fluid volume and observed associations with mortality<sup>9-11</sup>. Longer dialysis sessions allow for a more gradual rate of fluid removal during dialysis, and rapid removal of fluid has been linked to mortality presumably because of hemodynamic alterations<sup>12,13</sup>. During dialysis, transient regional wall motion abnormalities in the heart have been documented, a phenomenon referred to as myocardial "stunning" that is thought to result from transient under-perfusion via the coronary circulation. The occurrence of such "stunning" episodes has been associated with increased mortality<sup>14</sup>. The incidence of intra-dialytic myocardial stunning is higher when the fluid removal rate is rapid<sup>14</sup>. Additionally, the slower rate of fluid removal made possible by extending treatment time may result in better control of blood pressure<sup>8,15</sup>, and lower blood pressure has been associated with less left ventricular hypertrophy (LVH)<sup>16,17</sup>. LVH is a surrogate outcome, but one that is strongly associated with increased mortality in patients treated with dialysis<sup>18</sup>. In a recently completed randomized trial conducted by the NIH-sponsored Frequent Hemodialysis Network (FHN), the co-primary outcome, LVH, was decreased among patients randomized to a regimen of six dialysis sessions per week compared to those randomized to three dialysis sessions per week<sup>19</sup>. Increased dialysis frequency in this trial resulted in longer total dialysis treatment time (12.7±2.2 hours per week in the frequent group compared with 10.4±1.6 hours per week in the control group).

### **Data relating treatment time to survival**

Several large *observational* studies of conventional thrice weekly hemodialysis have found associations between hemodialysis session length and patient survival<sup>20;21;22;23,24</sup>. In these studies the risk of death increased by 19-42% with dialysis sessions less than 4 hours compared with sessions 4 hours or longer. Two of these studies utilized the databases of Fresenius Medical Care<sup>21</sup> and DaVita<sup>24</sup>, the two dialysis provider organizations participating in the TiME trial. In both analyses, longer dialysis session length was associated with improved patient survival, independently of URR. A retrospective study from New Zealand also found that increased dialysis time was associated with lower mortality independent of URR, and that the lowest mortality was found with the longest session lengths which were 4.5-4.9 hours<sup>22</sup>. The findings of the FHN daily dialysis trial support the concept that increased dialysis time, which was achieved in the FHN trial by increasing the frequency to six times per week, is beneficial<sup>19</sup>. However, the FHN trial was not powered to evaluate hard outcomes and frequent (i.e., 6 times per week) dialysis is not practicable for most patients.

One analytical problem in assessing the relationship between dialysis dose (URR) and mortality in observational studies is that the magnitude of the dose effect far exceeds the maximum likely effect calculated from the randomized comparison in the HEMO study, the largest randomized trial conducted thus far evaluating dialysis treatment approaches (N=1,846)<sup>25,26</sup>. Thus, even though some observational studies suggest a strong benefit of increased dialysis session lengths, the apparent advantages may be overestimated due to a dose-targeting bias that is difficult to remove even with statistical adjustment for measured factors related to the patient's health status. In an analysis of CMS ESRD Clinical Performance Measures Project data that incorporated adjustment for anthropometric volume of distribution for urea, a benefit of longer time was not evident and there was a non-statistically significant trend toward worse outcomes with longer treatment times, a finding attributed by the authors to confounding by indication<sup>27</sup>. Thus, a beneficial effect of increasing dialysis session duration in the routine thrice-weekly hemodialysis schedule is not definite and requires a well-powered randomized trial to confirm or refute.

### **Treatment time and body size**

We will employ the clustered-trial design in the proposed TiME trial to examine the effect of increasing dialysis session duration on mortality. In this design, the prescription of dialysis session durations based on randomization assignment of the dialysis facility will be applied to all patients initiating dialysis in that facility. However, because large patients typically receive dialysis sessions of at least 4 hours, and thus little difference in treatment time can be expected between the Intervention and Usual Care groups among such patients, the *primary analysis* will estimate the effectiveness of longer dialysis time among small and average-size patients, i.e., those with a body water volume (estimated from age, height, weight and sex) of less than or equal to 42.5 Liters. Current data from the USRDS indicate that nearly 70% of incident patients in the US, including almost all women and close to 50% of men, have body water volume less than 42.5 Liters, [personal communication, Beverly Forest, USRDS Coordinating Center]. Any observed differences in outcomes between treatment groups among the larger patients will also be of interest because they will likely reflect indirect effects possibly at the dialysis facility level related to trial participation. Regardless, this design incorporates the advantages of both feasibility of trial implementation and generalizability of the results.

### **Why women and smaller patients often have shorter treatment times**

Several decades ago, the usual hemodialysis treatment regimen was 6 8-hour sessions three times per week. As dialyzers became more efficient, and as determination of dialysis adequacy focused on urea reduction, a small readily-dialyzable solute<sup>28</sup>, it became possible to achieve high degrees of urea removal during much shorter treatment periods, e.g., 2.5-4 hours<sup>29</sup>. Current U.S. clinical practice guidelines define minimally adequate dialysis for a 3 times per week schedule as a treatment that achieves a urea reduction ratio or Kt/V of at least 65% or 1.2, respectively. A minimum treatment duration of 3 hours is recommended, but not

mandated. Because smaller individuals and those with lower muscle mass (and thus smaller total water volume) can achieve a given urea reduction ratio in less time than larger, more muscular individuals, in the United States today, many smaller patients, including most women, have treatment times shorter than 4 hours, often in the range of 3.0 - 3.5 hours or less. These treatments usually meet the guideline target of a URR  $\geq 65\%$ , or  $Kt/V \geq 1.2$  but do not take into account removal of fluid and uremic toxins with larger molecular weights and may be suboptimal in terms of survival and quality of life.

**HEMO Study results: treatment time, women, and body size**

The only recent, large randomized trial of hemodialysis therapy, the HEMO study, compared dialytic URRs of approximately 65% and 75% and found no overall benefit in terms of survival or hospitalization in the higher URR group<sup>30</sup>. The increase in URR in the higher-dose group was achieved by increasing dialysis efficiency through use of higher dialyzer blood flow rates and larger dialyzers, while limiting dialysis time to the minimum. Therefore, the trial was truly a test of urea removal, but not dialysis session time or larger-molecule removal. Nonetheless, the higher-URR group required an average of 30 minutes more than the lower-URR group in order to achieve its URR target. When the HEMO study results were analyzed using an intent-to-treat comparison for women and men separately, the higher dialysis URR (and the accompanying longer time) showed a beneficial effect on all-cause mortality for women but not for men; there was a statistical interaction between sex and URR on mortality. Among the female participants, those assigned to the high URR group had a mean dialysis session duration of 3.5 hours compared with 3.0 hours in the controls. When results were analyzed according to body size (as estimated body water), smaller patients also seemed to benefit from assignment to the higher URR (and treatment time)<sup>30</sup>.

**Survival of women and smaller patients with ESRD**

The survival advantage of females seen in the general population is completely lost among patients treated with maintenance hemodialysis, as men and women have similar mortality rates. Furthermore, regardless of sex, smaller patients, defined by low estimated body water volume<sup>25</sup>, have a markedly lower survival than their larger counterparts. Reasons for this are likely multifactorial, but part of the reason may be the shorter dialysis times typically prescribed for smaller patients.

**Safety of the TiME Trial intervention**

The dialysis session duration being evaluated in the TiME Trial is well within the range of session durations administered in routine clinical practice. While there have not been clinical trials designed specifically to evaluate the safety of treatment sessions of 4 – 4.5 hours, there is not a theoretical basis for concern about reduced safety with 4.25-hour sessions compared with shorter sessions, nor have such concerns arisen from observational studies<sup>20-23</sup>, including studies of treatments of 6 – 8 hours<sup>32,33,34</sup>. Dialysis sessions that are of longer duration are expected to generate less hemodynamic stress than shorter treatments because of slower

removal of fluid<sup>31</sup>. 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.

### **Summary of rationale for the TiME Trial intervention**

There is considerable skepticism about whether urea-based determination of dialysis adequacy (i.e., URR or Kt/V) provides a sufficient approach to prescribing hemodialysis session duration, although this is the current practice standard in the United States. Physiological considerations and observational data provide a rationale for session durations that are longer than many patients currently receive. Daily hemodialysis appears to confer benefits with respect to several important surrogate outcomes; however, patient acceptance of frequent therapies is not very high, even in a highly selected and motivated sub-population<sup>35</sup>. Additionally, there are operational barriers to instituting more frequent therapy, such that 97% of hemodialysis treatments in the United States are administered on a thrice-weekly schedule. Given this reality, optimizing the prescription parameters for a thrice-weekly schedule has the potential of providing benefits to a large proportion of patients. Moreover, if women and small patients are receiving inadequate dialysis it is critical to address this. Although several thought leaders in dialysis care have proposed broad implementation of longer dialysis sessions, there is enough uncertainty about the benefits of longer treatment times that evaluation through an adequately-powered randomized trial is warranted before widespread changes in practice are recommended.

### **1.2. Rationale for the Pragmatic Trial Design**

The TiME Trial is being conducted as part of the NIH Health Care Systems Research Collaboratory pragmatic trial initiative. The overall goal of HCS Research Collaboratory is to strengthen the national capacity to implement cost-effective large-scale research efforts that engage health care delivery organizations as research partners. The pragmatic trial demonstration projects are intended to be large clinical trials that provide findings that are highly generalizable to “real world settings” and thus are 1) conducted within the clinical care environment, 2) evaluate interventions implemented by care providers, and 3) rely as much as possible on data obtained as part of routine clinical care. Dialysis care provides a setting that is highly suited to pragmatic trials. Dialysis units across the United States provide dialysis in a fairly standardized manner; patients have frequent (typically thrice weekly) contact with medical personnel; and highly granular clinical, demographic, treatment, and laboratory data elements are captured electronically. The large dialysis provider organizations participating in the TiME Trial care for a large number of patients that are representative of the overall U.S. dialysis patient population and have tremendous diversity with respect to geography, race, ethnicity, age, and socioeconomic characteristics.

## **2. Trial Objectives**

### **2.1. Primary Objective**

The primary objective of the TiME Trial is to determine whether, compared with usual care, dialysis facility implementation of a minimum hemodialysis session duration of 4.25 hours for patients with end-stage renal disease initiating treatment with thrice weekly maintenance hemodialysis:

1. Increases survival
2. Reduces hospitalizations
3. Improves quality of life

### **2.2. Secondary Objectives**

#### **2.2.1. Secondary Effectiveness Objectives**

Secondary objectives of the TiME Trial are to determine whether thrice weekly hemodialysis with session durations of at least 4.25 hours:

1. Improves blood pressure control
2. Reduces the incidence of post-dialysis hypotension
3. Reduces inter-dialytic fluid intake
4. Maintains or improves adherence to dialysis treatments
5. Has benefits that are linked to rate of fluid removal (ultra-filtration rate)

#### **2.2.2. Pragmatic Trial Demonstration Objectives**

The TiME Trial is one of the pragmatic trial demonstration projects of the Health Care Systems (HCS) Research Collaboratory funded by the NIH Common Fund. The overall goal of HCS Research Collaboratory is to strengthen the national capacity to implement cost-effective large-scale research efforts that engage health care delivery organization as research partners. The pragmatic trial demonstration projects are intended to be large clinical trials conducted within the clinical care environment evaluating interventions implemented by care providers and relying as much as possible on data obtained as part of routine clinical care. As secondary objectives the TiME Trial will:

1. Determine the extent to which the TiME Trial adheres to the principles of a pragmatic trial
2. Assess the experience of health care providers at participating facilities with respect to TiME Trial implementation



### **3. Study Organization**

#### **3.1. Health Care Systems (HCS) Research Collaboratory**

The HCS Research Collaboratory is one of the Roadmap initiatives of the Office of the Director of the National Institutes of Health. Roadmap initiatives are intended to address roadblocks to research and to transform the way biomedical research is conducted by overcoming specific hurdles of filling defined knowledge gaps. The HCS Research Collaboratory will engage health care systems as research partners in conducting large-scale clinical studies. Initial grant awards issued in September 2012 established a Collaboratory Coordinating Center based at Duke University and seven pragmatic clinical trial demonstration projects, one of which is the TiME Trial. Although each pragmatic trial demonstration project is fully responsible for implementing a clinical trial, there will be activities of the full Collaboratory aimed at creating generalizable knowledge, tools and resources for use by the broader research community to facilitate a broadened base of research partnerships with health care systems. The HCS Collaboratory Coordinating Center is comprised of seven working groups including: 1) Health Care Systems Interactions 2) Electronic Health Records, 3) Stakeholder Engagement, 4) Ethics and Regulatory, 5) Biostatistics and Design, 6) Phenotyping, and 7) Patient Reported Outcomes. Each of these working groups has representation from the pragmatic trial demonstration projects.

#### **3.2. TiME Trial Study Group**

The TiME Trial Study Group is comprised of investigators from academic institutions, investigators and research personnel from two large dialysis provider organizations, DaVita and Fresenius Medical Care, investigators and research personnel from the Clinical Research Computing Unit (CRCU) at the University of Pennsylvania, and project officers from the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). The primary governing body of the TiME Trial is the Steering Committee which is comprised of investigators from the academic institutions, investigators from DaVita and Fresenius Medical Care, the Penn DCC Project Manager, and the NIDDK project officers. Laura M. Dember, M.D., at the University of Pennsylvania, is the Chair of the Steering Committee. The Steering Committee is responsible for developing the study protocol, study policies, publications and presentations, and overseeing the trial conduct and progress. The external (non-Penn) members of the TiME Trial Steering Committee are:

- Steven Brunelli, M.D., M.S.C.E., DaVita Inc.
- Alfred Cheung, M.D., University of Utah
- John Daugirdas, M.D., University of Illinois
- Tom Greene, Ph.D., University of Utah
- Csaba Kovesdy, M.D., University of Tennessee
- Eduardo Lacson, Jr. M.D., M.P.H., Tufts University
- 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

### **3.3. Dialysis Provider Organizations**

The dialysis provider organizations for the TiME Trial are DaVita and Fresenius Medical Care, the two largest dialysis providers in the United States. DaVita operates approximately 1,800 dialysis facilities in the United States and serves approximately 140,000 patients undergoing treatment with maintenance hemodialysis. Fresenius Medical Care operates approximately 2,100 dialysis facilities in the United States and serves approximately 166,000 patients undergoing treatment with maintenance hemodialysis. Both organizations have active research divisions that coordinate and support internally and externally initiated research.

### **3.4. Data Coordinating Center**

The DCC for the TiME Trial is based at the Clinical Research Computing Unit of the Center for Clinical Epidemiology and Biostatistics at the Perelman School of Medicine of the University of Pennsylvania. The DCC is responsible for the overall management of the trial and works closely with the research teams at the dialysis provider organizations to coordinate trial activities, develop training materials and lead protocol training sessions for participating facilities. The DCC is responsible for regulatory oversight and submissions to the Institutional Review Board. The DCC will plan, test and implement the data transfer processes with input from the information technologists at the dialysis provider organizations. The DCC will create the trial database, and plan and perform the data analyses. The DCC will oversee the quality assurance activities, generate data reports, monitor study progress, and prepare progress reports for the NIH and reports for the Data and Safety Monitoring Board.

### **3.5. Subcommittees**

The following subcommittees or groups have been or will be established to address specific aspects of the trial conduct and analyses.

- Executive Subcommittee
- Design and Intervention Subcommittee
- Facility Identification and Implementation Subcommittee
- Ethics and Regulatory Subcommittee
- Publication and Dissemination Subcommittee
- Information Technology Group
- Evaluation Subcommittee
- Analysis Group
- Trainee Subcommittee

## **4. Study Design**

### **4.1. Overview**

The TiME Trial is a cluster-randomized, parallel-group pragmatic clinical trial for patients initiating treatment with maintenance hemodialysis. Four hundred and two dialysis facilities will be randomized in a 1:1 distribution to the Intervention arm or the Usual Care arm.

Facilities randomized to the Intervention arm will adopt the practice of recommending dialysis session durations of at least 4.25 hours for all patients initiating hemodialysis treatment regardless of body size or dialysis solute clearance measurements. Facilities randomized to Usual Care will maintain their existing approaches to prescribing dialysis session duration. Participants will be followed for up to 3 years. The primary endpoint is mortality; major secondary endpoints are hospitalization rate and quality of life. Pragmatic features of the TiME Trial include 1) high generalizability due to non-restrictive eligibility criteria and broad representation of participating facilities, 2) implementation of the intervention by clinical care providers rather than by research personnel, and 3) reliance on data obtained through routine clinical care rather than through research activities.

## **4.2. Study Setting**

The trial will be conducted in 402 dialysis facilities operated by two large dialysis provider organizations, DaVita and Fresenius Medical Care. Approximately half of the participating facilities will belong to each organization. The dialysis facilities will be distributed throughout the United States.

## **4.3. Eligibility Criteria**

### **4.3.1. Facility Eligibility**

Dialysis facilities will be eligible for participation if they meet the following criteria:

1. Willingness of the Medical Director, nephrologists and the clinical leadership to adopt a facility approach of prescribing dialysis sessions of at least 4.25 hours for patients initiating treatment with maintenance hemodialysis (“incident” patients) contingent upon randomized allocation.
2. Ability of the facility to accommodate longer dialysis treatment times for new patients.
3. Facility use of the electronic data systems of the dialysis provider organization. This issue may be relevant to dialysis facilities that have recently been acquired by a provider organization and have not yet fully transitioned to the electronic systems that will be utilized for the TiME Trial.

### **4.3.2. Patient Eligibility**

The eligibility criteria are broad in order to maximize the generalizability of the trial findings.

#### **Inclusion Criteria**

1. Initiation of maintenance dialysis within the past 120 days.
2. Treatment with maintenance dialysis in a participating facility.
3. Age  $\geq 18$  years.

## **Exclusion Criteria**

1. Unwillingness to participate. Of note, patients receiving dialysis in facilities in the Intervention arm can participate without agreeing to a minimum dialysis session duration of 4.25 hours. Data collection for such participants will be identical to those who receive the session duration of  $\geq 4.25$  hours.
2. Patients who are unable to provide consent for dialysis care will be excluded from trial participation.

## **4.4. Randomization**

Randomization of dialysis facilities will be performed by the Data Coordinating Center after a facility has agreed to participate in the trial. Facilities will be randomized to the Intervention group or the Usual Care group in a 1:1 ratio. The allocation sequence will be based on a permuted randomization procedure stratified by 1) dialysis provider organization, 2) proportion of prevalent patients at a dialysis facility receiving dialysis via a central venous catheter ( $\leq 20\%$  or  $> 20\%$ ), and 3) the proportion of patients at the dialysis facility self-identified as black in the provider organization electronic data system ( $\leq 50\%$  or  $> 50\%$ ).

The stratification will be based on facility data for the six-month period prior to randomization. Stratification by dialysis provider organization is important because of potential practice differences between provider organizations that might affect implementation of the intervention, adherence to the intervention, or outcomes. Stratification by prevalence of central venous catheters will be implemented because of the well-established increased risk of death with central venous catheter use, and by race because of the lower risk of death among black individuals treated with dialysis and the large variation in the proportion of black patients across dialysis facilities. Randomization assignment will be transmitted to the dialysis provider organization research team via computer.

## **4.5. Intervention**

Dialysis facilities randomized to the Intervention arm will adopt an approach of recommending that all patients who are initiating treatment with maintenance hemodialysis have a treatment session duration of at least 4.25 hours even if urea clearance and fluid removal are considered adequate with shorter treatment durations.

### **4.5.1. Role of the Treating Nephrologist**

Although the dialysis facilities in the Intervention arm will adopt an approach of recommending a minimum session duration of 4.25 hours, the specific treatment time will be prescribed by the treating nephrologist(s) thus allowing for individualization of the prescription based on other considerations. Also consistent with standard practice, patients can have input into the prescribed session duration through discussions with the treating nephrologist(s). Patients will also be able to reduce the duration of any particular dialysis session just as they would if they

were not participating in the trial. Thus, in the Intervention facilities, the treatment durations will be influenced, but not dictated, by randomization to the Intervention group.

In the Usual Care facilities, there will be no attempt to influence dialysis session length. It is anticipated that a subset of the patients in control facilities will be prescribed dialysis sessions of 4.25 hours or longer; such patients might be larger in size, have higher inter-dialytic fluid intake, and/or be perceived by the treating nephrologist as feeling better with longer treatment times.

#### **4.5.2. Governing Body Approval**

After the facility treatment assignment is made, facilities randomized to the Intervention group will hold a meeting of the facility's governing body to approve adoption of a facility approach of prescribing dialysis session treatment time of at least 4.25 hours for patients who meet the trial eligibility criteria. A governing body is a CMS-required entity, either a group or an individual, with legal authority and responsibility for the governance and operation of the facility. The governing body adopts and enforces rules and regulations relative to its own governance and to the health care and safety of patients, to the protection of the patients' personal and property rights, and to the general operation of the facility. A dialysis facility governing body is typically comprised of the medical director and facility administrator and nursing director. The TiME Trial Intervention will not be implemented without approval by the governing body.

### **4.6. Adherence**

#### **4.6.1. Intervention Group Facilities**

One of the principles of pragmatic trial design is that adherence to the intervention be assessed in a non-obtrusive manner or in a manner that best replicates the clinical practice setting. Because of the detailed information available in the electronic health systems, the DCC can non-obtrusively monitor adherence to the intervention, both in terms of prescribed dialysis session time and delivered dialysis session time. Reports generated by the DCC about performance of participating facilities will be provided to the dialysis provider organization research teams who, in turn, can communicate with the clinical leadership at the dialysis facilities. Additionally, the DCC can generate reports comparing adherence rates between participating dialysis units for review at monthly dialysis unit quality improvement meetings. Monitoring and reporting comparisons across dialysis facilities has been found to lead to broad performance improvements in process-of-care measures<sup>36</sup>.

As standard practice, members of the multi-disciplinary care teams in dialysis units pay close attention to adherence by patients to the prescribed dialysis session duration along with many other aspects of their care. The multi-disciplinary care teams will be encouraged to review adherence to the intervention 1) during routine monthly multidisciplinary care rounds, 2) during monthly quality improvement meetings which occur routinely in all dialysis facilities, or

3) via direct communication from the dialysis provider organization's TiME Trial project managers (and/or other quality assurance and improvement officers) to the dialysis unit clinical leadership. To encourage adherence at the individual patient-level, informational materials about the TiME Trial will be provided to the Intervention group facilities and the treating nephrologists will be encouraged to discuss the hypothesized benefits of longer treatment times with trial participants and clinical staff.

#### **4.6.2. Participant and Facility Incentive Programs (Initiated June 2016)**

A Participant Incentive Program will be implemented at Intervention facilities to encourage patient adherence to longer treatment times. Participants will receive a monetary incentive if they achieve a specified increase in their session duration. The criteria for receiving the incentive payments will be provided to participants in writing.

A Facility Incentive Program will also be implemented. Intervention facilities will receive a monetary award if the facility meets specified session durations for their participants.

The DCC will determine on a monthly basis which patients and facilities meet the incentive criteria. The payments will be distributed by the research teams at the dialysis provider organizations. Incentive programs will be piloted at 10 Intervention facilities to assess the impact and optimize the implementation before initiating a study-wide roll-out of the program.

#### **4.6.3. Usual Care Facilities**

Dialysis facilities randomized to the Usual Care arm will not adopt a trial-driven approach to dialysis session duration. In the Usual Care facilities, the dialysis provider organizations will have flexibility with respect to monitoring and encouraging, at the facility level, adherence to prescribed dialysis session durations. As standard practice, members of the multi-disciplinary care teams in dialysis units pay close attention to adherence by patients to the prescribed dialysis session duration along with many other aspects of their care. The multi-disciplinary care teams will be encouraged to review general adherence to therapy 1) during routine monthly multidisciplinary care rounds, 2) during monthly quality improvement meetings which occur routinely in all dialysis facilities, or 3) via direct communication from the dialysis provider organization's quality assurance and improvement officer to the dialysis unit manager. Nephrologists are generally encouraged by the provider organizations to promote adherence behavior in the dialysis facility by periodically educating patients and clinical staff.

### **4.7. Outcomes**

#### **4.7.1. Primary Outcome: Mortality**

The primary outcome for the TiME Trial is time to death, and the trial hypothesis is that time to death will be longer in facilities randomized to the Intervention compared with facilities randomized to Usual Care. In keeping with the pragmatic nature of the trial, ascertainment of

death will utilize systems that are already in place for provision of dialysis care. The principal source of death data will be the electronic data systems of the dialysis provider organizations. The accuracy and completeness of death data in the electronic data system is anticipated to be high given the frequent contact between the dialysis facility and patient. Unlike other outpatient health care settings where attempts may or may not be made to reschedule the patient for a missed appointment, a missed dialysis treatment triggers immediate inquiry by the dialysis unit staff.

In addition to the electronic data systems of the dialysis provider organizations, another potential source of death data is the ESRD Death Notification Form (CMS Form 2746). All dialysis facilities that receive payment from the Centers for Medicare and Medicaid Services (CMS) are required to notify their ESRD Network of all deaths the CMS Form 2746. ESRD Networks are contracted by CMS to oversee chronic dialysis facilities. The completeness and accuracy of Form 2746 submissions has been previously demonstrated through comparisons between prospectively collected data using research personnel (e. g., the NIH HEMO Study) and data in the United States Renal Data Systems<sup>38</sup>. For the TiME Trial, the electronic data systems of the dialysis provider organizations are preferable to the CMS Form 2746 as the source of death information, as there are delays and costs for obtaining CMS data. Additionally, Social Security numbers must be transmitted to query the CMS databases, which adds complexity from a research regulatory standpoint. Moreover, because the CMS 2746 form is generated by the dialysis facility staff, the death information in the electronic data system and information provided via the CMS 2746 form originates from the same source and is likely to have similar accuracy.

For participants who transfer care to another facility or change dialysis modality from hemodialysis to peritoneal dialysis, the death outcome will be able to be ascertained if the transfer is to another facility within the same dialysis provider organization. If a participant transfers care to a different provider organization or receives a kidney transplant it will not be possible to obtain death outcomes and follow-up will end at the time of transfer or transplantation, respectively.

## **4.7.2. Secondary Outcomes**

### **4.7.2.1. Hospitalization Rate**

Hospitalization rates are a major secondary outcome of the TiME Trial and the trial hypothesis is that, in comparison with the Usual Care facilities, hospitalization rates will be lower for the facilities randomized to the Intervention group. As part of standard operations, staff members at the dialysis units of both provider organizations enter dates of hospitalizations into the electronic data system. Dialysis providers have contact with patients three times per week and, a missed dialysis treatment triggers immediate inquiry by the dialysis unit staff. Additionally, hospitalization rates are used as quality indicators and dialysis facilities track hospitalizations

for internal quality improvement efforts. For these reasons, we expect the hospitalization data in the electronic data systems of the dialysis provider organizations to be reasonably complete. Reasons for hospitalizations will not be collected for the TiME Trial because they cannot be ascertained from information available through routine care or operations.

#### **4.7.2.2. Health-Related Quality of Life (HRQOL)**

Quality of life is an important secondary outcome of the TiME Trial. The trial hypothesis is that extension of treatment time will improve hemodynamic stability during dialysis and increase solute clearance, and that these effects will lead to improvement in physical aspects of health-related quality of life. The HRQOL questionnaire used for the TiME Trial will be 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 the CMS requirement that quality of life be assessed at least once per year. The investigator team considered other QOL instruments and decided, based in part on logistical advantages, to use the survey that is already being administered as part of routine care delivery at the dialysis facilities.

#### **4.7.2.3. Other Secondary Effectiveness Outcomes**

Pre-dialysis blood pressure, post-dialysis blood pressure, and inter-dialytic weight gain are secondary outcomes that will be used to evaluate the hypothesis that longer dialysis treatment sessions improves blood pressure control, reduces intra-dialytic hypotension, and reduces post-dialysis fluid intake because of less hemodynamic instability. Dialysis attendance will be compared between treatment groups to determine the effect of longer prescribed session duration on adherence to scheduled dialysis treatments.

#### **4.7.3. Pragmatic Trial Demonstration Outcomes**

The TiME Trial is one of the pragmatic trial demonstration projects of the NIH Health Care Systems (HCS) Research Collaboratory. These demonstration projects are intended to be large clinical trials conducted within the clinical care environment evaluating interventions implemented by care providers and relying as much as possible on data obtained as part of routine clinical care. In order to assess the extent to which the TiME Trial adheres to the principles of a pragmatic trial, the members of the TiME Trial study group will complete an assessment before and after completion of the trial using the “Pragmatic-explanatory continuum indicator summary (PRECIS)” tool<sup>39</sup>. This tool is designed to display the position of trials within a spectrum of a pragmatic-explanatory trial continuum. Additionally, the experience of a sample of care providers at participating facilities will be explored through anonymous surveys that address the burden of participating in the trial and challenges associated with implementing the trial intervention.



## **4.8. Data Collection**

The electronic data systems of both 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 DCC database at scheduled intervals. No laboratory studies will be performed specifically for the trial. While standard outpatient dialysis unit procedures using currently approved dialysis devices (Fresenius 2008K, 2008T, 2008H Series; Braun Dialog Series; Gambro Phoenix System) will be used in the trial, neither dialysis provider has the capability to track the type of device or machine characteristics used for individual treatments.

The following data elements will be obtained from clinical care data for all trial participants at the indicated frequency:

### **Demographic and Comorbidity Data: all at study entry**

1. Age
2. Sex
3. Weight
4. Height
5. Race
6. Ethnicity
7. Co-morbid illnesses noted on admission to the dialysis facility (ICD-9/10 codes)
8. Cause of end-stage renal disease
9. Extremity amputation present on admission to the dialysis facility

### **Dialysis treatment data**

1. Session length (delivered): every session
2. Pre-dialysis weight: every session
3. Post-dialysis weight: every session
4. Pre-dialysis systolic and diastolic blood pressure: every session
5. Post-dialysis systolic and diastolic blood pressure: every session
7. Vascular access type (presence or absence of catheter): once per month

### **Adherence data**

1. Prescribed dialysis session duration: every session
2. Delivered dialysis session duration: every session

## **Health-Related Quality of Life**

1. KDQOL™36: each of 5 component summary scores annually

## **Laboratory Data: once per month**

In alignment with usual practice, the following laboratory test results will be made available to the DCC by electronic data transfer once per month. It is expected that periodically some lab results will be missing and that repeated lab values will be present.

1. Pre-dialysis blood urea nitrogen
2. Post-dialysis blood urea nitrogen
3. Hemoglobin
4. White blood count
5. Albumin
6. Creatinine
7. Sodium
8. Potassium
9. Bicarbonate
10. Chloride
11. Calcium
12. Phosphorus
13. Glucose

## **Laboratory Data: once every 3 months**

1. Intact parathyroid hormone

## **Hospitalizations dates: all**

## **Status Change: all**

1. Date of transfer to another dialysis facility
2. Date of kidney transplantation
3. Date of transfer to peritoneal dialysis
4. Date of withdrawal from dialysis
5. Date of death

## **4.9. Participant Timeline**

Participants will be followed for 3 years.

## **5. Trial Implementation**

All of the TiME Trial processes will be described in detail in the Manual of Procedures (MOP). The MOP will include trial activities occurring at the dialysis facilities, dialysis provider organization data warehouses, and the DCC. The DCC is responsible for maintaining the manual and any associated documents and ensure that all relevant collaborators are informed about study procedures.

### **5.1. Centralization of Research Activities**

One of the innovative aspects of the TiME trial is the reliance on centralized research personnel rather than local study staff. This model is possible because of the infrastructure of the dialysis provider organizations, and is necessary because dialysis unit staff members at the large number of participating facilities will not be engaged in the research. The project managers and the IT personnel from the dialysis provider organizations will work closely with the DCC to implement the trial and extract the specified data elements from existing data acquired through routine clinical practice. Most of the direct interfacing between the TiME Trial Study Group and participating dialysis units will be performed by the research personnel of the dialysis provider organizations. The DCC project manager will team with each dialysis provider organization project manager who, in turn, will initiate the dialysis facilities into the trial. Dialysis facilities will be enrolled and activated in stages such that problems can be identified early after the trial begins and solutions can be applied uniformly across units. Steady communication between project managers at the dialysis provider organization and the research team at the DCC will be required to ensure that standard operating procedures for the trial are used at all dialysis facilities.

### **5.2. Facility Selection**

Each dialysis provider organization will identify dialysis facilities within the respective organizations that meet the eligibility criteria and are interested in participating in the TiME Trial. Effort will be made to have broad geographical representation within the United States although there will not be strict distribution requirements. Characteristics of facilities that will be incorporated into prioritization include the anticipated number of patients initiating dialysis (goal of 12 – 20 per year), distribution of dialysis session durations during the past 6 months, and capacity to accommodate the Intervention arm session duration. Preference will be given to dialysis facilities with median dialysis session duration of  $\leq 3.5$  hours in order to achieve separation between the randomized treatment groups.

The medical directors, nephrologists, clinical leadership, and facility administrators for potentially eligible facilities will be invited to learn more about the TiME Trial through educational materials developed and delivered by the TiME Trial Study Group. The leadership teams of interested dialysis facilities will be asked to provide affirmation that the medical director(s), facility administrator (or equivalent), nursing director (or equivalent), and admitting

nephrologists are willing to implement the TiME Trial intervention should the facility be randomized to the Intervention arm. After a facility has joined the TiME Trial, if the facility is randomized to the Intervention arm, formal approval of adoption of the intervention by its governing body will be required.

### **5.3. Participant Enrollment**

#### **5.3.1. Waiver of Informed Consent**

The TiME Trial will be conducted under 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 (the “Common Rule”):

1. The research involves no more than minimal risk to subjects.
2. The waiver will not adversely affect the rights and welfare of the subjects.
3. To the extent possible, the subjects will be provided with pertinent information after participating in the trial.
4. The research cannot be practicably conducted without a waiver of the requirement for informed consent.

The risk to subjects of participating in the TiME Trial is no more than minimal :

- a) the intervention consists of a dialysis session duration that is within the range of usual care administered in the United States as well as in many other countries;
- b) there are not anticipated safety concerns related to dialysis sessions of 4.25 hours; and
- c) identifying information is not transmitted to the Data Coordinating Center.

The waiver of the requirement for informed consent will not adversely affect the rights and welfare of the subjects because

- a) patients initiating dialysis treatment at a participating facility will be provided information about the trial at the time they initiate dialysis,
- b) dialysis session duration will be prescribed by a participant’s treating nephrologist with opportunity for individualization of the prescription based on other considerations including patient input;
- c) patients will be provided with an opportunity to opt out of trial participation; and
- d) participant confidentiality will be protected.

To the extent possible, subjects will be provided pertinent information about the findings from the trial after participating.

Dissemination of pertinent information can be accomplished by distributing information documents at participating facilities after the trial is over.

The research question cannot be practicably answered without a waiver of informed consent.

A major objective of the trial is to evaluate effectiveness of the intervention for the overall population of patients receiving maintenance hemodialysis rather than to evaluate efficacy of the intervention for a selected, non-representative subset. Because the randomized treatment assignment for the dialysis facility will be determined before patients are enrolled, a requirement for patient-level informed consent would likely result in important differences in the characteristics of participants in the two treatment groups (intervention patients would be those who *a priori* are interested in having longer dialysis sessions and the usual care cohort would be “all comers”). These differences would substantially undermine the objectives of the TiME Trial.

### **Patient Options**

Patients initiating dialysis will be informed about the TiME Trial when they are admitted to a participating dialysis facility or shortly thereafter. A brief “information sheet” will be given to the patient by the dialysis facility staff. The information sheet describes the purpose of the trial and what participation involves. The content differs for Intervention facilities and Usual Care facilities. The information sheet for both types of facilities contains a toll-free telephone number to allow the potential participant to obtain more detailed information about the trial if desired and to opt-out of participation if desired. Trained research staff at the dialysis provider organizations will respond to these telephone calls, provide additional information requested by the potential participant, and inform the dialysis provider organization information technology team about any patients who opt out of the transmission of their data to the DCC.

### **5.3.2. Waiver of HIPAA Authorization**

The TiME Trial will be conducted with a waiver of HIPAA authorization. Justification for waiving HIPAA authorization is based on the following factors:

1. The researchers require access to protected health information (PHI) in order to conduct the research. The only PHI that will be transmitted from the clinical data warehouses of the dialysis providers to the DCC is a limited dataset comprised of dates of dialysis sessions, death, hospitalizations, transplantation, and transfer out of a participating hemodialysis facility. 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. The members of the TiME Trial research team *within the dialysis provider organizations* (who are employees of the covered entities) will require access to PHI in order to implement the research protocol (e.g., for assigning unique identification codes to participants, for monitoring dialysis facility adherence to the intervention and for other communication with dialysis facilities). No PHI other than dates will be distributed outside the individual provider organizations. The identity or location of dialysis facilities will not be linked to individual participants. The number of participating facilities is sufficiently large

(approximately 400) that, without a link between participants and dialysis facilities, it is extremely unlikely that an individual could be identified from dates transmitted to the DCC.

2. The research cannot be practicably conducted without the waiver. The TiME Trial is designed 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. This trial is being conducted within a health care delivery setting at hundreds of facilities with routine dialysis care delivered by physicians, nurses and dialysis technicians. During the course of each dialysis session, information about patient status and dialysis session characteristics, obtained as part of routine care, will be used as the trial data. The health care providers at the dialysis facilities who will be generating trial data through routine clinical care are not trained in research practices and are not able to administer and explain research documents to patients such as a HIPAA waiver of authorization. Under this implementation model, obtaining authorization for disclosure of PHI from study participants is not reasonably practicable.
3. The use or disclosure of PHI poses no more than minimal risk to participants 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. Data that are transmitted to the DCC from the dialysis provider organizations will be maintained securely with access limited to authorized users. All PHI (i.e., dates) will be removed from the data set prior to any possible transfer of data from the DCC to investigators or to NIH data repositories.

The Privacy Officer at each dialysis provider organization has provided a HIPAA waiver determination to cover the work of employees with identifiable data for the purpose of creating the limited data set for research.

### **5.3.3. Participant Identification**

Patients who are incident to dialysis, defined as initiation of maintenance dialysis within 120 days, and receiving care at participating dialysis facilities will be identified through the electronic data systems of the dialysis provider organizations by the TiME Trial Information Technology (IT) teams at the provider organizations. A unique research participant identifier (PID) for each participant will be generated by the dialysis provider organizations. 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 unique identifiers for participants enrolled from their organizations. The keys to the unique identifiers will not be transmitted to the DCC. During the data extraction process, all personal identifiers will be replaced by the PID.

### **5.3.4. Participant Withdrawal**

Participants may decide to withdraw from the study at any time. Patients who decide not to participate in the trial will have no data transmitted to the DCC. Patients who initially do not opt-out of trial participation and later elect to withdraw from the trial will have no data transmitted to the DCC after the date of withdrawal. Data transmitted to the DCC prior to withdrawal will remain in the trial database. Contact information for the research personnel from the relevant dialysis provider organization will be available at participating dialysis facilities throughout the duration of the trial to facilitate communication such as a decision to withdraw from the trial. It should be noted that participants in Intervention facilities who elect to discontinue the dialysis session duration of  $\geq 4.25$  hours will remain as trial participants and continue to have data transmitted to the DCC unless they withdraw from the trial.

## **5.4. Data Management**

### **5.4.1. Data Extraction and Transfer**

During the data extraction process, all personal identifiers will be replaced by the unique research participant identifier (PID). The relevant data fields in the electronic medical records of trial participants will be tagged for export from the data warehouses of the dialysis provider organizations. (See Figure 1.) A secure file transfer protocol (sftp) site at the dialysis provider organization will be used to deliver data files. The DCC will programmatically upload these files into the DCC relational database. Automated processes will be used to review completeness of the transactions and to identify any corruption. During the initial period after the trial begins data transmission will be performed frequently in order to refine the process and identify and resolve any unanticipated problems. After all facilities are initiated and patient enrollment reaches a steady pace, the frequency of data transfer may be changed. Data and system requirements will describe the attributes of the data file exports: field, description, format, limitations, and user notes.

The dialysis provider organizations will provide a standard limited data set and an accompanying data dictionary based on the clinical data elements extracted from the dialysis provider organization data warehouse. Data extraction specialists from each of the dialysis provider organizations will query the data warehouse for the pre-determined data elements. The dialysis provider organizations will use a secure server environment for exporting data. The DCC will be responsible for ensuring the security and completeness of the data transfer and import process and the continuous security of data stored at the DCC.

The DCC central database repository will be constructed such that all imported data will retain the original structure and integrity. The transfer process will be tested according to the CRCU SOP # 9 – Data Integrity of Laboratory and Other Electronically Transferred Data. This process will ensure the secure transfer and confirmation/validation of uploaded data.

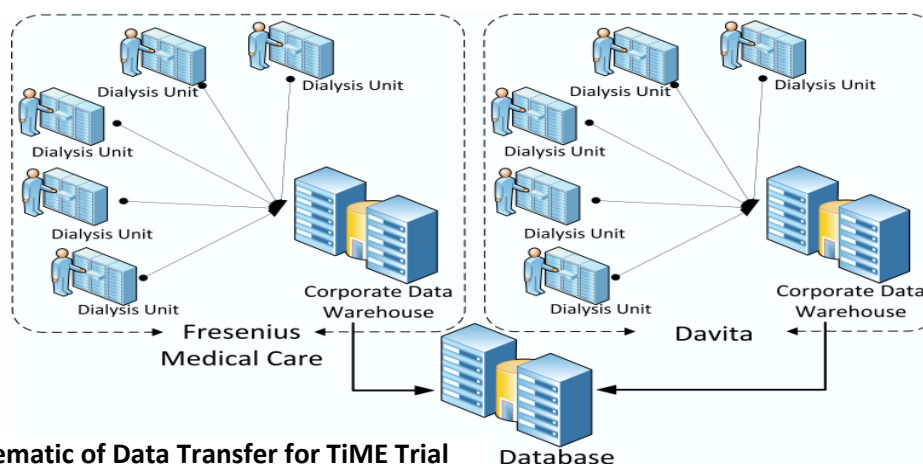


Figure 1. Schematic of Data Transfer for TiME Trial

### 5.4.2. Data Quality Procedures

Primary responsibility for data quality will reside with the data warehouse teams of the dialysis provider organizations. For both organizations, it is routine practice to regularly transmit data for inclusion in their central data warehouses. The data warehouse teams have processes to ensure that data are captured appropriately from the various originating facilities. The data extracted and transmitted from these central warehouses to the DCC is expected to be an accurate representation of the source data collected at each dialysis facility. The DCC will utilize a module to ensure that records transmitted from the central warehouse are accurately incorporated into the trial database. This module, at a minimum, will verify expected record counts and examine anomalous data based on expected data characteristics as defined by the TiME Trial study group. Data quality standards and processes for confirming missing data will be developed by the DCC in collaboration with the research teams at the dialysis provider organizations.

The clinical systems within the dialysis provider organizations are constructed with data restrictions and checks at the point of data entry for most of the primary data elements. Additional restrictions and quality checks exist at the transfer of data from the clinical system to the data warehouse. Automated measures are in place to reasonably ensure that the nightly data load process is successful and complete. If the process fails to run to completion, troubleshooting is done to identify and resolve the issue, and the process is resumed to completion. Additional quality assurance work is performed by end data users within the dialysis provider organizations as they analyze and report the data for operational purposes. These measures ensure that the database is an accurate representation of the source data collected at each dialysis clinic.

Clinical research activities at the DCC are performed in accordance with a set of standard operating procedures (SOPs) that have been implemented to promote compliance with applicable human subject protection regulations and guidelines. These SOPs are reviewed and renewed every two years. The SOP which applies to the electronic health record data



transmitted from the dialysis provider organizations describes requirements for ensuring that the integrity of electronically supplied data is maintained during the transfer and download process. It describes a systematic process of data and transfer method definition, use of scanning software to detect file corruption, encryption techniques, discrepancy management, process testing, validation procedures and documentation.

### **5.4.3. Data Security**

The data management system is designed to prevent unauthorized access to trial data and to prevent data loss due to equipment failure or catastrophic events. This is accomplished through user account management, user privilege assignment, data loss prevention (database backup), computer systems validation, performance monitoring, and Data Management System change management. User access will be controlled by assignment of confidential usernames, passwords and role assignment. The system will meet the applicable Federal regulatory requirements and those described in the E6 Good Clinical Practice Guidelines to ensure the confidentiality of trial subjects.

Data are transmitted over secure connections, authenticated by the use of digital certificates and encrypted during transmission via the Internet to the DCC using secure FTP technology.

## **6. Sample Size and Analysis Plan**

### **6.1. Analysis Population**

In current practice dialysis prescriptions are typically written to target urea removal. For this reason there is usually a strong association between prescribed dialysis time and estimated urea distribution volume or total body water volume (V) which usually averages 50% in women

and 60% in men<sup>40</sup>. A detailed analysis of 2,922 patients on dialysis  $\leq 3$  years in the Renal Research Institute database in January 2012, demonstrates the expected association between treatment time and V (**Table 1**). Thus, one can foresee that for most patients with V > 42.5 L, the prescribed dialysis times will be close to 4 hours, even when such

**Table 1. Treatment time and body water volume**

<b>Estimated body water volume V (L)</b>	<b>Median Treatment Time (min)</b>
< 27.5	185
27.5-32.5	206
32.5-37.5	211
37.5-40	213
40-42.5	224
> 42.5	235

patients are receiving their initial prescriptions in a Usual Care rather than Intervention dialysis unit. Hence, for such larger patients, the times prescribed in intervention units are not expected to differ importantly from controls.

Analysis of the same Renal Research Institute data sample suggests that about 35% of enrolling patients will have V values greater than 42.5 L and thus unlikely to be meaningfully participating

in the “time” prolongation intervention. Accordingly, the direct effects of the TiME Trial intervention will be evaluated in the *Primary Treatment Assessment Population*, which will consist of those patients with V (estimated from sex, age, and entry weight and height)  $\leq 42.5$  L.

In addition to the direct effects of treatment time, indirect effects of being enrolled in an Intervention facility versus a Usual Care facility are also possible. For example, assignment of a given dialysis facility to the Intervention group may lead to changes in unit practices that are unrelated to dialysis time but that may still affect patient outcomes. The *Extended Population* will consist of all patients in the trial and will be used to evaluate the combined direct and indirect effects of the cluster-administered intervention.

## **6.2. Sample Size**

The sample size calculation is based on the comparison of mortality rates between the Intervention and Usual Care arms in the primary treatment assessment population (participants with body water volume  $\leq 42$ L). The sample size requirements depend on the following factors: the minimum clinically important effect size, the mortality rate among incident patients (patients who have initiated dialysis within the past 120 days), the annual rate of loss to follow-up, type one error rate, and desired power. Since randomization for this trial will be at the level of the dialysis facility rather than at the patient level, the sample size also depends on the average number of participants enrolled within each dialysis facility and the intra-class correlation coefficient (ICC) (i.e., the correlation between two participants from the same dialysis facility, which describes the extent of similarity of mortality risk between two participants from the same dialysis facility).

Data from the two dialysis provider organizations from January 2011 to May 2012 suggests an overall mortality rate of 18% per year among incident patients. Other assumptions include a loss to follow-up rate of 5% per year. Loss to follow-up is expected to occur because of kidney transplantation, conversion from hemodialysis to peritoneal dialysis, and transfer to dialysis facilities belonging to a different dialysis provider organization. Based on data provided by both dialysis provider organizations, an ICC for mortality of 0.03 is expected. Based on the number of incident patients per facility at the two provider organizations, the average cluster size is expected to be 16, and it is expected that an average of approximately 10 (63%) of these patients will belong to the primary treatment assessment population.

**Table 2** shows sample size requirements under different scenarios based on an enrollment period of one year and a total study duration of three years. For the primary analysis, the desired detectable hazard ratio for mortality risk is 0.85 comparing the Intervention arm to the Usual Care arm in the primary treatment assessment population. To achieve 80% power with two-sided alpha level of 0.05, the trial requires 402 dialysis facilities (201 in each randomization arm) and a total of 6432 patients (of whom 4020 belong to the primary treatment assessment

population), assuming an ICC of 0.03. With this sample size the trial will also have 80% power to detect a HR of 0.88 in the extended population with a two-sided alpha level of 0.05.

**Table 2. Sample Size Requirement**

Hazard Ratio	Intra-class Correlation Coefficient	Number of Dialysis Facilities	Sample Size for Primary Assessment Population	Total Sample Size
0.9	0.04	1038	10380	16608
	0.03	970	9700	15520
	0.02	902	9000	14432
0.85	0.04	432	4320	6912
	0.03	402	4020	6432
	0.02	374	3740	5984
0.8	0.04	230	2300	3680
	0.03	216	2160	3456
	0.02	200	2000	3200

For the secondary outcome of hospitalization, a hospitalization rate of at least one per patient per year is expected. Conservatively estimating the minimum detectable effect size using only the first hospitalization, and assuming an ICC of 0.03, the study has 80% power to detect a hospitalization risk ratio of 0.90 in the primary treatment assessment population and 0.92 in the extended population. For the quality of life outcome, estimating, based on data from the HEMO trial, that the standard deviation of the change of the Physical Health Composite is approximately 10 units from baseline to year one, and assuming that 50% of the participants will complete the KDQOL™36, the study has 80% power to detect a difference of 1.4 for the change in the physical composite score (PCS) or mental composite score (MCS) in the primary efficacy population and a mean difference of 1.1 in the extended population. In repeated measures analyses, the actual minimum detectable effect size will be even smaller because quality of life will be assessed once per year during the follow-up period.

### **6.2.1. Revised Sample Size (incorporated June 2016)**

Sample size calculations were repeated after the trial was underway to incorporate the following changes to assumptions that affect study power. These changes include the following:

- 1) Facility enrollment did not begin until just prior to participant enrollment rather than being carried out and completed during the 12 months prior to participant enrollment. As a result the duration of participant enrollment increased from 1 year to 3 years. The duration of the trial was increased to 4.5 years to maintain a median follow-up of 2.5 years.
- 2) A total of 266 rather than 402 facilities agreed to participate and 10 facilities withdrew from the trial after randomization resulting in a smaller number of clusters and larger size of clusters.
- 3) The percentage of participants who were lost to follow-up because of transplantation or facility transfer was higher than anticipated.

- 4) The observed intra-cluster correlation coefficient (ICC) for mortality determined during the trial after approximately 5000 participants were enrolled was lower than anticipated with observed ICC of approximately 0.01 rather than 0.03.

**Table 2R** shows sample size requirements under scenarios that incorporate the modifications described above including enrollment period of 36 months and a total study duration of 54 months, a cluster number of 256 and cluster size standard deviation (SD) of 10 or 16, a loss to follow-up rate of 10%, and an ICC for mortality of 0.012 or 0.015. For the primary analysis, the desired detectable hazard ratio for mortality risk is 0.85 comparing the Intervention arm to the Usual Care arm in the primary treatment assessment population. A sample size of 6,880 (4250 in primary analysis population) provides 77 – 82% power to detect a HR of 0.85 with a two-sided alpha of 0.05.

**Table 2R. Revised Sample Size Requirement**

Enrollment Time/Total Study Time (mos)	# Clusters	SD for Cluster Size (1° Analysis Population)	Annual Loss to F/U	Annual Mortality Rate	ICC for Mortality	Sample Size for 1° Analysis Population	Total Sample Size	Power to detect HR 0.85
12/36	402	0	5%	18%	0.03	4020	6432	80%
36/54	256	10	10%	18%	0.015	4020	6432	78%
36/54	256	16	10%	18%	0.015	4020	6432	76%
36/54	256	10	10%	18%	0.012	4020	6432	80%
36/54	256	16	10%	18%	0.012	4020	6432	78%
36/54	256	10	10%	18%	0.015	4250	6800	80%
36/54	256	16	10%	18%	0.015	4250	6800	77%
36/54	256	10	10%	18%	0.012	4250	6800	82%
36/54	256	16	10%	18%	0.012	4250	6800	80%

### 6.3. Statistical Analyses

In addition to the analyses described in this section, descriptive statistics will be used during the conduct of the trial as part of data management plan for monitoring data quality. An overview of the statistical methods used both for descriptive purposes and in analyses of the primary research questions, is summarized in the following sections. More comprehensive plans for data management and statistical analyses will be provided as formal Data Management and Statistical Analysis Plans.

#### Descriptive Analyses

Standard descriptive statistics will be used to summarize baseline characteristics and study outcome measures at each follow-up visit, both overall, and within each treatment arm. Summary statistics such as means, medians, and ranges will be produced for all continuous variables. Frequencies will be computed for all categorical and ordinal variables. Graphical methods including histograms, stem-and-leaf diagrams and boxplots will be used to examine distributions, identify potential influential points, and guide in the choice of transformations, if warranted. The balance of baseline measures across the two treatment arms will be compared with robust variance estimate to take in account the clustering effect.

**Intent-to-Treat Analysis of Mortality**

The primary outcome is time to death and the primary analyses will include participants in the primary treatment assessment population only. The primary and main secondary analyses of treatment effectiveness will be intention-to-treat, i.e., each participant will be included in the group in which her/his dialysis facility was randomized, regardless of adherence to the assigned strategy. The primary analysis will be performed using Cox proportional hazards model to compare the survival rates between the Intervention and usual care arms stratified by the stratification variables (see section 4.4). Variance estimation will be calculated by the robust variance estimator to adjust for clustering by facility. In secondary analyses of mortality, time by treatment interaction terms will be applied to determine whether the treatment effect on mortality varies as a function of the amount of time the patient has been on the intervention. In addition, treatment by body size and treatment by sex interaction terms will be considered to assess whether treatment effects differ by body size or gender subgroups. Multivariable Cox regression will also be used to assess the sensitivity of the results to adjustment for baseline patient and center characteristics that are not balanced between the two treatment arms and that are predictive of the death outcome.

In additional secondary analyses of mortality, each of the above analyses will be performed in the extended population including all participants in the study, as well as in the large-size subgroup of patients >42.5 L to address any indirect effects of the intervention.

**Analyses of Secondary Endpoints**

Several secondary analyses will be conducted, both to evaluate the secondary outcomes and to supplement the primary endpoint comparison. Secondary outcomes include hospitalization data collected during the follow-up period and quality of life measured every year. Generalized estimating equations (GEE) will be used to model repeated quality of life data. GEE can account for the correlation of repeated measures within subject and also the correlation of repeated measures within cluster. Hospitalization data will also be analyzed using a GEE approach assuming a Poisson distribution with an offset term to account for the length of follow-up for each participant.

**Analyses Accounting for Non-Adherence**

Non-adherence is one of the most common causes complicating the application of causal inference to results from randomized trials. This is particularly the case for pragmatic trials, where the biological effect of the treatment received may differ greatly from the effectiveness of the intervention as estimated using intent-to-treat analyses. While the primary statistical analyses will be performed using standard intent-to-treat approaches to estimate effectiveness, we will perform additional explanatory analyses using modern methods of causal inference to assess the biological effect of the treatment received.

There are many reasons patients may not be adherent to the study protocol. For example, patients may switch from a dialysis facility in the treatment arm to a dialysis facility in the control arm, or patients in a dialysis facility assigned to the treatment may decline to increase their treatment time. In the trial, we will collect adherence information for all participants during the entire follow-up period in the form of the length of each dialysis treatment (both prescribed and delivered) and relevant time-updated covariates (see section 4.10). Modern causal modeling methods including marginal structural models<sup>41</sup> and structural nested models will be used to estimate the treatment efficacy assuming all participants are adherent to the study protocol.

#### **6.4. Managing Missing Data**

Given the nature of end-stage renal disease and dialysis practices, it is possible that missing data will be above the anticipated rate of 5% per year due to transfer of care, and kidney transplantation. Extensive efforts will be made to collect complete mortality data. For example, if a patient transfers his/her care to a different dialysis facility, hospitalizations and mortality outcomes will still be collected if the dialysis facility is part of the same provider organization.

For the primary analyses of mortality, patients will be censored at the time of loss to follow-up, which can lead to bias if censoring is informative – i.e., the censoring mechanism is associated positively or negatively with survival. The major projected source of censoring is receipt of a kidney transplant, which tends to occur in healthier patients with a relatively good prognosis. The potential implications of censoring of participants who undergo kidney transplantation will be explored by estimating the cumulative incidence of both death and kidney transplantation. For the secondary quality of life outcomes, missing data may be anticipated due to death, loss to follow-up for transplant and other reasons, and dependence on participants completing the questionnaires. In secondary analyses, different strategies will be used to handle missing data due to loss-to-follow-up and death. For the former, comparisons will be made between subjects with complete follow-up and those lost to follow-up, with respect to observed characteristics, and discrepancies will be pursued to shed light on the reasons for missing data in subjects with incomplete follow-up. Inverse probability weighting (IPW)<sup>41</sup> will be used when fitting GEE models. For missing data due to death, the use of statistical models based on the modern framework of principle stratification in which statistical inferences are restricted to participants who would survive in both arms (called “survivor average causal effect” (SACE) in causal inference literature) will be explored<sup>43</sup>.

## 7. Data and Safety Monitoring

### 7.1. Adverse Event Reporting

Hemodialysis sessions of 4.25 hours are not experimental procedures and there are no anticipated severe adverse effects associated with dialysis session durations of 4.25 hours compared with sessions which are shorter in duration. For this reason, the TiME Trial will not collect or report adverse events. 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. Further, should they occur, such events will be captured as hospitalization or death outcomes. Longer hemodialysis sessions are expected to produce gentler treatments with less fluctuation in intravascular volume. Therefore, it is anticipated that physical tolerability of dialysis sessions of 4.25 hours will be similar or better than shorter treatments.

### 7.2. Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) has been convened by the NIDDK to oversee the TiME Trial. The DSMB is comprised of individuals with expertise in dialysis, clinical trial conduct, and biostatistics. Members of the DSMB will not be involved in the conduct of the trial. The DSMB will review trial progress, data quality, and interim analyses throughout the course of the trial in accordance with a Data and Safety Monitoring Plan. The DSMB will meet regularly and make recommendations to the trial sponsor (NIH) about study progress and safety and will make recommendations about trial continuation. DSMB reports will be submitted to the IRB.

### 7.3. Reports and Interim Analyses

The study will be monitored routinely for issues of data quality and study conduct including facility and participant enrollment and follow-up rates. Patient enrollment is expected to be completed in approximately 3 years. An interim analysis will be performed when participants reach 50% information-time. The results of these analyses will be provided to the DSMB. To avoid inflating the overall Type I error rate for the primary analysis of effectiveness, an O'Brien-Fleming boundary will be used to calculate the nominal significance level to which the interim p-value is compared. The DSMB will have the authority to recommend that the trial be stopped early based on efficacy, futility, or safety concerns. **Table 3** outlines the proposed reporting schedule.

**Table 3. Study Reports**

Report	Prepared By	Provided To	Frequency
Enrollment	DCC	SC	q 2-4 weeks
Data Quality, Timeliness	DCC	SC, DSMB	q 3-4 mos
Demographics (combined)	DCC	SC, DSMB	q 3-4 mos
Interim Analysis	DCC	DSMB	12 and 24 mos
Primary Analysis	DCC	DSMB	36 mos
Abbreviations: DCC – Data Coordinating Center; SC – Steering Committee; DSMB – Data and Safety Monitoring Board			

## **8. Regulatory Issues**

### **8.1. Institutional Review Board**

The University of Pennsylvania Institutional Review Board will serve as the IRB of record for the TiME Trial and provide regulatory oversight for the trial activities at the dialysis provider organizations, the dialysis facilities and the DCC.

### **8.2. Protocol Changes**

All modifications to the protocol will be approved by the Steering Committee and submitted to the IRB for approval prior to implementation. Changes will be incorporated into the protocol as amendments. The protocol changes and new versions of the protocol will be distributed to all members of the TiME Trial Study Group.

### **8.3. Declaration of Interests**

Financial and other competing interests for the investigators are documented, provided to the Institutional Review Board, updated annually, and maintained at the DCC.

### **8.4. Data Sharing**

A data sharing policy will be developed by the TiME Trial Study Group. The policy will be consistent with the data sharing policy of the NIDDK. Data that can potentially be linked to a specific participating dialysis provider organization will not be transmitted to NIH data repositories. This includes all data elements that are collected by only one of the two dialysis provider organizations and data categories with counts below a specified threshold. All PHI will be removed from any shared data sets including dates, ages >89 years and any other sparsely represented values that could potentially be identifying.

### **8.5. Record Retention**

The clinical data generated at the dialysis facility is retained at the data warehouse of the dialysis provider organization in accordance with each organizations standard operating procedures. The trial database at the University of Pennsylvania will be maintained for a period of 5 years following completion of the study, after which it will be archived. A copy of the data will be transferred to the NIDDK data repository in accordance with NIDDK policy. Data elements that are unique to one of the dialysis provider organizations, infrequent values, or any other elements that have potential for identifying provider organization, dialysis facility, or participant will not be included in the repositied data.



## **9. References**

1. U S Renal Data System, USRDS 2012 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2012.
2. Wilson SM, Robertson JA, Chen G, et al. The IMPACT (Incident Management of Patients, Actions Centered on Treatment) program: a quality improvement approach for caring for patients initiating long-term hemodialysis. *American Journal of Kidney Diseases* 2012;60:435-43.
3. Wingard RL, Pupim LB, Krishnan M, Shintani A, Ikizler TA, Hakim RM. Early intervention improves mortality and hospitalization rates in incident hemodialysis patients: RightStart program. *Clinical journal of the American Society of Nephrology* 2007;2:1170-5.
4. Strippoli GF, Craig JC, Schena FP. The number, quality, and coverage of randomized controlled trials in nephrology. *Journal of the American Society of Nephrology* 2004;15:411-9.
5. KDOQI Hemodialysis Adequacy 2006 Work Group. Clinical practice guidelines for hemodialysis adequacy, update 2006. *Am J Kidney Dis* 48 (Suppl 1): S2-90, 2006
6. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *Journal of the American Society of Nephrology* 2004;15:2208-18.
7. U.S. Renal Data System, USRDS 2011 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2011.
8. Charra B, Chazot C. Volume control, blood pressure and cardiovascular function. Lessons from hemodialysis treatment. *Nephron Physiol* 2003;93:p94-101.
9. Wizemann V, Wabel P, Chamney P, et al. The mortality risk of overhydration in haemodialysis patients. *Nephrology, Dialysis, Transplantation* 2009;24:1574-9.
10. Agarwal R. Hypervolemia is associated with increased mortality among hemodialysis patients. *Hypertension* 2010;56:512-7.
11. Agarwal R, Light RP. Intradialytic hypertension is a marker of volume excess. *Nephrology, Dialysis, Transplantation* 2010;25:3355-61.
12. Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. *Kidney International* 2011;79:250-7.

13. Flythe JE, Curhan GC, Brunelli SM. Disentangling the Ultrafiltration Rate-Mortality Association: The Respective Roles of Session Length and Weight Gain. *Clinical Journal of the American Society of Nephrology* 2013.
14. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clinical Journal of the American Society of Nephrology* 2009;4:914-20.
15. Katzarski KS, Charra B, Luik AJ, et al. Fluid state and blood pressure control in patients treated with long and short haemodialysis. *Nephrology, Dialysis, Transplantation* 1999;14:369-75.
16. Koc Y, Unsal A, Kayabasi H, et al. Impact of volume status on blood pressure and left ventricle structure in patients undergoing chronic hemodialysis. *Ren Fail* 2011;33:377-81.
17. Chan CT, Greene T, Chertow GM, et al. Determinants of left ventricular mass in patients on hemodialysis: Frequent Hemodialysis Network (FHN) Trials. *Circ Cardiovasc Imaging* 2012;5:251-61.
18. Zoccali C, Benedetto FA, Mallamaci F, et al. Left ventricular mass monitoring in the follow-up of dialysis patients: prognostic value of left ventricular hypertrophy progression. *Kidney International* 2004;65:1492-8.
19. Chertow GM, Levin NW, Beck GJ, et al. In-center hemodialysis six times per week versus three times per week. *N Engl J Med* 2010;363:2287-300.
20. Saran R, Bragg-Gresham JL, Levin NW, et al. Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. *Kidney International* 2006;69:1222-8.
21. Brunelli SM, Chertow GM, Ankers ED, Lowrie EG, Thadhani R. Shorter dialysis times are associated with higher mortality among incident hemodialysis patients. *Kidney International* 2010;77:630-6.
22. Marshall MR, Byrne BG, Kerr PG, McDonald SP. Associations of hemodialysis dose and session length with mortality risk in Australian and New Zealand patients. *Kidney International* 2006;69:1229-36.
23. Tentori F, Zhang J, Li Y, et al. Longer dialysis session length is associated with better intermediate outcomes and survival among patients on in-center three times per week hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrology, Dialysis, Transplantation* 2012;27:4180-8.
24. Flythe JE, Curhan GC, Brunelli SM. Shorter length dialysis sessions are associated with increased mortality, independent of body weight. *Kidney international* 2013;83:104-13.

25. Daugirdas JT, Greene T, Depner TA, Levin NW, Chertow GM. Modeled urea distribution volume and mortality in the HEMO Study. *Clinical Journal of the American Society of Nephrology* 2011;6:1129-38.
26. Greene T, Daugirdas J, Depner T, et al. Association of achieved dialysis dose with mortality in the hemodialysis study: an example of "dose-targeting bias". *Journal of the American Society of Nephrology* 2005;16:3371-80.
27. Ramirez SP, Kapke A, Port FK, et al. Dialysis dose scaled to body surface area and size-adjusted, sex-specific patient mortality. *Clinical Journal of the American Society of Nephrology* 2012;7:1977-87.
28. Gotch FA, Sargent JA. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney international* 1985;28:526-34.
29. Lacson E, Jr., Brunelli SM. Hemodialysis treatment time: a fresh perspective. *Clinical journal of the American Society of Nephrology* 2011;6:2522-30.
30. Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 2002;347:2010-9.
31. Basile C, Libutti P, Di Turo AL, et al. Haemodynamic stability in standard bicarbonate haemodialysis and long-hour slow-flow bicarbonate haemodialysis. *Nephrology, dialysis, transplantation* 2011;26:252-8.
32. Lacson E, Jr., Xu J, Suri RS, et al. Survival with three-times weekly in-center nocturnal versus conventional hemodialysis. *Journal of the American Society of Nephrology* 2012;23:687-95.
33. Charra B. From adequate to optimal dialysis long 3 x 8 hr dialysis: a reasonable compromise. *Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia* 2005;25 Suppl 2:19-24.
34. Rocco MV, Lockridge RS, Jr., Beck GJ, et al. The effects of frequent nocturnal home hemodialysis: the Frequent Hemodialysis Network Nocturnal Trial. *Kidney international* 2011;80:1080-91.
35. Halpern SD, Berns JS, Israni AK. Willingness of patients to switch from conventional to daily hemodialysis: looking before we leap. *Am J Med* 2004;116:606-12.
36. Lacson E, Jr., Wang W, Lazarus JM, Hakim RM. Hemodialysis facility-based quality-of-care indicators and facility-specific patient outcomes. *American Journal of Kidney Diseases* 2009;54:490-7.
37. <http://www.cms.gov/Medicare/CMS-Forms/CMS-Forms/downloads/cms2728.pdf>.

38. Michael V. Rocco, Guofen Yan, Jennifer Gassman, et al. Comparison of Causes of Death Using HEMO Study and HCFA End-Stage Renal Disease Death Notification Classification Systems. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2002;146-53.
39. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *CMAJ* 2009;180:E47-57.
40. Watson PE, Watson ID, Batt RD. Total body water volumes for adult males and females estimated from simple anthropometric measurements. *Am J Clin Nutr* 1980;33:27-39.
41. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11:550-60.
42. Robins J. Correcting for non-compliance in randomized trials using structural nested mean models. Vol 23. Philadelphia, PA, ETATS-UNIS: Taylor & Francis; 1994.
43. Frangakis CE, Rubin DB. Principal stratification in causal inference. *Biometrics* 2002;58:21-9.
44. Piantadosi S. *Clinical trials: a methodologic perspective*. 2nd ed. Hoboken, NJ: Wiley-Interscience; 2005

# **TiME Trial**

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

A LARGE, CLUSTER-RANDOMIZED, PRAGMATIC TRIAL TO EVALUATE THE EFFECTS ON  
MORTALITY, HOSPITALIZATIONS, AND QUALITY OF LIFE OF INCREASING THE DIALYSIS SESSION DURATION  
FOR THRICE WEEKLY MAINTENANCE HEMODIALYSIS

## **STATISTICAL ANALYSIS PLAN**

**Version 1.1**

**Prepared By:** Senior Biostatistical Scientist and the Data Coordinating Center  
Center for Clinical Epidemiology and Biostatistics (CCEB)  
Blockley Hall, 423 Guardian Drive  
Perelman School of Medicine at the University of Pennsylvania  
Philadelphia, PA 19104

Protocol Summary	
<b>Title</b>	Time to Reduce Mortality in End-Stage Renal Disease (TiME) Trial
<b>Short Title</b>	TiME Trial
<b>Protocol Number</b>	817911
<b>Sponsor</b>	National Institutes of Health: NIDDK, Office of the Director
<b>Design</b>	Cluster-randomized, open label, pragmatic clinical trial
<b>Principal Investigator</b>	Laura M. Dember, M. D.
<b>Objectives</b>	<ol style="list-style-type: none"> <li>1. To determine whether dialysis facility implementation of a minimum hemodialysis session duration of 4.25 hours (versus usual care) for patients with end-stage renal disease initiating treatment with thrice weekly maintenance hemodialysis has benefits on mortality, hospitalizations and health-related quality of life.</li> <li>2. To demonstrate the capacity to conduct a large, pragmatic clinical trial in partnership with two large dialysis provider organizations.</li> </ol>
<b>Intervention</b>	Intervention facilities will recommend a minimum hemodialysis session duration of 4.25 hours. Control facilities ("Usual Care") will not implement a trial-driven recommendation about dialysis session duration.
<b>Enrollment Period</b>	3 years
<b>Duration</b>	4.5 years
<b>Study Center(s)</b>	Dialysis facilities operated by DaVita and Fresenius Medical Care, two large dialysis provider organizations
<b>Data Coordinating Center</b>	Clinical Research Computing Unit, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine
<b>Number of Facilities &amp; Patients</b>	402 dialysis units 6880 patients
<b>Main Eligibility Criteria</b>	<b>Dialysis Facility Eligibility</b> <ol style="list-style-type: none"> <li>1. Willingness of the facility's Medical Director, nephrologists and clinical leadership to adopt a facility approach of prescribing dialysis sessions of at least 4.25 hours for patients initiating treatment with maintenance hemodialysis (incident patients).</li> <li>2. Capacity to accommodate treatment session durations of at least 4.25 hours for incident patients.</li> <li>3. Facility use of the electronic data systems of the dialysis provider organization.</li> </ol>

## Protocol Summary

	<p><b>Patient Eligibility</b></p> <p><b><u>Inclusion Criteria</u></b></p> <ol style="list-style-type: none"> <li>1. Initiation of maintenance dialysis within the past 120 days.</li> <li>2. Treatment with maintenance dialysis in a participating facility.</li> <li>3. Age <math>\geq 18</math> years.</li> </ol> <p><b><u>Exclusion Criteria</u></b></p> <ol style="list-style-type: none"> <li>4. Unwillingness to participate. Patients receiving dialysis in facilities in the Intervention arm can participate without agreeing to a minimum dialysis session duration of 4.25 hours. Data collection for such participants will be identical to those who receive the session duration of <math>\geq 4.25</math> hours.</li> <li>2. Patients who are unable to provide consent for dialysis care will be excluded from trial participation.</li> </ol>
<b>Outcomes</b>	<p><b>Primary Outcome:</b> death</p> <p><b>Major Secondary Outcomes:</b> hospitalizations, health-related quality of life</p>
<b>Duration of intervention</b>	Up to 3 years
<b>Analytic Approach</b>	<ol style="list-style-type: none"> <li>1. <b>Primary outcome:</b> intention to treat comparison of time to death between Intervention and Usual Care groups.  Analysis will include generation of the hazard ratio and 95% confidence interval for the intervention. Significance testing will be performed with two-tailed p values of <math>\leq 0.05</math> considered significant. Survival curves with 95% confidence intervals will be generated using the Kaplan-Meier method. Secondary analyses will incorporate adjustment for co-variables that are not balanced between randomization groups.</li> <li>2. <b>Secondary outcomes:</b> <ol style="list-style-type: none"> <li>a) comparison of hospitalization rates between Intervention and Usual Care groups</li> <li>b) comparison of change over time in KDQOL™36 domains between Intervention and Usual Care groups</li> </ol> </li> <li>3. <b>Primary analysis population:</b> patients with anthropometric volume <math>\leq 42.5</math> liters. Referred to as “Primary Treatment Assessment Population.”</li> <li>4. <b>Secondary analysis population:</b> all patients. Referred to as “Extended Analysis Population.”</li> </ol>
<b>Study Oversight</b>	An independent Data and Safety Monitoring Board (DSMB) appointed by NIH will review trial progress, data quality, and interim analyses throughout the course of the trial in accordance with a Data and Safety Monitoring Plan.

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## 1 STUDY DESIGN

The TiME Trial is a cluster-randomized, parallel-group pragmatic clinical trial for patients initiating treatment with maintenance hemodialysis. The trial is one of the pragmatic trial demonstration projects of the National Institutes of Health (NIH) Health Care Systems Research Collaboratory. The trial will be conducted in partnership with DaVita and Fresenius Medical Care, the two largest dialysis providers in the United States who together care for approximately 70% of the US dialysis population.

The primary objective of the TiME Trial is to determine whether, compared with usual care, dialysis facility implementation of a minimum hemodialysis session duration of 4.25 hours for patients with end-stage renal disease initiating treatment with thrice-weekly maintenance hemodialysis improves clinical outcomes including survival. The secondary objective is to demonstrate the feasibility of conducting a large, pragmatic clinical trial in partnership with two large dialysis provider organizations.

Participating dialysis units will be randomized to the Intervention group or the Usual Care group. Intervention facilities will adopt an approach of recommending dialysis session durations of at least 4 hours and 15 minutes (255 minutes) for eligible patients. Usual Care facilities will have no trial-driven approach to dialysis session duration. The trial will use an opt-out approach to participation in which all eligible patients initiating dialysis in participating facilities will be enrolled unless they opt out of allowing their clinical data to be included in the trial dataset.

Four hundred and two dialysis facilities will be randomized in a 1:1 distribution to the Intervention arm or the Usual Care arm. Facilities randomized to the Intervention arm will adopt the practice of recommending dialysis session durations of at least 4.25 hours for all patients initiating hemodialysis treatment regardless of body size or dialysis solute clearance measurements. Facilities randomized to Usual Care will have no trial-driven approach to dialysis session duration. Participants will be followed for up to 3 years. The primary endpoint is mortality; major secondary endpoints are hospitalization rate and quality of life. Secondary outcomes include hospitalization rates compared between treatment groups; health related quality of life (HRQOL) utilizing the kidney disease-specific questionnaire KDQL™<sup>36</sup>; and other secondary effectiveness outcomes such as pre-dialysis blood pressure, post-dialysis blood pressure, inter-dialytic weight gain, and dialysis attendance compared between treatment groups.

Pragmatic features of the TiME Trial include 1) high generalizability due to non-restrictive eligibility criteria and broad representation of participating facilities, 2) implementation of the intervention by clinical care providers rather than by research personnel, and 3) complete reliance on data obtained through routine clinical care rather than through research activities. The source of outcomes data will be the electronic data systems of the dialysis provider organizations.

## 2 DATA ACQUISITION, MANAGEMENT, AND APPROACH TO REPORTING

### 2.1 Data Acquisition

Facility and patient enrollment at the two dialysis provider organizations will be monitored by the Data Coordinating Center (DCC) at the University of Pennsylvania. The DCC has established a data transfer process with each dialysis provider organization in which pre-specified data elements will be extracted from the clinical data systems of the dialysis provider organizations by their information technology personnel. After internal data quality assessment, the data will be transferred electronically to the Data Coordinating Center once per month. The transfer of data will be cumulative rather than incremental – i.e., all trial data accumulated to date will be transmitted rather than only newly acquired data since the prior data transfer. Each month the DCC will combine the uploaded data from the two dialysis provider organizations into a single trial database and reviewed the data for completeness and implausible values. Reports will be generated and shared with the dialysis provider organizations and the Steering Committee to allow regular monitoring of adherence to the Intervention.

### 2.2 Session Duration

Because the trial relies on existing clinical data, the ability to query the dialysis providers for individual data elements is limited. The DCC will use the following approach for managing and validating session data for reporting.

- a. Reports of session duration exclude single dialysis sessions < 60 minutes in duration since these represent aborted sessions.
- b. Two dialysis sessions occurring on the same date are treated as a single session that was interrupted and resumed. The time records will be summed.
- c. When a pre-session dialysis record does not have a corresponding post-session record, it is treated as a session that was never initiated and the session is excluded from summary reports.

### 2.3 Missed Dialysis Sessions

A missed dialysis sessions is defined as a session that is missed despite the expectation that it would occur. The estimated missed sessions per month estimate how many sessions a participant has missed not attributable to hospitalization. The process for determining skipped sessions is as follows:

- a. Expected number of dialysis sessions per day: The TiME Trial enrolls participants who are prescribed thrice weekly dialysis sessions and thus the number of expected dialysis sessions per week is 3/7. In practice, the prescribed frequency occasionally changes, usually temporarily. Therefore, the expected number of dialysis sessions per day takes into account the prescribed frequency.

- b. Number of observed days in a week: For participants without hospitalization, this number is always 7. If a participant is hospitalized for  $x$  number of days in a week, the number of observed days in the week will be  $(7 - x)$ . The reason that the hospitalized days are removed is because participants receive dialysis during the hospitalization but the session data are not included in the dialysis provider clinical data and thus are not in the trial dataset.
- c. Expected number of dialysis sessions in a week: This is calculated by multiplying the expected number of dialysis sessions per day by the number of observed days in a week.
- d. Number of missed sessions in a week: For each participant, the number of missed sessions for each week is calculated by subtracting the number of delivered dialysis sessions from the expected number of dialysis sessions in that week.
- e. Total number of missed sessions: For each participant, the total number of missed sessions is calculated by summing numbers of missed sessions in all weeks.
- f. Gaps in dialysis session data are compared to hospitalization information [admission and discharge dates] in order to determine reason for missing session data.

## 2.4 Status Changes

The two dialysis provider organizations have different methods for identifying and recording patient status changes. Throughout the course of dialysis, participants may have experienced multiple events of status change. For the purpose of the statistical analyses, only the current event of status change will be considered. Events of status change happened prior to any dialysis session will not be considered as the event of status change; i.e., only the event of status change resulting in no dialysis data transferring to DCC will be considered. As a result we have examined and consolidated all of the information transmitted into the following status change categories to represent each participant's current status:

Participant Status Categories	Details
Study cutoff	Alive
Death	
Modality change	To peritoneal dialysis, to other modality
Loss-to-follow-up	Prison/Abroad, became ineligible, hospitalized, Termination/loss-to-follow-up/opt-out, Recovery, Transfer to a facility outside of the dialysis provider organization
Transplantation	
Transfer to a non-participating facility within the dialysis provider organization	

### **3 INTERIM ANALYSES FOR THE DATA AND SAFETY MONITORING BOARD**

The protocol includes a plan for an interim efficacy analysis when the participants reach 50% information time to be provided to the DSMB. To avoid inflating the overall Type I error rate for the primary analysis of effectiveness, an O'Brien-Fleming boundary will be used to calculate the nominal significance level to which the interim p-value is compared. The DSMB will have the authority to recommend that the trial be stopped early based on efficacy, futility, or safety concerns.

#### **3.1 DSMB-Requested Interim Analysis**

A mid-course interim analysis, including a futility analysis, was requested by the DSMB. The interim analysis was conducted using data through October 2016 when the information time was approximately 50%. The following plan was provided to the DSMB before the interim efficacy analysis and the futility analysis were conducted:

The TiME Trial design provides 80% power to detect a hazard ratio of 0.85 from a Cox proportional hazards model at a type 1 error rate of 5%. To account for the interim analysis of accumulated data in the TiME Trial, the Lan-DeMets alpha spending function method will be used to determine the O'Brien-Fleming boundary to maintain an overall type 1 error rate of 5%. All confidence intervals will be adjusted for the interim analysis with one-look at information time of 50% (i.e., the O'Brien-Fleming boundary for a two-sided test would be  $\{-2.96, 2.96\}$ ). In other words, the null hypothesis that the hazard ratio equals 1 would be rejected if the test statistic is less than -2.96.

### **4 FINAL DATA ANALYSIS UPON COMPLETION OF TRIAL**

#### **4.1 General Approach**

Upon completion of the trial, after all data has been entered in the database and query resolution is complete, description of the data and the primary statistical analysis will be performed. The DCC will produce a final report outlining all analyses and interpretation of the results. The report will be used as the basis of the primary results manuscript to be prepared for publication. Details of the analyses and statistical methods to be included in the final report are outlined in this Statistical Analysis Plan. All statistical tests described will be conducted using a two-sided level of significance.

Before proceeding with inferential analyses, the data for this study will be fully described. Data will be examined for the primary outcome and all covariates to assess distributional assumptions, and balance of covariates among the study arms.

In this normal theory framework, we will first test for any difference between the trial arms, using a multivariable linear model. The multivariable model will be implemented where the interest is on testing the two arms using a Wald test. The assessment of the primary hypothesis of no difference between the arms will be conducted using a two-sided test.

Since randomization will be implemented at the site level, the intra-cluster correlation will be addressed in the models for all analyses. The design factors, stratification on each site's racial distribution (black vs non-black) and catheter use, not included in the primary analysis will be assessed in secondary analyses.

## **4.2 Baseline Data**

Descriptive statistics will be used to summarize baseline characteristics both in overall and in each treatment arm. Summary statistics such as means, standard deviations, medians and interquartile ranges will be produced for all continuous variables. Frequencies and percentages will be computed for all categorical and ordinal variables. Graphical methods including density plots, histograms, and boxplots will be used to examine distributions, identify potential influential points, and guide in the choice of transformations, if warranted. The balance of baseline measures across the two treatment arms will be compared with robust variance estimate to take in account the clustering effect.

## **4.3 Primary Efficacy Analysis**

The primary outcome is time to death and the primary efficacy analyses will be an intention-to-treat (ITT) analysis on mortality for the primary analysis population, referred to as "Watson  $\leq 42.5L$ ". Each participant will be included in the arm in which her/his dialysis facility was randomized, regardless of adherence to the assigned strategy. The analysis will be performed using Cox proportional hazards models to compare the hazard rates between the Intervention and Usual Care arms. Intra-cluster correlation (ICC) between participants within the same facility will be modeled by using a random component for the hazard function (i.e. frailty models). The hazard ratio (HR) for mortality between Intervention and Usual Care arms will be reported by calculating the exponential function of the estimated parameter of the treatment effect from the Cox models. The test statistic will be calculated to test the null hypothesis that the hazard ratio equals 1 versus the 2-sided alternative hypothesis that the hazard ratio is greater than and/or less than 1. To examine the proportionality between the Intervention group and the Usual Care group, an interaction term between treatment and a function of time will be included in the model; i.e., to determine whether the treatment effect on mortality varies as a function of time that a participant has been under the treatment. The same approach will be used for the primary outcome analysis for the extended analysis population (all participants regardless of Watson V) as well as in the stratified analyses and the large-size subgroup of participants, referred to as "Watson  $>42.5L$ ".

## **4.4 Secondary Analyses of the Primary Outcome**

### **4.4.1 Stratified Analyses**

Secondary analyses of the primary outcome of mortality will include stratified analyses 1) participant's self-identified race (black, non-black); and 2) participant's use of a central venous catheter at baseline (yes, no).

In addition, interaction terms between treatment and body size and treatment and sex will be considered to determine whether treatment effects differ by body size or sex subgroups.

#### **4.4.2 Exploratory As-Treated Analyses**

##### **4.4.2.1 Rationale**

Non-adherence to the trial intervention is one of the most common factors complicating the application of causal inference to results from randomized trials. This is particularly the case for pragmatic trials, where the biological effect of the treatment received may differ greatly from the effectiveness of the intervention as estimated using intent-to-treat analyses. While the primary analyses will be performed using standard intent-to-treat approaches to estimate effectiveness, additional explanatory analyses using modern methods of causal inference will be performed to assess the biological effect of the treatment received; i.e., as-treated analyses.

Non-adherence to the TiME trial intervention may occur as a result of unwillingness by patients to undergo longer dialysis sessions, preference of the treating nephrologist to prescribe shorter sessions for specific patients, operational barriers for facilities, and patient transfer to non-participating facilities. Adherence information for participants will be collected during the entire follow-up period in the form of the both prescribed and delivered duration of each dialysis session and relevant time-updated covariates.

To monitor patient adherence, we use an aggregated metric, average session duration within each patient, as well as a graphical tool, lasagna plot, at session-level for each patient. In the as-treated analysis, we will use the previously described Cox models with frailty to investigate the effect of session duration (prescribed and delivered) on mortality rate.

One disadvantage of the as-treated analysis for mortality is that, for example, a difference in mortality for a 30-minute increase in delivered session duration is potentially confounded by unmeasured confounders (e.g. healthier patients may be more likely than sicker patients to have longer sessions). Therefore, the difference in mortality in such an analysis infers association, but not necessarily causation; or, equivalently, it is a result from an observational study, not a randomized trial. An advantage of the TiME Trial is its randomization. Consequently, we will conduct instrumental variable (IV) analyses using the randomization assignment as an instrument. The property of the instrument (randomization) is to provide a proper way to adjust for the unmeasured confounders (e.g. indication bias), and to provide a causal interpretation of the difference in mortality for a 30-minute increase in delivered session duration among compliers (those patients who, because of the randomization, increase their dialysis session duration from x minutes to x+30 minutes). Although the strength of the instrument within an IV analysis may be determined by the separation in delivered session duration between Intervention and Usual Care arms (which will be decreased by non-adherence), this will affect the precision of the causal interpretation (i.e. wider confidence interval for the hazard ratio), but not the accuracy of the causal interpretation (i.e. unbiased hazard ratio).

## **4.5 Secondary Outcomes**

Secondary outcomes include hospitalization rates using data collected during the follow-up period, pre- and post-dialysis blood pressure using data from each dialysis session, and ultra-filtration rate calculated using data from each dialysis session, laboratory data measured every month, and quality of life measured approximately annually. Analyses of the secondary outcomes will be performed for the primary analysis population (Watson V  $\leq 42.5$ L), for the extended analysis population (all participants regardless of Watson V), and for the subgroup of participants with Watson V  $> 42.5$ L, as well as in the stratified analyses.

### **4.5.1 Hospitalizations**

Hospitalization data will be analyzed in two ways. First, time to the first hospitalization will be compared between treatment groups using multivariable Cox proportional hazards models adjusting for clustering. Second, to compare the hospitalization rates between treatment groups, a generalized estimating equations (GEE) approach will be used assuming a Poisson distribution with an offset term to account for the length of follow-up for each participant and an independent correlation structure to account for participants within the same facility. Similar to the analyses of the primary endpoint, analyses will be performed for the primary treatment assessment population and the extended analysis population.

### **4.5.2 Quality of Life**

Quality of life as assessed by the Kidney Disease Quality of Life Short Form-36 (KDQOL 36™), a kidney disease specific instrument administered by both dialysis provider organizations at least once per year as part of routine practice and in accordance with CMS requirements. The KDQOL consists of five

sub-domains: SF12 physical scores, SF12 mental scores, burden of kidney diseases scores, symptoms/problems scores and effects of kidney diseases scores. For each sub-domain, the baseline measurement is determined by the average of all available measurements collected between 90 days before and 120 days after the date of the first transferred dialysis session; and the follow-up measurement is determined by the average of all available measurements collected beyond 120 days after the first transferred dialysis session. Changes in the KDQOL sub-domains between treatment arms will be compared using linear mixed effects models to account for participants within the same facility.

#### **4.5.3 Safety Parameters**

Five safety events of interests are defined by the laboratory data measured every month and the blood pressure measured at every dialysis session: potassium, phosphorus, bicarbonate, albumin and post-dialytic systolic blood pressure. For monitoring by the DSMB, the thresholds for defining each safety event were determined based on the distribution of the in the Usual Care arm for laboratory measures, and based on clinical significance for post-dialysis blood pressure. The five safety events are (1) hypokalemia defined as potassium < 3.6 mEq/L; (2) hypophosphatemia defined as phosphorus < 3.0 mg/dL; (3) hyperbicarbonatemia defined bicarbonate > 26 mEq/L; (4) hypoalbuminemia defined as albumin < 3.2 g/dL; and (5) hypotension defined as post-dialytic systolic blood pressure < 90 mmHg. The safety events are summarized as events per 100 participant-years. The difference in event rates between treatment arms will be compared using the GEE models as previously described.

#### **4.5.4 Blood pressure**

The pre- and post-dialysis blood pressures during each dialysis session will be summarized by the weighted average to account for the unequal number of dialysis sessions per participant. The differences in overall mean and slope over the study period between treatment arms will be compared using linear mixed effects models to account for both participants within the same facility and repeated measurements within the same participant.

#### **4.5.5 Ultrafiltration rate**

Ultrafiltration rates for each dialysis session will be calculated as milliliters of fluid removed per kilogram body weight per hour (ml/kg/hr). The ultrafiltration rates will be summarized by the weighted average to account for the unequal number of dialysis sessions per participant. The differences in overall mean and slope over the study period between treatment arms will be compared using linear mixed effects models to account for both participants within the same facility and repeated measurements within the same participant.

### **5 LOSS TO FOLLOW-UP**

Given the nature of end-stage renal disease and dialysis practices, it is possible that loss-to-follow-up will be above the anticipated loss-to-follow up rate of 5% per year due to transfer of care and kidney



transplantation. Extensive efforts will be made to collect complete mortality data. If a participant transfers his/her care to a non-participating dialysis facility that is within the same dialysis provider organization, all data elements for the patient will continue to be included in the data transfers from the dialysis provider organization.

For the primary analyses of mortality, participants will be censored at the time of loss to follow-up, which can lead to bias if censoring is informative – i.e., the censoring mechanism is associated positively or negatively with survival. The major projected source of censoring is receipt of a kidney transplant, which tends to occur in healthier patients with a relatively good prognosis. The potential implications of censoring of participants who undergo kidney transplantation will be explored by estimating the cumulative incidence of both death and kidney transplantation. For the secondary quality of life outcomes, missing data may be anticipated due to death, loss to follow-up for transplant and other reasons, and dependence on participants completing the questionnaires. In secondary analyses, different strategies will be used to handle missing data due to loss-to-follow-up and death. For the former, comparisons will be made between participants with complete follow-up and those lost to follow-up, with respect to observed characteristics, and discrepancies will be pursued to shed light on the reasons for missing data in subjects with incomplete follow-up. Inverse probability weighting (IPW) will be used when fitting models.