Health Effects of oral Protein Supplements in HD (The HELPS-HD Trial)

NCT02933151

Final Protocol, Version November 11, 2019

Health Effects of oraL Protein Supplements in HD (The HELPS-HD Trial)

An Open-Label Cluster Randomized Pragmatic Trial Evaluating the Effectiveness of Oral Intradialytic Nutritional Supplements on Mortality in Hemodialysis Patients

1. SPECIFIC AIM:

To conduct a pragmatic randomized clinical trial in which we will determine the mortality impact of a protocol whereby all hemodialysis patients receive an oral, protein-based nutritional supplement during the dialysis procedure as compared to the existing nutritional protocol whereby only hemodialysis patients with serum albumin below 3.5 g/dL and incident hemodialysis patients during the first months of care receive an oral, intradialytic protein-based nutritional supplement during the dialysis procedure.

2. BACKGROUND:

Hemodialysis, the most common form of kidney replacement therapy, is a lifesaving procedure for people with kidney disease, but is accompanied by high rates of morbidity and mortality, some of which may reflect the catabolism induced by the hemodialysis procedure itself. Most people in the United States receive hemodialysis thrice weekly at dialysis facilities, where their entire blood volume cycles through the hemodialysis circuit between 5 and 10 times per hour over a hemodialysis session lasting between 3 and 4.5 hours. The purpose of dialysis is to remove small proteins that can no longer be cleared by the kidneys, control volume overload, and maintain electrolyte balance. The hemodialysis procedure, not surprisingly, induces considerable stress on dialysis patients, through both hemodynamic and metabolic challenges. It is this metabolic challenge that the current trial is addressing.

2.1 Protein Catabolism during Hemodialysis

The dialysis procedure itself results in amino acid loss. In several elegant balance studies of hemodialysis patient volunteers, Ikizler and colleagues demonstrated that:
1) Muscle catabolism occurs during dialysis in people not given oral or intravenous protein during dialysis;[3] 2) Plasma amino acid levels drop during hemodialysis in the absence of protein supplementation and do not return to normal immediately post hemodialysis while being maintained near normal in participants being given oral nutritional supplements (Figure 1);[1] and 3) A low dose of amino-acid supplementation can adequately counteract HD-associated catabolism.[1] In

our proposed pragmatic clinical trial, noting these results and the loss of amino acids from the circulation, we will replace estimated losses with 15 g of protein administered during dialysis.

Critically, as shown by Sundell and colleagues,[1] the protein loss and subsequent catabolism induced by hemodialysis is potentially modifiable and represents an attractive target for interventions to improve the overall prognosis and well-being of patients with kidney failure treated with hemodialysis. This is not an insubstantial issue, as mortality rates are extremely high among hemodialysis patients, with approximately 50% dying within three years of initiating kidney replacement therapy.[4] Notably, poor nutritional status and nutrient deficiency are common among patients treated with maintenance dialysis, with prevalence ranging from 18-75%.[5] Although neither sensitive nor specific, serum albumin, the most prevalent protein circulating in the body, is the most common marker used to estimate nutritional status, and a low serum albumin level, which may indicate both poor nutritional status and heightened systemic inflammation, is a powerful marker of increased mortality risk.[6-9]

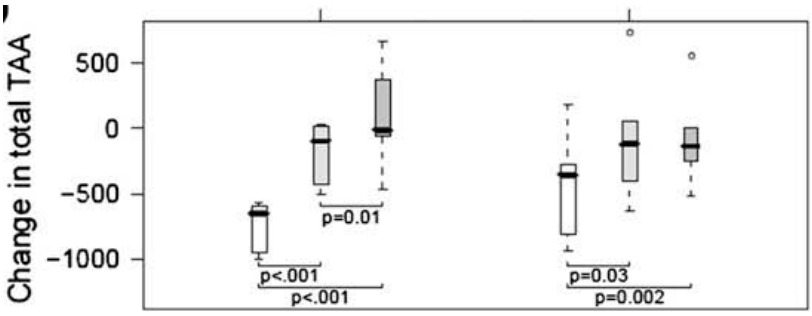

Figure 1. Box-and-whisker plot of changes in total amino acid (TAA) levels (μmol/L) during HD vs pre-HD (left plots) and post HD-pre-HD (right plots). Open boxes represent the control group that received no nutritional supplements, light gray boxes represent Pro-Stat lower dose group, and dark gray boxes represent Pro-Stat higher dose group.[1]

The relationship between serum albumin and outcomes may reflect causality, as anorexia and dysgeusia can lead to in inadequate protein and calorie intake, resulting in malnutrition and adverse outcomes, particularly in the context of increased nutritional needs that occurs in the catabolic milieu that is characteristic of hemodialysis; however, this relationship may be substantially more complicated since nutritional markers including serum albumin also reflect underlying inflammation or illness burden.[10,11] In contrast to hypoalbuminemia and weight loss, both of which are associated with poor outcomes, clinical characteristics that suggest better nutrition or nutritional reserve and therefore better ability to cope with the catabolic effects of hemodialysis, such as higher serum creatinine and higher body mass index, are associated with improved survival.[6,12,13]

As discussed above, while comorbid conditions common in patients treated with hemodialysis are associated with catabolism, the hemodialysis procedure itself also induces a catabolic state.[2,14-16] Studies that explored amino acid losses occurring during dialysis are summarized in Table 1 below,[17-21] reprinted from Lim et al,[2] consistently demonstrate amino acid losses and negative protein balance during the hemodialysis procedure. Importantly, several small studies, including those described in more detail above, demonstrate that oral intradialytic supplement administration early in the dialysis session appears to ameliorate this catabolic state.[1,3]

Author (Reference)	Isotope	Flux	Pre-HD/HD					Pre-HD/Post-HD			
			B	O	S	D	NB	B	O	S	NB
Lim (11)	^{13}C leucine	μmol/kg per h→	118/117	17/14	101/88	14.4	−17/−29	118/115	17/19	101/95	−17/−19
		Fractional Δ→	↓1%	↓18%	↓13%	(12%)	↓71%	↓3%	↑12%	↓ 6%	↓12%
Ikizler (8)	^{13}C leucine	mg/kgFFM per min→	3.4/3.7	0.5/0.4	2.9/2.7	0.61	−0.5/−1.0	3.4/3.8	0.5/0.6	2.9/3.2	−0.5/−0.6
		Fractional Δ→	↑9%	↓19%	↓7%	(16%)	↓96%	↑11%	↑21%	↑11%	↓20%
Raj (9)	$^{13}C_6$ phenyl-alanine	nmol/kg per min→	0.8/0.7	—	—	—	—	—	—	—	—
		Fractional Δ→	↓15%	—	—	—	—	—	—	—	—
Veeneman (12)	^{13}C valine	μmol/kg/h→	70/65	15/9	62/50	21.0	−8/−21	—	—	—	—
		Fractional Δ→	↓7%	↓40%	↓19%	(26%)	↓87%	—	—	—	—
Pupim (14)	^{13}C leucine	mg/kgFFM per min→	3.4/3.8	0.54/0.52	2.9/2.8	—	−0.5/−1.0	3.4/3.7	0.54/0.65	2.9/3.0	−0.5/−0.6
		Fractional Δ→	↑10%	↓4%	↓3%	—	↓81%	↑7%	↑20%	↑5%	↓20%

Table 1. As shown in 5 balance studies performed in hemodialysis patients, during HD, although whole-body protein degradation is minimally changed from baseline, net protein balance is substantially reduced because of a combination of dialysate protein loss and decreased protein synthesis. After dialysis, net protein balance because less negative due to cessation of dialysate losses and improved protein synthesis.[2]

Under column 'Flux' are the absolute values of the flux rates and fractional changes in each experiment. The latter represents increment or decrement comparing during HD with pre-HD and comparing post-HD with pre-HD. Two values are entered into the columns of breakdown (B), oxidation (O), synthesis (S), and net balance (NB) representing before and during and before and after HD. Column D lists the absolute amounts of unlabeled dialysate amino acid (the study amino acid) loss, and values in parentheses represent losses expressed as % of total flux.

Presumably, if catabolism can be interrupted and protein balance maintained at a stable baseline through the hemodialysis procedure, protein-energy wasting, which is common in hemodialysis, could be ameliorated.[10,22] Conceptually, as shown in the schematic figure (Figure 2), interrupting catabolism could result in less sarcopenia and better overall health through both direct effects on anabolism as well as subsequent indirect effects on anorexia, inflammation and other states that predispose to wasting.

2.2 Observational Data Supporting Protein Supplement Use

To date no large clinical trials have addressed patient outcomes associated with supplemental protein administration; however, dialysis providers have leveraged quality improvement activities to evaluate cohort data using quasi-experimental designs in order to inform this question.

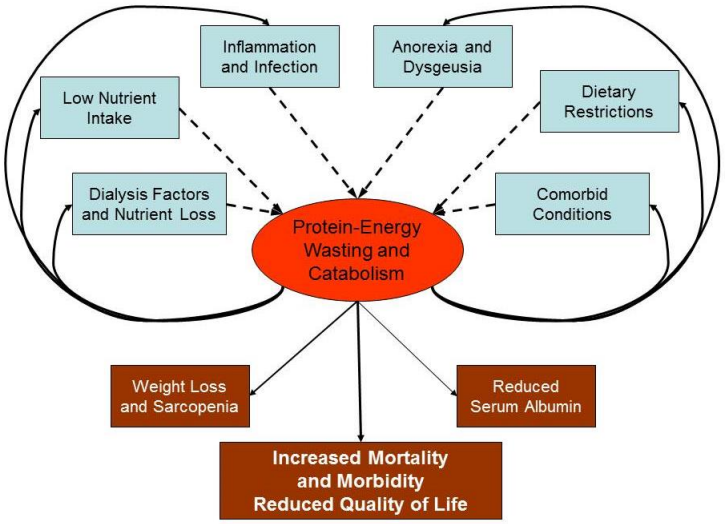

Figure 2. Concept figure of the interplay among protein loss, clinical symptoms and signs, and patient outcomes in dialysis.

In one report, Lacson and colleagues evaluated the potential utility of intradialytic nutritional supplements in a large quality improvement project conducted in patients treated with maintenance hemodialysis at facilities operated by Fresenius Medical Care North America.[23] In their protocol, maintenance hemodialysis patients with a baseline serum albumin ≤3.5 g/dL were eligible to receive oral nutritional supplements (ONS) thrice weekly during the hemodialysis procedure until serum albumin was ≥4 g/dL, at which time the ONS would be discontinued. The ONS used was variable based on individual facility preferences, ranging from liquid protein concentrates to protein drinks and protein bars. Specific choices included NeproCarb Steady, Prostat RC, ZonePerfect, and VitalProteinRx. Due to variable adoption of the protocol by facilities, Lacson and colleagues were able to divide their population into treated and untreated groups, matching individuals between groups using a propensity score. Among patients receiving ONS, as compared to those never receiving ONS, there was a 34% reduced risk of all-cause mortality in adjusted analyses. Critically, Lacson and colleagues were unable to examine change in serum albumin during the study period due to an assay change.

In 2010, Dialysis Clinic, Inc. (DCI) widely implemented a similar nutritional supplement protocol (NSP), such that, when serum albumin was ≤3.5 g/dL, patients were administered 15g of oral protein during each dialysis session; this was largely accomplished using Prostat, a liquid supplement with 15g of protein per 30 ml of supplement, although other supplements are available for use. In this observational study, also using propensity score matching to evaluate mortality in NSP users versus non-users, prescription and receipt of the NSP protocol was associated with a significant reduction in mortality for in-center maintenance hemodialysis patients,[24] consistent with results from the Fresenius study.[23] The effect of NSP prescription and receipt was substantial in all analyses, regardless of propensity matching and incorporation of time-dependent variables, suggesting that, although the impact of NSP prescription appears 'too good to be true', at a

minimum there is no indication of harm and there potentially is a marked mortality benefit, ranging between a 20-50% relative reduction in mortality associated with its use, depending on the method of analysis.

2.3 Provision of Hemodialysis Care in the US

In the United States, hemodialysis is most often performed in free-standing facilities, ranging in size from approximately 30 to 200 patients, with patients typically receiving hemodialysis thrice weekly for 3 to 4.5 hours. Hemodialysis units are highly structured and much of the care provided is administered following physician-prescribed protocols, such that most patients are managed with similar in-center medications at similar doses and receive similar treatments. In the US, dialysis care is funded largely by Medicare through the End-stage Renal Disease (ESRD) entitlement. Recent payment reforms within the ESRD program resulted in the 2011 expansion of the ESRD bundled payment; this sum, on average ~$240 per treatment depending on patient factors and geographic location, covers almost all aspects of hemodialysis care, including all dialysis-related medications and treatments administered in the dialysis facility.[25,26]

Included within this bundle would be nutritional supplements administered during dialysis. In a 2009 opinion regarding whether expansion of a program to provide nutritional supplements to "malnourished end-stage renal disease patients who are on dialysis", the US Office of the Inspector General (OIG) concluded that the requestor would not be violating the Federal anti-kickback statute by providing nutritional supplements for this purpose, assuming that they were discontinued when the serum albumin reached 4.0 g/dL, the target level established by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines.[27] The OIG report specifically supported the statement that, in these circumstances, supplements could be considered an "integral part of the clinical care provided to a patient" and cited as supporting data the requestor's comment that many patients *"only consume them with the active encouragement and support of the patient's treating physician and/or the dialysis facility's patient care team*."[27] Of note, the 3.5 g/dL threshold for initiation was a semi-arbitrary level that was chosen based on likelihood of regulatory acceptance and there is little reason to think that protein handling during hemodialysis differs markedly based on serum albumin levels. Of note, in the study by Sundell and colleagues discussed above, participants had mean baseline serum albumin levels of 3.9 g/dL and all would have been ineligible for current nutritional supplement protocols used widely at dialysis facilities in the US.[1]

Furthermore, in observational data, there is no inflection point at which the association between higher serum albumin level and reduced risk of mortality is attenuated (Figure 3).[6]

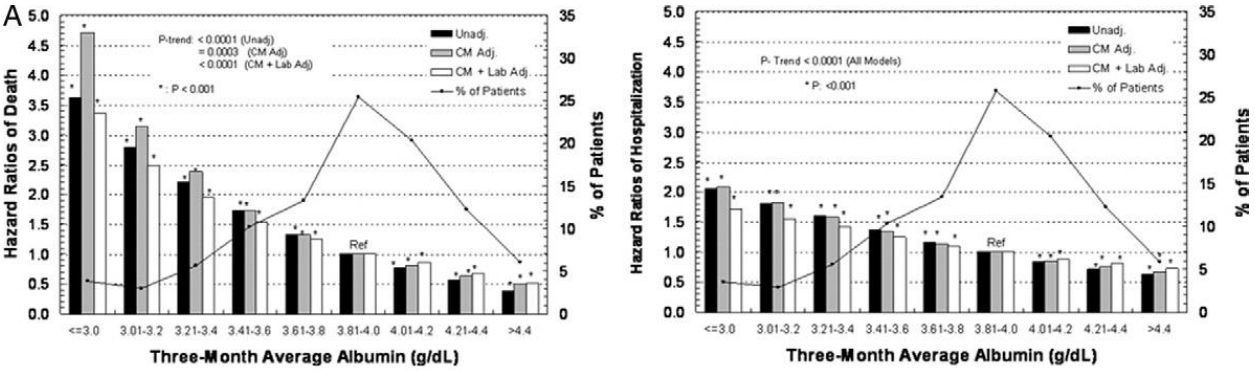

Figure 3. Association between serum albumin and mortality (left panel) and hospitalization (right panel). *, p-value <0.001. Grey bars are case mix adjusted (age, sex, race, diabetes, and dialysis vintage) while white bars are adjusted for case mix and laboratory values, including eKt/V, hemoglobin, calcium, phosphorus, creatinine, intact parathyroid hormone, and white blood cell count as well as body surface area. Data encompass 78,420 prevalent hemodialysis patients in treated at Fresenius Medical Care facilities in 2004.

In sum, the current threshold of 3.5 g/dL to define nutritional supplement eligibility is based on regulatory guidance rather than on medical science. As shown, **there is no threshold level in observational studies for albumin above which there is not a lower risk of mortality or hospitalization. Broadening supplement eligibility such that all dialysis patients can receive protein supplements is supported by metabolic balance experiments in dialysis patients. Critically, with albumin only measured monthly by dialysis facilities, by the time a drop in serum albumin is ascertained, increased catabolic challenges and their sequelae may have already occurred.**

2.4 Pragmatic Trials in Dialysis

Given the nature of hemodialysis, specifically that dialysis is conducted similarly across the country in facilities that typically vary in size from serving approximately 30 to 200 patients and that dialysis facilities, as a part of routine care, measure laboratory tests, collect demographic information and track patient outcomes, dialysis facilities are well situated for pragmatic clinical trials. Nephrology, among medical subspecialties, has the fewest randomized clinical trials (Figure 4).[28] This is particularly notable in dialysis, where a review of the NIH eReporter on September 24, 2015 revealed only three R01 or U01 mechanism clinical trials addressing therapies in dialysis patients, all of which are designated as pilot studies. Given that care of dialysis patients comprises more than 5% of all Medicare expenditures and that mortality rates, hospitalization rates and

rehospitalization rates among dialysis patients remain very high, adequately powered randomized trials in nephrology are urgently needed to identify effective and safe treatments for this population. Similarly, a search of Clinicaltrials.gov on September 24, 2015 of active intervention trials in dialysis reveals 120 trials, almost all of which are either very small or are evaluating new pharmacologic agents for treating anemia or mineral and bone disorder, areas where there is substantial financial potential for pharmaceuticals.

The largest ongoing clinical trial in dialysis is an exception to this trend in the United States. Titled '*A Cluster-randomized, Pragmatic Trial of Hemodialysis Session Duration (TiME)*', this trial (clinicaltrials.gov: NCT02019225) is a joint undertaking by Fresenius Medical Care, DaVita, the University of Pennsylvania and the National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases. A cluster-randomized, parallel-group pragmatic clinical trial, the purpose of the TiME Trial is 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. The investigators are targeting an enrollment of more than 6000 incident hemodialysis patients through randomization at the level of the dialysis facility.

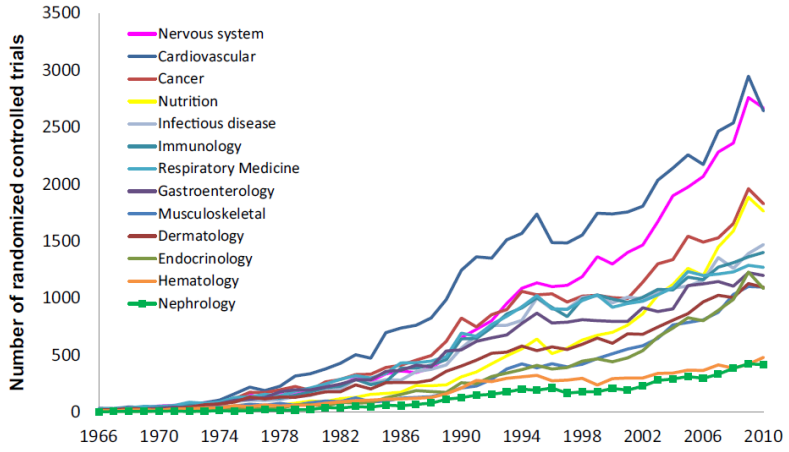

Figure 4. Randomized controlled trials published in nephrology and 12 other medical subspecialties. Nephrology is represented by the green line at the bottom of the figure.

The dialysis facility is a setting where randomized, non-blinded studies are faced with unique challenges due to the open environment. This reflects the reality in dialysis facilities that: 1) surrounding patients are fully aware of interventions and treatments provided to other patients; 2) there is a group mentality prevalent among dialysis patients such that they expect to receive similar treatment and interventions; 3) almost all counseling occurs in the semi-public dialysis setting; 4) all patients in a facility get their routine care from the same key providers, specifically nurses,

technicians, social workers and dieticians, with most patients in each unit cared for by only a handful of physicians; and 5) patients spend considerable time interacting with each other before, during and after the dialysis procedure comparing details of their care. Recognizing these factors, rather than randomizing individuals, the TiME Trial uses cluster randomization, randomizing approximately 400 facilities in the United States in a 1:1 distribution to the long duration treatment time intervention versus usual care arm.

Participants in the TiME trial will be followed for up to 3 years, using data capture mechanisms currently in place at Fresenius and DaVita dialysis facilities. 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. This strategy results in a trial that is feasible and that should yield generalizable results.

The TiME Trial is conducted under a cooperative agreement between the NIH and the University of Pennsylvania. The IRB at the University of Pennsylvania is the IRB of record for the trial and approved the human subjects' protection plan, which includes an independent Data Safety Monitoring Board. Notably, the TiME Trial is being conducted under a waiver of consent. Criteria for facility eligibility included a willingness of the facility's medical director, nephrologists and clinical leadership to adopt the facility randomization approach, ability to administer the intervention, and use of the provider's electronic data system for clinical data capture. The dialysis facilities randomized to a 4.25 hour treatment session implemented this as follows: 1) The approach was formally approved by the facility's governing body prior to implementation; and 2) While the 4.25 hour session time was stressed, treating nephrologists could individualize the session duration based on other considerations including patient characteristics and patient preferences.

The following paragraph of this proposal discusses information provided to patients and the opt-out mechanism present in the TiME Trial as well as the rationale for waiver of consent, based on criteria set forth in HHS 45 CFR part 46):

a. Information for Patients and Opt-Out Mechanism

In the TiME trial, all patients initiating therapy in participating facilities, regardless of whether the facility was randomized to usual care or the longer dialysis intervention received an information sheet that includes the following:

a. Trial sponsor information
b. Description of the purpose of the trial
c. The group to which the facility was randomized
d. The role of the physician in prescribing dialysis duration
e. A description of data safety procedures (the data coordinating center was not affiliated with the dialysis providers in TiME)
f. A statement that there is no additional testing performed for the trial
g. A toll-free number to contact research personnel to obtain additional information about the trial and opt out if desired

b. Rationale for Waiver of Consent in the TiME Trial
    a. *The research involves no more than minimal risk to subjects*. Specifically, in justifying the trial, the investigators noted that there was only a minimal risk to loss of privacy due to data analyses. Additionally, for those individuals in the group randomized to longer dialysis sessions, the investigators cite the ongoing extensive role of the treating physicians in ensuring that individualized care remain a readily available option as well as that extending dialysis sessions does not pose additional medical risk. For the latter, an extensive observation literature was described noting that outcomes are typically better with longer hemodialysis sessions.
    b. *The waiver will not adversely affect the rights and welfare of the subjects*. All patients within the TiME trial retain their rights to alter their care, including, after a discussion with their physicians regarding risks and benefits of various dialysis duration, to individualize their treatment regimens and/or to opt out of trial participation. Additionally, all patients are provided written information about the trial at the time they initiate dialysis, written information about the trial is posted in dialysis facilities for the duration of the trail, and all patients are provided with contact information to obtain more information about the trial.
    c. *Whenever appropriate, subjects will be provided with pertinent information after participating in the trial*. At the completion of the trial, the researchers will prepare a summary of major findings that will be distributed to patients receiving treatment at participating facilities.

d. The research cannot practicably be conducted without the waiver. The TiME investigators raised multiple factors as to why the trial could not be conducted without the waiver. These included:
    i. The trial is designed to evaluate effectiveness rather than efficacy and therefore aims to enroll as broad a group of patients as possible in a large number of dialysis facilities rather than a highly selected subset.
    ii. Cluster randomization by dialysis facility is necessary in order to implement the intervention without contamination of the usual care arm, in which the intention is not to influence the duration of the dialysis session.
    iii. An important objective of this research is to implement the trial using the routine clinical care delivery model of the health care setting in which participants are receiving care. The TiME trial is being conducted at approximately 400 facilities across the US with routine dialysis care being delivered by physicians, nurses and dialysis technicians with no active data collection. Because the clinical care providers at the dialysis facilities do not conduct research and do not have training in protection of human subjects, relying on these individuals to obtain consent for research is not appropriate and not consistent with NIH requirements for NIH-sponsored research.

The completed TiME Trial offered an important template for the conduct of pragmatic cluster randomized trials in dialysis and a precedent for waiver of consent for large, minimal-risk trials. While we feel that the our proposed trial of oral protein supplements in dialysis patients is similar enough to the TiME trial to warrant consideration of a waiver of need for consent, the current proposal for HELPS-HD relies on a waiver of consent documentation rather than a waiver of consent

3. RESEARCH METHODS

3.1 Study Design

This will be a pragmatic, cluster randomized clinical trial comparing the effectiveness of two different oral nutritional supplement protocols and accompanying education. All participants in participating facilities will be asked to participate in the study unless they do not qualify. Reflecting the pragmatic study design targeting broad generalizability, inclusion criteria are broad and exclusions are minimal.

3.2 Intervention

1. Usual Care versus Intensive Protocols

Facilities will be cluster randomized into one of two protocols:

a. Usual care protocol which will continue the current nutritional supplement protocol for all patients at the dialysis facility, whereby those with albumin below 3.5 g/dL receive supplement
b. Intensive nutritional supplement protocol, which will prescribe nutritional supplements for all patients at the dialysis facility regardless of serum albumin levels

The majority of DCI facilities currently have the majority of their patients prescribed the usual care oral nutritional supplement protocol, with 20-30% of patients at any given time receiving an in-center oral nutritional supplement. Of note, all patients are offered the protocol, but approximately 10-20% refuse the protein supplement, often due to taste and individual preference. Being prescribed the protocol does not affect a patient's ability to consume food or other supplements of their choosing before, during (depending on facility and state regulations) or after dialysis; it simply means that they receive an oral nutritional supplement for consumption during dialysis from the dialysis facility included as a part of their routine dialysis care. The specific nutritional supplement is not specified in the protocol, although many facilities currently use Prostat due to pricing and availability. The protocol prescribes approximately 15 g of oral protein supplement; when Prostat is used, this is accomplished by drinking 30 mL of Prostat. In cases of facility or patient preference, including taste fatigue, other supplements can be used in the current usual care protocol in lieu of Prostat (as was the case in the quality improvement report published by Lacson and colleagues).[23] For example, the PI's facility currently has some patients receiving Prostat while others receive BodyQuest Protein Ice Cream, reflecting patient preference. Nutritional supplements utilized during the trial will vary, but should contain approximately 15 g (range 12 to 20 g) of protein with low sodium, potassium and phosphorus content. Based on current use within DCI and availability as well as prior experiences and cost, we anticipate the following protein supplements will be utilized:

a) BodyQuest Protein Ice Cream, which contains 16 g of protein and 120 kcal per serving
b) Prostat, Sugar Free, which contains 15 g of protein and 100 kcal per serving
c) LiquaCel Liquid Protein, which contains 16 g of protein and 90 kcal per serving
d) ZonePerfect Nutrition Bars (flavor varied to avoid taste fatigue), which contain ~ 15 g of protein and ~ 210 kcal per serving
e) Nepro, which contains 19 g of protein and 425 kcal per serving.

2. Implementing the Intervention

As occurs currently in practice, the serum albumin level from routinely drawn monthly labs will automatically feed into the electronic centralized nutritional supplement prescribing protocols, from which supplements are then prescribed and administered. The DCI electronic oral nutritional supplement protocol will be used in the same manner as in current practice and follow the same rules for dosing and stoppage for the usual care arm, while protocol-based administration will continue regardless of serum albumin level for the intensive protocol arm. All new patients at the time of dialysis initiation (first dialysis session) will receive an oral nutritional supplement if prescribed the protocol by their physician. The specific supplement is typically based upon what the individual facility has available and on storage space within facilities. For example, one supplement is a frozen protein supplement (BodyQuest Protein Ice Cream) that can only be used in facilities that have adequate space for food freezers.

As a non-blinded study, the treating physicians will be aware of the study allocation of the facility. In facilities assigned to the intensive oral nutritional supplement intervention, an order will be generated in the DCI MIS by DCI Information Services for administration of an oral protein supplement at each dialysis session. Similarly, in patients assigned to the standard oral nutritional supplement intervention, a renewal order of the current supplement protocol will be generated. As with all orders pertaining to in-center hemodialysis care, the order for intensive versus standard nutritional supplement protocol will need to be signed electronically by the physician caring for the patient. If the physician does not sign this order, the patient will not receive nutritional supplements. The physician, regardless of randomization, can elect to discontinue the supplement order at any time.

As is currently done in practice, the dialysis nurse will record in the treatment record that the nutritional supplement has been dispensed and whether and when it was consumed. Supplements should be distributed and consumed within the first 30 minutes of initiation of a dialysis session.

3.3 Facility and Patient Education Efforts

Within all facilities, patients will receive information regarding the nutritional supplement trial. These are described in further detail below. Educational posters will be displayed in public waiting areas, including signs and posters that inform patients that the site is participating in the trial as

well as signs and posters that promote the importance of nutrition and adequate protein intake in recipients of hemodialysis. Every dialysis facility, as a condition for coverage by CMS, is required to have a dietician who provides nutritional information to patients. Regardless of randomization assignment, this individual will continue to encourage appropriate protein intake for dialysis patients, including recommendations for protein and other hemodialysis-appropriate diet consumption at home.

Facilities randomized to usual care and to intensive supplements will have slightly different approaches. First, facilities randomized to the usual care arm will have different signs and posters than those randomized to the intensive arm. Usual care arm materials will promote the need for nutrition and encourage supplement consumption when the albumin is low. Patients are informed of their serum albumin levels monthly at dialysis when they receive feedback from the dietician. In these conversations, the dietician will continue to emphasize protein consumption as per prior routine. For intensive facilities, materials will focus on the catabolic stresses induced by dialysis regardless of baseline albumin level, and emphasize that oral nutritional supplements taken early during dialysis may be able to impact catabolism. Reflecting the open nature of dialysis facilities, if neighboring patients are on different treatment regimens, they are likely to overhear the specific counseling given to other patients and are likely to appreciate that others are receiving more or less supplements than they are. Finally, there is a group mentality prevalent among dialysis patients such that they expect to receive similar treatment and interventions. These factors reinforce the hemodialysis environment as best suited to cluster randomization.

3.4 Blinding

Patients, investigators, and dialysis unit physicians and staff will not be blinded to study arm assignment. The endpoints committee will be blinded to facility (and therefore patient) treatment assignment.

3.5 Eligibility

To maintain broad generalizability and the pragmatic nature of the trial, eligibility and exclusion criteria are minimal and based largely on common sense. The following criteria will identify potential study participants:

<u>1. Inclusion Criteria</u>

a. Receipt of in-center hemodialysis in a facility participating in the trial
b. Able to consume oral nutritional supplements
c. Age ≥18 years

2. Exclusion Criteria

a. Tube feed or intravenous feed dependent
b. Unable to feed oneself or request help with feeding if a supplement is provided
c. Known allergy to ingredient(s) of the supplement

3. Pregnancy

Pregnancy is rare in hemodialysis patients but pregnancy will not be an exclusion criterion as this is a minimal risk protocol and research has shown that protein supplements may actually be beneficial to the mother.[29]

4. Cognitively Impaired

Cognitively impaired patients will not be excluded as this is a minimal risk protocol and these patients' legally authorized representative will be asked whether they can be in the study.

5. Racial and Ethnic Origin

DCI is a nationally representative dialysis organization, with dialysis clinics in 27 states across the US. Consistent with the racial/ethnic mix of the DCI population, we expect to enroll approximately 50-55% Caucasians, 40-45% African Americans, 5% Asians, and less than 5% of other racial background; 5% to 10% will likely be Hispanic. No racial / ethnic group will be excluded from participating.

6. Other Vulnerable Subjects

Prisoners typically do not receive dialysis in any potential participating facilities, and, if this does occur, it is usually temporary until sentencing to a correctional facility where dialysis is available. Accordingly, prisoners will not be included in the trial.

3.6 Recruitment

The study intervention is considered minimal risk given the nature of the intervention (roughly comparable to the amount of protein consumed with 2 large hard boiled eggs). To achieve

adequate power to evaluate mortality, we will need to recruit more than 5000 HD patients; this will require participation of more than 80 dialysis units throughout DCI, which nationally provides hemodialysis care to approximately 13,000 individuals. Given the pragmatic design of the trial, the high risk of cross-contamination between the usual care and the intensive intervention due to patient-patient interactions, other patient observed patient-dietician and patient-dialysis staff interactions, and our plan to promote the study to the entire facility, it is not practicable to conduct this research without a waiver of informed consent documentation.

Following education of facility staff, patients will receive study information sheets. Patients will have the opportunity to review the study information sheets and ask any questions they may have by contacting the study staff listed in the information sheets. Dialysis staff will note whether the patient agrees to be in the study by documenting it in their medical record. The process for initiating study sites is as follows:

1) Send the trial protocol to the governing body for each dialysis facility that is a potential trial participant. The governing body, which typically consists of the facility medical director(s), administrator, nurse manager(s) and chief technician, will review the protocol and have an opportunity to discuss the trial with the PI and central study personnel. Following this, they will need to approve of their facility's participation in the trial before their facility can be considered for inclusion.
2) Dialysis staff will participate in one to two pre-study conference calls, receive local facility materials such as posters and patient information sheets, and, at their discretion, have the opportunity to participate in study-wide conference calls that will occur monthly during the first several months of the trial before becoming quarterly thereafter.
3) All patients receiving dialysis in a participating facility prior to the start of the trial (but after the facility has been assigned randomly to a study arm) will receive an information sheet about the trial. These will be made available in multiple languages and will also be available to patient proxies. Information sheets and posters will also be posted in clinical areas of the dialysis facility. As with other information that is communicated to patients as a part of clinical practice, facility personnel will read forms to visually impaired or illiterate patients. All new patients who initiate dialysis at a participating facility will receive the information sheet that applies to their clinic at their initial treatment in the facility and will be asked whether they wish to participate

4) Patients can withdraw from the study at any time, regardless of intervention arm, by informing personnel at the dialysis unit that they do not want to take supplements or by simply not taking the supplement.

3.7 Trial Outcomes

All trial outcomes are ascertained as a part of usual dialysis care and will not require additional efforts by the dialysis facility. Following randomization, facilities will remain in the study for three years. Trial outcomes are:

1. Primary outcome

All-cause mortality.

2. Secondary outcomes:

a. Hospitalization rate
b. 30-day re-hospitalization rate
c. Infection, defined by a bloodstream infection, receipt of IV antibiotics in an outpatient DCI dialysis unit at three or more hemodialysis sessions, or hospitalization for a primary cause of infection
d. Infection as defined by the above plus infection as a primary cause of hospitalization
e. Serum albumin (in analyses exploring mediation if there is a benefit associated with the more intensive protocol)
f. Economic analysis

3. Outcomes Ascertainment

Outcomes ascertainment balances the structure of a pragmatic trial with data needs for safety and effectiveness. In routine clinical practice, each facility reconciles events, including deaths, hospitalizations, and infections monthly. These clinical data will define outcomes in the study.

3.8 Randomization:

Facilities will be randomized 1:1 to study arms, blocked by region and facility size (small, medium, large). If possible, randomization will occur concurrently for all participating facilities and with protocols available for prescribing immediately by physicians in the facility in the medical information system. Alternatively, depending on the time needed for facilities to approve the trial, we will randomize facilities over several months. Randomization will be performed by DCI's

Information Services (IS) personnel. DCI's IS personnel have experience with randomized clinical trials (RCTs), having designed and overseen an electronic algorithm that randomized patients to treatments arms across 3 strata in a past RCT conducted within DCI. They will create the master file of the treatment assigned to each facility. During the course of the trial, although facilities and patients and providers at those facilities will know their own randomization assignment, this information will not be made widely available to other dialysis units, physicians, patients, or staff, with the exception of the Data Safety Monitoring Board.

Approximately within four weeks following randomization, either treatment to usual care will be continued or treatment to the intensive protocol will begin depending on which protocol the unit has been assigned to as well as whether the patient agreed to be in the study. This gap is to allow sufficient time for patients in facilities to receive and review the information sheets as well as allow for educational materials to be posted in dialysis facilities.

3.9 Data Analysis

We will examine the effects of a liberal oral nutritional supplement protocol versus the current standard of care in DCI facilities, which consists of administration of oral nutritional supplements only to those patients with low serum albumin levels, even though balance studies show that dialysis procedure associated catabolism still occurs in patients with albumin levels above this threshold.[1] The primary outcome of all-cause mortality will be assessed using a time-to-event model. Hospitalization and infection rates will be assessed in time-to-event models that allow for repeated events.

3.9.1. Sample Size Considerations:

Given that the study, due to its pragmatic nature, will be relatively inclusive, we anticipate a death rate consistent with the general dialysis population. For incident dialysis patients in 2010, based on USRDS data, the mortality rate peaked at 440 deaths per 1,000 patient years at risk in month two then fell to 201 in month 12. Given that most patients will be prevalent patients and that most patients who are incident will receive nutritional supplements regardless of randomization assignment, we estimate a mortality rate closer to 15-17% and have considered the lower end of this range, in our power calculations to be conservative.

To determine the sample size, many assumptions are needed. Assuming a non-linear median 4 year

survival for hemodialysis patients, we used a two-sided logrank test with an overall sample size of 3351 subjects (1675 in the usual care group and 1676 in the intensive supplement group) followed for 3 years, achieving 80% power at a 2-sided 0.05 significance level to detect a hazard ratio of 0.85 when the usual care group hazard rate is considered 0.173. This power calculation assumes all subjects begin the study together (no accrual periods). The proportion dropping out of the usual care group is 0.05, and the proportion dropping out of the intensive supplement group is also 0.05. Accounting for the cluster randomized design and an intraclass coefficient of 0.01, based on blocking by facility size and region, approximately 5500 patients in 86 facilities of average size of 65 participants will be needed. This sample size is liberal, as, once a facility is randomized to a treatment arm, new patients will continue to initiate dialysis within that facility. Through study completion, patients initiating dialysis in a facility will receive that facility's treatment. Those initiating dialysis in the final nine months of the study will not be included in primary analyses as patients receive nutritional supplements during the first 90 – 120 days of maintenance hemodialysis regardless of facility randomization arm. Factoring in 2 interim analyses using an O'Brien Fleming Test to allocate the alpha over three analyses inflates the sample size by factor of 1.017. Thus, the total sample size is 5597 patients, a small increase that will readily be accounted for with inclusion of incident patients in participating facilities over the first year of the trial.

3.10 Internal Data and Safety

Dialysis staff at all participating facilities will have all central research staff contact information in case of questions. Periodic study updates may occur in a variety of ways, some examples may include, during study phone calls which will be open to any staff at participating facilities if they wish to participate, through newsletters from the study office to participating units, and in person during the DCI spring medical directors' meeting, which is attended by a majority of DCI facility medical directors, as well as at the annual DCI meeting, which is attended by medical directors, nurse managers, administrators, and charge and education nurses.

3.11 External Data and Safety Monitoring

An external Data and Safety Monitoring Board will be appointed prior to study start, consisting of nephrologists with experience in caring for dialysis patients, and, preferably, with experience in clinical trials, as well as a statistician with clinical trial experience. The DSMB will review separation across treatment arms and adverse events (deaths and hospitalization rates) tabulated by treatment arm once during the course of the trial. These data will be extracted from DCI's MIS at

the time of analysis. There will be one planned interim analyses of death and all-cause hospitalization. The first interim analysis was conducted after approximately 18 months from the time the first facility is randomized. A second interim analysis was initially planned; however, following the DSMB's interim analysis and after reviewing the time frame for the second analysis relative to the first analysis, including that the trial would essentially be complete by the time the DSMB's analysis would occur, the DSMB supported the PI's plan to reduce the number of interim analyses to a single analysis. Under the O'Brien Fleming test, the p values that will be required to reject the null hypothesis at each interim analysis must be less than 0.0005 at the first interim analysis; 0.0142 at the second interim analysis; and 0.0456 at the final analysis. Investigators will remain blinded to these interim analyses. The DSMB will advise the Sponsor and Principal Investigator about continuation of the study after the interim analysis.

3.12 Data Confidentiality and Storage

All data pertaining to treatment and follow-up of study patients, including labs drawn as a part of routine care and outcomes, will be based on the data that is generated in routine practice currently. There will be no paper data collection forms and no additional data collected outside of that routinely collected in clinical practice. All of these data exist in electronic form within the MIS and will transfer into the research database for analysis. Patient level data within the research database will be identified by study identification number. The link between the DCI medical record number and the study identification number along with the patient's treatment assignment will be maintained by DCI's Information Services. Electronic data within the MIS and the research database are secured behind DCI's firewalls. The DSMB will be provided with a de-identified dataset for interim analyses.

3.13 Transition at Closeout of the Study

Enrollment is scheduled to end in January 2020. Given that all patients at DCI facilities receive oral nutritional supplements for their first 90 days, the exposure does not differentiate until after this incident period. In this context, we will end all new enrollment at the end of 2019, continuing participants within their facility-assigned study stratum for an additional six months. To avoid patient frustration with the change in management at intervention sites, we will intensify communication with additional patient facing study materials at the facilities randomized to the intensive nutritional supplement protocol. The administrative censoring date for primary analyses would be April 30, 2020, allowing for a minimum of 1 month of separation among those consented

in late 2019, with secondary analyses extending to June 30, 2020 to maximize available data. The 2 month interval between these will allow preliminary results to be shared with study participants at the time of termination of the intervention.

This will result in one of two conclusions being relayed to study participants in this cluster randomized pragmatic trial: 1) there is no significant effect on mortality with continuing nutritional supplements once albumin is sustained in a normal range and therefore it is reasonable to revert to the usual care protocol; or 2) nutritional supplements were effective but intensive supplementation must end until the OIG has revised their opinion stating that continued intensive supplement is not in violation of the Federal anti-kickback statute. Given the increase in practice models being promulgated by CMS and the Centers for Medicare and Medicaid Innovation (CMMI) and active review of anti-kickback regulation by Health and Human Services, we are hopeful that, if data are positive, we would be able to obtain a waiver to allow oral nutritional supplement administration regardless of serum albumin levels as a part of these programs with a minimal interval between study termination and wider implementation in usual clinical care.

After the six month extension, all enrolled patients will be treated per their primary nephrologist's direction; for patients receiving usual care, this will continue unless the physician elects to discontinue this prescription. For those randomized to the intensive protocol, the intensive protocol order will be discontinued and an order generated for the usual care protocol that will need to be electronically signed by the physician prior to prescription. These procedures have been reviewed with the three member DSMB, who have approved of these changes.

3.14 Risk/Benefit Assessment

Hemodialysis is a catabolic procedure, associated with amino acid loss and protein-energy wasting. Mortality and morbidity are high among hemodialysis patients, many of whom face nutritional challenges due to anorexia, fatigue, intercurrent illness and demands on time. Currently, the Office of the Inspector General, in an opinion rendered to a single dialysis provider, views administration of oral nutritional supplements in the dialysis facility as permissible under federal regulations to individuals with low serum albumin; this policy motivates the usual care arm in this research protocol, and this usual care protocol is currently used throughout DCI and, with only slight differences, in many dialysis facilities operated by other providers across the United States. The broadening of supplement administration in this research trial has no known medical risks and

may have considerable benefits, reflecting many factors. Among these factors are: 1) replacement of amino acid losses that occur as a result of the dialysis session itself; 2) a drop in serum albumin, which is only measured monthly by dialysis facilities, may be a late marker of increased catabolic challenge to an individual dialysis patient; and 3) there is no threshold level shown in observational studies for albumin above which there is not a lower risk of mortality or hospitalization.

Included in this study will only be facilities who are currently utilizing the existing nutritional supplement protocol in the majority of patients, further reinforcing that there will be no change in care for those facilities randomized to the usual care arm.

1. Potential Benefits to Participating Dialysis Patients

There are no personal benefits to participants. However, all dialysis patients are faced with the metabolic challenges inherent to dialysis treatments and, at one point or another, will face challenges associated with protein loss and protein-energy wasting. The benefit of participating is that this study will attempt to determine whether more aggressive oral nutritional supplementation administration during dialysis improves outcomes; if so, this inexpensive and feasible intervention may be able to be used across dialysis facilities throughout the United States, pending additional advisory opinions by the OIG.

2. Potential Risks to Participating Dialysis Patients

We are not aware of any potential healthcare risks associated with consumption of a small dose of protein supplement. There is a theoretical albeit small risk associated with loss of data confidentiality; however, given that this study is being run by DCI in DCI facilities, data will not be handled differently, aside from periodic dissemination to the DSMB, than it would be in usual clinical and quality improvement activities.

3. Costs to Participating Dialysis Patients

There are no costs for patients to participate in the trial.

3.15 Regulatory Issues

The NIH-sponsored TiME trial sets a useful important precedent for the conduct of large, pragmatic clinical trials in the dialysis setting, an environment that is unique in healthcare due to the frequent contact between patients and the dialysis facility, the continuous interactions among patients, and

the lack of evidence base to guide treatment decisions. The proposed trial comparing two different nutritional supplement strategies follows the spirit of Sugarman and Califf in their recent viewpoint in JAMA describing the role of pragmatic clinical trials in evidence generation to inform care practices.[30] This study will be requesting a waiver of documentation of consent.

1. *The research involves no more than minimal risk to subjects*.

   The most common currently utilized oral nutritional supplement within DCI is Prostat. Pro-Stat is a sugar free liquid protein supplements (medical food), with protein derived from hydrolyzed collagen. In our review at DCI of observational data using a natural experiment to inform a pseudo-randomization cohort design, we found impressive benefits and, critically, no sign of harm associated with Prostat use.[24] Similarly, using similar methodology, Lacson and colleagues found impressive benefits and, critically, no signal of harm with four different protein supplements, including Prostat and ZonePerfect Protein bars.[23] Both Pro-Stat and BodyQuest Protein Ice Cream have very low sodium, potassium and phosphorus content, while ZonePerfect bars selected will be their lowest phosphorus and potassium containing options.

   For patients in the intensive supplement group, many will receive more doses of the oral nutritional supplement than they otherwise would have received with usual care. There is no known risk associated with the intake of these supplements. Although there are data in pre-dialysis populations suggesting that high protein intake may be associated with more rapid progression of kidney disease and more uremic symptoms, for patients treated with hemodialysis, this concern is no longer present.

   For patients in the usual care group, there is no effect of trial participation on medical care and the risk of loss of confidentiality is minimal. These patients will still be allowed to consume other food items during dialysis as they had previously and will still be administered an oral nutritional supplement if their serum albumin is low.

   Regardless of treatment assignment and as they currently do when prescribed the usual care protocol in current clinical practice, patients will have the ability to withdraw from the study, either by stating they do not wish to participate or simply by not taking the oral supplement. This will not in any way affect any other aspect the care delivered to these patients. Lastly, through the MIS, physicians will be aware of treatment assignment and, if desired, have the ability to discontinue the intensive nutritional supplement protocol.

2. *The research involves no procedures for which written consent is normally required outside of the research context.*

   Only facilities that are currently utilizing DCI's nutritional supplement protocol will be approached to participate in the study. Therefore, patients will already be familiar with protein supplements either because they took them themselves or saw others taking it in the unit as part of routine care. All data pertaining to treatment and follow-up of study patients, including labs drawn as a part of routine care and outcomes, will be based on the data that is generated in routine practice currently. There will be no paper data collection forms and no additional data collected outside of that routinely and currently collected in clinical practice.

3.16 Statistical Analyses

The primary outcome will be analyzed per intent-to-treat principles as a time to event analysis. For incident dialysis patients, time 0 will begin at day 90 as all patients are provided nutritional supplements during the first 90 days of hemodialysis. Hospitalization and infection will be analyzed as multiple events as well as using a time to first event approach. There are a large number of patients in this study, and it is unlikely that mortality risk factors will be differentially distributed across treatment arms; however, we will evaluate the distribution of key facility and patient factors by allocation group and, if there are differences in these parameters, secondary analyses using multivariable regression will be performed.

References

1. Sundell MB, Cavanaugh KL, Wu P, Shintani A, Hakim RM, Ikizler TA. Oral protein supplementation alone improves anabolism in a dose-dependent manner in chronic hemodialysis patients. *J Ren Nutr.* Sep 2009;19(5):412-421.
2. Lim VS, Ikizler TA, Raj DS, Flanigan MJ. Does hemodialysis increase protein breakdown? Dissociation between whole-body amino acid turnover and regional muscle kinetics. *J Am Soc Nephrol.* Apr 2005;16(4):862-868.
3. Pupim LB, Majchrzak KM, Flakoll PJ, Ikizler TA. Intradialytic oral nutrition improves protein homeostasis in chronic hemodialysis patients with deranged nutritional status. *J Am Soc Nephrol.* Nov 2006;17(11):3149-3157.
4. Collins AJ, Foley RN, Chavers B, et al. 'United States Renal Data System 2011 Annual Data Report: Atlas of chronic kidney disease & end-stage renal disease in the United States. *Am J Kidney Dis.* Jan 2012;59(1 Suppl 1):A7, e1-420.
5. Fouque D, Kalantar-Zadeh K, Kopple J, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int.* Feb 2008;73(4):391-398.
6. Lacson E, Jr., Wang W, Hakim RM, Teng M, Lazarus JM. Associates of mortality and hospitalization in hemodialysis: potentially actionable laboratory variables and vascular access. *Am J Kidney Dis.* Jan 2009;53(1):79-90.
7. Mehrotra R, Duong U, Jiwakanon S, et al. Serum albumin as a predictor of mortality in peritoneal dialysis: comparisons with hemodialysis. *Am J Kidney Dis.* Sep 2011;58(3):418-428.
8. Cohen LM, Ruthazer R, Moss AH, Germain MJ. Predicting six-month mortality for patients who are on maintenance hemodialysis. *Clin J Am Soc Nephrol.* Jan 2010;5(1):72-79.
9. Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, et al. Revisiting mortality predictability of serum albumin in the dialysis population: time dependency, longitudinal changes and population-attributable fraction. *Nephrol Dial Transplant.* Sep 2005;20(9):1880-1888.
10. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. *Am J Kidney Dis.* Nov 2003;42(5):864-881.
11. Kalantar-Zadeh K, Kopple JD. Relative contributions of nutrition and inflammation to clinical outcome in dialysis patients. *Am J Kidney Dis.* Dec 2001;38(6):1343-1350.
12. Ricks J, Molnar MZ, Kovesdy CP, et al. Racial and ethnic differences in the association of body mass index and survival in maintenance hemodialysis patients. *Am J Kidney Dis.* Oct 2011;58(4):574-582.
13. Molnar MZ, Streja E, Kovesdy CP, et al. Associations of body mass index and weight loss with mortality in transplant-waitlisted maintenance hemodialysis patients. *Am J Transplant.* Apr 2011;11(4):725-736.
14. Gutierrez A, Bergstrom J, Alvestrand A. Hemodialysis-associated protein catabolism with and without glucose in the dialysis fluid. *Kidney Int.* Sep 1994;46(3):814-822.
15. Raj DS, Adeniyi O, Dominic EA, et al. Amino acid repletion does not decrease muscle protein catabolism during hemodialysis. *Am J Physiol Endocrinol Metab.* Jun 2007;292(6):E1534-1542.
16. Gutierrez A. Protein catabolism in maintenance haemodialysis: the influence of the dialysis membrane. *Nephrol Dial Transplant.* 1996;11 Suppl 2:108-111.
17. Ikizler TA, Flakoll PJ, Parker RA, Hakim RM. Amino acid and albumin losses during hemodialysis. *Kidney Int.* Sep 1994;46(3):830-837.
18. Lim VS, Bier DM, Flanigan MJ, Sum-Ping ST. The effect of hemodialysis on protein metabolism. A leucine kinetic study. *J Clin Invest.* Jun 1993;91(6):2429-2436.

19. Pupim LB, Flakoll PJ, Brouillette JR, Levenhagen DK, Hakim RM, Ikizler TA. Intradialytic parenteral nutrition improves protein and energy homeostasis in chronic hemodialysis patients. *J Clin Invest.* Aug 2002;110(4):483-492.
20. Raj DS, Sun Y, Tzamaloukas AH. Hypercatabolism in dialysis patients. *Curr Opin Nephrol Hypertens.* Nov 2008;17(6):589-594.
21. Veeneman JM, Kingma HA, Boer TS, et al. Protein intake during hemodialysis maintains a positive whole body protein balance in chronic hemodialysis patients. *Am J Physiol Endocrinol Metab.* May 2003;284(5):E954-965.
22. Carrero JJ, Stenvinkel P, Cuppari L, et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). *J Ren Nutr.* Mar 2013;23(2):77-90.
23. Lacson E, Jr., Wang W, Zebrowski B, Wingard R, Hakim RM. Outcomes associated with intradialytic oral nutritional supplements in patients undergoing maintenance hemodialysis: a quality improvement report. *Am J Kidney Dis.* Oct 2012;60(4):591-600.
24. Weiner DE, Tighiouart H, Ladik V, Meyer KB, Zager PG, Johnson DS. Oral intradialytic nutritional supplement use and mortality in hemodialysis patients. *Am J Kidney Dis.* Feb 2014;63(2):276-285.
25. Chambers JD, Weiner DE, Bliss SK, Neumann PJ. What can we learn from the U.S. expanded end-stage renal disease bundle? *Health Policy.* May 2013;110(2-3):164-171.
26. Weiner DE. The 2011 ESRD prospective payment system: welcome to the bundle. *Am J Kidney Dis.* Apr 2011;57(4):539-541.
27. Department of Health and Human Services. Office of the Inspector General. OIG Advisory Opinion No. 09-07. Issued June 23, 2009.
28. Palmer SC, Sciancalepore M, Strippoli GF. Trial quality in nephrology: how are we measuring up? *Am J Kidney Dis.* Sep 2011;58(3):335-337.
29. Ota E, Hori H, Mori R, Tobe-Gai R, Farrar D. Antenatal dietary education and supplementation to increase energy and protein intake. *The Cochrane database of systematic reviews.* 2015;6:CD000032.
30. Sugarman J, Califf RM. Ethics and regulatory complexities for pragmatic clinical trials. *JAMA.* Jun 18 2014;311(23):2381-2382.