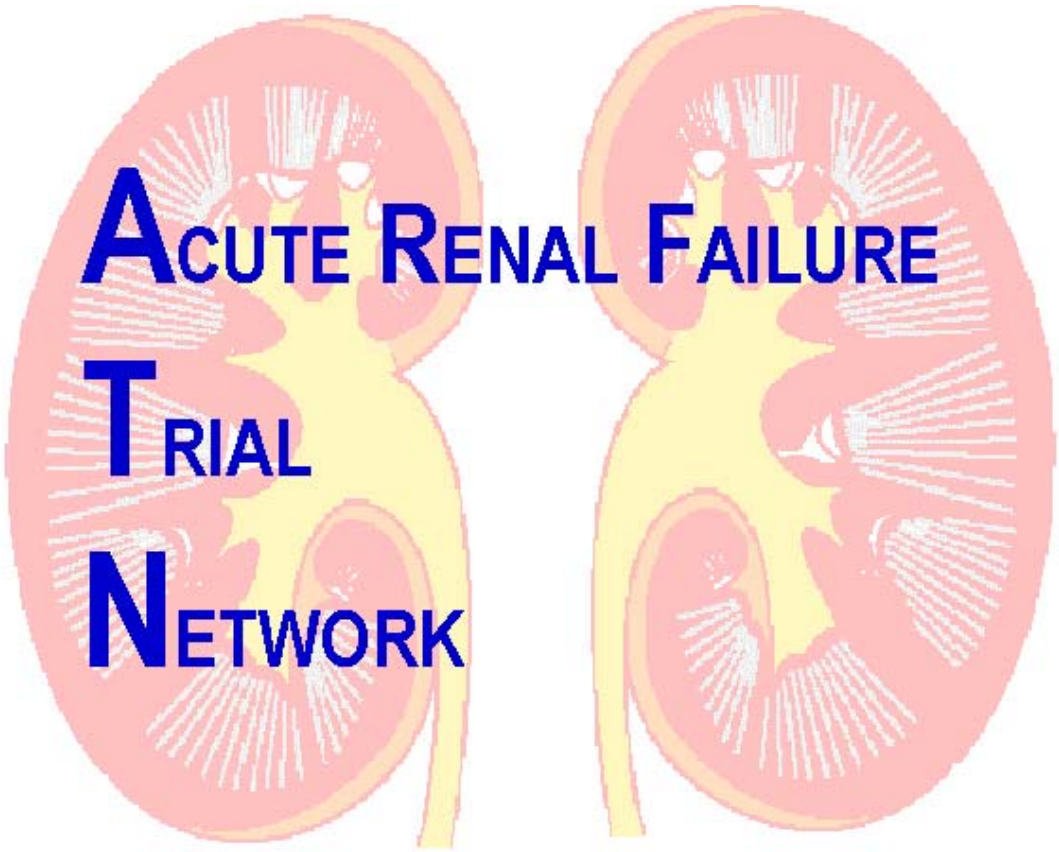
VA COOPERATIVE STUDY #530:

Intensive vs Conventional Renal Support in Acute Renal Failure



Department of Veterans Affairs
COOPERATIVE STUDIES PROGRAM

National Institute of Diabetes & Digestive & Kidney Diseases

Study Protocol and Amendments

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Executive Summary/Abstract

Acute renal failure (ARF) is the abrupt loss of kidney function resulting in the failure to excrete urea and other nitrogenous waste products. The incidence of ARF in hospitalized patients varies between 1% and 15%, depending upon the population at risk and the criteria used for defining renal failure. Based on a review of ICD-9 codes of discharge diagnoses from the Austin Automation Center Patient Treatment File for Fiscal Year 1999, the incidence of ARF within the VA is approximately 3.1%. No pharmacologic therapy is effective in ARF; management is primarily supportive, with renal replacement therapy serving as the cornerstone in patients with severe ARF. The mortality rates associated with ARF have remained very high despite advances in the use of hemodialysis and other renal replacement therapies over the past 50 years. Mortality rates from recent series continue to exceed 50%. Many fundamental issues in the management of renal replacement therapy in ARF remain to be resolved including the indications for and timing of initiation of therapy, the optimal dose and modality of therapy, the selection of dialysis membranes, the composition of dialysate and replacement fluids, and indications for the discontinuation of therapy. Several recent clinical studies have suggested that more intensive renal support may result in improved survival. These studies, however, have had significant limitations and have not been widely accepted in clinical practice. We therefore propose to compare a strategy of intensive renal support to conventional management of renal replacement therapy in critically ill patients with acute renal failure.

Our primary hypothesis is that intensive renal support decreases mortality in critically ill patients with acute renal failure as compared to conventional management of renal replacement therapy. Secondary hypotheses are that intensive renal support in critically ill patients with acute

renal failure will shorten the duration of ARF and decrease the incidence and duration of non-renal complications as compared to conventional management.

The proposed study is a multi-center, prospective, randomized, parallel-group trial of two strategies for the management of renal support in acute renal failure in critically ill patients. For the purpose of this study, acute renal failure will be defined as an increase in serum creatinine of ≥ 2 mg/dL (≥ 1.5 mg/dL in women) over a period of ≤ 4 days or acute oliguria (urine output < 20 mL/hour) for > 24 hours. Patients will be enrolled if they have ARF clinically consistent with a diagnosis of acute tubular necrosis and if the primary treatment team is planning on initiating renal support. Patients with chronic kidney disease, defined as a pre-morbid serum creatinine > 2.0 mg/dL (1.5 mg/dL in women), and patients with acute renal failure not due to ATN based on clinical criteria will be excluded. In addition, in order to exclude patients with relatively mild disease, in whom ATN is not associated with high mortality, patients will be included only if they have evidence of at least one non-renal organ failure or the presence of sepsis.

Patients will be randomized in a 1:1 ratio to be treated using either a strategy of intensive renal support or conventional management of renal replacement therapy for their ARF. In both arms of the study, dialysis will be initiated using the same criteria. In the intensive therapy arm, renal support will be provided as intermittent hemodialysis on a 6-times per week basis (target delivered spKt/V of 1.2/treatment), as compared to a 3-times per week basis (target delivered spKt/V of 1.2/treatment) in the conventional therapy arm. In both arms, for hemodynamically unstable patients (cardiovascular SOFA score: 3-4), renal support will be provided as continuous venovenous hemodiafiltration (dosed at 35 mL/kg/hr in the intensive dose arm and 20 mL/kg/hr in the conventional dose arm) or as sustained, low-efficiency dialysis (SLED) provided 6-times per week in the intensive therapy arm and 3-times per week in the conventional therapy arm.

Protocol therapy will be continued until renal function recovers or until day 28. Patients who remain dialysis dependent when ready for discharge from acute care, or after day 28, whichever comes first, will be taken off of protocol treatment and will be prescribed further dialysis at the discretion of their treating physician.

The primary study end-point will be 60-day all-cause mortality. Secondary end-points will include all-cause hospital mortality, 1-year all-cause mortality, and recovery of renal function. Duration of renal support, ICU and hospital length of stay, discharge to "home" not requiring dialysis, and the development and/or recovery of non-renal organ failure (assessed by SOFA organ system scores) during renal support will also be assessed. An economic analysis of the treatment strategies will also be performed.

We postulate that the intensive treatment strategy will result in a 10% reduction in mortality from 55% to 45%. Using a 2-sided test of significance with $\alpha = 0.05$, a sample size of 1164 will be required to test the primary hypothesis with 90% power, assuming a 10% drop-out rate.

This study will be jointly funded by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) through an interagency agreement. Eighteen VA sites and nine non-VA sites are expected to participate in order to accrue 1164 patients. Each VA site will be expected to enroll 27 patients (9 patients per year), and each non VA-site will be expected to enroll 84 patients (28 per year), during 3 years of intake.

Four amendments to the protocol have been approved. These amendments are not reflected in the body of the protocol, but are appended to the end of the protocol. Amendment 1 modifies the eligibility criteria, updating the definition of sepsis to be consistent with the most recent published consensus definition, and operationalizing the definitions of etiologies of ARF

other than ATN. Amendment 2 establishes a biorepository for serum and plasma samples obtained on study days 1 and 8. Amendment 3 establishes an observational cohort to clarify the process of care provided to patients receiving dialysis for ARF outside of the study. Amendment 4 further modifies the eligibility criteria, the criteria of selecting modality of therapy within each treatment group and the criteria for discontinuing study therapy.

Figure 1: Overview of Study Design

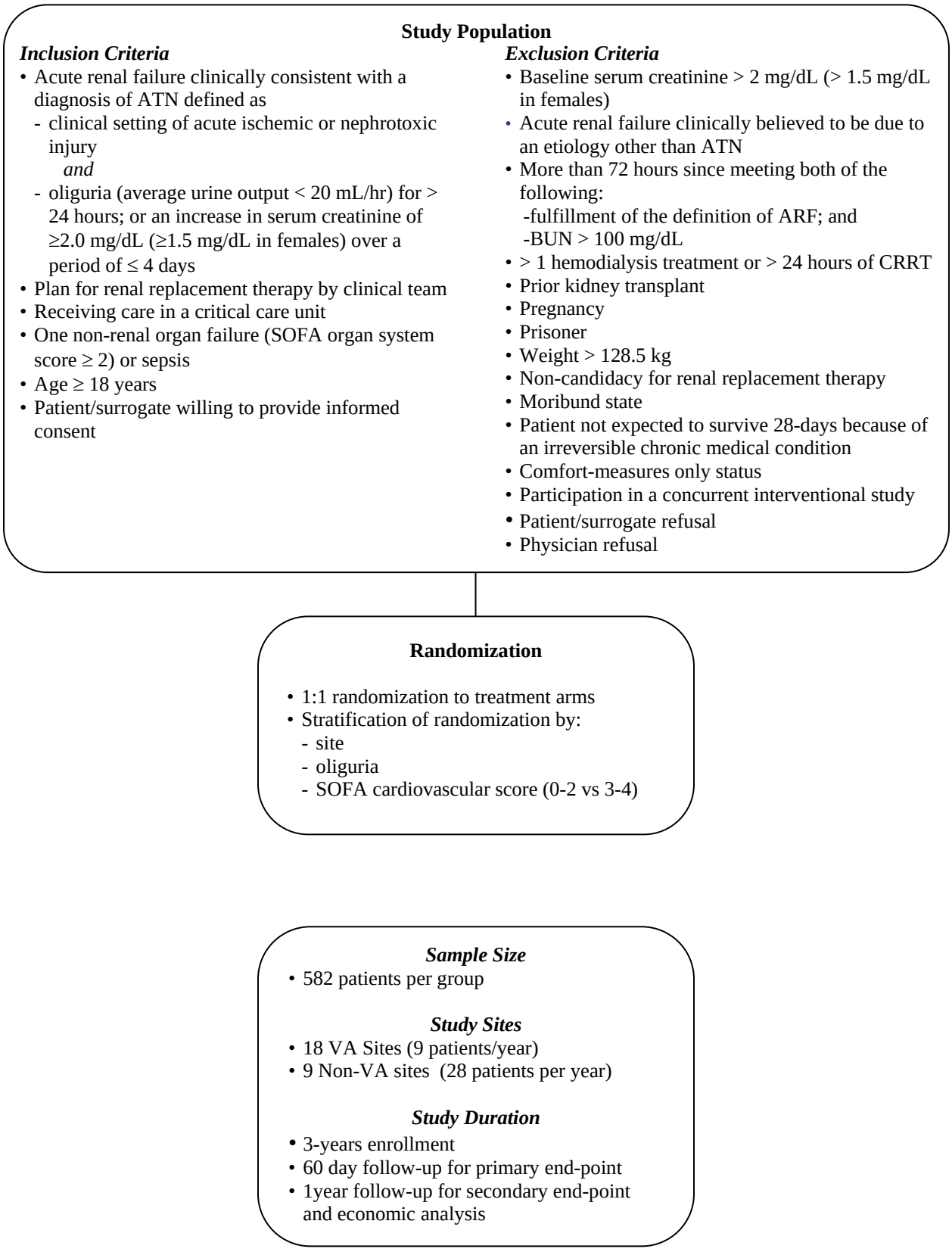
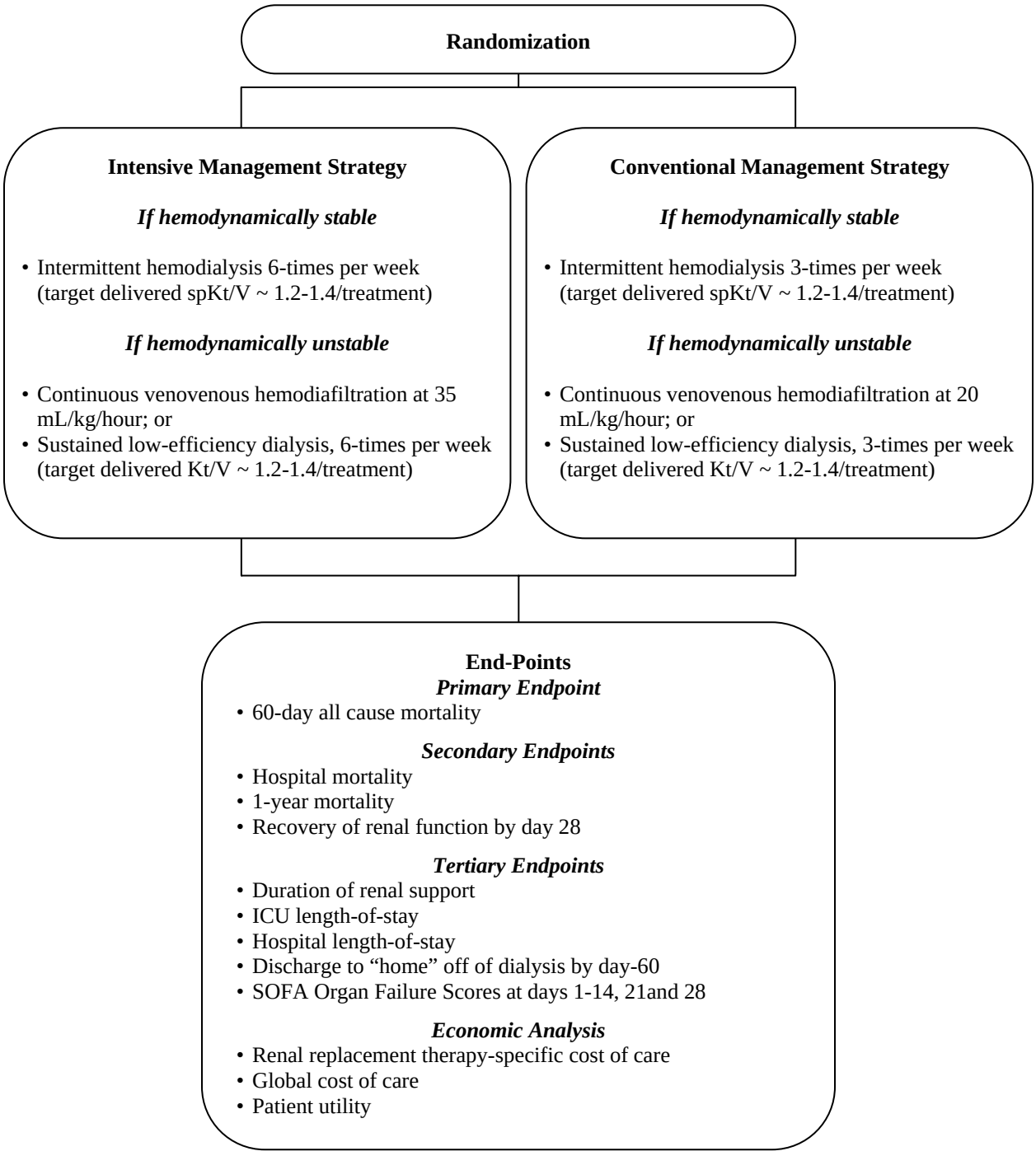


Figure 2: Overview of Study Design (continued)



I. Introduction

Acute renal failure (ARF) is defined by the abrupt loss of renal function resulting in the failure of the kidney to excrete urea and other nitrogenous waste products. Although there have been substantial advances in our understanding of the pathogenesis of ARF, clinical advances in its treatment have been limited. Multiple pharmacologic interventions have shown promise in animal models of ARF, however no agents have been demonstrated to be efficacious in clinical practice. As a result, the management of ARF remains primarily supportive, with renal replacement therapy serving as the cornerstone of therapy in patients with severe renal failure.

Despite more than a half-century of experience in the use of hemodialysis and other renal replacement therapies in the management of ARF, mortality remains high and many fundamental issues remain to be resolved. These include the indications for and timing of initiation of therapy, the optimal dose and modality of therapy, the selection of dialysis membranes, the composition of dialysate and replacement fluids, and indications for the discontinuation of therapy. Although there is substantial variation in how renal replacement therapy is provided for patients with acute renal failure, renal support is commonly initiated in response to overt manifestations of renal failure (i.e., uremic symptoms, volume overload, hyperkalemia and metabolic acidosis) or in response to progressive azotemia, when the blood urea nitrogen (BUN) concentration reaches ~100 mg/dL (1). Intermittent hemodialysis is the most commonly prescribed form of renal support, usually provided on a 3-4 times per week schedule, although the continuous renal replacement therapies (CRRT) have been gaining increasing acceptance in the management of critically ill patients. Several recent clinical studies (see Section III) have suggested that more intensive renal support may result in improved survival. These studies have had significant limitations and have not been widely accepted in clinical practice. We therefore

propose to compare a strategy of intensive renal support to conventional management of renal replacement therapy in critically ill patients with acute renal failure.

II. Specific Objectives

A. *Primary and Secondary Hypotheses*

Our primary hypothesis is that intensive renal support decreases mortality in critically ill patients with acute renal failure as compared to conventional management of renal replacement therapy. Our secondary hypotheses are that intensive renal support in critically ill patients with acute renal failure will shorten the duration of ARF and decrease the incidence and duration of non-renal complications as compared to conventional management. We also hypothesize that although the renal replacement therapy-specific cost of intensive therapy will be higher than that of conventional therapy, that the global cost of care will be increased by no more than $75,000 per life saved (i.e., cost effective) if not actually reduced by intensive therapy.

We therefore propose the following primary and secondary objectives:

B. ***Primary Objective***

To determine if a strategy of intensive renal support decreases 60-day all cause mortality in critically ill patients with acute renal failure as compared to conventional management of renal replacement therapy.

C. ***Secondary Objectives***

To determine if a strategy of intensive renal support for acute renal failure, as compared to conventional management of renal replacement therapy:

- Decreases all-cause hospital mortality;
- Decreases 1-year all cause mortality; and
- Increases the recovery of renal function.

D. Tertiary Objectives

To determine if intensive renal support for acute renal failure, as compared to conventional renal replacement therapy:

- Decreases the duration of renal support;
- Decreases ICU length-of-stay;
- Decreases hospital length-of-stay;
- Increases the incidence of discharge to “home” off of dialysis; and
- Decreases the incidence and duration of non-renal organ failure.

E. Economic Analysis

To determine the costs associated with intensive renal support as compared to conventional renal replacement therapy for acute renal failure and to evaluate the health economic impact of intensive as compared to conventional management of renal replacement therapy.

III. Background

Acute renal failure is a heterogeneous condition that encompasses acute intrinsic renal failure, pre-renal azotemia and obstructive uropathy. Acute intrinsic renal failure is most commonly due to acute tubular necrosis, which results from hypotension and ischemia in approximately 50% of patients and from exposure to nephrotoxins in an additional 35% of patients (2,3). In many, if not most cases, acute tubular necrosis in critically ill patients is multifactorial (4). Less frequent etiologies of acute intrinsic renal failure include acute interstitial nephritis and acute or rapidly progressive glomerulonephritis (2,3).

Studies of the incidence of acute renal failure yield widely varying results depending on the clinical setting and the definition used to define acute renal failure. Commonly used definitions include an increase in serum creatinine of $\geq$ 0.5 mg/dL from base-line, an increase in the serum creatinine by more than 50 percent from base-line, a reduction in the calculated creatinine clearance by more than 50 percent, or a decrease in renal function necessitating dialysis (2). Using these varied definitions, the reported frequency of acute renal failure has ranged from 1 percent at hospital admission (5), to 2 to 5 percent during hospitalization (6,7), to as high as 4 to 15 percent after cardiopulmonary bypass (8). Based on DRG coding of hospital discharges, it has been estimated that there were 275,000 cases of acute renal failure in the United States in 1997, of which 115,000 cases were due to intrinsic renal disease (4), giving an incidence of intrinsic acute renal failure of approximately 400 to 450 cases per million population. The prevalence of acute renal failure within the VA is similar to these described rates. In a review of ICD-9 diagnosis codes recorded in the VA's Austin Automation Center Patient Treatment File for Fiscal Year 1999, we identified 11,187 patients out of the 359,608

patients receiving in-patient care (3.1%) who had a discharge diagnosis of acute renal failure (Appendix F).

Specific therapy for acute intrinsic renal failure is primarily supportive. Although treatment with corticosteroids and other immunomodulatory agents may be of benefit in patients with acute interstitial nephritis and acute glomerular syndromes, no effective pharmacologic therapy exists for acute tubular necrosis (2,4). A wide variety of possible agents, including loop-acting diuretics, mannitol, dopamine, atrial naturetic peptide, thyroid hormone and insulin-like growth factor-1, have shown promise in animal models, however they have not proven to be efficacious for either the prevention or treatment of acute renal failure in the clinical setting (2).

The morbidity and mortality of acute renal failure are highly variable, depending upon the etiology, severity, clinical setting and co-morbid conditions (1,3). Uncomplicated acute renal failure, in the absence of other underlying illness, is associated with mortality rates of 7 to 23 percent, whereas the mortality of acute renal failure in the postoperative or critically ill patient with multisystem organ failure may be as high as 50 to 80 percent (2,4,8-12). Before the development of renal replacement therapies, the most common causes of death were uremia, electrolyte disturbances (primarily intractable metabolic acidosis and hyperkalemia), complications of volume overload, and hemorrhagic diatheses. Although mortality rates remain elevated despite the advent of dialysis, the cause of death in patients with acute renal failure has changed, with sepsis, gastrointestinal bleeding, cardiovascular and pulmonary dysfunction and withdrawal of life-support measures now being most common (2,13,14).

A. Timing of Initiation of Renal Support

The use of hemodialysis in acute renal failure entered clinical practice in the decade following World War II (15-20). In its initial application, hemodialysis was applied to patients

with advanced symptoms of renal failure, including clinical uremia, severe hyperkalemia and pulmonary edema (15,20,21). Although control of uremic symptoms and volume overload were achieved, a clear reduction in mortality could not be demonstrated (21). Paul Teschan and colleagues introduced the concept of "prophylactic" dialysis, initiated prior to the onset of overt symptoms, in the treatment of acute renal failure in military patients in Korea (21). Multiple studies in the intervening four decades have attempted to define the appropriate timing, modality and dose of renal replacement therapy in acute renal failure.

In their landmark report, Teschan et al. described a prospective, uncontrolled series of 15 patients with oliguric acute renal failure treated with "prophylactic" hemodialysis, defined as initiation of dialysis before the BUN reached 100 mg/dL (21). Patients received daily dialysis (average duration 6 hours) using twin-coil cellulosic dialyzers at a blood flow of 75 to 250 mL/min to maintain a pre-dialysis BUN of less than 75 mg/dL. Caloric and protein intake were unrestricted. All-cause mortality was 33% with mortality due to hemorrhage or sepsis of 20%. Although no control group was studied, the authors reported that the results contrasted dramatically with their own past experience in patients in whom dialysis was not initiated until "conventional" indications were present.

In a series of 45 patients with acute renal failure, Easterling and Forland reported similar results (22). Although they lacked a control group and were therefore unable to draw any conclusions regarding improved survival with early dialysis, they also concluded that the prevention of uremic symptoms in acute renal failure was desirable.

Parsons et al. retrospectively analyzed 33 patients with postoperative acute renal failure who were treated with hemodialysis during the periods 1956-1958 and 1959 (23). Survival in

patients initiated on dialysis "early" (BUN between 120 and 150 mg/dL) was 75% as compared to 12% survival in patients in whom dialysis was initiated "late" (BUN > 200 mg/dL) ($p<0.001$).

Fischer et al. described 162 patients requiring hemodialysis between 1950 and 1964 (24). Patients initiated when the BUN reached 150 mg/dL or when clinical deterioration was first observed had a 57% mortality compared to 74% mortality in patients in whom dialysis was not initiated until the BUN was greater than 200 mg/dL.

Similar retrospective results were described by Kleinknecht et al. who reported on 500 patients with acute renal failure requiring dialysis during the period 1966 to 1970. All patients were maintained on similar caloric (30 kcal/kg/d) and protein (1 g/kg/d) intake (25). Patients receiving "prophylactic" dialysis (defined as early and frequent dialysis to maintain pre-dialysis BUN less than 93 mg/dL) had a mortality of 27% as compared to 42% mortality in patients in whom dialysis was initiated only if the BUN was greater than 163 mg/dL or if severe electrolyte disturbances were present ($p<0.05$). The authors observed a marked reduction in mortality due to sepsis and gastrointestinal bleeding in the more aggressively dialyzed group.

The first prospective evaluation of "prophylactic" dialysis in acute renal failure was reported by Conger in 1975 (26). He described 18 patients with post-traumatic acute renal failure sustained during the Vietnam War and treated on the Naval Hospital Ship USS Sanctuary between April and October 1970. Patients were alternately randomized to an intensive dialysis regimen which maintained the pre-dialysis BUN and creatinine at less than 70 mg/dL and 5 mg/dL, respectively, or a non-intensive regimen in which dialysis was not carried out until the BUN approached 150 mg/dL, the creatinine reached 10 mg/dL, or the patient developed clinical indications for dialysis (hyperkalemia, volume overload or uremic encephalopathy). All dialysis treatments were provided using coil dialyzers. A minimum nutritional intake of 25 kcal/kg/d

was provided as parenteral glucose and patients capable of oral feeding received a minimum of 0.75 g/kg/d of protein. Survival was 64% (5 of 8 patients) in the intensive treatment group as compared with 20% (2 of 10 patients) in the non-intensive dialysis group ($p<0.01$). In addition, complications of hemorrhage (36% versus 60%) and gram-negative sepsis (50% versus 80%) were less frequent in the intensive treatment group.

Expanding on this study, Gillum et al. studied 34 patients with acute renal failure who were randomized to receive either intensive hemodialysis (5 to 6 hours daily or every other day to maintain a pre-dialysis BUN < 60 mg/dL and serum creatinine < 5 mg/dL) or non-intensive dialysis (5 hours daily to every third day, allowing the BUN to reach 100 mg/dL and the serum creatinine to reach 9 mg/dL) (27). Patients were stratified based on etiology of acute renal failure (trauma-surgery or medical) and randomized in paired fashion when the serum creatinine reached 8 mg/dL. All patients were dialyzed using hollow fiber cellulosic dialyzers. Although the mean age of the patients in the two groups were similar, the age distribution was skewed in the intensive dialysis group, with clustering of the youngest (< 40 years) and oldest (>60 years) patients. Protein intake was lower in the intensively dialyzed group (0.55±0.32 g/kg/d) as compared to in the non-intensive group (0.77±0.28 g/kg/d), however the difference was not statistically significant. Mortality was higher in the intensively dialyzed group (58.8% versus 47.1%), but given the small sample size, this was not statistically significant ($p=0.73$). Hemorrhagic and septic complications were more common in the non-intensively dialyzed group (hemorrhage: 24% versus 59%; sepsis: 47% versus 65%), however these differences also did not reach statistical significance.

Gettings et al. have reported the results of a retrospective analysis of early (BUN < 60 mg/dL) versus late (BUN > 60 mg/dL) initiation of continuous renal replacement therapy

(CRRT) in 100 adult patients with post-traumatic acute renal failure (28). The 41 patients who were "early" starters were younger (40.5±17.9 years versus 48.0±18.9 year; p=0.051), but otherwise comparable to the 58 "late" starters. Patients had similar Injury Severity Scores (early: 33.0±13.5 versus late: 37.2± 15.0; p=0.178) and Glasgow Coma Scale scores (early: 11.8±3.8 versus late: 12.5±3.7; p=0.349) on admission. No other indices of severity of illness were reported. CRRT was initiated on day 10.5±15.3, when the BUN was 42.6±12.9 in the "early" group as compared to day 19.4±27.2 ($p<0.0001$), when the BUN was 94.5±28.3 ($p<0.0001$) in the "late" group. Survival was 39.0% in the "early" group as compared to 20.3% in the late group (p=0.041).

B. Quantification of Dose of Renal Support in ARF

In end stage renal disease, multiple studies have established a clear inverse relationship between dialysis dose and both morbidity and mortality. Based on the mechanistic analysis of the National Cooperative Dialysis Study (29), the unitless term Kt/V, where K is the dialyzer urea clearance, t is the duration of dialysis and V is the volume of distribution of urea, is generally accepted as an index of dialysis dose (29). Multiple urea kinetic models have been developed for the calculation of Kt/V, including both single-pool and multiple-pool kinetic models. The National Kidney Foundation's Dialysis Outcomes Quality Initiative (NKF-DOQI) clinical practice guidelines hemodialysis adequacy establishes a delivered single-pool Kt/V of 1.2 as the minimum adequate dose of dialysis for thrice weekly therapy in chronic hemodialysis for end stage kidney disease (30).

Although multiple investigators have attempted to apply urea kinetic modeling to renal support in ARF, many of the fundamental assumptions used in developing these models for end stage kidney disease are violated in ARF (31, 32). The primary assumption in all of these

models is that urea, as a low molecular weight solute, is a surrogate marker for the toxic metabolites of renal failure. In end stage kidney disease, there is robust data to correlate low molecular weight solute clearance with long-term outcomes. However, other data suggest that higher molecular weight species, such as β_2-microglobulin, also contribute to long-term toxicity. A similar link between low molecular weight solutes and outcome is not established in acute renal failure, especially in the setting of multisystem organ dysfunction.

Urea kinetic modeling assumes the existence of a relative steady state during the modeling period – i.e., that the patient is in neutral nitrogen balance, and that the pre-dialysis state remains relatively stable over a repetitive cycle of dialysis treatments. These assumptions are not valid in the ARF patient. Unlike end stage kidney disease patients, the majority of patients with ARF are hypercatabolic and are in negative nitrogen balance (33). Alterations in regional blood flow, especially in patients who are hemodynamically unstable and require support with vasoactive medications, may produce disequilibrium in urea distribution between body fluid compartments, invalidating standard single-pool models (33). Finally, the volume of distribution of urea in ARF is altered, and varies widely, as compared to the chronic kidney disease patient. Himmelfarb et al. compared the volume of distribution of urea calculated based on both double-pool and equilibrated blood-side urea kinetics with estimates of total body water based on both anthropometric measurements and bioelectrical impedance analysis (34). The volume of distribution of urea calculated in this fashion exceeded the calculated values of total body water by between 7 percent and 50 percent (34). Similar results have also been reported in abstract form by the PICARD Study Group (35).

Other methods for quantifying hemodialysis dose have also been evaluated in acute renal failure. The solute removal index (SRI) measures the amount of urea removed during a dialysis

treatment based on dialysate quantification. In stable end stage kidney disease patients, there is good correlation between SRI and equilibrated Kt/V (36). In contrast, in acute renal failure, significant mass balance errors are observed between dialysate quantification and blood-side kinetic measurements (37). Although dialysate quantification is a more accurate technique for measurement of solute removal, it is not practical for routine clinical use.

Urea kinetic modeling has recently been applied to sustained low-efficiency dialysis (SLED) in critically ill patients with acute renal failure (38). Good correlation was observed between kinetic parameters, including Kt/V, SRI and equivalent renal urea clearance (EKR), calculated from direct dialysate quantification, and the same parameters calculated using blood-side single-pool kinetic models (38).

Quantification of dose in continuous renal replacement therapy is more straightforward than in intermittent hemodialysis (39). In continuous venovenous hemofiltration (CVVH), clearance is equal to the ultrafiltration rate if replacement fluids are administered post-hemofilter. When replacement fluids are administered pre-hemofilter (predilution) clearance is reduced due to the dilution of solutes reaching the hemofilter. Mathematically, this reduction in clearance is equal to $Q_B/(Q_B+Q_R)$ where Q_B and Q_R are the blood and replacement fluid flow rates, respectively. Experimentally, at a blood flow of 150 mL/min and an ultrafiltration rate of 2000 mL/hour, predilution reduces urea clearance by approximately 15 percent (40). In continuous venovenous hemodialysis (CVVHD), equilibration of urea between blood and dialysate is nearly complete and clearance is proportional to dialysate flow rate (40). In hemodiafiltration, there is no significant interaction between diffusive and convective urea clearance (40). Thus, clearance in continuous therapy is proportional to the total effluent flow rate. There is no validated method, however, for normalizing clearance between patients. A

value for Kt/V can be estimated based on the total time of therapy divided by an estimated volume of distribution of urea. Since this latter value cannot be reliably predicted, normalization to body surface area, as used for assessment of glomerular filtration rate, or body mass (ml/kg/hour) has been suggested.

There are also no reliable methods for relating the dose of intermittent hemodialysis delivered on a three times per week schedule to treatments delivered on a more frequent or continuous schedule. In end-stage renal disease, the outcomes achieved with continuous ambulatory peritoneal dialysis provided at a weekly Kt/V of 2.0 are similar to the outcomes associated with hemodialysis dosed to provide a spKt/V of 1.2 per treatment delivered on a three-times per week schedule despite the fact that the arithmetic sum of the weekly delivered dose of hemodialysis (Kt/V of 3.6) is substantially greater than the "equivalent" weekly dose of peritoneal dialysis. There are many possible reasons for this lack of arithmetic equivalency. In intermittent hemodialysis, urea concentration fluctuates in a saw-tooth pattern, with a rapid fall during treatment and a slow rise during the intra-dialytic interval. Since the quantity of urea removed per unit time is proportional to the blood urea concentration, the absolute rate of urea removal is greatest at the start of treatment, and falls continuously throughout the treatment. Thus, during the latter portion of a conventional hemodialysis treatment, urea removal becomes relatively inefficient. A higher dose of therapy is required to compensate for this inefficiency (42). In addition, the mechanism of toxicity in uremia is poorly understood. To the extent that toxicity correlates with the peak blood urea concentration, the efficiency of treatment increases as the interval between treatments decreases. Maximal efficiency is achieved by continuous therapy (43). The exclusive use of urea kinetic modeling in the dosing of therapy discounts the

contribution of higher molecular weight solutes to the toxicity of uremia. The clearance of these solutes correlates better with duration of therapy than with urea kinetics (42).

Three mathematical models have been proposed for correlating the doses of continuous and intermittent renal replacement therapies. These models differ with regard to how they correlate the steady state urea concentration achieved by continuous therapy and the pattern of peak and trough urea concentrations observed with three-times per week intermittent hemodialysis. In the first model, the target steady state urea concentration is equal to the peak pre-dialysis urea concentration during the weekly hemodialysis schedule (43); in the second model, this concentration is set equal to the mean pre-dialysis urea concentration (44); and in the third model to the time-averaged urea concentration (45). At the present time, all three of these equivalency models must be considered theoretical as none have been rigorously validated in clinical practice.

C. Relationship Between Dose of Renal Support and Outcome in ARF

Evanson et al. evaluated the delivery of hemodialysis to 40 patients with acute renal failure at two tertiary care medical centers (46). Seventy percent of patients received hemodialysis three-times per week with the remaining patients receiving hemodialysis four-times per week. The prescribed Kt/V was calculated based on the *in vivo* dialyzer clearance, dialysis prescription time and estimated total body water. The delivered Kt/V was calculated as a logarithmic function of the urea reduction ratio. The mean prescribed Kt/V was 1.25±0.47 whereas the mean delivered Kt/V was 1.04±0.49. More recent studies by the same authors have suggested that the blood-based kinetic measurements used in this study substantially overestimate the total urea removal quantified using dialysate-based kinetics (47). Thus,

assessment of practice suggests that the delivery of dialysis to the acute renal failure population falls short of the targets for stable ESRD patients.

Paganini et al. assessed the outcome of 844 critically ill patients with acute renal failure requiring renal replacement therapy at the Cleveland Clinic (10). Severity of illness was assessed using the authors' Cleveland Clinic Foundation ARF severity score. There was no correlation between the delivered dose of dialysis and outcomes in patients with either very low (<4) or very high (>13) severity scores. However, in patients with intermediate severity scores (5-12), delivery of a Kt/V > 1.0 per treatment, three-times per week was associated with improved survival as compared to patients receiving a lower delivered dose of dialysis.

Schiffl et al. have reported on 160 critically ill patients with severe ischemic or nephrotoxic acute tubular necrosis who were assigned, in alternating order, to daily or every other day hemodialysis (48). Patients were excluded from the study if they had an indication for continuous renal replacement therapy. Indications for initiation of hemodialysis were volume overload, electrolyte imbalance, uremic symptoms, acid-base disturbances or severe azotemia. Although the target Kt/V was 1.2 per treatment, the delivered Kt/V was 0.94±0.11 per treatment in the alternate day hemodialysis group (weekly Kt/V 3.0±0.6) and 0.92±0.16 per treatment in the daily hemodialysis group (weekly Kt/V 5.8±0.4). The primary end-point for the study was all-cause mortality 14 days after the last hemodialysis session. The authors observed a reduction in mortality from 46 percent in the alternate day treatment group to 28 percent in the daily treatment group (p=0.01). In addition, there was an increased incidence of infections and gastrointestinal bleeding in the alternate day treatment group. The duration of renal failure decreased from 16±6 days to 9±2 days with the more intensive therapy (p=0.001). While this study is supportive of a more intensive dialysis prescription in acute renal failure, there are many

problems with this study's design and implementation. The exclusion of patients with an indication for continuous renal replacement therapy eliminated the sickest patients and diminished the generalizability of the study. The non-random assignment of patients to groups may have introduced bias, although the reported baseline characteristics of the two groups appear similar. Most importantly, the delivered dose of therapy in the alternate-day group was substantially lower than accepted "adequate" hemodialysis for chronic kidney disease, resulting in a mean pre-dialysis BUN of 104 mg/dL in this group and an increased incidence of uremic complications, including infection and gastrointestinal bleeding. In an editorial accompanying this manuscript, Bonventre urged caution in instituting changes in practice on the basis of this study and suggested the need for further studies to evaluate whether daily hemodialysis would have benefit as compared to alternate-day hemodialysis at a higher delivered dose (49).

Ronco et al. assessed the impact of dose of therapy in 425 patients with acute renal failure treated with continuous venovenous hemofiltration (CVVH) at a single center in Vicenza, Italy (50). Since clearance in CVVH is directly proportional to ultrafiltration rate, patients were randomized to one of three treatment doses: ultrafiltration at 20 mL/kg/hr, ultrafiltration at 35 mL/kg/hr or ultrafiltration at 45 mL/kg/hr. The primary endpoint was survival at 15 days after stopping hemofiltration using an intention to treat analysis. Survival was 41% in the 20 mL/kg/hr group versus 57% in the 35 mL/kg/hr group and 58% in the 45 mL/kg/hr group ($p<0.001$).

Despite these results, an observational study of renal support in ARF, which included 54 centers in 21 countries (BEST Kidney Study) conducted after the publication of the Ronco study demonstrated that the majority of patients were not prescribed CRRT based on body weight. At the six participating academic medical centers in the United States, the mean prescribed effluent

flow rate was approximately 28 mL/minute, with a delivered dose of therapy of only 20.4±8.0 mL/kg/hour (R. Bellomo, personal communication).

D. Intermittent Hemodialysis versus Continuous Renal Replacement Therapy

The majority of studies comparing conventional intermittent hemodialysis and continuous renal replacement therapy have been non-randomized or retrospective studies (51-55). Swartz et al. analyzed the survival data of 349 patients with acute renal failure who received either CRRT or intermittent hemodialysis at a single center (56). Although the initial univariate analysis showed the odds of death for patients receiving CRRT to be more than twice that of patients receiving intermittent hemodialysis (risk of death, 2.03; $p<0.01$), multivariate risk adjustment to control for severity of illness yielded an adjusted risk of death of 1.09 (95% CI: 0.67-1.80; $p=0.72$) for CRRT as compared to intermittent hemodialysis (56).

In a small, randomized, prospective study, published only in abstract form, Sandy et al. compared the outcome in 39 patients with ARF treated with continuous venovenous hemodialysis (CVVHD) to 40 patients treated with intermittent hemodialysis (57). The two groups were well matched in terms of acuity of illness. Mortality was 71.4% in the continuous therapy group versus 60% in the intermittent dialysis group ($p>0.05$).

Mehta et al. performed a multicenter prospective randomized trial comparing CRRT to intermittent hemodialysis in 166 patients with ARF (58). An intention-to-treat analysis found a 28-day all-cause mortality of 59.5% in patients randomized to CRRT as compared to 41.5% in patients randomized to hemodialysis ($p<0.02$) and an in-hospital mortality of 65.5% versus 47.6% ($p<0.02$). However, this study was flawed by unbalanced randomization, resulting in significantly higher APACHE III scores (96.4 versus 87.7; $p<0.045$) and a significantly greater percentage of patients with liver failure (42.9% versus 29.3%; $p<0.05$) in the CRRT group.

Using multivariable stepwise logistic-regression analysis, hepatic failure, APACHE III score and organ system failure (OSF) score were all independently related to ICU mortality. Based on this analysis, the adjusted odds of death associated with CRRT was 1.58 (95% CI: 0.7 to 3.3). Similarly, a time-to-event analysis using a Cox proportional hazards model demonstrated an adjusted hazard ratio associated with CRRT of 1.35 (95% CI: 0.89 to 2.06; p=0.16). Despite the higher mortality in the CRRT group, patients initially treated with CRRT had higher rates of recovery of renal function than patients treated with intermittent hemodialysis (58).

Kellum et al. have performed a meta-analysis of 13 studies encompassing a total of 1400 patients with acute renal failure comparing continuous to intermittent renal replacement therapy (59). Only three of the 13 were prospective, randomized studies. Overall there was no difference in mortality (RR: 0.93; 95% CI: 0.79-1.09; p=0.29), however study quality was poor and only six of the studies compared groups with equal severity of illness at baseline. Adjusting for study quality and severity of illness, the authors calculated a relative risk of death in patients treated with CRRT of 0.72 (95% CI: 0.60-0.87; p<0.01). In the six studies with similar baseline severity of illness, unadjusted relative risk of death with CRRT was 0.48 (95% CI: 0.34-0.69; p<0.0005). The authors concluded that, given the weakness in study quality, the current evidence was insufficient to draw strong conclusions regarding the mode of renal support in critically ill patients with acute renal failure, but that the data suggests a potential benefit of continuous as compared to intermittent therapy (59).

Extended daily dialysis (EDD) and sustained low efficiency dialysis (SLED) are hybrid therapies, bridging standard intermittent hemodialysis and continuous therapy (60, 61). In these treatments, blood flow and dialysate flow rates are reduced from those used in conventional hemodialysis and treatment times are prolonged to between 8 and 24 hours per day, thereby

providing greater hemodynamic stability than conventional intermittent hemodialysis. There are no studies comparing outcomes with these modalities to outcomes with either conventional hemodialysis or continuous renal replacement therapy.

Given the results of these studies, there is insufficient data to favor either intermittent hemodialysis or CRRT as a superior mode of therapy in acute renal failure. There is consensus, however, that in hemodynamically unstable patients, CRRT can be more safely performed due to a lesser tendency to exacerbate hypotension. In centers that are not equipped to perform CRRT, SLED has gained increasing usage in hemodynamically unstable patients. For the purposes of this protocol, intermittent hemodialysis will be the primary therapeutic modality, with CRRT or SLED reserved for use in patients with significant hypotension requiring support with vasopressor medications.

E. Membrane Biocompatibility

The impact of membrane bioincompatibility on the activation of humoral and cellular pathways at the blood-dialyzer interface has also been postulated to have a significant impact on the outcome of acute renal failure (62,63). In animal models of acute renal failure, white blood cell and platelet activation and activation of a variety of humoral mediators, including the complement and coagulation pathways, can be demonstrated to delay the recovery of renal function (62,64).

Clinical trials evaluating the impact of membrane bioincompatibility on outcomes in acute renal failure have yielded conflicting results. Schiffl et al. have demonstrated an increased mortality and increased incidence of “lethal sepsis” in acute renal failure patients dialyzed using cuprophan (bioincompatible) and compared to AN69 (biocompatible) membranes (65,66). Hakim et al. demonstrated a reduction in mortality from 80% to 20% (p=0.01) and an increased

recovery of renal function (85% versus 40% p=0.003) in patients with non-oliguric acute renal failure hemodialyzed using biocompatible polymethylmethacrylate membranes as compared to bioincompatible cuprophan dialyzers (67). No benefit was observed, however, in patients with oliguric renal failure. Himmelfarb et al. expanded this study from a single center to multiple sites, using multiple biocompatible membrane types, and again demonstrated an improvement in survival (74% versus 48%, p=0.003) and recovery of renal function (79% versus 46%, p=0.0004) in patients with non-oliguric acute renal failure (68). As in the original trial, there was no benefit observed in patients with oliguric ARF. Kurtal et al. observed a reduction in mortality from 36% to 28% using polyamide and compared to cuprophan hemodialyzers, however this study was underpowered and this difference did not reach statistical significance (69). In contrast, studies by Jorres et al. (70), Gastaldo et al. (71) and Albright et al. (72) have not demonstrated any benefit to the use of synthetic biocompatible membranes as compared to bioincompatible dialyzers. Thus, the issue of the most appropriate dialysis membrane for use in renal support in ARF remains unresolved, with some data supporting the use of biocompatible membranes and other studies demonstrating no benefit, but with no studies suggesting a detrimental effect associated with biocompatible synthetic membranes.

F. Risk Stratification in Critically Ill Patients with Acute Renal Failure

Many investigators have attempted to develop risk stratification systems for patients with acute renal failure or to validate existing ICU scoring systems in this subset of patients. Chertow et al. retrospectively reviewed the records of 132 consecutive patients at a single medical center who required renal support for ARF (9). The strongest association that they identified was the need for mechanical ventilation (81% mortality in patients requiring mechanical ventilation versus 29% in patients not requiring mechanical ventilation; p<0.0001). They also observed a

significant correlation between in-hospital mortality and the number of failed non-respiratory organ systems, with an odds ratio of death of 1.7 (95% CI: 1.1-2.6; p=0.014) per each additional organ failure.

Numerous studies have attempted to validate general ICU severity scoring systems as prediction models for patients with acute renal failure (73-81). One of the most widely used severity of illness scoring systems is the second generation Acute Physiology and Chronic Health Evaluation (APACHE II) score (82). Van Bommel et al. found that the APACHE II score on the day of initiation of dialysis (area under the receiver operator curve (ROC): 0.78) and the ratio of scores calculated on the day of initiation of dialysis and the day of ICU admission (area under the ROC: 0.92) were predictors of mortality in critically ill surgical patients with ARF (74). In a multicenter trial of 153 patients dialyzed for ARF, Parker et al. also found the APACHE II score to be a reliable predictor of survival, especially when stratified by the presence or absence of oliguria (77). El-Shahawy et al. evaluated the APACHE II score in 222 patients with renal failure due to acute tubular necrosis. Mortality in patients with APACHE II scores of ≤14, 15-18, 19-23, or ≥24 were 67%, 47%, 39% and 0%, respectively, at 6 months. Other predictors of mortality included the need for dialysis, the presence of oliguria, the need for mechanical ventilation, the presence of sepsis and the number of failed organs (79).

In contrast, Radovic et al. did not find a correlation between APACHE II score and outcome in 33 patients with acute renal failure requiring hemodialysis following severe polytrauma (75). Similarly, Halstenberg et al. found that the APACHE II score did not discriminate between survivors and non-survivors in either cardiac or non-cardiac patients with ARF at the Cleveland Clinic (76). Fiaccadori et al. found that the APACHE II model, version II of the Simplified Acute Physiology Score (SAPS II) and version II of the Mortality Probability

Model at 24 hours (MPM_{24} II) did not adequately predict mortality in individual ARF patients (78).

The Sequential Organ Failure Assessment (SOFA) Score was developed as a prognostic index in patients with sepsis, but has been validated as a general prognostic model in critically ill patients (83-85). The SOFA score has been evaluated as a predictor of the development and outcome of ARF in 1411 patients without underlying chronic kidney failure treated in 40 ICU's in 16 countries (81). Risk factors for the development of acute renal failure included age ≥65 years, infection on admission to the ICU, cardiovascular failure, cirrhosis, respiratory failure, chronic heart failure and a history of lymphoma or leukemia. Risk factors for death in acute renal failure patients included oliguria (OR: 1.59; 95% CI: 1.23-2.06; $p<0.01$), maximum cardiovascular score (OR: 1.37; 95% CI: 1.18-1.60, $p<0.01$), number of organ failures on admission (OR: 1.24; 95% CI: 1.03-1.50; $p=0.02$), age ≥65 years (OR: 1.22; 95% CI: 1.01-1.49; $p=0.04$) and a past history of lymphoma or leukemia (OR: 2.31; 95% CI: 1.03-5.16; $p=0.04$).

Using a discriminant function on data collected prospectively from 328 patients**,** Liano et al. have developed a prediction model for patients with acute renal failure due to acute tubular necrosis (86). The major predictors of mortality that they identified were age, male gender, presence of oliguria, hypotension, jaundice, level of consciousness and ventilator dependence. The correlation between their prediction equation (Acute Tubular Necrosis – Individual Severity Score; ATN-ISS) and outcome (survival or death) was highly significant ($r=0.607$, $p<0.001$). Applying this scoring system to their series of patients with ARF due to multiple trauma, Radovic et al. found better correlation with the outcome of ARF than they observed with the APACHE II score (75). Schor observed a strong correlation between the ATN-ISS score and

outcome in 205 patients, with an area under the ROC of 0.94 ($p<0.001$) in critically ill patients, as compared to 0.66 ($p=0.006$) for the APACHE II scoring system in the same population (87).

Paganini et al. have also developed an ARF-specific prediction model (CCF-ARF Score) based on a registry of 512 ICU patients requiring dialysis for acute renal failure at the Cleveland Clinic between 1988 and 1992 (88). Identified risk factors for death included male gender; requirement for mechanical ventilation; platelet count < 50,000/mm^3, leukocyte count < 2,500/ mm^3 or bleeding diathesis; bilirubin > 2.0 mg/dL; non-surgical disease; number of organ failures; serum creatinine at initiation of dialysis; and increment in blood urea nitrogen concentration. The model has been validated using registry data on an additional 148 patients and prospectively tested in an additional 130 patients at the Cleveland Clinic. The model provides a strong correlation with observed mortality, with an odds ratio of death of 1.30 (95% CI: 1.16-1.46; $p=0.0001$) for each unit increment in score (10).

Using a database of 605 critically ill patients with acute renal failure, Mehta et al. have compared previously reported generic and acute renal failure-specific predictive models including APACHE II, APACHE III, SOFA, ATN-ISS and CCF (89). None of the previously reported predictive models performed as well as the logistic regression model developed by the authors, incorporating age, gender, BUN, serum creatinine, urine output, heart rate and respiratory, hepatic and hematologic failure at the time of nephrology consultation.

Thus, although many generic and disease-specific predictive models have been developed and applied to patients with acute renal failure, none of these models have proven to be optimal. In the generic models, indicators of renal function heavily influence overall score, and impair the performance of the model in a population consisting exclusively of patients with ARF. The disease specific models vary with regard to the population studied (e.g., ATN versus all causes of

ARF), and the timing of the scoring (e.g., time of consultation versus initiation of dialysis). The generalized applicability of these models is therefore limited.

G. Impact of Interventions on Outcomes in Critically Ill Patients

One concern in designing studies to evaluate interventions in critically ill patients is that the complexity and severity of illness in this patient population may mask the impact of any individual intervention. In addition, critically ill patients tend to be highly heterogeneous, making it difficult to ensure comparability between study arms, as was the case in the study by Mehta et al. comparing continuous and intermittent therapy in ARF (58). Despite these concerns, several recent studies have demonstrated profound effects of non-renal interventions on outcomes in critically ill patients (90-93).

The Acute Respiratory Distress Syndrome Network (ARDS Net) compared two strategies for management of mechanical ventilation in patients with acute lung injury and acute respiratory distress syndrome (90). In this multicenter, prospective, randomized trial, "traditional" ventilation management (initial tidal volume of 12 mL/kg, reduced in 1 mL/kg steps to maintain a plateau pressure ≤50 cm H_2O) was compared to low tidal volume ventilation (initial tidal volume of 6 mL/kg, adjusted to maintain a plateau pressure of 25-30 cm H_2O). The trial was stopped after the fourth scheduled interim analysis (n=861 patients) due to a reduced mortality in the low-tidal volume group as compared to the "traditional" ventilator management group (31.0% versus 39.8%, p=0.007). In addition, the number of ventilator-free days during the first 28 days after randomization was greater in the low tidal volume group (12±11 days versus 10±11days, p=0.007).

The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study was a multicenter, randomized, double-blind, placebo-controlled evaluation

of recombinant human activated protein C (drotrecogin alfa activated, 24 µg/kg/hour for 96 hours) in critically ill patients with systemic inflammatory response syndrome (SIRS) and organ failure due to acute infection (91). The study end-point was 28-day all-cause mortality. The study was terminated at the time of the scheduled second interim analysis. A total of 1690 patients were enrolled in the study. Mortality in the treatment group was 24.7 percent as compared to 30.8 percent in the control group (p=0.005), a reduction of the relative risk of death of 19.4 percent (95% CI: 6.6-30.5).

Van den Berghe et al. performed a single-center, prospective, randomized trial of intensive insulin therapy (maintenance of a blood glucose level between 80 and 110 mg/dL) as compared to conventional treatment (initiation of insulin infusion for blood glucose > 215 mg/dL, maintenance of a blood glucose level between 180 and 200 mg/dL) in patients admitted to the surgical intensive care unit who required mechanical ventilation (92). The study was stopped at the fourth 3-month interim analysis after 1548 patients were enrolled. Intensive insulin therapy reduced ICU mortality in all patients from 8.0 percent to 4.6 percent ($p<0.04$) with the observed reduction in mortality observed exclusively in the subgroup of patients requiring more than 5 days of ICU care (20.2% versus 10.6%, p=0.005). The greatest reduction in mortality involved deaths due to multiple-organ failure with a proven septic focus. Intensive insulin therapy was also associated with a 34 percent reduction in overall in-hospital mortality, a 46 percent reduction in bacteremia and a 41 percent reduction in ARF requiring extracorporeal support.

The Early Goal-Directed Therapy Collaborative Group randomized patients with severe sepsis or septic shock, treated at a single urban emergency department, to receive either 6 hours of protocol-driven goal-directed therapy (GDT) to provide early optimization of hemodynamic

status, or 6 hours of standard therapy, prior to admission to the intensive care unit (93). The clinicians who assumed treatment of the patients once they were admitted to the ICU were blinded to the treatment assignment. The primary study end-point was in-hospital mortality. A total of 263 patients were enrolled in the study over a 3-year period. APACHE II scores were similar at baseline (GDT: 21.4±6.9; Control: 20.4±7.4; p=0.27), but were lower at 6 hours (GDT: 16.0±6.9; Control: 17.6±6.2; p<0.001) and from hours 7 to 72 (GDT: 13.0±6.3; Control: 15.9±6.4; p<0.001) in the goal-directed therapy group. In-hospital mortality was reduced from 46.5 percent in the control group to 30.5 percent in the early goal-directed therapy group (p=0.009).

These four studies, along with the previously discussed trials of intermittent hemodialysis by Schiffl et al. (48) and CVVH by Ronco et al. (50) provide strong support for the viability of intervention trials in critically ill patients with ARF. The intensive insulin and early goal-directed therapy trials also provide support for the hypothesis that early and intensive correction of derangements in critically ill patients, such as the hemodynamic and metabolic disturbances of ARF, can be associated with clinically significant reductions in morbidity and mortality.

The proposed study is distinct from the prior studies of renal support in ARF described above, in that it is a prospective, randomized, multi-center trial that is sufficiently powered to identify a clinically-meaningful treatment effect. The study is designed to reflect the real-world practice of nephrology, permitting the use of different modalities of therapy as dictated by changes in patients' clinical status. Unlike the recent comparison of daily to every-other-day hemodialysis, the conventional therapy arm will provide a dose of dialysis that is at least equivalent to the recommended practice guidelines for patients with chronic kidney disease.

The study is also unique in that it has been prospectively designed to provide an analysis of the economic impact of more intensive therapy.

IV. Significance of Proposed Research to the VA

Acute renal failure is a significant problem within the VA patient population. Based on ICD-9 diagnosis data from the Austin Automation Center Patient Treatment File over 3% of patients receiving in-patient care at the VA (11,187 of 359,608 patients) develop acute renal failure, with over 12% of these patients identified as requiring renal replacement therapy. Based on a limited audit of known patient records, incomplete coding may result in a failure to identify all patients who actually required dialysis support. Although robust mortality data for ARF in the VA population is not available, in the cohort of patients identified in the PTF file, mortality was 27.1% for all patients with ARF and 43.8% in patients coded as receiving dialysis (M Smith, personal communication). Acute renal failure is also a common complication among military casualties. Thus research to improve care for this population is highly relevant to the VA's mission.

V. Overview of Study Design

The study is a multi-center, prospective, randomized, parallel- group trial of two strategies for the management of renal support in acute renal failure (ARF) secondary to acute tubular necrosis (ATN) in critically ill patients. For the purpose of this study, acute renal failure will be defined as an increase in serum creatinine of ≥ 2 mg/dL (≥ 1.5 mg/dL in women) over a period of ≤ 4 days or acute oliguria (urine output < 20 mL/hour) for > 24 hours. Patients will be enrolled if they have ARF clinically consistent with a diagnosis of acute tubular necrosis and if the primary treatment team is planning on initiating renal support. Patients with chronic kidney disease, defined as a pre-morbid serum creatinine > 2.0 mg/dL (1.5 mg/dL in women), and patients with acute renal failure not due to ATN on clinical criteria (e.g., pre-renal azotemia, obstructive uropathy, interstitial nephritis, glomerulonephritis, vasculitis, hepatorenal syndrome), will be excluded. In addition, in order to exclude patients with relatively mild disease, in whom ATN is not associated with high mortality, patients will be included only if they have evidence of at least one non-renal organ failure, defined as an individual SOFA organ system score of 2-4 (83), or the presence of sepsis, defined as known or suspected infection accompanied by two or more of the modified ACCP/SCCM SIRS criteria (91, 94).

Patients will be randomized in a 1:1 ratio to be treated using either a strategy of intensive renal support or conventional management of renal replacement therapy for their ARF. In both arms of the study, dialysis will be initiated using the same criteria. In the intensive therapy arm, renal support will be provided as intermittent hemodialysis on a 6-times per week basis (target delivered spKt/V of 1.2/treatment), as compared to a 3-times per week basis (target delivered spKt/V of 1.2/treatment) in the conventional therapy arm. In both arms, for hemodynamically unstable patients (cardiovascular SOFA score: 3-4), renal support will be provided as continuous

venovenous hemodiafiltration (dosed at 35 mL/kg/hr in the intensive dose arm and 20 mL/kg/hr in the conventional dose arm) or as sustained, low-efficiency dialysis (SLED) provided 6-times per week in the intensive therapy arm and 3-times per week in the conventional therapy arm). Protocol therapy will be continued until renal function recovers or until day 28. Patients who remain dialysis dependent when ready for discharge from acute care, or after day 28, whichever comes first, will be taken off of protocol treatment and will be prescribed further dialysis at the discretion of their treating physician. Patient survival will be monitored until day 60; one-year survival will be assessed by telephone contact as well as from data reported to vital registries, including the VA Beneficiary Identification and Records Locator System (BIRLS), the National Center for Health Statistics' National Death Index database and the Social Security Administration's Death Master File.

The primary hypothesis to be tested is that the intensive management strategy for renal support will decrease 60-day all cause mortality as compared to conventional management of renal replacement therapy in acute renal failure. The primary study end-point will be 60-day all-cause mortality. Secondary end-points will include all-cause hospital mortality, 1-year all-cause mortality, and recovery of renal function. Duration of renal support, ICU and hospital length of stay, discharge to "home" not requiring dialysis, and the development and/or recovery of non-renal organ failure (assessed by SOFA organ system scores) during renal support will also be assessed. An economic analysis of the treatment strategies will be performed based on both the renal replacement therapy-specific cost of care as well as the global cost of patient care. The economic analysis will also evaluate patient utility.

The mortality associated with the conventional management strategy in this population of patients with acute renal failure is approximately 55%. We postulate that the intensive treatment

strategy will result in a 10% reduction in mortality to 45%. Assuming a 2-sided test of significance at a significance level of 0.05 with 10 percent of patients lost to follow up, a sample size of 1164 will be required to test the primary hypothesis with 90% power.

Tentative agreement has been reached with the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) to provide partial funding for this study through an interagency agreement. Twenty-four VA sites and seven non-VA sites are expected to participate in order to accrue 1164 patients. Each VA site will be expected to enroll 24 to 30 patients (8 to 10 patients per year), and each non VA-site will be expected to enroll 75 to 90 patients (25 to 30 per year), during 3 years of intake. Each patient will be followed for a maximum of 60 days, for an overall study duration of 38 months.

VI. Patient Recruitment

A. Recruitment Strategy

All adult patients fulfilling the inclusion and exclusion criteria will be offered enrollment in the study. No patient will be excluded from the study on the basis of gender, race, ethnicity or sexual preference. Patients will be identified for recruitment by screening patients receiving care in the critical care units of participating centers on a daily basis.

B. Inclusion and Exclusion Criteria

The target population for this study is critically ill patients with acute renal failure due to acute tubular necrosis who require renal replacement therapy. Multiple definitions of acute renal failure have been utilized in prior studies. These definitions have ranged from mild increments in serum creatinine, to provide a high degree of sensitivity in detecting ARF at the expense of decreased specificity, to imprecise definitions based on the need for renal replacement therapy. Unfortunately, there are no clinically available biochemical markers of renal epithelial cell injury that can be used as both sensitive and specific markers for acute renal failure and that correlate with severity of disease. The operational definition that will be utilized was selected to maximize specificity while not requiring an excessive prolongation in the time to diagnosis. Thus, the definition of ARF used for this study requires a substantial increase in serum creatinine (2.0 mg/dL in men, 1.5 mg/dL in women) over a relatively brief period of time (≤ 4 days) or the presence of prolonged (> 24 hours) oliguria. The study population will be restricted to patients with a clinical diagnosis of ATN, by requiring that the renal failure must occur in a clinical setting consistent with this and by excluding patients in whom the renal failure is clinically suspected to be due to a condition other than ATN. Clinical settings consistent with a diagnosis of ATN include recent renal ischemia, nephrotoxin exposure or sepsis, or a urine sediment with

many granular casts and/or tubular epithelial cells. Patients clinically suspected to have pre-renal azotemia, based on hemodynamic status, improvement with volume loading, the presence of high renal tubular sodium avidity (fractional excretion of sodium < 0.01), and/or a decreased fractional excretion of urea (<0.35), will be excluded. Obstructive uropathy will be considered to be present based on findings of urinary tract dilatation (e.g., new or progressive hydronephrosis on ultrasound or an elevated urinary bladder post-void residual volume) and/or improvement following decompression of the urinary collecting system. Acute (allergic) interstitial nephritis will be clinically suspected based on the clinical setting and presence of the typical constellation of findings including pyuria, eosinophiluria, leukocyte casts, eosinophilia and/or skin rash. A diagnosis of acute or rapidly progressive glomerulonephritis will be clinically suspected based on the clinical history and urine microscopy demonstrating red blood cell casts and dysmorphic red blood cells. Vasculitis, hemolytic-uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), malignant hypertension and scleroderma renal crisis will be suspected based on clinical presentation. Atheroembolism will be clinically suspected on the basis of the clinical setting and the presence of livedo reticularis, digital ischemia, and other cutaneous findings. Hepatorenal syndrome will be diagnosed based on the criteria of the International Ascites Club (95).

Patients with uncomplicated ATN (e.g., ATN due to contrast nephropathy without other organ failure) have a good prognosis, with an expected mortality of < 10 percent (4). In contrast, multiple studies have documented that mortality in ARF correlates with the number of failed non-renal organ systems (9,81,86,88). The inclusion criteria therefore require the presence of at least one non-renal organ system failure or the presence of sepsis.

The prognosis of patients with chronic kidney disease who develop acute renal failure is different than that of other patients with ARF. The mortality associated with acute renal failure in this setting is lower, however there is decreased recovery of renal function (3, 96). For this reason, patients with chronic kidney disease manifested by a baseline serum creatinine of greater than 2 mg/dL (1.5 mg/dL in women) will be excluded from the study. Patients with history of prior kidney transplant also represent a unique population with multiple confounding factors, and will be excluded from the trial. Patients with morbid obesity (weight > 120 kg), in whom it is difficult to achieve the targeted doses of therapy, will also be excluded from the trial.

In addition, patients who are not candidates for renal replacement therapy, patients who are not candidates for aggressive medical treatment (comfort measures only status), patients who are moribund in whom death is perceived to be imminent, and patients who are not expected to survive 28-days because of uncorrectable medical conditions will also be excluded.

In order to prevent the logistics of obtaining informed consent from delaying the initiation of treatment, patients will be permitted to have no more than one hemodialysis treatment or 24-hours of CRRT prior to enrollment and randomization.

The specific inclusion criteria are:

- Acute renal failure clinically consistent with a diagnosis of acute tubular necrosis, defined as:
  - Clinical setting of ischemic or nephrotoxic injury

    and
  - oliguria (urine output < 20 mL/hour) for > 24 hours, or an increase in serum creatinine of $\geq$ 2 mg/dL ($\geq$ 1.5 mg/dL in females) over baseline over a period of $\leq$ 4 days.

- Plan for renal replacement therapy by the clinical team
- Receiving care in critical care unit (e.g., MICU, SICU, CCU)
- One non-renal organ failure (SOFA organ system score ≥2) or the presence of sepsis (using modified ACCP/SCCM SIRS criteria)
  - $PaO_2/FiO_2 \leq 300$ mmHg;
  - Platelet count ≤ 100,000 mm^3;
  - Bilirubin ≥ 2.0 mg/dL;
  - Hypotension (MAP < 70 mmHg) requiring any pressor support;
  - Glasgow Coma Scale ≤ 12; or
  - Known or suspected infection accompanied by two or more of the following
    - Temperature > 38°C or < 36°C;
    - Heart rate > 90 beats per minute except in patients with a medical condition known to increase the heart rate;
    - Respiratory rate > 20 breaths per minute, a $PaCO_2$ < 32 mm Hg or the use of mechanical ventilation for an acute respiratory process; and
    - WBC > 12,000 per mm^3 or < 4,000 per mm^3 or > 10% immature neutrophils.
- Age ≥ 18 years
- Patient/surrogate willing to provide informed consent

The specific exclusion criteria are:

- Baseline serum creatinine > 2 mg/dL (> 1.5 mg/dL in females)
- Acute renal failure clinically believed to be due to an etiology other than ATN:
  - Pre-renal azotemia;
  - Obstructive uropathy;

  - Allergic interstitial nephritis;
  - Acute or rapidly progressive glomerulonephritis;
  - Vasculitis;
  - Hemolytic-uremic syndrome (HUS)/Thrombotic thrombocytopenic purpura (TTP);
  - Malignant hypertension;
  - Scleroderma renal crisis;
  - Atheroembolism;
  - Functional or surgical nephrectomy; or
  - Hepatorenal syndrome
  - Cyclosporin or tacrolimus nephrotoxicity
- > 1 hemodialysis treatment or > 24 hours since starting CRRT
- Prior kidney transplant
- Pregnancy
- Prisoner
- Weight > 120 kg
- Non-candidacy for acute renal replacement therapy
- Moribund state
- Patient not expected to survive 28-days because of an irreversible medical condition
- Comfort-measures only status
- Participation in a concurrent interventional study
- Patient/surrogate refusal
- Physician refusal

C. Enrollment window

The window for patient enrollment and initiation of renal support will be 48-hours after one of the specified criteria for initiating renal replacement therapy has been met. The majority of these criteria (volume overload, hyperkalemia, metabolic acidosis, and uremic symptoms) represent urgent indications for renal support. In order to not delay the initiation of therapy while informed consent is being obtained, patients will be permitted to receive one hemodialysis treatment or up to 24-hours of CRRT prior to enrollment and randomization. The additional criterion for initiation of renal replacement therapy, a BUN ≥ 60 mg/dL, when combined with this 48-hour window, will permit initiation of renal support at a level of azotemia consistent with usual practice while excluding patients in whom severe azotemia, which may be an independent factor affecting outcome, has been permitted to develop.

The definition of the enrollment window is:

- Within 48-hours of first meeting any of the following criteria for initiation of renal replacement therapy
  - BUN ≥ 60 mg/dL
  - Volume overload
  - Persistent hyperkalemia (K^+ > 6.2 mEq/L or the presence of ECG changes)
  - Severe metabolic acidosis (pH < 7.20 or tCO_2 < 15 mEq/L)
  - Uremic signs or symptoms
- No more than one hemodialysis treatment or 24-hours of CRRT may be provided prior to enrollment.

VII. Description of Treatment Groups

A. Intensive Renal Support Arm

In patients randomized to the intensive renal support (experimental) arm who are hemodynamically stable (SOFA Cardiovascular Score: 0-2), intermittent hemodialysis will be provided 6 days per week (Monday through Saturday) with a targeted delivered spKt/V of 1.2 per treatment. In hemodynamically unstable patients (SOFA Cardiovascular Score: 3-4) either continuous renal replacement therapy (CRRT) or sustained low-efficiency dialysis (SLED) will be utilized, based on the modality of therapy available at each study site. CRRT will be dosed to achieve a total effluent flow rate (i.e., the sum of dialysate and ultrafiltrate flow rates) of 35 mL/kg/hour. SLED will be provided 6-times per week with a targeted delivered spKt/V of 1.2 per treatment.

B. Conventional Renal Support Arm

Patients randomized to the conventional management of renal replacement therapy (control) arm who are hemodynamically stable (SOFA Cardiovascular Organ Failure Score: 0-2), will be provided intermittent hemodialysis on a three-times per week schedule (Monday-Wednesday-Friday or Tuesday-Thursday-Saturday) with a targeted delivered spKt/V of 1.2 per treatment. If required, isolated ultrafiltration will be provided on non-dialysis days for volume management. In hemodynamically unstable patients (SOFA Cardiovascular Score: 3-4) either continuous renal replacement therapy (CRRT) or sustained, low-efficiency dialysis (SLED) will be utilized, based on the modality of therapy available at each study site. CRRT will be dosed to achieve a total effluent flow rate (i.e., the sum of dialysate and ultrafiltrate flow rates) of 20 mL/kg/hour. SLED will be provided on a three-times per week schedule (Monday-Wednesday-Friday or Tuesday-Thursday-Saturday) with a targeted a minimum delivered Kt/V of 1.2 per

treatment. As with patients on intermittent therapy, patients treated with SLED will receive isolated ultrafiltration on non-treatment days, if needed for volume management.

VIII. Treatment Assignment

A. Stratification of Randomization

All patients fulfilling the inclusion and exclusion criteria and providing informed consent will be randomized in a 1:1 ratio to the two treatment arms. Randomization will be stratified by site, and within sites by SOFA Cardiovascular Organ Failure Score (0-2 versus 3-4) and by the presence or absence of oliguria. Randomization will be performed by an automated phone randomization system using a computer generated randomization scheme produced by the West Haven CSPCC.

Stratification on the basis of SOFA Cardiovascular Organ Failure Score is necessary for several reasons. A score of 3-4 identifies the subgroup of patients with profound hemodynamic instability, manifested by hypotension requiring vasopressor support (83). Since hemodynamic instability will be used as the criterion for use of CRRT (or SLED at sites that do not perform CRRT) as opposed to intermittent hemodialysis, stratification on the basis of the Cardiovascular SOFA Organ Failure score will permit balanced distribution of the initial modality of therapy. In addition, hypotension has been identified as an independent poor prognostic indicator in studies of ARF; the cardiovascular organ failure being the only organ failure independently associated with mortality by the SOFA score in patients with ARF (81).

The operational definition of ARF for this study requires either an increase in serum creatinine of 2 mg/dL (1.5 mg/dL in women) over a period of four or fewer days or the presence of persistent oliguria. Since oliguria is an independent predictor of mortality in ARF (77,79,81,86) stratification of randomization based on the presence or absence of oliguria is necessary.

B. Randomization Method

Treatment assignment will be accomplished using a 24-hour automated phone randomization system located at the CSPCC in Perry Point, Maryland. Patients will be randomized by site, and within site by combinations of cardiovascular SOFA score level (0-2 or 3-4) and presence or absence of oliguria. An adaptive randomization procedure (98) will be used to generate the treatment assignment within each site in order to achieve the best balance of combinations of treatment, cardiovascular SOFA score level (0-2 or 3-4) and presence or absence of oliguria. The operational details of the randomization process will be given in the Operations Manual. Patients will enter the treatment protocol immediately after randomization. The West Haven CSPCC will monitor and review the randomization process during the entire enrollment phase of the study.

C. Blinding

Neither the patient nor the study personnel at the treating site will be blinded as to the treatment assignment. If adjudication of endpoints (e.g., renal recovery) or complications is required, the individual(s) involved in adjudication will be blinded to treatment assignment.

IX. Treatment Protocol

A. General Management of Renal Support

In order to ensure uniformity of treatment between sites and between patient groups, all renal support provided during the study will follow specific protocols for the management of intermittent hemodialysis, CRRT and SLED. Intermittent hemodialysis will be the primary therapeutic modality in both study groups. CRRT and SLED will be reserved for patients in whom hemodynamic instability (SOFA Cardiovascular Organ Failure Score of 3-4), manifested by a mean arterial blood pressure < 70 mmHg requiring the use of pressor agents (e.g., dopamine > 5 mcg/kg/min, norepinephrine, epinephrine, phenylephrine, vasopressin) proscribes the use of intermittent hemodialysis. Patients receiving CRRT or SLED will be converted to intermittent hemodialysis when hemodynamic instability has resolved (SOFA Cardiovascular Organ Failure Score of 0-1 for > 24 hours). Each study site will use either CRRT or SLED, based on standard site-specific practice.

The inclusion of CRRT and SLED for the treatment of hemodynamically unstable patients is necessary, since many practitioners would consider it unethical to prohibit the use of these modalities in hemodynamically unstable patients. However, since the use of these therapies will be determined by the patient's hemodynamic status, their use does not create a multi-armed study and comparison between continuous and intermittent therapy is not a goal of this study. Since the allocation of hemodynamically unstable patients to CRRT or SLED will not be random, this study is also not designed to provide rigorous comparison between these modalities.

B. Management of Hemodialysis

Hemodialysis will be provided using biocompatible synthetic hollow-fiber dialysis membranes (e.g., polysulfone, polyamide, polymethylmethacrylate, polyacrylonitrile). Bicarbonate-buffered dialysate will be used for all treatments. Electrolyte composition (e.g., sodium, potassium, and calcium) will be adjusted by the treatment team as appropriate. All intermittent hemodialysis will be provided using ultrafiltration-controlled dialysis machines. Ultrafiltration goals will be prescribed by the treating physicians. Since reduced blood flow due to catheter malfunction is a common reason for failing to achieve the desired dialysis prescription, the total volume of blood processed (liters processed), will be monitored each dialysis treatment.

The initial prescribed dialysis dose will be based on a target spKt/V of 1.4 per treatment in order to provide a delivered dose of 1.2 per treatment. The value of V will be calculated assuming that the volume of distribution of urea is normally approximately 55% of body weight and that any acute increase in patient weight is due to an increased total body water. Thus, V will be estimated as 0.55 x Pre-Morbid Weight + (Current Weight – Pre-Morbid Weight). In obese patients (>30% above ideal body weight) V will be calculated based on adjusted body weight, calculated as ideal body weight plus 25% of the difference between ideal and actual weight.

The delivered dialysis dose will be monitored based on blood-side urea kinetics three-times per week (each treatment in the conventional therapy arm, every other treatment in the intensive therapy arm) for the first two weeks, and at least weekly thereafter. Blood samples for blood urea nitrogen will be obtained immediately pre-dialysis using standard technique (30). The post-dialysis blood urea nitrogen sample will be obtained using the slow flow/stop pump

techniques to prevent sample dilution with recirculated blood and minimize the confounding effects of urea rebound (30). The spKt/V will be calculated as:

spKt/V = -Ln (R - 0.008 x t) + (4 - 3.5 x R) x 0.55 UF/V

where Ln is the natural logarithm; R is the post-dialysis BUN ÷ pre-dialysis BUN; t is the dialysis session length in hours; UF is the ultrafiltration volume in liters; and V is the patient's estimated volume of distribution of urea, calculated as 0.55 x Pre-Morbid Weight + (Current Weight – Pre-Morbid Weight) (97). The dialysis prescription will be adjusted as necessary to achieve a target spKt/V of 1.2 to 1.4.

C. Management of Continuous Renal Replacement Therapy

Continuous renal replacement therapy will be provided using automated equipment with integrated ultrafiltration control. All therapy will be provided as continuous venovenous hemodiafiltration (CVVHDF) with a 1:1 ratio of dialysate and replacement fluid administration. All hemodiafilters will be comprised of biocompatible synthetic hollow-fiber membranes. Hemodiafilters will be changed at least every 48 hours. Dialysate and replacement fluids will be bicarbonate-buffered unless citrate-anticoagulation is utilized. The electrolyte composition of the dialysate and replacement fluids and fluid removal parameters will be prescribed by the treating physicians. Effluent flow rate in each group will be based upon pre-morbid body weight. In obese patients (>30% above ideal body weight) calculations will be based on adjusted body weight, calculated as ideal body weight plus 25% of the difference between ideal and actual weight.

D. Sustained Low-Efficiency Dialysis

Sustained low-efficiency dialysis (extended daily dialysis) will be performed using standard ultrafiltration dialysis machines that have been adapted to provide reduced dialysate

flow rates. Biocompatible synthetic hollow-fiber dialysis membranes will be used for all treatments. Blood flow rates will be maintained at 200 mL per minute. Dialysate flow rate will be maintained between 100 and 300 mL per minute. Bicarbonate-buffered dialysate will be used for all treatments with the electrolyte composition adjusted by the treatment team as appropriate. Ultrafiltration goals will be prescribed by the treating physicians. The delivered dialysis dose will be monitored based on blood-side urea kinetics three-times per week (each treatment in the conventional therapy arm, every other treatment in the intensive therapy arm) for the first two weeks, and at least weekly thereafter as described for intermittent hemodialysis. Treatment prescription will be modified as necessary to achieve a target spKt/V of 1.2 to 1.4.

E. Discontinuation of Renal Support

Renal replacement therapy will be continued as per study protocol until there is recovery of renal function, a decision is made by the patient or surrogate decision-maker to withdraw life-sustaining therapy or the patient dies. All patients who have persistent renal failure when ready for discharge from the acute care setting, or at Day 28 post-randomization, whichever comes first, will be taken off of protocol treatment and will be prescribed further dialysis at the discretion of the treating physicians.

In patients who are oliguric (urine volume < 20 mL/hour), recovery of renal function is heralded by an increase in urine volume. In patients who are non-oliguric, urine volume is not an adequate indicator of recovery of renal function. In patients who are being dialyzed on a three-times per week schedule, increased solute clearance may be detected based on a decline in the pre-dialysis blood urea nitrogen or serum creatinine concentrations. In patients dialyzing six-times per week, and patients on CVVHDF, extracorporeal solute clearance may mask changes in blood levels of these markers resulting from increased endogenous clearance. For this reason,

recovery of renal function will be assessed in patients with a urine output of > 30 mL/hour based on 6-hour urine collections for creatinine clearance. Clearance studies will be performed three-times per week (on non-dialysis days for patients in the conventional arm), with the urine collection obtained at the time of daily blood work. Creatinine clearance (Cl_{Cr}) will be calculated as:

$$Cl_{Cr} = (U_{Cr} \times V / P_{Cr}) \times 2.8x10^{-3}$$

where U_{Cr} and P_{Cr} are the urine and serum creatinine concentrations, respectively, in mg/dL and V is the 6-hour urine volume, in mL. Renal function will be considered to have recovered sufficiently to discontinue renal replacement therapy when the creatinine clearance is > 20 mL per minute.

F. Nutrition

All patients will be prescribed a nutritional intake that will provide at least 25-30 kcal/kg/day, depending on mechanical ventilation and other factors. Protein intake will be at least 1.2 g/kg/day. In patients receiving parenteral nutrition, carbohydrate infusion rates will not exceed 5 mg/kg/min. Water-soluble vitamins will be supplemented to replace dialysis-related losses.

G. Other Medical Care

The patient's primary physicians will determine the remainder of patient management consistent with established best practices with the management of critically ill patients. In patients with acute lung injury or the acute respiratory distress syndrome, tidal volume for mechanical ventilation will be approximately 6 mL per kilogram of predicted body weight and adjusted to maintain a peak plateau pressure between 25 and 30 cm of water (90). Ventilator associated pneumonia will be evaluated and treated in accordance with published clinical

practice guidelines and consensus statements (99, 100). All medications will be dose adjusted for renal failure and renal replacement therapy in accordance with standard dosing guidelines (101).

H. Withdrawal from Study Protocol

A patient/surrogate may request to be withdrawn from the study protocol at any time, for any reason, without prejudice. A patient may also be withdrawn from the protocol at the request of his/her physician, for any reason. Patients who withdraw from active study participation will be requested to permit continued data collection for the remainder of the follow-up period.

X. Outcome Measurements

A. Primary Endpoint

The primary study endpoint is 60-day all cause mortality.

The ultimate goal of therapeutic interventions in acute renal failure is to decrease the high mortality associated with this condition. Prior studies have selected a variety of endpoints for assessing mortality in acute renal failure, including ICU mortality, hospital mortality and mortality at a fixed time-point following discontinuation of renal support. There are, however, methodological difficulties associated with the selection of an endpoint that is less than entirely objective. The decision to discharge a patient from the ICU or from the hospital is not entirely objective and may be affected by issues other than the patient's medical status such as local practice patterns, differences in insurance coverage, and the use of intermediate (transitional) care facilities. Thus, the criteria for hospital discharge may be somewhat variable and arbitrary between institutions, and even between patients within a single institution.

The use of a time-delimited endpoint obviates many of these issues and has been utilized in prior studies in critically ill patients (91, 93). For example, twenty-eight-day all cause mortality was the primary end-point in the PROWESS Study, evaluating the efficacy of activated protein kinase C in critically ill patients with sepsis (91). However, some studies have suggested that a 28-day or 30-day endpoint may miss a significant percentage of total disease-related mortality (102).

Prior studies of acute renal failure support the use of a mortality endpoint between 30 and 60 days. The duration of acute renal failure is usually no more than several weeks, and the majority of mortality associated with acute renal failure is observed within this time frame. In the study by Mehta et al., mean hospital length-of-stay was 17.1 days in patients treated with

CRRT and 26.3 days in patients treated with intermittent hemodialysis, with a longer length of stay in survivors than in non-survivors (58). The mean duration of therapy in the study comparing three doses of CVVH by Ronco et al. ranged between 11±6 days and 13±8 days (50). All of the reported observed mortality in this study occurred prior to day 35, however follow-up was limited to 15-days following discontinuation of renal replacement therapy (50). Similarly, in the comparison of daily versus every-other day hemodialysis by Schiffl et al., mean duration of therapy ranged between 9±2 and 16±6 days in the two groups (48). In a study by Gastaldo et al. comparing two different dialysis membranes, the majority of observed mortality occurred within the first 4 weeks, however mortality rates did not plateau until after day 50 (71).

The use of a 60-day time-point will, however, increase the risk of patients being lost to follow-up following hospital discharge. It is felt, however, that based on the population being studied and the ability to track patient survival using vital registry data, that loss to follow-up will not impact significantly on the ability to track 60-day all cause mortality.

B. Secondary Endpoints

Secondary endpoints include:

- All-cause hospital mortality by day 60

Hospital discharge will be defined as discharge from acute care, whether to acute rehabilitation, transitional care, long-term care or home.

- 1-year all cause mortality
- Recovery of renal function by day 28.

Recovery of renal function will be defined as lack of need for continuing dialysis support, and will be classified as complete recovery, partial recovery or no recovery. Complete recovery of renal function will be defined as a serum creatinine that is no more than 0.5 mg/dL

greater than baseline. Partial recovery will be defined as a serum creatinine > 0.5 mg/dL greater than baseline but not dialysis-dependent. Patients who remained dialysis dependent at study completion or at time of death will be categorized as having no recovery of renal function. Multiple studies have demonstrated that the majority of patients who recover renal function following ARF do so within the first 4 weeks (48, 50, 58, 65, 68), justifying the use of the 28-day time point.

C. Tertiary Endpoints

Tertiary endpoints to be evaluated include:

- Duration of renal support

The duration of renal support will be defined as the number of days from the initiation of renal replacement therapy to final dialysis treatment. Duration of renal support will be censored if the patient is still dialysis dependent at the time of death. Duration of renal support will be evaluated on the basis of both the mean number of days of renal support and Kaplan-Meier survival, censored for patient death

- ICU length-of-stay
- Hospital length-of-stay

Both ICU and hospital length-of-stay will be defined based on the ICU and acute hospital admissions during which the patient was randomized. Length-of-stay will be evaluated on the basis of both the mean number of days of ICU/hospital stay following randomization and Kaplan-Meier survival, censored for patient drop out or death. Hospital discharge will be defined as discharge from acute care, whether to acute rehabilitation, transitional care, long-term care or home.

- Discharge to “home” off of dialysis by day 60

The optimal outcome in acute renal failure is the ability of the patient to return to his or her prior living situation ("home") not requiring renal replacement therapy on an ongoing basis. This will be assessed using an endpoint defined as return to pre-morbid living situation (e.g., if residing in a skilled nursing facility prior to the index hospitalization, than discharge back to a skilled nursing facility will be considered to be discharge to "home") and not requiring renal replacement therapy, by day 60.

- SOFA Organ Failure Scores at days 1-14, day 21 and day 28

Non-renal organ system failures will be assessed on the basis of SOFA Organ Failure Scores at days 1-14, day 21 and day 28 following randomization. Organ failure will be defined as an individual SOFA organ failure score ≥ 2. Parameters to be monitored will include the maximum number of non-renal organ failures, the rates of individual non-renal organ-system failures, the time course of non-renal organ failures, and the overall non-renal SOFA score.

D. Economic Analysis

An economic analysis will be conducted to evaluate:

- Renal replacement therapy-specific cost of care
- Global cost of care
- Patient utility

The Health Economics objectives will be measured and analyzed as described in the Health Economics Component section of the protocol (Section XXII).

XI. Data Collection and Monitoring

The data collection schedule is shown in Tables 1 and 2. Treatment data will be collected on a daily basis while patients remain dialysis-dependent. Follow-up outcome data will be collected at Day 60 (primary end-point) and at hospital discharge. It is anticipated that most patients will not be hospitalized at Day 60 and that this data will be collected by telephone or mail. Follow-up at 1-year will be performed by telephone or mail. In addition, survival at 1-year will be ascertained based on vital statistic registries, including the VA Beneficiary Identification and Records Locator System (BIRLS), the National center for health Statistics' National Death Index database and the Social Security Administration's Death Master File.

Table 1
General Data Collection

	Screening	Baseline	Study Days 1-14, 21, 28	Day 28	Day 60	1-Year
Screening Evaluation Baseline Serum Creatinine Etiology of ARF Duration of ARF	X					
History		X				
Physical Examination		X				
Charlson Score		X				
Laboratory Assessment CBC Comprehensive Chemistry Panel Basic Chemistry Panel		 X X	 X X			
Hemodynamic Assessment		X	X			
Pressors		X	X			
24-Hour Urine Volume	X	X	X			
SOFA Score	X	X	X			
APACHE II Score		X				
CCF ARF Score		X				
SIRS Score		X	X			
Nutrition Management		X	X			
Medication Usage			Days 7 & 28			
Renal Replacement Therapy Data			See Below			
Assessment of Renal Function				X		
Survival Status				X	X	X
ICU LOS				X	X	
Hospital LOS				X	X	
Economic and Utility Data					X	X

Table 2 Renal Replacement Therapy Data Collection				
	Initiation of RRT	Each Treatment	3x/week for 2 weeks, then weekly	Discontinuation of RRT
Indications for RRT Volume status Serum potassium Acid-base status Symptoms BUN Hemodynamic status	X			
Hemodialysis / SLED Dialyzer Duration Blood Flow Dialysate flow Pre-dialysis weight Fluid removal		X		
Hemodialysis / SLED Adequacy Assessment BUN at initiation BUN at termination			X	
CVVHDF Hemodiafilter Blood flow Dialysate flow Replacement fluid rate Ultrafiltration rate Hours of therapy 24-hour effluent volume Anticoagulation		X		
Complications of Therapy First use reaction Hypotension requiring discontinuation of treatment Air embolism Bleeding (e.g. due to system disconnection or dialyzer rupture) New onset of serious arrhythmia during treatment Iatrogenic fluid and/or electrolyte disturbance Seizures Catheter insertion complication		X		
Indications for termination of renal support				X

A. Schedule of Observations

All subjects will be followed daily until hospital discharge, death, or day 28 post-randomization, whichever occurs first. Vital status of study subjects will be determined on day 60 post-randomization and at one year post-randomization.

1. All acute renal failure patients in intensive care unit (ICU) settings:

Screening/Eligibility Form 01.

2. All eligible patients (or the patient's surrogate) before randomization:

Consent Form VA 10-1086 (Form 02)

3. All patients for whom initial consent was provided by a surrogate and who regain decision-making capacity:

Consent Form VA 10-1086 (Form 02-R)

Reconsent Form R

4. All eligible patients who sign the informed consent or who have the consent form signed for them by a surrogate:

Randomization Form 03

Baseline Form 04

Patient Contact Information Form 05

Baseline Scores and Laboratory Data Form 06

5. All randomized patients on study days 7 and 28:

Medications Data Form 08

6. *All randomized patients on study days 1 through 14, 21 and 28:*

Study Days Scores and Laboratory Data Form 07

7. *Each time renal replacement therapy is received:*

Renal Replacement Therapy – Each Treatment Form 09

8. *Each dialysis catheter insertion:*

Catheter Insertion Data Collection Form 15

9. *If renal replacement therapy is discontinued:*

Discontinuation of Study Therapy Form 10

10. *Twenty-eight days post-randomization:*

Day 28 Status Form 11

11. *Sixty-days post-randomization:*

Day 60 Status Form 12

Day 60 Economic Data Form 17V and 17N

Health Utilities Index Form 19

12. *At the time of any serious adverse event which may be related to study treatment from randomization through death, termination of study treatment, or day 30 after randomization, whichever comes first:*

Serious Adverse Event Form 16 (see specific instructions in Operations Manual)

13. *At time of withdrawal or exit from study through 60 days post-randomization:*

Study Exit Form 13

14. For release of patient records from another medical facility:

Release of Patient Information Form 14 (This form will be signed once by the patient and copies of it will be used for all requests for release of patient records from another facility for a period of one-year following randomization)

15. One-year follow-up:

One-year Economic Data Form 18V and 18N

Health Utilities Index Form 19

Follow-up at day-28, day-60 and at one-year will be performed by site staff using telephone and/or mail follow-up. After study closure (i.e., 38 months after study start-up), all remaining 60-day and 1-year follow-up will be performed by staff at the Chairman's office using telephone and/or mail follow-up. Survival data on patients who cannot be contacted will be obtained using the VA Beneficiary Identification and Records Locator System (BIRLS), the National Center for Health Statistics' National Death Index database and the Social Security Administration's Death Master File.

XII. Patient Follow-up Procedures

A. Follow-up of subjects for 28-day vital status

At 28-days post-randomization, an assessment of renal function and vital status will be made for all subjects enrolled in the study. Hospital and ICU discharge information for the hospitalization during which the subject was enrolled in the study, including dates of admission and discharge, and primary and secondary discharge diagnoses will also be obtained. The date of the most recent dialysis treatment will be determined and, if the patient has been discharged from the hospital, the patient's current living situation (e.g., home, skilled nursing facility, rehabilitation center) will be identified.

B. Follow-up of subjects for 60-day vital status, medical resource utilization, and quality of life

At 60-days post randomization, an assessment of renal function, vital status, medical resource utilization and quality of life will be made for all subjects enrolled in the study. Hospital and ICU discharge information for the hospitalization during which the subject was enrolled in the study, including dates of admission and discharge, and primary and secondary discharge diagnoses, will also be obtained. The date of the most recent dialysis treatment will be determined and, if the patient has been discharged from the hospital, the patient's current living situation (e.g., home, skilled nursing facility, rehabilitation center) will be identified. Medical resource utilization will be assessed by telephone and/or mail survey as described in Health Economics and Cost Analysis (Section XXII).

C. Follow-up of subjects for recovery of renal function

Information regarding recovery of renal function will be collected on the Discontinuation of Study Form (Form 10), as well as on the 28-day and 60-day Vital Status Forms (Forms 11 and 12).

D. Follow-up of subjects at one year for vital status, medical resource utilization and quality of life

Mortality and quality of life will be determined by telephone or mail survey at one year. Mortality of patients who cannot be contacted will be determined from the VA Beneficiary Identification and Records Locator System (BIRLS), the National Center for Health Statistics' National Death Index database and the Social Security Administration's Death Master File. Medical resource utilization will be assessed by telephone and/or mail survey as described in Health Economics and Cost Analysis (Section XXII).

E. Reporting of Adverse Events

Adverse Events: Given the severity of illness of the patient population for this study, it will not be possible to separate study-related adverse events from the natural progression of disease. For this reason, for the purpose of this study, only serious adverse events will be monitored.

Serious Adverse Events: Serious adverse events to be reported for this study are defined by the ICH Harmonized Tripartite Guideline E2A for Clinical Safety Data Management as untoward medical occurrences that result in death, are life-threatening (actually place the patient at risk of death at the time of the event), result in prolonged existing hospitalization, result in persistent or significant disability or incapacity, or are felt to be serious by the investigator **and**

are thought by the investigator to be related to the investigative treatment (intensive or conventional renal support).

Both expected and unexpected serious adverse events need to be reported by the investigator. An expected adverse event is what is expected to occur by nature, frequency or severity in a number of patients given the study intervention and is consistent with available information. Unexpected events may be not previously observed or may add information on the specificity or severity of an already known adverse event.

Patients will be monitored for serious adverse events until death, discharge from the hospital, or for 30 days after randomization, whichever comes first.

Examples of serious adverse events may include, but are not limited to:

1. Major complications from dialysis catheter insertion meeting the definition of serious.
2. Complications associated with dialysis treatment:
    a. anaphylactic reaction to dialyzer ("first-use" reaction)
    b. hypotension requiring discontinuation of therapy
    c. air embolism
    d. bleeding (e.g. due to system disconnection or dialyzer rupture)
    e. new onset of serious arrythmia requiring discontinuation of therapy (e.g. rapid supraventricular tachycardia with hypotension, ventricular tachycardia)
    f. iatrogenic fluid and/or electrolyte imbalances
    g. seizures
3. Any other major important medical event considered serious by the investigator and felt to be <u>related to the investigative treatment</u>. Serious adverse events with a reasonable causal relationship will be reported.

All serious adverse events will be reported on the Serious Adverse Event Form. Information on catheter complications will be collected on the Catheter Insertion Data Collection Form. Catheter complications that are serious should be reported on the Catheter Insertion Data Collection Form and the Serious Adverse Event Form.

Directions on how to complete the Serious Adverse Event Form will be available in the Operations Manual. All serious adverse events will be faxed to the West Haven CSPCC within 72 hours from the time they are identified by the site. Investigators will be notified of new hazards or other trends involving patient safety.

The Study Chairman, Coordinating Center (CSPCC) West Haven Biostatistician, and Clinical Research Pharmacy Coordinating Center (CSPCRPCC) Research Pharmacist will review all serious adverse events. Serious events that are related to the treatment strategy and unexpected or those that warrant special attention will be reported to VA CSP Headquarters, study investigators, the Data and Safety Monitoring Board and the West Haven Human Rights Committee.

Adverse Event Data Summaries

The West Haven CSPCC and CSPCRPCC will provide periodic summaries of all serious adverse events reported. These summaries will be available to the Study Chairman, VA CSP Headquarters, and the Data and Safety Monitoring Board.

XIII. Human Rights Issues and Informed Consent

A. Informed Consent Procedure

Informed consent will be obtained from all patients, or their legally authorized representative (surrogate), prior to participation in this study. Informed consent requires that the patient or patient's surrogate understand the details of the study and agree, without coercion, to participation in the study. In order to obtain informed consent, the following information shall be provided to each patient or patient's surrogate:

1. The name of the study
2. The name of the Principal Investigator
3. An explanation that the study involves research
4. An explanation that the purpose of the study is to determine whether a strategy of more intensive renal replacement therapy (dialysis) in patients with acute kidney failure results in increased survival as compared to the conventional management of renal replacement therapy in acute kidney failure.
5. An explanation that the active treatment portion of the study will last up to 4 weeks and that additional follow-up by telephone or mail will occur over a period of one year.
6. A description of the intensive and conventional treatment strategies.
7. A description of randomization.
8. A description that participation in the study may require additional dialysis treatments over usual therapy.
9. A description that participation in the study will require additional blood tests.

10. A description that the patient's Social Security number will be used to identify records of medical care and to track the patient's survival after hospital discharge.
11. A description that the alternative to participation in this study will be to receive renal replacement therapy (dialysis) not as part of the study.
12. A description that all records will be kept confidential, but that records may be examined by representatives of the VA and or the National Institutes of Health.
13. An explanation of whom to contact for answers to questions about the research and about research subjects' rights.
14. An explanation of whom to contact in the event of research-related injury.
15. A statement that participation in the study is voluntary and that a decision not to participate or to withdraw from the study after initially agreeing to participate will involve no penalty, loss of benefits or reduction in access to medical care.
16. A statement that there will be no cost for the treatments provided as part of this study.
17. A statement that there will be no payment for participation in this study

Merely obtaining signature consent from the patient, or the patient's surrogate, does not constitute informed consent. However, the use of a standardized consent form aids in assuring that subjects/surrogates receive adequate and consistent information about the trial and have consented to participate.

The study coordinator at each site will introduce and explain the study to the patient (or the patient's surrogate) and present him/her with the detailed consent form and supplementary material to read and review. Subsequently, the participating investigator (or a designated physician) will review and discuss the study with the patient/surrogate and answer any questions

that the patient/surrogate might have. The investigator will sign and date the consent form on the day the meeting with the patient/surrogate occurred.

The two strategies for renal support will be clearly described. The general intent of the study will be delineated. The randomization process and the risks associated with all procedures will also be described to the patient/surrogate. It will be explained to the patient/surrogate that no experimental drugs will be utilized in this study. The patient/surrogate will be informed that the patient's Social Security number will be recorded in the research records as a unique patient identifier. The patient/surrogate will also be informed that, at the data-coordinating center, any personal identifying information will be kept in a data-file separate from the files containing his/her other study data.

The informed consent process will be documented in a detailed progress note prior to study participation, i.e., prior to any procedure associated with risk or discomfort performed for study purposes rather than for patient care. In addition, the patient/surrogate will sign the informed consent in the presence of an independent witness not associated with the study. It must be ensured that the patient/surrogate understands every aspect of the trial, including its risks and benefits, prior to signing the informed consent.

The consent of the patient to participate in the study will be recorded on the study consent form VA 10-1086 (Appendix A and Form 2, Appendix I). The original will be placed in the patient's medical record. Copies of the signed consent firm will be provided to the patient, the Research Office at the participating site (if required by the IRB), and will also be placed in the patient's study file. A copy of the informed consent will also be sent to West Haven CSPCC at the time of enrollment in the study.

B. Surrogate Consent

Patients eligible for this trial will be critically ill and the majority will be unable to provide informed consent due to acute delirium or pharmacologic sedation (103). For this reason, as is the case in most trials involving critically ill patients, it is anticipated that for the majority of patients, informed consent will be obtained from the patient's legally authorized representative (surrogate).

Patients with impaired decision making capacity constitute a vulnerable population for research studies and require special protection. VHA Directive 1200.5 Appendix D (March 12, 2001) details four criteria that are required for approval of surrogate consent. The following details each of the criteria and the corresponding justification for inclusion of patients with impaired decision making in this study:

(1) *Only incompetent persons or persons with impaired decision making capacity are suitable as research subjects. Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision making capacity as subjects. Incompetent persons or persons with impaired decision making capacity must not be subjects in research simply because they are readily available.*

Patients with critical illness are generally incapable of providing informed consent. As stated previously, decision making capacity is generally present in less than 10 percent of critically ill patients due to delirium from their underlying illness or from sedative medications that are part of the standard of care. Restricting a clinical trial of critically ill patients with acute renal failure to the small minority of patients with intact decision-making capacity would

severely compromise the generalizability of the study results by limiting the study to a patient population not representative of the spectrum of critically ill patients with acute renal failure.

(*2*) *Favorable risk/benefit ratio. The proposed research entails no significant risks, tangible or intangible or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people or persons with impaired decision making capacity will not be subjects of research that imposes a risk of injury unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.*

The purpose of this study is to evaluate whether a strategy of intensive renal replacement therapy results in decreased mortality compared to conventional management of renal support in critically ill patients with acute renal failure. The patients enrolled in this trial will receive renal replacement therapy regardless of whether they participate in this trial. The intervention consists of increasing the frequency or the dose of renal replacement therapy. If an individual patient is randomized to the conventional strategy arm, management will be similar to the management of patients not participating in the trial. If an individual patient is randomized to the intensive therapy arm, the risk of more frequent dialysis treatments is outweighed by the potential survival benefit.

(3) Voluntary participation. Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.

This is unlikely to be an issue in this study population where the loss of decision-making capacity will result from acute delirium of sedation. No patient will be forced or coerced to participate.

(4) *Well-informed representatives. Procedures have been devised to assure that participant's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity. Health care agents (appointed under Durable Power of Attorney for Health Care) and next-of-kin or guardians must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.*

Surrogate decision-makers will be fully informed of the risks and benefits associated with participation in this study. They will be instructed that as a surrogate decision-maker, their obligation is to provide substituted judgment for the patient, based on their determination of what the patient would have done if they were able to express their opinion. If they do not know what the patient would have decided, they are to provide or refuse consent on the basis of what they believe is in the patient's best interest.

At VA sites, surrogate consent may be obtained from court-appointed guardian of the patient or from a health care agent appointed by the patient in by a Durable Power of Attorney for Health Care (DPAHC) or similar document (104). In the absence of such a legally appointed representative, surrogate consent may be obtained from next-of-kin in the following order of priority: spouse; adult child (18 years of age or older); parent; and adult sibling (18 years of age

or older) (104). At non-VA sites, identification of the patient's legally authorized representative for surrogate consent will be in accordance with prevailing state law.

In order to obtain surrogate consent, two physicians will determine and document in the medical record that the patient lacks decision-making capacity and that there is little or no likelihood that the patient will regain decision-making capacity within the time-frame required for enrollment in this study.

Patients regaining decision-making capacity during or after completion of active treatment will be notified of their participation in the study and formal reconsent for continued participation will be obtained. Decision making capacity will be assessed based on clinical evaluation including documentation of mental status using an objective tool, such as the Mini Mental Status Examination (105) or the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (106,107), and documentation of sufficient judgment to understand the design, risks and benefits of participation in this study. For patients who do not regain decision-making capacity by day 28, the individual providing surrogate consent will be contacted for the day 60 and or 1-year follow-up to determine if the patient is able to provide consent. If the patient is able to provide consent, the patient will be contacted and reconsent will be obtained by telephone and/or mail.

C. Risks and Benefits

All patients participating in this study will have been determined to require renal replacement therapy by their treating physicians prior to study enrollment, and may have already been initiated on renal replacement therapy. The risks of inserting a dialysis catheter and the risks of initiating renal replacement therapy are therefore not risks attributable to this study.

The major risk attributable to this study is the risk of complications associated with more frequent dialysis treatments. The complications associated with dialysis include low blood pressure, allergic reactions, bleeding, air embolization, rapid heart rates and, rarely, death. The most frequent complication of dialysis, particularly in the acutely ill patient is dialysis-related hypotension. Paradoxically, this risk may be reduced in the intensive therapy arm due to the decreased ultrafiltration that will be required during each dialysis session.

In order to ensure that the delivered dose of dialysis corresponds to the study protocol, blood samples will be obtained pre- and post-dialysis up to 8 times during the study. The total volume of blood samples will be less than 180 mL. Since these samples will be obtained through the dialysis catheters, there will be no discomfort or significant risks from blood sampling. As a result of this monitoring of the dialysis dose, it is likely that patients randomized to the conventional therapy arm will receive a higher delivered dose of therapy than would be provided to patients not being treated on the study protocol.

The study hypothesis is that patients treated in the intensive therapy arm will have decreased mortality, and may therefore have direct benefit from participation in the study. It will be possible, however, that there will be no benefit or even increased mortality associated with the experimental study arm. For this reason, we cannot state that any direct benefit will accrue to patients based on participation in this study.

XIV. Quality Assurance Procedures

A. Data Quality Control

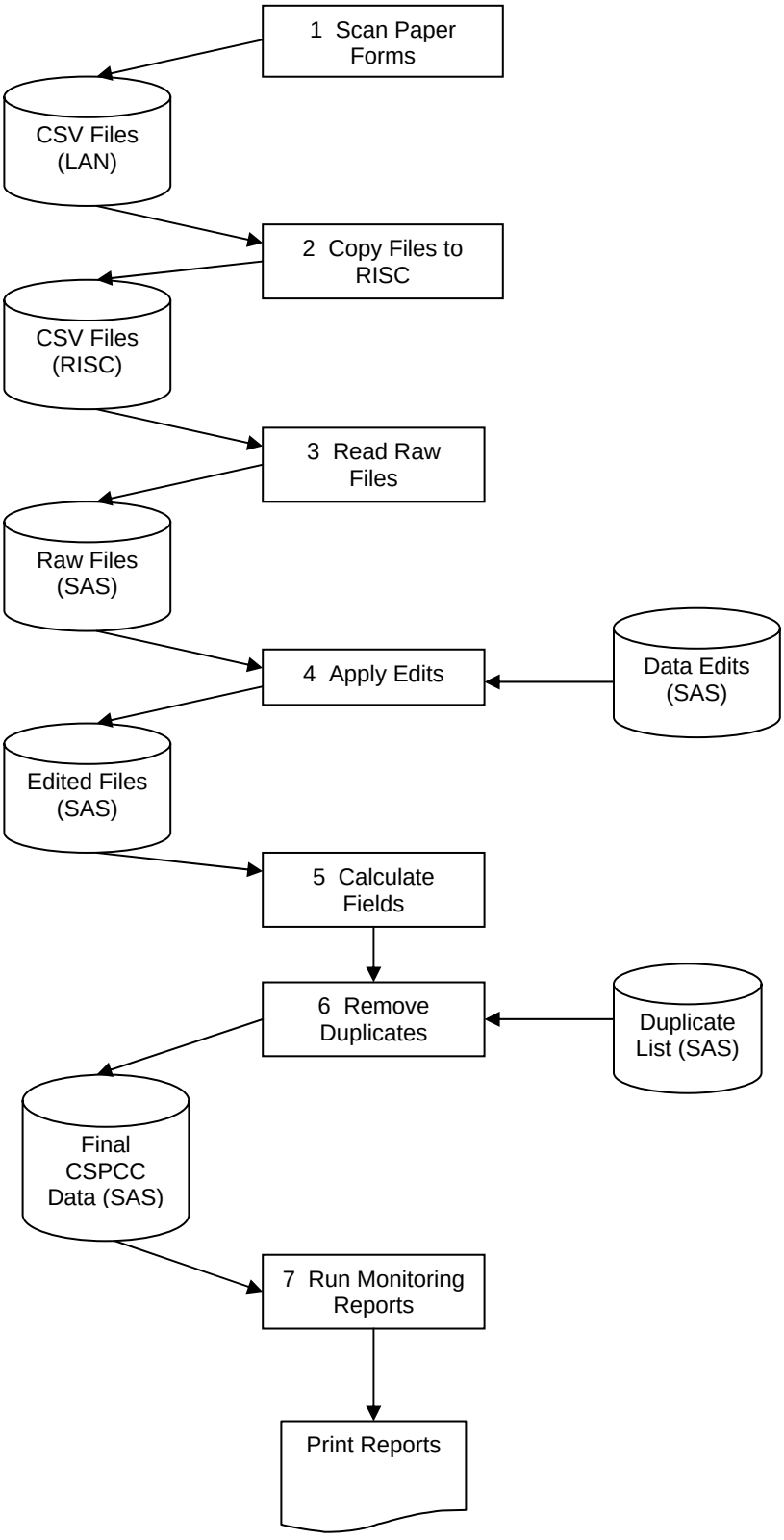
After the study is approved, the Case Report Forms (CRFs) will be field-tested. Data forms will be readable by a scanner. Printed scanner-readable forms will be sent to the sites for data collection. Alternatively, computer-based versions of the data forms in PDF format may be completed on a personal computer at the study site. If a form is completed on a personal computer, two copies of it must be printed – one for the patient file at the site and one to be sent to the West Haven Coordinating Center.

The study personnel at each participating medical center will complete and assemble the CRFs, send the originals to the West Haven Coordinating Center and file a copy of the forms at the participating investigator's office. If the site completes computer-based versions of the forms, printed copies will be sent to CSPCC and printed copies will be filed in patient study folders at the site. The participating investigator has the overall responsibility for the integrity of the data from the site.

A research assistant at the Coordinating Center will review the forms for consistency and completeness in conjunction with the Study Chairman's Office. Problems discovered will be resolved by telephone calls to the site coordinators. The completed forms will then be scanned and entered into a data file. The West Haven CSPCC Standard Data Processing System is illustrated in Figure 3.

Data files on the in-house standard computer containing the accumulated patient information will be updated at regular intervals. Tested and validated computer programs will check newly entered forms for missing or out-of-range values. Computer-generated notices will be mailed to the participating investigators requesting completion, correction, or verification of

Figure 3.


1 Scan Paper Forms
CSV Files (LAN)
2 Copy Files to RISC
CSV Files (RISC)
3 Read Raw Files
Raw Files (SAS)
4 Apply Edits
Data Edits (SAS)
Edited Files (SAS)
5 Calculate Fields
6 Remove Duplicates
Duplicate List (SAS)
Final CSPCC Data (SAS)
7 Run Monitoring Reports
Print Reports

specific data items. A computer-generated edit message indicating the questionable (e.g., out-of-range or missing values) data will be used to monitor coding errors and to edit the data on the main computer file when the requested information is returned. A computerized record of the types of errors will be kept in order to ensure a high level of data integrity.

At periodic intervals, a cumulative record of errors and data quality progress reports will be sent to investigators and the Study Chairman. Data edits and removal of duplicate records will be applied to the data files on a regular basis, and cleaned (final) files through the time of the most recent running of data edits will be created. These final files will be used to run monitoring reports on a regular basis.

The progress of data collection will be monitored with computerized data form inventory programs that will produce a profile of all forms expected and received for each study patient. Missing-forms reports will be generated and sent to the sites periodically. To assist sites in the 60-day patient follow-up, the Coordinating Center will provide a computer generated reminder to the site 2 weeks prior to the 60-day post randomization date for every subject enrolled at the site.

B. Quality Control of the Process

After the study is approved, the principal proponent and the West Haven Coordinating Center will prepare an Operations Manual that will be provided to the investigators as a guide to the operation and management of the study as well as a technical reference manual. A training session will be held at the study kick-off meeting for all study personnel in order to: (1) assure uniformity in patient management and data collection procedures, and (2) train the personnel in study procedures and criteria.

Study procedures will be reinforced by the use of regular conference calls, particularly in the first few months of the study and by the periodic distribution of a study newsletter. All study personnel will attend group meetings during the enrollment period when study procedures again will be discussed in detail. The Study Chairman's Office will be available to clarify study procedures by telephone, fax and e-mail.

If the Executive Committee (see Section XVIII) determines that a procedure must be changed, the participating sites will be informed by conference call and/or newsletter and an updated section of the Operations Manual pertinent to the changed procedure will be provided to all sites.

The trial will be conducted in compliance with Good Clinical Practices (see Section XV).

XV. Good Clinical Practices

This trial will be conducted in compliance with the Good Clinical Practice (GCP) procedures. Study site personnel will receive GCP training at the study organizational meeting. Monitoring of sites participating in the trial will be executed according to Cooperative Studies Program Guidelines. A GCP Reviewer from the Site Monitoring and Review Team (SMART) will visit all study centers at least once during the course of the study. The purpose of these visits is to encourage and assess compliance with Good Clinical Practice requirements. These GCP requirements will be set out and described in detail in the operations manual, and will include a description of: investigator study files, Institutional Review Board (IRB) – investigator interactions, the informed consent procedure to be followed in this study, inspections of investigator sites, and the archiving of study records.

SMART reviewers will examine patient study files, including source documents, in both the clinic files and the patients' hospital medical records and will also review regulatory/essential documents such as correspondence with the IRB and the Sponsor (CSP). Areas of particular concern will be patient informed consent issues, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, patient records, and investigator supervision and involvement in the trial. Reports will be prepared following the SMART visit to a site and will be forwarded to the investigator, the Study Chairman, and the CSPCC director.

A. Good Clinical Practices and Human Subjects Protection Training

All site personnel involved with the conduct of this study will be certified in Good Clinical Practices (GCP) and Human Subjects Protection training. GCP training will be conducted at the organizational (kick-off) meeting and subsequent annual meetings. Human Subjects Protection training certification will be obtained by completing approved training, such

as the online computer based training offered by the NIH Office of Human Subjects Research (http://ohsr.od.nih.gov). Site personnel who already have certification in Human Subjects Protection from an appropriate outside source may use this certification. Written verification of GCP and Human Subjects Protection training of site personnel will be submitted to the West Haven CSPCC prior to the start of patient enrollment at each site. Any site personnel who are hired after the organizational meeting will have three months to complete certification. Re-certification of GCP and Human Subjects Protection training is required every three years.

B. Patient Informed Consent

Protection of the rights and welfare of patients is a primary concern of the VA Cooperative Studies Program (Section XIII). Informed consent will be documented in this trial by the use of a consent form prepared by each investigator and approved by the investigator's IRB. The prototype consent form provided in the protocol may be adapted to meet local needs (Appendix A and Form 2, Appendix I). This form has been reviewed by the central HRC at the CSPCC and contains the basic required elements of informed consent. The consent form, as revised and approved by the local IRB, must be sent to the CSPCC before the trial may begin.

C. Inspections of Investigator Sites

Routine site visits by clinical trials monitors are not planned for this trial. Each site, however, may expect to be visited at least once during the trial by a GCP reviewer from the SMART team in Albuquerque. The investigator will be contacted prior to the visit to arrange a mutually agreeable time for the visit. The reviewer will be at the site for approximately two days to review study records and discuss the conduct of the trial. Following the site visit, a summary of findings and observations will be sent to the investigator. The CSPCC HRC will conduct annual human rights site visits at selected sites during the course of the study.

D. Data Security

All patient data will be stored in locked files. Computers with research subject data will be password protected to ensure confidentiality of patient records.

E. Archiving Study Records

At the close of the trial, investigators will be instructed about record retention. No records shall be destroyed without CSP authorization. The current CSP policy is that participating medical centers can, after consultation with the CSPCC, discard study files five years after the study is completed. In some cases, it may be necessary to retain study files longer, depending on local policy. The participating site will be encouraged to contact the CSPCC if record storage becomes a problem at the site. The CSPCC will authorize records disposal or discuss alternative storage location.

XVI. Biostatistical Considerations

A. Study Design

The study is a multi-center, prospective, randomized, parallel group trial comparing 60-day all-cause mortality in patients with acute renal failure (ARF) who are treated using a conventional strategy for the management of renal replacement therapy to those who are managed using a strategy of intensive renal support. Patients will be screened to determine if they are eligible for entry into the study. Eligible patients who consent to participate will be randomized into either the conventional therapy arm or the intensive therapy arm. The randomization will be stratified by site and within sites by cardiovascular SOFA score (0 – 2 and 3 - 4) and urine volume (oliguric versus non-oliguric renal failure) using an adaptive randomization procedure (98). Patients will be enrolled over a three-year period and the maximum length of follow-up is 60-days.

B. Study Objectives and Outcome Measures

Primary Objective: The primary objective is to determine if a strategy of early initiation and intensive dosing of renal support decreases 60-day all cause mortality in critically ill patients with acute renal failure as compared to conventional management of renal replacement therapy.

The primary outcome measure is 60-day all cause mortality.

Secondary Objectives: The secondary objectives are to compare the effect of a strategy of intensive renal support to standard management of renal replacement therapy on:

1. All cause hospital mortality by day-60,
2. One-year all cause mortality, and
3. Recovery of renal function by day-28.

Tertiary Objectives: The tertiary objectives are to compare the two treatment groups with respect to:

1. The duration of renal support,
2. ICU length-of-stay,
3. Hospital length of stay,
4. Discharge to "home" off of dialysis by day-60, and
5. Non-renal organ failures as classified by the SOFA Organ Failure Score.

The Health Economics Objectives are to compare the intensive treatment group to the standard treatment group with respect to:

1. Global cost of care,
2. Renal replacement therapy-specific cost of care, and
3. Patient utility.

The Health Economics objectives will be measured and analyzed as described the Health Economics Component section of the protocol (Section XXII).

C. Expected Treatment Effect

From the literature, the event rate for all-cause mortality in patients with acute renal failure varies between 39% (81) and 79% (11) (Table 3). A weighted-summary of these studies provides an estimated mortality rate in acute renal failure of 48% (N=3,827). When patients identified as not being critically ill and patients in the daily hemodialysis and high-dose CVVH arms of the intervention studies of Schiffl et al. (47) and Ronco et al. (48) are excluded from the

Table 3: Reported Mortality in Studies of Patients with ARF

Study	N	Mortality
Liano, 1996 (3)	All Patients	
	748	45%
	Patients with ATN	
	337	60%
Liano, 1998 (1)	ICU Patients	
	192	79%
	Non-ICU Patients	
	186	37%
Chertow (9)	132	70%
Paganini (10)	844	66%
Schiffl (48)	Alternate day HD	
	80	46%
	Daily HD	
	80	28%
Ronco (50)	Low-dose CVVH	
	146	59%
	High-dose CVVH	
	279	42%
Mehta (58)	166	57%
Van Bommel (74)	104	51%
Fiaccadori (78)	425	39%
De Mendonca (81)	348	43%
Johnson (96)	97	62%

meta-analysis, the mortality rate is 57% (N=2534). Since this latter group is representative of the proposed conventional management arm, we hypothesize that the 60-day mortality rate in this study for subjects treated using a strategy of conventional management of renal replacement therapy will be 55%. Our primary hypothesis is that a strategy of intensive renal support will reduce this rate by 10%, to 45%.

D. Sample Size and Power

The sample size for the primary outcome of the study has been calculated using the method described in Fleiss (108) for comparing two proportions. The sample size and power considerations are based on the proportion dead at 60 days using the binomial distribution. The following assumptions are used in the determination of sample size and power for the study:

1. The mortality rate using a conventional strategy for the management of renal support in critically ill patients with acute renal failure is estimated to be 55%.

2. The strategy of intensive renal support will provide a 10% absolute reduction in mortality rate relative to the conventional treatment strategy.

3. A two-sided significance level of 0.05.

4. A drop-out rate of 10%.

Table 4. Sample Size Estimation Table

60 -Day All Cause Mortality		Power		
Conventional Renal Replacement Therapy (Control Arm)	Intensive Renal Support (Experimental Arm)	0.80	0.85	0.90
65%	60% 55% 50%	1634 418 189	1869 478 216	2188 559 252
60%	55% 50% 45%	1704 431 192	1949 492 220	2281 577 257
55%	50% 45% 40%	1739 436 192	1989 498 220	2328 582 257
50%	45% 40% 35%	1739 431 189	1989 492 216	2328 577 252
45%	40% 35% 30%	1704 418 181	1949 478 207	2281 559 241
40%	35% 30% 25%	1635 396 169	1869 453 194	2188 530 226

Table 5. Power Sensitivity Analysis Using Sample Size of 582 per Treatment Group With 10% Drop-Out, and α=0.05

60-Day All Cause Mortality		Power
Conventional Renal Replacement Therapy (Control Arm)	Intensive Renal Support (Experimental Arm)	
65%	60%	39%
	59%	52%
	58%	64%
	57%	**76%**
	56%	85%
	55%	91%
60%	55%	37%
	54%	50%
	53%	63%
	52%	**74%**
	51%	84%
	50%	90%
55%	50%	37%
	49%	49%
	48%	62%
	47%	**74%**
	46%	83%
	45%	90%
50%	45%	37%
	44%	49%
	43%	62%
	42%	**74%**
	41%	83%
	40%	90%
45%	40%	37%
	39%	50%
	38%	63%
	37%	**75%**
	36%	84%
	35%	91%
40%	35%	39%
	34%	52%
	33%	65%
	32%	**77%**
	31%	86%
	30%	92%

Based on these assumptions, the primary analysis of mortality requires at least 582 patients in each treatment arm to achieve 90% power (see Table 4).

A power sensitivity analysis based on a sample size of 582 patients per group with 10 percent lost to follow-up rate and α=0.05 using two-sided tests is shown in Table 5. If the 60-day all cause mortality rate in the conventional management strategy group is in the range of 40% to 65% and the absolute decrease in the mortality rate in the intensive management strategy group is 8% rather than 10%, the study will still have 74% or greater power to detect this difference with our proposed sample size of 582 per group.

E. Power for Secondary Endpoints

1. One-year all cause mortality – Power estimates are calculated based on the same assumptions as were made for the primary endpoint. Based on these assumptions the study has more than 90% power at the two-sided α=0.05 level to detect a 10% reduction in one-year all cause mortality with the intensive treatment strategy as compared to conventional treatment.

2. All cause hospital mortality – Assuming the same hypothesis as for the primary endpoint, the target sample size will provide at least 90% power at the two-sided α=0.05 level to detect a 10% reduction in hospital mortality with the intensive treatment strategy as compared to conventional treatment.

3. Recovery of renal function – Previous studies have not shown a significant difference in recovery of renal function among surviving ARF subjects comparing different doses or modalities of renal replacement therapy. Mehta et al. observed complete recovery of renal function in 70.7% and partial recovery in an additional 18.8% of

surviving patients (58). Similarly, Ronco et al. observed 90% to 95% recovery of renal function in surviving patients treated with low or high dose CVVH (50). Nineteen to twenty percent of patients who ultimately died, recovered renal function prior to death (50). In this trial we will examine the recovery of renal function by treatment arm but do not expect to see any significant differences in recovery of renal function in patients who survive. We anticipate that 70% of surviving patients in each arm will have complete recovery of renal function (defined as a serum creatinine that is no more than 0.5 mg/dL greater than baseline) and that an additional 20% of surviving patients will have partial recovery of renal function (defined as a serum creatinine > 0.5 mg/dL greater than baseline but not dialysis-dependent).

F. Duration of Study/Feasibility/Number of Participating Sites

It is anticipated that 24 VA sites and 7 to 8 NIH funded sites will be needed to participate in the study in order to accrue 1164 patients in 3 years. The average participating VA center admits 20 to 40 patients per year to the ICU with ARF (see Appendices A and G). We estimate that about 40% will not meet the study eligibility criteria and that about 40% of the remainder will refuse. This results in approximately 8 to 10 patients enrolled per year from each VA site, for a total of approximately 582 subjects enrolled from 24 VA centers in 3 years. NIH funded sites would also need to enroll 582 subjects in the 3 year enrollment period. If each NIH site can enroll 3 times as many subjects per year (25-30) as each VA site, or 75 to 90 subjects in 3 years, a total of 7 to 8 non-VA sites will be needed to enroll 582 patients. All patients will be followed for a maximum of 60 days.

G. Statistical Analysis

1. Interim Monitoring and Analysis

Interim monitoring will focus on efficacy, safety and feasibility of the study.

a. Interim Analysis for Potential Early Study Termination for the Primary Endpoint

Two interim looks at the primary endpoint, incidence of death within 60 days of randomization, will be proposed to the DSMB for making the decision about whether or not to continue the trial based on the results of the interim analyses of the primary endpoint. It is proposed that the first interim analysis will be done when at least 600 subjects have been enrolled and followed for more than 60 days and the second interim analysis will be done when at least 900 subjects have been enrolled and followed for more than 60 days. For both interim analyses, it is proposed that a very wide boundary such as that proposed by Haybittle and Peto (109) be used. It is suggested that the significance level for the interim analyses be 0.001 and the two-sided significance level for the final analysis be 0.05. The inflation of the overall type I error will be negligible.

At the first interim analysis, there will be approximately 81% power to detect a 17% absolute reduction in mortality rate relative to the conventional treatment strategy (assuming the mortality rate for conventional treatment strategy is 55%). At the second interim analysis, there will be approximately 82% power to detect a 14% absolute reduction in mortality rate relative to the conventional treatment strategy.

b. Safety Monitoring

Trial safety will be monitored by CSPCC and reported to the DSMB after enrollment and 60-day follow-up of each 200 patient block (i.e., after 200, 400, 600, 800 and 1000 patients), or

every 6 months, whichever comes first. The distribution of complications of dialysis catheter insertion, including vascular injury requiring surgical intervention, pneumothorax requiring chest-tube, protracted bleeding, stroke, and death, will be summarized by treatment and site. Complications associated with dialysis treatment, including anaphylactic reaction to dialyzer ("first-use" reaction), hypotension requiring discontinuation of therapy, air embolism, bleeding (e.g., due to system disconnection or dialyzer rupture), new onset of serious arrhythmia requiring discontinuation of therapy (e.g., rapid supraventricular tachycardia with hypotension, ventricular tachycardia), iatrogenic fluid and/or electrolyte disturbance, and seizures also will be summarized by treatment and site.

A Chi-square test or Fisher's Exact test, as appropriate, will be run on each of the safety outcomes by comparing the intensive treatment vs. conventional treatment. The 95% confidence intervals of the treatment difference will also be provided for DSMB review. In the event that severe adverse reactions or increased mortality are noted to be excessive in the intensive renal support arm relative to the conventional strategy arm, the DSMB may consider stopping the trial. At two planned interim analyses, if a higher mortality is observed in the intensive treatment group compared to the conventional treatment group and reaches statistical significance at the two-sided 0.01 level, then the DSMB may recommend stopping the study.

It is our intention to set up an asymmetric upper and lower monitoring boundary. For the purpose of overall trial safety, we want to notify the DSMB if we observe the intensive treatment having higher mortality than the conventional treatment at the two-sided 0.01 level, although we are using a 0.001 level for efficacy in favor of intensive treatment.

c. Administrative Data Monitoring

The administrative monitoring will focus on patient intake (overall and within medical center), adequacy of randomization, adherence to protocol and operational aspects of the study. The number of patients screened (overall and by site) will be tabulated. The combined, as well as site-specific, proportion of enrolled/eligible patients will also be examined, along with the balance of important baseline variables between treatment groups (see below). Strict adherence to the protocol will be expected of every participating center. Adherence will be monitored by CSPCC and reported to the DSMB. The parameters used to monitor adherence will include patient intake, timely submission of data, completeness of follow-up and errors in randomization.

d. Feasibility Monitoring

At the time of the two interim analyses, a feasibility analysis will be performed to assess the likelihood of eventual success based on the observed data. The conditional power (116) to fulfill the study will be provided to the DSMB as either an exact value of power or through a Yes/No question. If the conditional power is too low, such as less than 50%, then the DSMB may recommend stopping the study.

2. Final Analysis

a. Baseline Comparability

In order to assess the adequacy of randomization, the distribution of baseline characteristics will be compared between the two treatment groups. These include: age, gender, ethnicity, baseline serum creatinine, ARF etiology, duration of ARF prior to randomization, medical history, oliguric status, chronic morbidity (Charlson Index), and acuity of illness (APACHE II score, SOFA score, Cleveland Clinic Foundation ARF score, and SIRS criteria).

The distribution of baseline patient characteristics between the randomization groups will be evaluated using descriptive statistics (means, medians, quartiles, percents, etc.) and graphical methods. *A priori* baseline variables which will be used for covariate adjustment include gender, age at randomization, primary diagnosis (medical or surgical), Charlson score, etiology of acute renal failure (ischemic, nephrotoxic, multifactorial, sepsis), severity of acute renal failure (oliguric, non-oliguric), acuity scores (SOFA score, SOFA organ system sub-scores, and Cleveland Clinic Foundation ARF score), mechanical ventilation, and sepsis.

b. Analysis of Primary Outcome Measure

The analysis of the primary endpoint, 60-day mortality, will be done according to the intent-to-treat principle, that is, according to the original treatment assignment, regardless of adherence. The primary outcome is the comparison of 60-day mortality between the intensive treatment strategy arm and the conventional treatment strategy arm. A p-value of 0.05 (two-sided) will be used as the level of significance for the primary outcome.

The generalized linear model developed by Wolfinger and O'Connell (110) will be used for the analysis since it is appropriate for a binary endpoint and mixed effects. Based on the study design, treatment, cardiovascular SOFA score and oliguria will be considered as fixed effects and study site will be considered as a random effect because of the large number of sites. Two analyses will be done:

1. Treatment adjusted for the study design (random site + fixed effects)

2. Treatment adjusted for study design and for the set of prespecified baseline covariates to examine their influence on the treatment comparison.

Treatment by covariate interactions will be examined in exploratory analyses from among the baseline covariates. These baseline covariates are gender, age at randomization, primary diagnosis (medical or surgical), Charlson score, etiology of acute renal failure (ischemic, nephrotoxic, multifactorial, sepsis), severity of acute renal failure (oliguric, non-oliguric), acuity scores (SOFA score, SOFA organ system sub-scores, and Cleveland Clinic Foundation ARF score), mechanical ventilation, and sepsis.

Sub-Group Analysis: Analysis of the primary endpoint will also be performed within the following, prospectively identified subgroups: oliguric/non-oliguric status, presence or absence of sepsis at randomization, cardiovascular SOFA score 0-2/3-4, and gender.

c. Analysis of Secondary Outcomes

A p-value of 0.05 (two-sided) will be used as the level of significance for all secondary outcomes.

All-cause hospital mortality by day 60: The same method of analysis as for primary outcome will be used for this secondary outcome.

1-year all-cause mortality: Kaplan-Meier survival curves, adjusted for censoring due to lost to follow-up, will be used to present treatment effects for 1-year all-cause mortality. Treatment group comparisons will be based on the log-rank test (111). The Cox proportional hazards model (111) will also be used to test the effect of treatment adjusted for the study design and for the prespecified set of covariates. Test of the proportional hazard assumption, including log (log) plots with visual examination, will be done to assure the validity of this analysis, and if the assumption is not valid, appropriate adjustments will be made, such as adding time by

covariate interaction terms or use of stratification. We will conduct a similar analysis for 60-day all-cause mortality.

Recovery of renal function by 28 days: This outcome is a three level discrete ordinal measurement – none, partial recovery (defined as a serum creatinine > 0.5 mg/dL greater than baseline but not dialysis-dependent) and complete recovery (defined as a serum creatinine no more than > 0.5 mg/dL greater than baseline). The generalized linear model with a cumulative logit link function (112) will be used to investigate the effect of treatment on recovery of renal function if the proportional odds assumption holds. Otherwise, a weighted-least-squares analysis developed by Koch (113, 114) will be used to assess the mean score of recovery of renal function for each treatment arm. As for the primary outcome, treatment comparisons will be adjusted for both the study design and the prespecified set of baseline covariates.

d. Analysis of Tertiary Objectives

A p-value of 0.05 (two-sided) will be used as the level of significance for all tertiary outcomes.

Duration of renal support: This outcome will be analyzed as both a continuous measurement, using the linear model (110), and as time to discontinuation of renal support using survival methods. Since some of the censoring, such as death, may be informative, we will conduct the analyses both with and without adjusting for the possibility of informative censoring. First, the analysis will be done on the actual duration of renal support, regardless of whether the censoring is informative or not. Then, we will assign 28 days as the duration of renal support for patients who died within 28 days (115) and analyze the data adjusted for the informative censoring as a sensitivity analysis.

Duration of hospitalization and length of ICU stay: The same analysis method as for duration of renal support, including the use of informative censoring, will be used to analyze these two secondary outcomes.

Discharge to "home" off of dialysis by day-60: The same method of analysis as for the primary outcome will be used for this tertiary outcome.

SOFA Organ Failure Score: Five individual SOFA organ scores will be collected on days 1 through 14, day 21 and day 28. They are respiratory, coagulation, liver, cardiovascular and central nervous SOFA scores. The scores will range from 0 to 4, for the individual organ SOFA scores, and to 20, for the total SOFA score (sum of the five individual SOFA scores except renal SOFA score). Organ failure will be defined as an individual SOFA organ failure score ≥ 2. Since some of the censoring, such as death, may be informative, we will evaluate all of the SOFA score related outcomes both with and without adjusting for the possibility of informative censoring. There are many ways to impute informative censoring data, e.g. fill in all non-observed SOFA scores after the patient dies with the highest possible value or fill them in with the last observed value before the patient died. Exploratory and sensitivity analyses using different imputation methods will be conducted to determine their impact on the treatment comparisons.

a. Overall non-renal SOFA score: The overall non-renal SOFA score is defined as the sum of the respiratory, coagulation, liver, cardiovascular and central nervous system organ SOFA scores and ranges between zero and twenty. Depending on the actual distribution of the outcome, we will use either a linear mixed model or a generalized linear mixed model to assess the treatment effect on the overall non-renal SOFA score, the time effect and the

treatment-by-time effect. The maximum non-renal SOFA score, defined as the highest daily score attained on days 1 through 14, day 21 or day 28 for each individual patient, will also be analyzed by treatment. The data will be analyzed with adjustment for the study design and for the prespecified set of baseline covariates, both with and without adjustment for deaths (i.e., potential informative censoring) as described above.

b. Individual non-renal organ SOFA scores and organ failures: For each individual non-renal SOFA score, we will use the same analytical strategy as for the overall SOFA score. In addition, individual organ failure will be defined as an individual SOFA organ failure score ≥ 2. For this binary outcome, the same method will be applied as used to analyze the primary outcome to assess the treatment effect, time effect and treatment-by-time effect with and without adjustment for deaths.

c. Number of non-renal organ failures: Using the definition of organ failure as an individual SOFA organ failure score ≥ 2, the number of organ failures will be calculated for each patient on days 1 through 14, day 21 and day 28. The range of possible number of non-renal organ failures on each day will be 0–5. For this six level discrete ordinal measurement we will assess treatment effect, time effect and treatment-by-time effect with the same strategy and methodology as used to analyze the overall non-renal SOFA score. In addition, the maximal number of organ failures, defined as the maximal number of organ failures on days 1 through 14, day 21 and day 28, will be

analyzed by treatment using the same strategy and methodology as described above.

The therapy specific cost of care, global cost of care, and patient utility analyses are described in the Health Economics Component of the protocol (Section XXII).

XVII. Potential Pitfalls of Proposed Study Design and Alternative Study Designs

A. Potential Pitfalls of the Proposed Study Design

1. Secular Trends in Management of Renal Support in ARF

The proposed study design compares two strategies for the management of renal replacement therapy in acute renal failure, a conventional management arm, designed to approximate the current approach to management of patients with acute renal failure, and an intensive therapy arm, which increases the intensity of renal support by increasing the frequency of intermittent hemodialysis in hemodynamically stable patients and increasing the clearance per unit time by increasing effluent flow rate in hemodynamically unstable patients treated with continuous renal replacement therapy. The use of these strategies to intensify the treatment of acute renal failure is supported by the recent studies by Schiffl et al. (48) and Ronco et al. (50), although, as discussed previously, these studies have significant limitations. We recognize however, that as a result of these preliminary studies, there may be a change in practice patterns that alters the definition of "conventional" therapy in the community at large.

2. Assessment of Dose of Intermittent Hemodialysis

In this protocol, we propose to assess the delivered dose of hemodialysis based on a single-pool, variable-volume model of urea kinetics, calculating Kt/V using the second-generation natural logarithmic equation developed by Daugirdas (97). We recognize that there are many theoretical problems with this approach. Formal urea kinetic modeling is predicated upon a number of steady-state assumptions that are violated in critically ill patients with acute renal failure, including non-steady-state urea generation rate (G) and treatment-to-treatment variability in the post-dialysis volume of distribution of urea (V). In addition, alterations in regional blood flow may accentuate the compartmentalization of urea distribution, undermining

the validity of a single-pool model. Although the formula that we propose to use for calculation of Kt/V has been validated in the ESRD population, it has not been validated in acute renal failure.

We have chosen to use this technique for assessing the delivered "dose" of dialysis despite these multiple technical shortcomings for a variety of reasons. Our goal is not to provide a rigorous urea kinetic description of the dialysis treatments. Rather, the goal of this measurement is to provide a simple assessment of dialysis "dose" to provide assurance that patients are not being inadequately treated. Such assessments are not part of the routine care of patients receiving renal replacement therapy for ARF and the inclusion of this monitoring in the trial will likely result in patients in the conventional therapy arm actually receiving more intensive therapy than if they did not participate in the study.

Alternative techniques for this assessment that were considered included measurement of urea reduction ratios, formal single-pool urea kinetic modeling and calculation of equilibrated Kt/V, to correct for multi-compartment kinetics. The urea reduction ratio would have provided the advantage of simplicity, however it would have been an even less robust index of dialysis delivery since it does not take into account the effect of volume removal during dialysis. Formal single-pool urea kinetic modeling, on the other hand, would have introduced substantial technical complexity, including assessment of residual renal function and urea generation for each modeled treatment. Adjustment for multi-compartment kinetics would provide an even more rigorous description of urea kinetics, but at the expense of even greater complexity – including measurement of delayed post-dialysis BUN, to correct for the immediate post-dialysis disequilibrium between compartments. While these techniques provide greater "rigor" in the

characterization of the dose of dialysis based on small solute kinetics, they are not validated in the critically ill patient with acute renal failure.

An additional strategy that was considered for monitoring the delivered dialysis dose was the use of on-line ionic dialysance. While this technique permits real-time assessment of dialysis dose, it is neither readily available nor validated in this population.

3. Difficulty in Delivering the Targeted Dose of Hemodialysis

We anticipate that the targeted dose of therapy will not be achieved in all dialysis treatments. The catheters used for intermittent hemodialysis may not provide the desired blood flow for all treatments. We will monitor for this by measuring the volume of blood processed (liters processed), for each treatment. This index integrates duration of therapy with blood flow rate. Comparison between the prescribed and delivered liters processed will provide an index of catheter malfunction. Operationally, when significant catheter malfunction is observed, the treatment should be interrupted and the catheter replaced.

Catheter recirculation will also impair the ability to deliver the targeted dose of therapy. Catheter recirculation occurs when blood returning from the extracorporeal circuit through the "venous" limb of the catheter re-enters extracorporeal circuit through the "arterial" limb of the catheter without passage through the circulation. Recirculation is usually less than 5%, but may increase to greater than 50% of total extracorporeal blood flow as the result of catheter malposition, impaired blood flow, and clot or fibrin sheath formation around the catheter. Increased recirculation decreases the efficiency of treatment. Recirculation will be suspected based on changes in extracorporeal circuit pressure profiles and/or unexplained decreases in the delivered dose of therapy.

The large volume of distribution of urea (V) that may be seen in obese patients and in patients with marked volume overload may also contribute to difficulty in achieving the target delivered dose of therapy in patients on hemodialysis. Since Kt/V is inversely proportional to V, increases in V decrease Kt/V. To compensate, patients with large values of V may require prolonged dialysis treatments (potentially in excess of 5 hours) using dialyzers with high urea clearance.

In patients treated with CVVHDF, the major barrier to the delivered dose of therapy will be time off of treatment due to clotting of the extracorporeal circuit or the need to interrupt therapy for diagnostic tests (e.g., radiologic procedures) or surgical interventions. While interruptions to therapy will be discouraged, they will occur. Overall compliance with the treatment prescription will be monitored by measurement of the daily effluent volume.

4. Non-Comparability of "Dose" Between Continuous and Intermittent Therapy

The selection of the doses of therapy for intermittent hemodialysis and continuous therapy within each treatment arm are not equivalent. The treatment regimens selected for the conventional therapy arm, however, were selected because they represent the current approach of dosing these two modalities of renal support in the community. We acknowledge, however, that based on urea kinetics, the doses of continuous renal replacement therapy in each arm will provide a higher "dose" of therapy than the corresponding dose of intermittent hemodialysis. If we assume 85% equilibration between blood and effluent in CVVHDF, and a volume of distribution of urea of 55% of body weight, a dose of 20 mL/kg/hr will provide a Kt/V of approximately 0.85 per day or 6.0 per week, as compared to 3.6 per week for the conventional dose of intermittent hemodialysis. Similarly, CVVHDF at a dose of 35 mL/kg/hr will provide a

Kt/V of 1.5 per day or greater than 10 per week, as compared to 7.2 per week for the intensive dose of hemodialysis.

Despite this increased dose of therapy, continuous renal replacement therapy has not been associated with improved survival as compared to intermittent therapy. In the randomized, controlled comparison of intermittent hemodialysis and continuous renal replacement therapy published by Mehta, et al. (58), there was no significant difference in mortality at doses similar to those proposed for the conventional therapy arm of this study.

5. Sample-Size Calculation

The key assumptions underlying the sample-size calculation are that the predicted 60-day all-cause mortality in the conventional therapy arm will be approximately 55 percent and the use of intensive renal support strategy will result in an absolute mortality reduction of 10 percent. While both of these assumptions are well supported by published studies (*vide supra*), deviations from the predicted mortality and effect-size will impact the power of the study.

The PICARD Study is a prospective, multi-center, observational study of acute renal failure. Preliminary data from the PICARD Study demonstrated a 42.3 percent ICU mortality rate in ARF patients in whom informed consent was obtained and who ultimately required renal replacement therapy (117). Several factors contributing to this unexpectedly low mortality rate are germane to the present study. The most important of these was the inability to obtain informed consent prior to patient death in patients with early mortality (118). Of patients who were eligible for study enrollment in whom informed consent was not obtained, 22 percent died prior to obtaining surrogate consent. We anticipate that the informed consent process for the present study may also operationally exclude patients with early mortality, and may result in a lower than predicted mortality in the conventional therapy group.

The impact of a reduction in baseline mortality on study power was evaluated by sensitivity analysis (Table 5), as discussed previously. If the mortality in the conventional therapy arm is as low as 40 percent, the projected sample size will provide a power of 0.92 to detect an absolute decrement in mortality of 10 percent. We recognize however, that this implies an increase in the relative effect-size from 18 percent to 25 percent. Using a constant effect size of 20 percent, our sample size of 582 patients per group will provide a power of 0.95 if the control group mortality is 55 percent, and a power of 0.77 if the control group mortality is 40 percent.

Our assumption of effect-size is conservative as compared to the two previously published studies comparing dosing of renal support in acute renal failure. In the study by Schiffl et al. comparing daily to alternate-day hemodialysis (48), the absolute reduction in mortality was 18 percent (relative reduction 39%). Similarly, in the study by Ronco et al. comparing three doses of CVVH (50), the absolute reduction in mortality was 16 percent, with a relative reduction in mortality of 27 percent. We therefore believe that even if the mortality in the conventional therapy arm (control group) is lower than predicted, that the study is adequately powered to detect a mortality change substantially smaller than observed in these prior studies.

6. Patient Recruitment

The feasibility of patient recruitment must be a major concern in a study of this complexity. In the PICARD Study, an observational study of ARF, only 54 percent of eligible patients were ultimately enrolled in the trial (118). Barriers to patient enrollment included death prior to the patient or surrogate providing informed consent (22%) and lack of available surrogate to provide consent in patients who were unable to consent (13%). Refusal to

participate in the study accounted for only 20 percent of non-enrolled patients (9.2 % of all patients). In 23 percent of potential subjects, the reason for non-enrollment was not known.

Since this is an interventional, rather than an observational trial, we assume that the rate of enrollment will be lower than observed in the PICARD Trial, with a higher rate of refusal of consent. Assuming that the rate of refusal to consent is 2-3 times that encountered in the PICARD trial (20 to 30 % of all patients), we anticipate an enrollment rate of 30% to 40% of eligible patients. For this reason, site selection has been driven by documentation of sufficient numbers of patients meeting the inclusion/exclusion criteria (Appendix G). Given the relatively low volume of ARF in the VA populations, we consider the inclusion of high-volume non-VA sites to be critical to the successful execution of this study.

7. Co-Intervention Bias

Since this study is non-blinded, there is the potential that the management of aspects of care other than renal replacement therapy will differ between the two groups. If systematic differences in the management of these "co-interventions" occur, this may introduce bias and either diminish or accentuate the differences between the two groups. This problem is inherent in any unblinded study and is of particular concern in patients with complex co-morbidities in which it is not possible to protocolize all aspects of patient management. Prior studies in the critically ill population, such as the ARDS Net trial (90) have demonstrated that it is possible to perform unblinded studies without undue confounding from co-intervention bias.

Several strategies will be employed to minimize the effect of co-intervention bias. Management of aspects of care that are thought to have a specific impact on outcomes in acute renal failure (e.g., nutrition) have been specified. Management of other aspects of care for which there is consensus regarding optimal management of critically ill patients (e.g., ventilator

management in ALI/ARDS, diagnosis and management of ventilator-associated pneumonia) will be provided in accordance with these standards of care.

Consensus on the management of many other aspects of critically ill patients (e.g., use of pulmonary artery catheters, selection of pressors) does not exist. The management of these aspects of care (e.g., hemodynamic monitoring, selection of vasopressor agents) has not been specified. Variation in management of these parameters, will occur between centers, and should be adjusted for by stratification by site. In addition, these aspects of care will be monitored during the trial to assure that significant differences are not present between groups. Similarly, we will monitor the use of selected pharmacologic therapies, including activated protein C (91), medications that have been postulated to have a salutary effect in acute renal failure (e.g., fenoldopam and N-acetylcysteine), and medications that are nephrotoxic and may prolong the duration of ARF (e.g., amphotericin, aminoglycosides, cyclosporine, tacrolimus. and radiocontrast agents).

Diuretic use will also be monitored. The impact on diuretic therapy on the outcome of established ARF is minimal. While diuretic therapy may increase urine output in oliguric patients, there is no evidence that these drugs alter dialysis requirements, renal recovery or survival in ARF (119)

B. Alternative Study Designs

Several alternative study designs were considered in addition to the design that we are proposing. In addition to the intensity of renal support, other potential factors that may impact on the outcome of renal support in acute renal failure are timing of initiation of therapy and modality of therapy. Several alternative designs that combined intensity of therapy with these variables were also considered.

As detailed in the Background section, there are data from retrospective trials that suggest that early initiation of renal support in acute renal failure may be associated with improved survival. In our initial planning request, we proposed comparison of a strategy of early initiation of renal support (within 48 hours of fulfilling criteria for a diagnosis of severe ARF, independent of biochemical or physiological parameters) combined with intensive management of renal replacement therapy as compared to a strategy of initiating renal replacement therapy when specific biochemical or physiological thresholds were met (e.g., volume overload, hyperkalemia, metabolic acidosis, uremic symptoms or a BUN $\geq$ 100 mg/dL) combined with conventional management of renal replacement therapy. This approach was abandoned because of concern on the part of members of the planning committee that the results of such a trial would not be widely accepted by the nephrology community because of the inability to separate out the effects of timing of therapy from the effects of intensity of therapy.

In order to separate out the effects of timing of therapy from the effects of intensity of therapy, the possibilities of a 2x2 factorial design or multi-armed study were considered. The 2x2 factorial design was rejected because it was felt that there was a high likelihood of interaction between timing and intensity of therapy on a single primary outcome of all-cause mortality. The possibilities of a four-arm study (early initiation/intensive management; early initiation/conventional management; conventional initiation/intensive management; conventional initiation/conventional management) or a three-arm study (early initiation/intensive management; conventional initiation/intensive management; conventional initiation/conventional management) were also considered, but rejected due to the excessive sample size that would be required to adequately power those study designs.

XIX. Publications

A. Publication Policy

Several major journals have limited the maximum allowed number of authors to between nine and twelve, and require that at least one person's name appear before a corporate author, so that someone is accountable for the manuscript (120), and require that all members of a corporate author fully meet the criteria for authorship (121). In keeping with these requirements, named authors of the principal study manuscripts will be those individuals who compile the data and write the manuscript (usually the Study Chairperson and Biostatisticians) followed by the corporate author **("***and the ARF Trial Network***")**, which will consist of all participating Investigators and Executive Committee members. Corporate authors will receive the manuscript for review and will sign the authorship form. The name of a corporate author is appropriately shown in brackets after the corporate byline on the author's Curriculum Vitae. Other study group members (i.e., Study Coordinators, statistical assistants, and members of the monitoring bodies) will be listed separately in the Appendix. Participating Investigators may propose ancillary studies and manuscripts for which they would serve and be listed as principal author. The Executive Committee must approve, in writing, ancillary studies and publications.

It is the policy of the Cooperative Studies Program that outcome data will not be revealed to the Study Chair or participating site investigators until the data collection and clean-up phase of the study is completed. This policy safeguards against possible biases affecting the data collection.

The presentation or publication of any data collected by participating investigators on patients entered into this VA cooperative study is under the direct control of the study's Executive Committee. This is true whether the publication or presentation is concerned with the

results of the principal undertaking or is associated with the study in some other way. No individual participating investigator has any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any of the data other than under the auspices and with the approval of the Executive Committee.

B. Publication Plan

An intended plan of the main publications is given below.

Manuscript	*Projected Time of Submission*
Design Paper	1-2 years after study begins
60-day mortality (primary) and Safety	6-12 months after end of year 4
1- year mortality	6-12 months after primary manuscript
Economic analysis	12-18 months after primary manuscript
Comparison of risk-stratification scoring systems in ARF	12-18 months after primary manuscript
The impact of RT management strategy on the development of other organ system failures	18-24 months after primary manuscript

XX. Sub-Studies

Sub-Studies are, as a rule, discouraged within the VA Cooperative Studies Program because they may divert resources from, or interfere with, the conduct of the primary study. Nevertheless, it is recognized that this study may provide a unique opportunity to examine other questions of scientific interest.

The following guidelines have been developed in accordance with the Cooperative Studies Program policies for sub-studies to CSP #530.

1. Any study specifically involving study patients will be considered a sub-study, even if it is limited to one site. Sub-studies will normally involve collection of additional data. Most 'ancillary' analyses of currently collected data (e.g., clinical factors associated with 60-day mortality, global cost of the two treatment strategies, etc) are already planned as part of the primary study.

2. Requests to perform sub-studies will be accepted only from Site Investigators at any of the designated study sites. Requests should be submitted initially as a letter of intent addressed to the Study Chairman. The letter should specify the objectives and general design of the proposed research, the proposed number of subjects and study sites, and an estimate of the funding, if any, that will be required.

3. Letters may be submitted at any time, but no study will be approved before the end of the first year of the primary study in order to ensure that recruitment is not hindered by the additional workload.

4. The Study Chairman and the Biostatisticians will review letters of intent. Although the scientific merit of the study will be considered, the primary purpose of this initial review is to

establish that the proposal in no way conflicts with the conduct of the primary study. Recruitment success and the overall performance of the proponent's site (and any proposed collaborating sites) will be one of the factors considered in this review. Sites that are struggling to meet recruitment goals for the primary study may be considered poor candidates for sub-studies.

5. If the proposal is acceptable, the proponents will be asked to submit a formal study protocol (including a human consent form, if appropriate) and a budget.

6. The Executive Committee, and possibly one or two additional reviewers with expertise in the area of interest, will review the protocol. The purpose of this review is to determine the scientific merit of the study and to determine if the proposed ancillary study conflicts with the goals and/or conduct of the primary study. All sub-studies require approval by the DSMB, HRC, and CRADO. Based on the required reviews, proposals will either be approved or disapproved.

7. Locating funding for approved studies is the responsibility of the proponents.

8. Any publications (including abstracts) resulting from sub-studies must conform to publication policies of the VA Cooperative Studies Program, as specifically outlined for CSP #530. This includes statistical review by the West Haven Coordinating Center and adherence to authorship policies. The proponent of the sub-study will normally serve as the principal author of any resulting manuscripts.

XXI. Qualifications of Participating Centers

All VA Medical Centers with active dialysis programs will be potential study sites. Centers will be selected to participate in the study based on the volume of acute renal failure treated at the facility, the interest in participation in the study by Nephrology and Critical Care staff at the facility, and prior experience in clinical trials. The Research and Development Committee and the Subcommittee on Human Studies (IRB) at each site must approve the protocol. The principal investigator at each VA site must be at least a $5/8^{th}$ FTEE employee, have completed human subjects protection training, and be approved by the Chief Research and Development Officer (CRADO).

Non-VA participating sites will be selected based on expertise in the treatment of critically ill patients with acute renal failure, patient volume, and the interest in participation of both Nephrology and Critical Care staff, and prior experience in clinical trials. Each non-VA site will also need to assure accessibility of financial data for the economic analysis component of this study. Participation will be dependent upon approval of the protocol by the Institutional Review Board (IRB) at each site. The principal investigator must demonstrate completion of human subjects protection training and be approved by the Chief Research and Development Officer (CRADO).

All site personnel involved with the conduct of this study must be certified in Good Clinical Practices (GCP) and human subjects protection training. A copy of these certificates must be mail or faxed to the West Haven CSPCC *before* patient enrollment begins at the study site. In addition, copies of the meeting minutes of the IRB and R&D committees at each participating site must be submitted to the West have CSPCCC prior to patient enrollment at the study site.

XXII. Health Economics and Cost Analysis

A. Overview

The proposed project will compare intensive management to conventional management of acute renal failure. The economic analysis will comprise two parts: a cost-outcome analysis and a cost-effectiveness analysis. The cost-outcome analysis will compare the difference in total costs between the two arms to the difference in the primary outcome, 60-day mortality. The cost-effectiveness analysis will compare the change in quality-adjusted life years (QALYs) between the arms to the difference in costs.

Four elements are needed to perform these analyses: clinical outcomes, health care utilization data, data for assigning costs to the utilization, and patient utilities. The methods may be summarized as follows. Vital status will be determined from hospital discharge records, patient/proxy interviews, and electronic mortality records. Health care utilization will be determined from hospital data systems, study forms, and patient/proxy reports. Cost data will be extracted from hospital data systems when possible and from published sources as needed. Utilities will be collected through surveys of patients or their proxies.

A societal viewpoint will be adopted for the analyses. The range of costs considered will include direct inpatient and outpatient care costs, indirect costs for travel, and the value of patients' and informal caregivers' time spent obtaining or delivering care. Adopting a societal viewpoint is recommended by a leading manual on cost-effectiveness research (122) and is standard practice in VA-sponsored clinical studies. We will also present an analysis from the perspective of the VA, one that does not include non-VA direct health care costs, indirect costs for travel or the value of patients' or informal caregivers' time. The VA perspective may be of greater interest to VA managers and administrators.

In the rest of the economic analysis plan, study sites funded by VA are called "VA sites" and patients enrolled there are "VA enrollees." Health care facilities outside the VA system are referred to as "non-VA" facilities. A subset of these, the study sites funded by NIH, are called "NIH sites." Patients enrolled there are "NIH enrollees."

B. Objectives

Total costs over a 60-day and 12-month horizon will be dominated by the cost of the initial hospitalization, which frequently lasts 30 days or longer for patients with ARF. *A priori* it cannot be known whether intensive therapy for ARF will increase or decrease hospital costs. Patients in the intensive therapy arm will have higher dialysis costs due to more frequent treatments (6 days per week versus 3 days per week for hemodialysis) or greater utilization of supplies (high-dose versus conventional dose CVVHDF), but the extra cost may be offset by savings from a reduced length of stay. Based on preliminary analyses using published sources and VA utilization data, we expect that on average patients receiving intensive therapy will have lower total costs, although the magnitude of the difference is unclear. The following hypotheses will therefore be tested:

1. Intensive therapy for ARF will reduce total direct and indirect costs over a 60-day period, relative to standard therapy;
2. Intensive therapy for ARF will reduce total direct and indirect costs over a 12-month period, relative to standard therapy.

Results will be discussed in terms of statistical significance and the magnitude of cost differences. A secondary outcome of interest is the impact on costs from the VA's perspective alone. This will be assessed using similar methods.

We will also determine life expectancies for patients in each study arm based on mortality rates of study patients and rates found in published studies. A standard survey instrument will be fielded to patients/proxies to determine patients' quality of life. The results will be used to determine the number of quality-adjusted life years (QALYs) gained under the two competing therapies. These calculations will allow us to calculate the incremental cost-effectiveness of intensive therapy relative to standard care and to test a third hypothesis:

3. Intensive therapy for ARF is cost-effective relative to usual care.

We will calculate a 95% confidence region all estimated cost-effectiveness ratios. The ratios will be discussed in light of the cost-effectiveness of other medical interventions.

C. Utilization and Cost Data – VA Care

1. Overview

The study will collect utilization and cost data for a 12-month period starting from the date of randomization. Data will be gathered from a variety of sources. Health care utilization will be determined from hospital data systems, bills from third-party vendors (providers not participating as study sites), and patient responses recorded on study forms. Mortality information will be obtained from study forms, VA electronic files, and publicly available death data files. Cost data will be extracted from hospital data systems, published studies, and Medicare payment schedules.

2. Utilization Data

There will be two sources of utilization data for inpatient stays. The first is the primary data collection forms. From these we will determine the following items: number, type and duration of dialysis treatments; length of stay for initial and any subsequent hospitalizations at VA and non-VA hospitals; and patient characteristics such as clinical background and

demographics. The second source of utilization data will be VA utilization databases. These include the Patient Treatment File (PTF) SAS files for inpatient procedures. We will look for all forms of VA care: inpatient hospitalization, nursing home stays, and domiciliary stays.

Outpatient care within the VA system will also be gathered from electronic data systems. The primary source for outpatient services will be the VA National Patient Care Database (NPCD) outpatient SAS files (also known as the outpatient Medical SAS files). These capture services at all VA facilities, not just the VA hospitals at which patients originally enrolled. All major types of outpatient care are captured, including outpatient dialysis, ARF-related doctor appointments, and visits for other purposes. We will also analyze a small number of VA sites to determine whether the local Decision Support System (DSS) contain visits not accounted for in the NPCD outpatient SAS files. An earlier study using the DSS National Data Extract found this to be the case (123), and we may assume that the local DSS systems contain all information found in the National Data Extracts. If our preliminary analysis reveals a notable discrepancy between the sources, we will draw on DSS data to complement the NPCD outpatient SAS files for every VA site.

Outpatient prescriptions will be found in the DSS Pharmacy Extract. If the Pharmacy Extract is found to be unreliable for particular sites, we will request the VA Pharmacy Benefits Management Strategic Healthcare Group (PBM/SHG) to create an extract from its national prescription database. There would be a nominal charge for doing so.

Among patients who survive the initial ARF episode, nearly all will regain normal kidney function. A few are expected to develop chronic renal insufficiency, however, marked by the need for regular outpatient dialysis. Because of its close relation to the treatments in question, outpatient dialysis visits will be queried separately from other outpatient visits on study forms.

Dialysis at VA facilities will be captured in the DSS and outpatient NPCD SAS files, as noted earlier.

Mortality information will be drawn from several sources. Most deaths will occur during the initial hospitalization and will be recorded in study forms. Subsequent deaths will be noted on study forms in the 60-day and 12-month follow-ups, by searching the VA Patient Treatment File and the VA Beneficiary Identification and Record Locator System (BIRLS) death file, and by searching the National Center for Health Statistics' National Death Index database and the Social Security Administration's Death Master File.

3. Cost Data

The cost of the index hospitalization at VA sites will be assigned as follows. The primary source will be extracts from the production-level detail of the local (VAMC) DSS system. Local extracts include costs of services and medications and allow differentiation between direct, indirect, and total (direct plus indirect) costs. A few items will be assigned costs in a different manner. Costs for inpatient dialysis will be drawn from DSS unless there is reasonable evidence to believe that it is unreliable. If it is, then we will model costs for inpatient dialysis treatments from the reliable sites. Alternatively, we may use a small number of reliable sites. From these we will develop a cost function that estimates the cost of an individual treatment based on its type, duration, and other factors. The cost function will be used to assign a cost to dialysis treatments from sites with unreliable DSS systems.

Costs beyond the index hospitalization, such as readmissions and outpatient care, will be determined from national-level VA databases. Inpatient stays will be valued using the DSS National Data Extract (NDE) inpatient files. Ambulatory care services, including renal dialysis, will be valued using the DSS NDE outpatient files. The cost of outpatient prescription

medications will come from the DSS Pharmacy Extract. If the PBM/SHG prescription database is used instead to determine outpatient pharmacy usage, we will draw prices from the VA contract price files maintained by PBM/SHG (124).

D. Utilization and Cost Data – Non-VA Care

1. Non-VA utilization by VA enrollees

VA patients may obtain health care outside the VA system during the study period, and the cost of such care must be taken into account. Two steps will be taken to capture non-VA services. When patients/surrogates complete the informed consent form, they will be given a diary form on which to record instances of non-VA care over the following 12 months (Form 20V). At the end of the 60-day study period, a study coordinator will call any patient who survived beyond the initial hospitalization. The coordinator will ask whether non-VA care was obtained. Respondents will be asked to refer to the diary form when answering the questions. Outpatient care will be recorded on the follow-up interview study forms (Forms 17V and 18V).

During the 12-month follow-up, patients will be asked how many prescriptions they obtained at non-VA pharmacies. This information, plus VA pharmacy data described in C.2 above, will be used to estimate models of total outpatient pharmacy expenditures. We will use the results to impute total pharmacy expenditures for VA enrollees who reported using non-VA pharmacies, as well as for all NIH enrollees.

The direct cost of non-VA outpatient care will be assigned the average price for similar VA care. Three average payments will be calculated and assigned: one for dialysis treatments, a second for doctor visits pertaining to ARF, and a third for all other outpatient visits. The three average costs will be derived from the DSS records of VA patients who obtain outpatient care within the VA system following their initial hospitalization. They will then be applied to

outpatient care at non-VA facilities received by both VA and non-VA patients. The HCFA Wage Index will be used to adjust for regional differences in health care prices.

We will estimate the indirect cost of outpatient care from the original hospital discharge date until 12 months after randomization. Time spent on health care activities will be queried on the 60-day and 12-month follow-up surveys. Time spent on home health care will be valued using the average national wage for home health care providers as estimated by the U.S. Dept. of Labor. Assigning a value to the time of patients and informal caregivers is problematic on theoretical grounds (122), but such costs should not be ignored or assumed to be zero.

Another aspect of indirect cost is travel to and from medical appointments. Travel distance to outpatient appointments will also be queried on the follow-up surveys. For inpatient stays that occur beyond the study sites, travel distance will be estimated by measuring the distance between the centroids of the zip codes of a patient's home and the provider's facility, as captured on study forms. The cost of travel will be estimated by multiplying the distance by the standard IRS mileage reimbursement rate.

If there was inpatient care, the patient will be asked to provide the name and address of the provider(s). The Release of Information form (Form 14) signed by the patient will be used when contacting the non-VA provider. A similar process will occur at the 12-month follow-up, when patients will be queried about use of non-VA facilities since the 60-day follow-up survey (Form 18V). Direct costs for such care will be queried in the letter that accompanies the Release of Information form. The letter will ask the provider for a copy of the billing statement. If they are not provided, we will assign a cost by the method described below.

In some cases it will not be possible to obtain billing statements and other information from non-VA providers. Patients may refuse to sign a release form or the non-VA provider may

not respond to the request letter. For outpatient care, we will assign an average cost for similar services at NIH sites or, barring those, at other non-VA sites. If costs are not available from non-VA sites, we will assign an average cost for similar services at VA sites as reported in the HERC Outpatient Average Cost datasets (125). As with VA enrollees, we will attempt to estimate three separate average costs: one for outpatient dialysis, a second for other ARF-related visits, and a third for all other visits.

For inpatient stays at hospitals and other facilities beyond the study sites, we will apply an average cost based on facility type (hospital, nursing home, hospice) and length of stay. Hospital stays will be valued using the HERC Inpatient Average Cost datasets. These datasets, described in detail in Wagner et al. (126), use a cost function based on length of stay and other characteristics to assign an average cost to VA inpatient stays. Nursing home stays will be valued at the cost paid by VA for community nursing home stays of similar lengths. Hospice stays, which are expected to be rare, will be valued based on published estimates of their daily costs.

2. Utilization at NIH sites by NIH enrollees

A substantial proportion of patients will be enrolled at sites funded by NIH. Inpatient costs for those patients will be captured through billing statements from the respective sites. (The ability to provide such information in electronic or paper format will be a requirement of participation in the study.) Patients who are living and not still hospitalized will be asked at the 60-day and 12-month follow-up periods whether any inpatient or outpatient care was received since discharge from the initial hospitalization. If a subsequent hospitalization has occurred at the study site, the site coordinator will obtain the bill.

3. Utilization at non-NIH facilities by NIH enrollees

We expect that some NIH enrollees will obtain care at non-NIH facilities. The process of obtaining billing statements for inpatient care by non-NIH providers will be handled in the same manner as for VA patients. Costs for outpatient care will likewise be assigned based on the average for similar services at NIH sites, other non-NIH sites, or VA sites. Forms 17N, 18N, and 20N will be used to gather requisite data from NIH enrollees.

Patients in this study are likely to take a significant number of prescription medications. Outpatient prescriptions will not be captured through the data systems of the NIH sites. We believe it would be too burdensome to ask patients to keep a log of every prescription they fill over a period of 10-12 months. Because VA and NIH enrollees should be similar in clinical characteristics, we will impute outpatient prescription costs for NIH enrollees using the model based on VA patients (see D.1, above).

E. Quality of Life

To estimate QALYs we must measure patients' utility levels, estimate the number of years remaining in their lives, and extrapolate utility levels over remaining life years. Major decisions and issues in QALY estimation include the following:

- the instrument used to measure utility
- the time points at which to measure utility
- methods for estimating length of remaining life
- methods for extrapolating utility over remaining life years

We will use the Health Utilities Index (HUI) Mark III to measure utility. It is a reliable instrument for measuring health-related utilities, validated for use by both patients and surrogates and for in-person or telephone administration (127). It strikes a good balance between

completeness and ease of use. The HUI Mark III and its predecessors have been used in dozens of studies and enjoy wide acceptance.

Cost-effectiveness analyses typically measure utility at study entry (baseline) and at a second point after the intervention has occurred. We plan instead to measure utility at 60 days and at 12 months following randomization. We chose to measure utility at 60 days rather than at baseline for two reasons. First, measuring utility at baseline would be uninformative. Because all patients in CSP 530 will have multiple organ failure, they are likely to have similar, very low qualities of life. After 60 days most patients who remain alive will have recovered to a significant extent, and so a 60-day utility measure will be more informative as a standard against which to measure the change by month 12. Second, we expect at least 40% of patients to die within 60 days. Measuring utility at baseline would constitute wasted effort for those who died during or soon after the treatment phase. Third, because the study concerns acute rather than chronic renal failure, the baseline does not represent the patient's typical pre-morbid state of utility.

The surveys will be administered by telephone if possible, or by mail for those who cannot be reached in person. Patients who have died will automatically receive a score of 0.0 and the HUI will not be administered.

HUI scores at 60 days and 12 months will be used to assign utility levels at other time points. For the period between the 60-day and 12-month follow-ups, we will assume that utilities rise gradually over time, rather than jumping discretely from one level to another. Utility extrapolations beyond the 12-month follow-up will be based on the HUI scores and published figures on life expectancies and QALYs among ARF survivors. We will assume that utility changes gradually over time and that most improvement following ARF will have

occurred by 12 months following randomization. If utilities appear to be fall into a small number of identifiable groups, our extrapolations will take that into account.

In sum, differences in utility between patients in the two study arms will be marked in three ways: differing mortality rates, differing 60-day HUI scores, and differing 12-month HUI scores. These data points will be used to interpolate and extrapolate utility to the intervening and remaining periods of life.

F. Cost-Effectiveness

The utility figures will be used in conjunction with cost data to determine the incremental cost-effectiveness ratio of the intervention. This represents the estimated cost of obtaining one additional quality-adjusted life year (QALY) from the intensive renal support strategy, relative to the conventional strategy. The ratio may be expressed as the difference in QALYs between the two groups divided by the difference in costs. A 95% confidence region surrounding cost-effectiveness ratios will be estimated using a bootstrapping method. Substantial developments in semiparametric and nonparametric statistical tests have occurred in recent years. If necessary, we will change our method for determining confidence regions based on research published by the study's end.

There are several possible outcomes of the cost-effectiveness analysis. If the intensive treatment strategy is both less expensive and yields greater utility, we may be certain that it is preferred to the conventional treatment. Conversely, if it is both more expensive and yields the same or lower utility, we may prefer the conventional treatment with confidence. A likely outcome is that the intensive treatment arm will be more expensive but yield greater utility and more QALYs.

We will present cost-effectiveness ratios for both 12-month and lifetime horizons. Because recovery from ARF typically occurs within a few months, we will assume that healthcare costs will be similar across treatment groups beyond the 12-month follow-up.

Life expectancies will be calculated on the basis of published studies of ARF patients (128) and the mortality rates of VA patients followed over the course of the study. A combination of VA and non-VA sources will be used to determine date of death, such as the VA Beneficiary Identification and Records Locator System (BIRLS) and the Social Security Death Index. Data from early enrollees will help us to estimate mortality beyond 12 months. By the time of the planned 12-month follow-up for the last enrolled patients, a period of about four years will have elapsed since the first patients were enrolled. A simple Markov-chain model will be used to estimate lifetime costs based on these inputs.

G. Inflation and Discounting

Dollar amounts in the study will be presented in terms of currency from a single year, most likely the last year of data collection. We will adjust costs for inflation using the Consumer Price Index for all urban consumers and all goods, the most common measure of nationwide inflation. Because money spent later is less valuable then money spent today, we will also discount expenditures at a rate of 3% per year. As noted earlier, the HCFA Wage Index will be used to adjust for regional differences in health care costs.

H. Sensitivity Analyses

We will test the sensitivity of our results to a number of assumptions. At a minimum, we expect them to include the elements described below.

Inpatient Costs. Inpatient costs will constitute the largest element of total healthcare costs for ARF patients. We also expect that VA and non-VA sites will have different levels of

typical inpatient costs. We will explore how our results vary depending on whether VA or non-VA costs are used for all patients. For example, we may calculate what the overall cost-effectiveness would be if all patients (including VA patients) were attributed the typical costs for non-VA patients. Doing so could increase the relevance of the cost-effectiveness analysis for non-VA decision-makers.

Lifetime Expectancies and Utility. As noted above, we must estimate lifetime expectancies for patients who are living at the time the data-collection period ends. We must also estimate utility beyond 12 months after randomization. We will vary these values, such as by one standard deviation in each direction, in order to determine how the results vary.

Patient-Incurred Costs. Patients and their caregivers incur costs for travel, for the time spent obtaining care, and for the time spent giving care (by unpaid caregivers). In the sensitivity analyses, we will vary the costs of that time. An example would be varying the assumed cost of caregiver time by $2/hour upward and downward.

Discount and Inflation Rates. Costs incurred in earlier years must be inflated over time to maintain a steady level of purchasing power. They must also be inflated over time to reflect the discount rate, the rate at which people value money today over the same amount of money next year. The inflation rate, which we will measure by changes in the Consumer Price Index (CPI), could be varied in two ways for a sensitivity analysis. One is to use an alternative inflation measure, such as changes in the Gross Domestic Product deflator. A second is to take the CPI and vary it by a small amount, such as +/- 1.0% per year. Likewise, we will vary the assumed 3% discount rate by using alternative rates, such as 2% or 5%.

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VA Cooperative Study #530

Intensive vs Conventional Renal Support in Acute Renal Failure

Protocol Amendment #1

July 2003

1. This Protocol Amendment revises the Inclusion and Exclusion Criteria to accommodate a change in the definition of sepsis and to clarify the exclusion criterion for acute renal failure believed to be due to an etiology other than ATN.

2. The proceeding of the 2001 International Sepsis Definitions Conference sponsored by the Society of Critical Care Medicine, European Society of Intensive Care Medicine, American College of Chest Physicians, American Thoracic Society and the Surgical Infection Society were recently published [1]. The consensus conference concluded that the diagnostic criteria for SIRS published in 1992 as part of the ACCP/SCCM Consensus Conference definition are overly sensitive and non-specific. As a result, they proposed a definition of sepsis based on the presence of documented or suspected infection (defined as a pathological process induced by a microorganism) in the setting of clinical evidence of a systemic inflammatory response (Table 1). The consensus conference further defined severe sepsis is defined as sepsis complicated by organ dysfunction. Since all patients entering the study will have at least one organ system failure – i.e., acute renal failure – the coexistence of renal failure with documented or suspected infection will fulfill the definition for severe sepsis.

   In order to ensure that the criteria used for sepsis are consistent with the most current literature, we will modify the definition of sepsis used as an inclusion criterion for the study. Rather than defining sepsis based on the 1992 ACCP/SCCM Consensus conference, we will define sepsis for the purpose of inclusion in this study as the presence of documented or suspected infection with the coexistence of ARF providing evidence of systemic inflammation with organ dysfunction.

3. The exclusion criterion of "acute renal failure clinically believed to be due to an etiology other than ATN" was accompanied by a list of 12 etiologies of ARF other than ATN. This list is not comprehensive. In order to eliminate confusion that any etiology of ARF other than the 12 listed would qualify patients for the study, this sub-list is being eliminated from the explicit exclusion criteria. In its place, detailed operational criteria for defining acute renal failure believed to be due to an etiology other than ATN will be provided in the Operations Manual (Appendix A).

4. The revised inclusion and exclusion criteria are listed in Table 2.

Reference:

1. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 2003; 29:530-538.

Table 1. Diagnostic criteria for sepsis[1]

Infection[a]

Documented or suspected *and* some of the following[b]**:**

General parameters

Fever (core temperature >38.3°C)
Hypothermia (core temperature <36°C
Heart rate >90 bpmor >2 SD above the normal value for age
Tachypnea: >30 bpm
Altered mental status
Significant edema or positive fluid balance (>20 ml/kg over 24 h)
Hyperglycemia (plasma glucose >110 mg/dl or 7.7 mM/l) in the absence of diabetes

Inflammatory parameters

Leukocytosis (white blood cell count >12,000/µl)
Leukopenia (white blood cell count <4,000/µl)
Normal white blood cell count with >10% immature forms
Plasma C reactive protein>2 SD above the normal value
Plasma procalcitonin >2 SD above the normal value

Hemodynamic parameters

Arterial hypotension[b] (systolic blood pressure <90 mmHg, mean arterial pressure <70, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age)
Mixed venous oxygen saturation >70%[b]
Cardiac index >3.5 l min^{-1} m^{-2}[c,d]
Organ dysfunction parameters
Arterial hypoxemia ($PaO_2/FIO2$ <300)
Acute oliguria (urine output <0.5 ml kg^{-1} h^{-1} or 45 mM/l for at least 2 h)
Creatinine increase ≥0.5 mg/dl
Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100,000/µl)
Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 mmol/l)

Tissue perfusion parameters

Hyperlactatemia (>3 mmol/l)
Decreased capillary refill or mottling

[a]Defined as a pathological process induced by a micro-organism
[b]Values above 70% are normal in children (normally 75–80%) and should therefore not be used as a sign of sepsis in newborns or children
[c]Values of 3.5–5.5 are normal in children and should therefore not be used as a sign of sepsis in newborns or children
[d]Diagnostic criteria for sepsis in the pediatric population is signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5°C or <35°C), tachycardia (may be absent in hypothermic patients) and at least one of the following indications of altered organ function: altered mental status, hypoxemia, elevated serum lactate level, and bounding pulses

[1]Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 2003; 29:530-538.

Table 2 Revised Inclusion/Exclusion Criteria

Inclusion Criteria

- Acute renal failure clinically consistent with a diagnosis of acute tubular necrosis, defined as:
  - Clinical setting of ischemic or nephrotoxic injury

  and
  - oliguria (urine output < 20 mL/hour) for > 24 hours, or an increase in serum creatinine of > 2 mg/dL (> 1.5 mg/dL in females) over baseline over a period of ≤ 4 days.
- Plan for renal replacement therapy by the clinical team
- Receiving care in critical care unit (e.g., MICU, SICU, CCU)
- One non-renal organ failure (SOFA organ system score ≥2) or the presence of sepsis
  - $PaO_2/FiO_2 \leq 300$ mmHg;
  - Platelet count ≤ 100,000 mm^3;
  - Bilirubin ≥ 2.0 mg/dL;
  - Hypotension (MAP < 70 mmHg) requiring any pressor support;
  - Glasgow Coma Scale ≤ 12; or
  - Known or suspected infection
- Age > 18 years
- Patient/surrogate willing to provide informed consent

Exclusion Criteria

- Baseline serum creatinine > 2 mg/dL (> 1.5 mg/dL in females)
- Acute renal failure clinically believed to be due to an etiology other than ATN:
- 1 hemodialysis treatment or > 24 hours since starting CRRT
- Prior kidney transplant
- Pregnancy
- Prisoner
- Weight > 120 kg
- Non-candidacy for acute renal replacement therapy
- Moribund state
- Patient not expected to survive 28-days because of an irreversible medical condition
- Comfort-measures only status
- Participation in a concurrent interventional study
- Patient/surrogate refusal
- Physician refusal

Protocol Amendment 1 - Appendix A

Clinical Criteria for Diagnosis of Etiologies of ARF other than ATN	
Etiology of ARF	**Clinical Criteria to Suggest Diagnosis**
Pre-renal azotemia	Primary: 1. Underlying absolute or effective (in setting of CHF or cirrhosis) hypovolemia, and 2. Improvement in renal function with volume loading or inotropic support Secondary (suggestive but not diagnostic): 1. Fractional excretion of sodium < 1% and/or fractional excretion of urea <35%; 2. Bland urine sediment
Obstructive uropathy	1. Bladder outlet obstruction diagnosed by elevated post-void residual bladder function; 2. New or progressive hydronephrosis on renal ultrasound or other imaging; or 3. Improvement in renal function following decompression of urinary collecting system
Allergic interstitial nephritis	1. Appropriate clinical setting (e.g., drug exposure, infection); 2. Clinical syndrome of fever and/or skin rash and/or eosinophilia; 3. Urine sediment with hematuria, pyuria, or leukocyte casts; and 4. Eosinophiluria (the negative predictive value of eosinophiluria is approximately 90%, however the positive predictive value is only ~50%)
Acute or rapidly progressive glomerulonephritis	1. Appropriate clinical setting (e.g., recent Strep infection, endocarditis, etc.…); 2. Positive serologic markers (e.g., low serum complement levels, positive anti-GBM antibodies, or positive ANCA); 3. Urine sediment with dysmorphic red blood cells or red blood cell casts; and/or 4. Renal biopsy demonstrating proliferative or crescentic glomerulonephritis
Vasculitis	1. Appropriate clinical setting (e.g., multisystem disease) 2. Positive serologic marker(s) (e.g., low serum complement levels, positive ANA, positive serum cryoglobulins, positive hepatitis B or hepatis C serologies) 3. Urine sediment with dysmorphic red blood cells or red blood cell casts; and/or 4. Biopsy of kidney or other tissue with acute vasculitis

Clinical Criteria for Diagnosis of Etiologies of ARF other than ATN	
Etiology of ARF	**Clinical Criteria to Suggest Diagnosis**
Hemolytic-uremic syndrome (HUS)/Thrombotic thrombocytopenic purpura (TTP)	1. Microangiopathic hemolytic anemia (with schistocytes on peripheral blood smear and elevated LDH); 2. Thrombocytopenia; 3. Absence of disseminated intravascular coagulation (DIC)
Malignant hypertension	1. Severe (Stage III) hypertension; 2. Neurologic changes; 3. Retinal hemorrhages, exudates or papilledema; and 4. Hematuria and/or red blood cell casts
Scleroderma renal crisis	1. Diagnosis of scleroderma; 2. Acute onset of renal failure; and 3. Abrupt onset of moderate to severe hypertension
Atheroembolism	1. Clinical setting (e.g., recent intra-arterial catheterization, recent vascular surgery or anticoagulation); 2. Presence of some or all of the following: - cutaneous manifestations (e.g., livedo reticularis, digital ischemia); - extra-renal visceral involvement; - atheroemboli visibile on retinal exam (Hollenhorst plaques); - eosinophilia; - eosinophiluria; - hypocomplimentemia; or - cutaneous or other biopsy positive for atheroemboli
Multiple myeloma	1. Known or suspected diagnosis of multiple myeloma 2. Presence of immunoglobulin light chains in the urine on UPEP 3. Serum paraprotein detected on SPEP

Clinical Criteria for Diagnosis of Etiologies of ARF other than ATN	
Etiology of ARF	**Clinical Criteria to Suggest Diagnosis**
Functional or surgical nephrectomy	1. Surgical nephrectomy; or 2. Bilateral renal infarction (secondary to thromboemboli, renal artery dissection or renal vein thrombosis) manifested by: - clinical presentation with flank pain, hematuria and/or elevated LDH - renal imaging by angiography, CT scan or MRI
Hepatorenal syndrome	Major criteria: 1. Chronic or acute liver disease with advanced hepatic failure and portal hypertension; 2. Absence of shock, ongoing bacterial infection, fluid loss and current or recent treatment with nephrotoxic drugs 3. Absence of ongoing GI fluid losses or renal fluid losses 4. Absence of sustained improvement in renal function after withdrawal of diuretics and expansion of plasma volume with 1.5 L of isotonic saline (administered over 4 to 6 hours); and 5. Absence of proteinuria > 500 mg/d, absence of ultrasound evidence of obstructive uropathy or parenchymal renal disease Minor criteria 1. Urine volume < 500 mL/d; 2. Urine sodium < 10 mEq/L; 3. Urine osmolality > plasma osmolality; 4. Urine red blood cells < 50 per high-powered field; 5. Serum sodium concentration < 130 mEq/L
Cyclosporin or tacrolimus nephrotoxicity	1. Elevated cyclosporin or tacrolimus drug levels as compared to prior baseline levels; and 2. Improvement in renal function following reduction in drug dose or discontinuation of drug.

VA Cooperative Study #530

Intensive vs Conventional Renal Support in Acute Renal Failure

Protocol Amendment #2

July 2003

1. This Protocol Amendment adds the banking of plasma and serum in a biological repository.

2. Background

   There is a paucity of data regarding serologic markers in patients with acute renal failure. Acute renal failure is a highly heterogenous disease characterized by the sudden loss of kidney function. Although there are multiple etiologies of acute renal failure, enrollment in this trial will be limited to patients with acute renal failure due to acute tubular necrosis. Acute tubular necrosis (ATN) may be due to either ischemic or toxic injury to the kidney. The pathogenesis of ATN is incompletely understood, but appears to be associated with the activation of multiple mediators including NO, endothelin, tumor necrosis factor-α (TNF-α), and a variety of cytokines, chemokines and growth factors [1-5].

   Iglesias et al. have recently shown that in patients with sepsis, elevated levels of soluble receptors to TNF-α (S-TNF-R) were strongly associated with the development of acute renal failure [6]. In the 112 patients who developed acute renal failure elevated S-TNF-R1 levels were associated with increased mortality ($P<0.02$) [6].

   In a multicenter, prospective observational study of acute renal failure, Himmelfarb et al. demonstrated that concentrations of both the pro-inflammatory cytokine interlukin-6 (IL-6) and the anti-inflammatory cytokine interlukin-10 (IL-10) were higher in non-survivors than in survivors, although all concentrations were markedly elevated as compared to healthy controls (IL-6: 201±224 pg/mL in survivors vs. 597±1056 pg/mL in non-survivors, $P<0.05$; IL-10: 5.6±8.9 in survivors vs. 25.6±82.0 in non-survivors, $P=0.09$) [7]. No association was observed between levels of interlukin-1b (IL-1b), interlukin-8 (IL-8), TNF-α, or C-reactive protein and survival [7].

   Increased levels of TNF-α, and IL-1 were found in the heart after renal ischemia in the rat [8]. This was associated with increased expression of intracellular adhesion molecule-1 (ICAM-1) mRNA in cardiac tissue. Evidence of apoptosis of cardiac cells was also observed after renal ischemia but not following bilateral nephrectomy, suggesting that soluble factors produced by the kidney after ischemia and not the uremic state mediated apoptosis. Blocking TNF-α limited the cardiac apoptosis. This data suggests that elaboration of inflammatory mediators by the kidney may play a significant role in non-renal organ dysfunction associated with ARF [8].

   Cytokine gene polymorphisms in patients with acute renal failure requiring dialysis have also been associated with survival in a preliminary study [9]. Promoter region polymorphisms of

pro-inflammatory (TNF-α and IL-6) and anti-inflammatory (IL-10) cytokines were prospectively evaluated and compared to clinical outcomes in a cohort of 63 patients [9]. Patients were stratified into three groups on the basis of APACHE II scores. In each group, high TNF-α producer genotype (G/A, A/A) was associated with an increased mortality as compared to low producer genotype (G/G) (P=0.03) [9]. Although no association between IL-6 or IL-10 genotype and mortality was observed, patients with a combination of high TNF-α and low IL-10 producer (ACC/ACC, ACC/ATA, ATA/ATA) genotypes had the highest mortality as compared to those with combined low TNF-α and high/intermediate IL-10 (high: GCC/GCC; intermediate: GCC/ACC, GCC/TAT) producer genotypes (P=0.04) [9]. These data suggest that cytokine gene polymorphisms are associated with clinical outcomes among patients with acute renal failure.

3. Biological Sampling

This study provides a valuable opportunity to develop a biological repository of plasma and serum samples from a large cohort of well-characterized patients with acute renal failure. We therefore propose to obtain 20 mL blood samples prior to dialysis at randomization (day 1) and a second 20 mL sample prior to dialysis on day 8. Two 10 mL samples will be drawn on each day. One sample will be drawn in a pyrogen-free vial containing EDTA for plasma and the second sample will be drawn without anticoagulation for serum. Samples will be immediately placed on ice and centrifuged at 4^{o} C. Plasma and serum will be aliquoted into microcentrifuge tubes, which will be labeled with pre-printed labels containing a coded ID without any patient identifiers. The aliquoted samples will be stored at -20^{o} C until they are shipped to the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC). Samples will be shipped on dry ice to MAVERIC where they will then be stored at -70^{o} C [10-13].

Samples from the biological repository will be available to qualified investigators from both within the VA and from outside of the VA. Requests for access to samples from the repository will be reviewed by the study Executive Committee and the Director of the West Haven CSPCC. In addition, the requesting investigator's institutional review board (IRB) must approve the proposed protocol for use of the biological samples. The MAVERIC laboratory will release samples to the investigator only after receiving a letter of approval from the Director of the West Haven CSPCC and a copy of the IRB approval for the study. MAVERIC will send the analytic laboratory only the amount of plasma or serum needed to perform the proposed analysis. If excess sample is sent in order to avoid repeated freeze-thaw cycles, the remaining sample must be returned to the biological repository.

Linkage to clinical information will be provided by the West Haven CSPCC using a de-identified dataset linked to the coded sample ID numbers. The clinical data provided in this dataset will include the minimum data elements required by the investigator. The investigator will complete a data-use agreement with the West Haven CSPCC prior to being provided with the de-identified clinical data.

4. Informed Consent

   This study modification will require the addition of specific language to the study consent form. Model language is provided in Appendix A.

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Protocol Amendment 2 - Appendix A

Insert the following language into the Study Consent Form at the end of the section "Description of The Study And The Procedures**"**

Blood Sample for Biological Repository

We will also obtain two blood samples, one obtained at the start of the study and the second on day 8 to be stored for future use. These samples will be used to measure chemicals in the blood, which play a role in inflammation and may play an important role in the recovery of renal function or the function of other organs in patients with acute renal failure. The samples may also be used to measure other chemicals in the blood that are thought to play a role in patients with acute renal failure. Each blood sample will be 20 ml (approximately 1½ tablespoons) for a total volume of 40 mL (approximately 3 tablespoons).

These samples will be stored at the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) in Boston, MA. The samples will be stored without identifying information about you (such as your name or Social Security number) but will be marked instead with a coded ID. Your personal information and the ID will be kept in a secure computer system that will only be available to the study investigators. Although use of your blood samples will be under the supervision of the investigators participating in this study, the samples may be used by investigators not associated with this study. No information identifying you will be provided to any investigator requesting access to your blood sample. The blood sample will be stored indefinitely, but you may request that it be destroyed at any time. This sample will not be used for any genetic studies.

I agree to storage of this sample: _____Yes _____No (Patient initials)

VA Cooperative Study #530

Intensive vs Conventional Renal Support in Acute Renal Failure

Protocol Amendment #3

October 2003

1. Purpose

This Protocol Amendment adds the collection of observational data on the delivery of renal replacement therapy to non-randomized patients in order to determine the prevailing practice patterns for the delivery of this therapy to patients with acute renal failure at participating study sites.

The primary purpose of this data collection is to ensure that the VA/NIH Acute Renal Failure Trial Network (ATN) Study (CSP #530) is conducted with maximal protection of the safety of patients in each of the two treatment arms. The Office for Human Research Protections (OHRP) of the US Department of Health and Human Services has specified that in all clinical trials there is a need to "assess the risks and potential benefits of each of the interventions for each arm…relative to concurrent routine clinical practice outside of the research context" (1). Since there is not a well-established standard of care for the management of renal replacement therapy in acute renal failure, it appears to be necessary to collect robust data on these processes of care provided for patients who are not participating in the ATN Study.

The data collected in this observational study will be reported to the study Data and Safety Monitoring Board (DSMB), to the West Haven CSPCC Human Rights Committee and to each participating institution's IRB.

2. Background

In a recent opinion, OHRP criticized trials organized by the Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network for failing to provide IRBs with "information adequate to assess the risks and potential benefits of each of the interventions for each arm…relative to concurrent routine clinical practice outside of the research context" (1). In each of the two trials reviewed by OHRP expressed concern that the trials reviewed actually consisted of two experimental arms and lacked a "routine" care control group. In its opinion, OHRP states:

> "…in order to have determined whether the risks to the subjects were minimized and reasonable in relation to the anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably have been expected to result, the IRBs should have received information adequate to assess the risks and potential benefits of each of the interventions for each arm of the …trial relative to concurrent routine clinical practice outside of the research context."

OHRP further stated that in order to make these determinations "…a clear, detailed description of concurrent routine clinical practice…" at the trial sites and "…a detailed comparison of the …management strategies that were to be used in the two experimental groups relative to concurrent routine clinical practice…" should have been provided.

In many ways, the ATN Study (CSP #530) is analogous to the ARDS Network trials. In particular, there are currently no accepted guidelines for the management of renal replacement therapy in acute renal failure and there appears to be wide variation in practice patterns both within individual institutions and between institutions. In developing the study protocol a survey of practice patterns for providing renal replacement therapy in acute renal failure at potential participating sites was performed. The data from this survey are presented in Appendix G of the protocol. This survey demonstrated wide variation in the utilization of modalities of therapy and of the dosing of therapy between institutions. The majority of sites reported that they provided intermittent hemodialysis on a daily or every-other day schedule; with only 8 of 46 sites indicating that they routinely provided intermittent hemodialysis more frequently than 4-times per week. Similarly, only 5 sites reported dosing CRRT at an effluent flow rate of 35 mL/kg/hour while 11 sites reported use of effluent flow rates of less than 2000 mL/hour. These data support that a state of clinical equipoise exists with regard to the most appropriate dosing strategy for renal replacement therapy and underlie the importance of the ATN Study. In order to better define treatment practices, a more detailed survey of providers at the 27 participating study sites is currently being performed (attachment A).

We believe, however, that these data, while providing some insight into the current patterns of care, may not be sufficiently robust to satisfy the standards established in the OHRP opinion. In order to satisfy OHRP's mandate for "…a clear, detailed description of concurrent routine clinical practice…" at the trial sites, patient level data on a cohort of patients matching those enrolled in the study but receiving renal replacement therapy "outside of the research context" needs to be collected. We are therefore proposing to obtain limited data on the actual renal replacement therapy provided to a sample of patients screened but not enrolled in VA Cooperative Study # 530.

3. Design of Observational Study

A. Patient Selection

The target sample population will be patients meeting all of the screening criteria for the ATN Study with the exception of informed consent for participation in the interventional trial. We anticipate that the most common reason for non-enrollment of otherwise qualified patients will be the inability to obtain consent from the appropriate surrogate decision-maker within the necessary time frame.

All patients selected for data collection in this observational cohort will need to have met all of the following five inclusion criteria for the study:

1. Acute renal failure clinically consistent with a diagnosis of acute tubular necrosis, defined as:
   - Clinical setting of ischemic or nephrotoxic injury

and

- oliguria (urine output < 20 mL/hour) for > 24 hours, or an increase in serum creatinine of > 2 mg/dL (> 1.5 mg/dL in females) over baseline over a period of ≤ 4 days.

2. Plan for renal replacement therapy by the clinical team
3. Receiving care in critical care unit (e.g., MICU, SICU, CCU)
4. One non-renal organ failure (SOFA organ system score ≥2) or the presence of sepsis
5. Age > 18 years

Patients excluded from the study based on the following exclusion criteria will also be excluded from the observational cohort:

1. Baseline serum creatinine > 2 mg/dL (> 1.5 mg/dL in females)
2. Acute renal failure clinically believed to be due to an etiology other than ATN
3. > 1 hemodialysis treatment or > 24 hours of CRRT prior to screening
4. Prior kidney transplant
5. Pregnancy
6. Prisoner
7. Weight > 120 kg
8. Non-candidacy for acute renal replacement therapy
9. Moribund state
10. Patient not expected to survive 28-days because of an irreversible medical condition
11. Comfort-measures only status
12. Participation in a concurrent interventional trial
13. Physician refusal to participation in the interventional trial

B. Data Collection

We propose to collect the following data on the patients entered into the observational cohort:

1. Demographic data including age, gender, race and etiology of ARF
2. Whether or not the patient received renal replacement therapy within 14 days of screening
3. If the patient received renal replacement therapy within 14 days of screening:
    a. Which day post-screening renal replacement therapy was initiated
    b. The indications for renal replacement therapy (e.g., volume overload, hyperkalemia, acidosis, uremic symptoms)
    c. The blood urea nitrogen (BUN) concentration on the day renal replacement therapy was initiated
    d. The SOFA Cardiovascular score at the time of initiation of renal replacement therapy
    e. The modality of renal replacement therapy provided on each day between day-1 and day-14 post screening

In addition, data on each renal replacement therapy treatment provided in the 14 days post screening will be collected using ***Study Form 09 – Renal Replacement Therapy – Each***

Treatment, to provide accurate data regarding the actual delivered treatments. In order to maintain a de-identified data set, this form will be modified for the observational cohort by the removal of prohibited identifiers, specifically patient initials and treatment date.

C. Data Analysis

The collected data will be analyzed to provide a description of the concurrent routine clinical practice for the delivery of renal replacement therapy for patients with acute renal failure. The descriptive analysis will include the indications for renal replacement therapy, the average BUN at time of initiation of therapy, the relationship between SOFA cardiovascular score and initial modality of therapy, the frequency of intermittent hemodialysis and SLED treatments, the estimated prescribed dose of intermittent hemodialysis and SLED, and the delivered dose of continuous renal replacement therapy. Data will be analyzed and compared to the patients in the two active treatment arms as the entire cohort and by study site.

D. Frequency of Data Collection

At a minimum, patient data will be collected on this observational cohort during the first and final years of study enrollment. Provisionally, we are proposing to collect data on the first 10 patients meeting the criteria for the observational cohort from each VA site, and the first 25 patients at each non-VA site. This data collection will be repeated at the start of year 3. Additional data collection will be at the discretion of the study Executive Committee and the study Data and Safety Monitoring Board (DSMB)

4. Ethical Concerns

We believe that the data collection for this observational cohort is eligible for approval for both a "waiver of consent" under the Common Rule (38 CFR16.116(d) and 45CFR46.116(d)) and a "waiver of authorization" under HIPAA.

Four criteria need to be satisfied to qualify for a "waiver of consent" under the Common Rule:

a. The research involves no more than minimal risk to the subjects

   Participation in the observational cohort will entail no tangible risk to the subjects. There will be minimal intangible risk resulting from loss of privacy as the result of the review of patient records by the data abstractor. This risk will be minimized, as all collected data will be de-identified.

b. The waiver will not adversely affect the rights or welfare of the subjects.

   There will be no impact on any of the rights or welfare of the subjects as a result of the data abstraction proposed. All data collected will be de-identified.

c. The research could not practicably be carried out without the waiver.

   The patients enrolled in the observational cohort will have not been enrolled in the interventional trial due to inability to obtain informed consent for the intervention trial. In the vast majority of these patients, the inability to obtain informed will have resulted from the subject's clinical condition resulting in an absence of decision-making capacity, combined with the absence of a surrogate decision-maker. This absence of a surrogate decision-maker will also impose a substantial barrier on obtaining informed consent for this prospective observational study. In a recently published observational study of ARF, refusal of consent by potential study subjects was infrequent; the most common reason for failure to enroll patients in that trial was the absence of a surrogate decision-maker to provide consent for patients lacking decision-making capacity (2).

   Limiting participation in the observational cohort to patients in whom consent is possible will significantly restrict the population of patients eligible for enrollment. Such a restriction could introduce biases into the study population and limit the generalizabilty of the collected data. Since the purpose of this observational cohort is to accurately characterize the processes of care provided to patients receiving "concurrent routine clinical practice outside of the research context" it is critical that such biases are avoided. Thus, we believe that without a waiver of consent, this study cannot practicably be performed and provide meaningful data.

d. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

   Since the collected data will be de-identified, it will not be possible to contact subjects after participation with additional pertinent information.

To qualify for a "waiver of authorization" under HIPAA the following additional criteria need to be satisfied to assure that the planned data use involves no more than minimal risk to each subject's privacy:

a. There is a plan to protect identifiers.

   The data collected will be de-identified

b. There is a plan to destroy identifiers at the earliest opportunity that is consistent with the goals of the study.

   The data collected will be de-identified

c. There is written assurance not to reuse the protected health information (PHI)

   The data collected will not be reused for analyses other than those stated in this protocol.

The primary purpose of this data collection is to help ensure the safety of subjects participating in the interventional trial by ensuring that there is adequate information available to the DSMB,

Human Rights Committee and IRBs to assess the risks and potential benefits of the interventions for each arm relative to concurrent routine clinical practice outside of the research context. We therefore believe that the minimal risks associated with this observational data collection are reasonable in relation to their anticipated benefits and that waivers of consent and authorization are justified.

5. Data and Safety Monitoring Board

These data are being collected in response to regulatory uncertainty regarding the relationship between "usual" care and the care provided in the two arms in the intervention trial. These data are being collected to assure that both study treatment arms fall within the broad range of usual care. These data, along with enrollment rates and physician refusal rates will help determine if clinical equipoise persists throughout the course of the trial. The DSMB will also monitor developments in the literature and clinical practice as the study progresses. If results of another clinical trial alter the state of clinical equipoise, then the study design may need to be altered or the study stopped. Changes in routine clinical practice occurring during the conduct of the study that are not supported by high-level scientific evidence should not, however, be grounds for altering or stopping the study. It is important to recognize that alterations in practice patterns at the study sites during the course of the study may reflect a Hawthorn effect rather than reflecting secular trends in the management of renal replacement therapy at non-study sites.

References

1. Borror K, Carome MA. Human research subject protections under federalwide assurance (FWA) 3136, multiple project assurances (MPA) M-1331, M-1363, and M-1338 and the OHRP-approved assurances for all ARDS Network institutions. Letter to Ronald S. Newbower, Massachusetts General Hospital, Lee E. Limbird, Vanderbilt University, and Robert Kay, the Cleveland Clinic Foundation. Rockville, MD: Office for Human Research Protections, July 3, 2003. (http://ohrp.osophs.dhhs.gov/detrm_letrs/YR03/jul03a.pdf.)

2. Chertow GM, Pascual MT, Soroko S, et al. Reasons for non-enrollment in a cohort study of ARF: The Program to Improve Care in Acute Renal Disease (PICARD) experience and implications for a clinical trials network.

Attachment A

Acute Renal Failure Trial Network
Survey of Practitioner Prescribing Practices

1. Which of the following best describes your specialty?
   [ ] Nephrologist
   [ ] Intensivist

2. Approximately how many critically ill patients with ARF do you treat who require renal replacement therapy?
   __ __ per month

3. Do you prescribe intermittent hemodialysis for critically ill patients with ARF
   [ ] Yes
   [ ] No (skip to question 10)

4. Approximately what percentage of critically ill patients with ARF who require renal replacement therapy do you treat with intermittent hemodialysis?
   __ __ %

5. For critically ill patients with ARF treated with intermittent hemodialysis, estimate the percentage of patients for whom you prescribe each of the following treatment schedules?
   __ __ % 2x/week
   __ __ % 3x/week
   __ __ % 4x/week
   __ __ % 5x/week
   __ __ % 6x/week
   __ __ % every other day
   __ __ % daily

6. What is the typical prescription that you use when prescribing intermittent hemodialysis in critically ill patients with ARF?
   Blood flow rate: __ __ __ mL/min
   Treatment duration: __ __. __ hours

7. What target dose of therapy do you aim for in prescribing intermittent hemodialysis for critically ill patients with ARF?
   __ .__ __ spKt/V or __ __% URR
   [ ] no specific target dose

8. Do you routinely measure the delivered dose of hemodialysis in critically ill patients with ARF?
   [ ] Yes
   [ ] No (skip to question 10)

9. How frequently do you measure the delivered dose of hemodialysis in critically ill patients with ARF?
    [ ] 1x/week
    [ ] 2x/week
    [ ] 3x/week
    [ ] more than 3x/week

10. Do you prescribe sustained, low-efficiency dialysis (SLED) or other forms of "slow" hemodialysis for critically ill patients with ARF?
    [ ] Yes
    [ ] No (skip to question 17)

11. Approximately what percentage of critically ill patients with ARF who require renal replacement therapy do you treat with SLED or other forms of "slow" hemodialysis?
    __ __ %

12. For critically ill patients with ARF treated with SLED or other forms of "slow" hemodialysis, estimate the percentage of patients who you prescribe each of the following treatment schedules?
    __ __ % 2x/week
    __ __ % 3x/week
    __ __ % 4x/week
    __ __ % 5x/week
    __ __ % 6x/week
    __ __ % every other day
    __ __ % daily

13. What is the typical prescription that you use when prescribing SLED or other forms of "slow" hemodialysis in critically ill patients with ARF?
    Blood flow rate: __ __ __ mL/min
    Dialysate flow rate: __ __ __ mL/min
    Treatment duration: __ __. __ hours

14. What target dose of therapy do you aim for in prescribing SLED or other forms of "slow" hemodialysis for critically ill patients with ARF?
    __ .__ __ spKt/V or __ __% URR
    [ ] no specific target dose

15. Do you routinely measure the delivered dose of SLED or other forms of "slow" hemodialysis in critically ill patients with ARF?
    [ ] Yes
    [ ] No (skip to question 17)

16. How frequently do you measure the delivered dose of SLED or other forms of "slow" hemodialysis in critically ill patients with ARF?
    [ ] 1x/week
    [ ] 2x/week
    [ ] 3x/week
    [ ] more than 3x/week

17. Do you prescribe continuous renal replacement therapy (CRRT) for critically ill patients with ARF?
    [ ] Yes
    [ ] No (skip to end)

18. Approximately what percentage of critically ill patients with ARF who require renal replacement therapy do you treat with CRRT?
    __ __ %

19. What modalities of CRRT do you utilize?
    [ ] Continuous arteriovenous hemofiltration (CAVH)
    [ ] Continuous arteriovenous hemodialysis (CAVHD)
    [ ] Continuous arteriovenous hemodiafiltration (CAVHDF)
    [ ] Continuous venovenous hemofiltration (CVVH)
    [ ] Continuous venovenous hemodialysis (CVVHD)
    [ ] Continuous venovenous hemodiafiltration (CVVHDF)

20. What blood flow rate do you usually prescribe for patients treated with CRRT?
    __ __ __ mL/min
    [ ] arteriovenous therapy – blood flow rate not specified

21. Do you prescribe CRRT based on patient weight?
    [ ] Yes (answer question 22 and then skip to question 24)
    [ ] No (skip to question 23)

22. What effluent flow rate (sum of replacement fluid, dialysate and net ultrafiltration rate) do you aim for in patients treated with CRRT?
    __ __ __ mL/kg/hr

23. What effluent flow rate (sum of replacement fluid, dialysate and net ultrafiltration rate) do you aim for in patients treated with CRRT?
    __ __ __ __ mL/hr

24. What fluid do you use for dialysate in patients treated with CRRT?
    [ ] Lactate-buffered dialysate
    [ ] Prismasate
    [ ] Normocarb
    [ ] Other: _____
    [ ] Do not use dialysate

25. What fluid do you use for replacement fluid in patients treated with CRRT?
    [ ] Lactate-buffered hemofiltration fluid
    [ ] Prismasate
    [ ] Normocarb
    [ ] Other: _____
    [ ] Do not use replacement fluid

26. Please identify your institution:

[ ] Ann Arbor VA
[ ] Buffalo VA
[ ] Dallas VA
[ ] Houston VA
[ ] Indianapolis VA
[ ] Little Rock VA
[ ] Long Beach VA
[ ] Los Angeles VA
[ ] Miami VA
[ ] Nashville VA
[ ] New Orleans VA
[ ] Pittsburgh VA
[ ] Portland VA
[ ] Richmond VA
[ ] San Diego VA
[ ] San Francisco VA
[ ] San Juan VA
[ ] Seattle VA
[ ] West Haven VA
[ ] Cleveland Clinic Foundation
[ ] Johns Hopkins Hospital
[ ] Massachusetts General Hospital
[ ] University of California, San Francisco
[ ] University of Miami/Jackson Memorial Hospital
[ ] University of Pittsburgh Medical Center
[ ] University of Texas at Houston
[ ] Wake Forrest University
[ ] Washington University in St. Louis

VA WEST HAVEN CSP530
ACUTE RENAL FAILURE TRIAL NETWORK (ATN STUDY)
Form 02-O
Entry Form for Observational Study

__ __ __ Hospital No. __ __ __ Patient ID.

A. Demographic Information

1. Age (years) __ __ years (indicate 90 if age ≥ 90 years)

2. Gender: __ male __ female

3. Racial/Ethnic Origin:
   __ White, not of Hispanic Origin
   __ Black, not of Hispanic Origin
   __ Hispanic
   __ Asian
   __ Pacific Islander
   __ American Indian/Alaskan Native
   __ Other

4. Etiology of Acute Tubular Necrosis
   a. Ischemic __ yes __ no
   b. Nephrotoxic __ yes __ no
   c. Sepsis __ yes __ no
   d. Multifactorial __ yes __no

B. Did patient receive Renal Replacement Therapy within 14 days of Screening?
__ yes __no

1. If no, please skip to the end of this form, enter date completed and staff initials, and send form to WH CSPCC.
2. If yes, complete the remainder of the form and send form to WH CSPCC

C. Renal Replacement Therapy (RRT) Data

1. Day post-screening that RRT was started. __ __(day 01=screening day)

2. Indication for RRT (choose all that apply).

   __ Volume overload [(severe peripheral edema or pulmonary edema or elevated right ventricular dysfunction) and unresponsive to diuretics]

   __ Persistent hyperkalemia ($K^+ > 6.2$mEq/L or the presence of ECG changes)

   __ Severe metabolic acidosis (pH < 7.2 or tCO_2 < 15 mEq/L)

   __ Azotemia

3. BUN on date RRT initiated: __ __ __ mg/dL

4. SOFA Cardiovascular Score at time of initiation of RRT: __

VA WEST HAVEN CSP530

ACUTE RENAL FAILURE TRIAL NETWORK (ATN STUDY)

Form 02-O

Entry Form for Observational Study

__ __ __ Hospital No. __ __ __ Patient ID

5. For days 1 through 14 post-screening, indicate whether RRT was provided and if provided, what modality was used. (day1=screening)

Day 1:	No RRT___	IHD ___SLED ___	CRRT ___
Day 2:	No RRT___	IHD ___SLED ___	CRRT ___
Day 3:	No RRT___	IHD ___SLED ___	CRRT ___
Day 4:	No RRT___	IHD ___SLED ___	CRRT ___
Day 5:	No RRT___	IHD ___SLED ___	CRRT ___
Day 6:	No RRT___	IHD ___SLED ___	CRRT ___
Day 7:	No RRT___	IHD ___SLED ___	CRRT ___
Day 8:	No RRT___	IHD ___SLED ___	CRRT ___
Day 9:	No RRT___	IHD ___SLED ___	CRRT ___
Day10:	No RRT___	IHD ___SLED ___	CRRT ___
Day11:	No RRT___	IHD ___SLED ___	CRRT ___
Day12:	No RRT___	IHD ___SLED ___	CRRT ___
Day13:	No RRT___	IHD ___SLED ___	CRRT ___
Day14:	No RRT___	IHD ___SLED ___	CRRT ___

6. Complete Form 9-O for each treatment provided in this 14 days post screening.

NOTE: Mail Form 02-O and all Forms 09-O for this patient to WH CSPCC.

__ __/__ __/__ __Date Form Completed __ __ __Staff Initials

VA Cooperative Study #530

Intensive vs. Conventional Renal Support in Acute Renal Failure

Protocol Amendment #4

July 2004

1. Purpose

This Protocol Amendment modifies several aspects of the study protocol based on issues encountered during the first six months of patient enrollment. These include:

a. Elimination of the enrollment window
b. Modification of the eligibility criteria
c. Timing of initiation of study therapy
d. Specification of modality of therapy
e. The criteria for discontinuation of renal replacement therapy

2. Elimination of the enrollment window

As currently written, the protocol specifies a specific "window" during which patients may be enrolled into the ATN Study. This window specifies that renal replacement therapy must be initiated within 48-hours of first meeting any of the following criteria for initiation of renal replacement therapy:

- BUN $\geq$ 60 mg/dL
- Volume overload
- Persistent hyperkalemia ($K^+ > 6.2$ mEq/L or the presence of ECG changes)
- Severe metabolic acidosis (pH < 7.20 or $tCO_2 < 15$ mEq/L)
- Uremic signs or symptoms

In addition, the protocol specifies that no more than one hemodialysis treatment or 24-hours of CRRT may be provided prior to enrollment.

The intent of this enrollment window was to ensure a degree of uniformity in the timing of initiation of renal replacement therapy in study subjects. A review of screening forms from patients excluded from the trial during the first six months of study enrollment has demonstrated, however, that the enrollment window has resulted in the exclusion of patients from the study who on review appear to have been appropriate candidates for the trial. ***This amendment therefore eliminates the enrollment window as currently specified.***

The majority of the criteria for initiation of renal replacement therapy specified in the enrollment window (volume overload, hyperkalemia, metabolic acidosis and overt uremic symptoms) represent urgent indications for initiation of RRT and have not posed a significant issue in study enrollment. However, the final criterion, initiation of renal replacement therapy within 48 hours of a BUN $\geq$ 60 mg/dL, has resulted in the exclusion of a substantial number of patients who, on review, appear to have been appropriate candidates for the study. The rationale for this criterion

was that delay in initiation of renal replacement therapy, as measured by severity of azotemia, has been suggested as an independent predictor of mortality in some prior studies. The intent of the enrollment window was to exclude patients in whom initiation of dialysis had been significantly delayed. However, the experience gained during the first six months of study enrollment demonstrates that this criterion is significantly discordant from current practice at the majority of participating sites; mandating the initiation of therapy at an earlier time point in the course of acute renal failure than is current clinical practice. As a result, in addition to being a barrier to patient enrollment, this criterion may potentially compromise the generalizabilty of the study's results.

This amendment eliminates the enrollment window. In place of the enrollment window, an additional exclusion criterion is added to the eligibility criteria (see below) to address the issue of inappropriate delay in initiation of renal support in ARF. This change will make the protocol more consistent with current practice patterns outside of the research setting for the management of renal replacement therapy in ARF.

3. Modification to the Eligibility Criteria (Table 1)

This amendment makes several modifications to the eligibility criteria for the purposes of clarification and to augment study enrollment. In addition, a new exclusion criterion is added, replacing the enrollment window, excluding patients in whom there is excessive delay in the initiation of renal replacement therapy. The revised inclusion and exclusion criteria are provided in Table 1.

The rationale for each change is provided below:

a. Inclusion criteria

The current definition of ARF used for the study includes oliguria, defined as a urine output of <20 mL/hour for > 24 hours. Given variability and errors in the recording of urine output, this is clarified as an ***average*** urine output of ≤ 20 mL/hour for > 24 hours.

b. Exclusion criteria

As described above, this amendment eliminates the enrollment window. Late initiation of renal support may, however, have an independent negative impact on the outcomes of patients with ARF. Although there is no general consensus regarding the optimal timing of initiation of renal replacement therapy in ARF, a threshold BUN of 100 mg/dL is commonly used in clinical practice. The prior enrollment window had utilized a threshold BUN of 60 mg/dL, requiring initiation of renal replacement therapy within 48 hours of reaching this level of azotemia. It has become apparent that this threshold for initiation of renal replacement therapy is not consistent with current practice patterns. The new exclusion criterion will exclude patients who have met the definition of ARF (as specified in the inclusion criteria) and have had a BUN > 100 mg/dL for more than 72 hours duration.

This amendment also modifies the exclusion based on weight from a pre-morbid weight of 120 kg to a pre-morbid weight of 128.5 kg, Although the exclusion for excessive weight is based on the difficulty achieving the target dose of therapy in morbidly obese patients, the exclusion weight of 120 kg was arbitrarily selected. The true maximal weight for patients enrolled in the study is dictated, however, by the technology of the most widely utilized equipment for CVVHDF, which provides a maximal flow rate for the sum of dialysate and replacement fluid of 4500 mL/hour. Given this limitation, the true upper weight limit for the study is 128.57 kg. This modification to the exclusion for excessive body weight will help facilitate patient recruitment without compromising study integrity.

This amendment clarifies the exclusion of patients not expected to survive at least 28 days because of an irreversible medical condition, by specifying that this exclusion is for expected mortality due to an irreversible ***chronic*** medical condition.

4. Timing of Initiation of Study Therapy

The protocol currently does not explicitly specify the timing of initiation of study therapy. ***This amendment therefore establishes the following guidelines for timing of initiation of study therapy:***

Study therapy is to be initiated within 24 hours of randomization. If this would necessitate initiation of IHD or SLED on a Sunday, initiation of study therapy may be deferred until the following Monday morning, if medically prudent.

If the renal replacement therapy is initiated prior to study enrollment and the initial treatment is IHD or SLED, protocol renal replacement therapy must be initiated:

- On the day subsequent to the initial treatment, if randomized to the intensive management arm (excluding Sunday for IHD and SLED); or
- Within two days of the initial treatment if randomized to the conventional management arm

If the renal replacement therapy is initiated prior to study enrollment and the initial treatment is CRRT, protocol renal replacement therapy must be initiated within 24 hours of the initiation of treatment.

5. Determination of Treatment Modality

The study protocol currently specifies that patients will be initiated on intermittent hemodialysis when the SOFA cardiovascular score is ≤ 2 and on CVVHDF or SLED when the SOFA cardiovascular score is 3 or 4. Patients treated with intermittent hemodialysis will be switched to CVVHDF or SLED if the SOFA cardiovascular score rises to 3 or 4. Patients treated with SLED or CVVHDF will be switched to intermittent hemodialysis when their SOFA cardiovascular score has fallen to 0 or 1 for at least 24 hours. The rationale for explicitly specifying criteria for selection of modality of therapy was to ensure that interconversion between modalities of therapy was uniform in the two treatment arms and did not introduce bias.

The rigidity of these criteria does not permit deviation in the selection of treatment modality when the modality specified by the protocol conflicts with the clinical judgment of the patient's treating physician. While ensuring uniformity in the selection of treatment modality is an important consideration, protection of patient safety, as perceived by the primary treating service is essential. ***This amendment modifies the criteria for selection of modality of therapy to allow deviation based on individual patient needs without constituting a protocol violation. Such deviations are to be reviewed by the Study Chairman or designee within 24 hours.***

6. Criteria for Discontinuation of Renal Replacement Therapy

The protocol establishes a measured creatinine clearance of 20 mL/min as the criterion for discontinuation of renal replacement therapy. Study sites have reported that this criterion has required the continuation of renal replacement therapy in patients with recovering renal function longer than is common in clinical practice outside of the research setting. ***This amendment therefore lowers the threshold for discontinuation of renal replacement to a measured creatinine clearance of at least 12 mL/min or the spontaneous decline in serum creatinine during an interdialytic interval. The end-point for recovery of renal function will remain unchanged, however, as a documented creatinine clearance > 20 mL/min.***

Table 1: Revised Inclusion and Exclusion Criteria

Inclusion Criteria

- Acute renal failure clinically consistent with a diagnosis of acute tubular necrosis, defined as:
    - Clinical setting of ischemic or nephrotoxic injury
      and
    - Oliguria (***average*** urine output ≤ 20 mL/hour) for > 24 hours, or an increase in serum creatinine of ≥ 2 mg/dL (males)/≥ 1.5 mg/dL (females) over a period of ≤ 4 days
- Plan for renal replacement therapy by the clinical team*
- Receiving care in a critical care unit
- One non-renal organ failure (SOFA organ system score ≥ 2) or the presence of sepsis
- Age ≥ 18 years
- Patient/surrogate willing to provide informed consent

****There are no precise, generally accepted, clinical criteria for the initiation of renal replacement therapy in patients with acute renal failure. Initiation of renal replacement therapy should therefore be based on the clinical expertise of the clinical treating services. For the purpose of this study, the following criteria are considered appropriate indications for initiation of renal replacement therapy in ARF:***

- ***Volume overload***
- ***Persistent hyperkalemia***
- ***Severe metabolic acidosis***
- ***Uremic signs or symptoms***
- ***BUN ≥ 40 mg/dL in absence of other specific indications***

Exclusion criteria

- Baseline serum creatinine > 2 mg/dL (males)/>1.5 mg/dL (females)
- Acute renal failure clinically believed to be due to an etiology other than ATN
- ***> 72 hours since meeting both of the following conditions:***
    - ***Fulfillment of the definition of ARF; and***
    - ***BUN > 100 mg/dL***
- > 1 hemodialysis treatment or > 24 hours since starting CRRT
- Prior kidney transplant
- Pregnancy
- Prisoner
- Weight ***> 128.5 kg***
- Non-candidacy for acute renal replacement therapy
- Moribund state
- Patient not expected to survive at least 28 days because of an irreversible ***chronic*** medical condition
- Comfort-measures only status
- Participation in a concurrent interventional study
- Patient/surrogate refusal
- Physician refusal

VA Cooperative Study #530

Intensive vs Conventional Renal Support in Acute Renal Failure

Protocol Amendment #5

June 2006

1. This protocol amendment extends the enrollment phase of the study by 8 months, from the originally planned 36 months to 44 months. No other aspects of the study are changed.

2. A total of 1164 subjects need to be enrolled into the study in order to be able to detect the hypothesized reduction in 60-day all-cause mortality from 55% in the conventional management arm to 45% in intensive management arm with 90% power with a two-sided α=0.05 and 10% subject attrition rate. The initial study design allocated 36 months to accrue the required study population. Based on current enrollment we project that at the end of this 36-month enrollment phase approximately 950 – 975 subjects will have been recruited. This amendment extends the enrollment phase by an additional 8 months to assure recruitment of the entire planned study cohort.