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

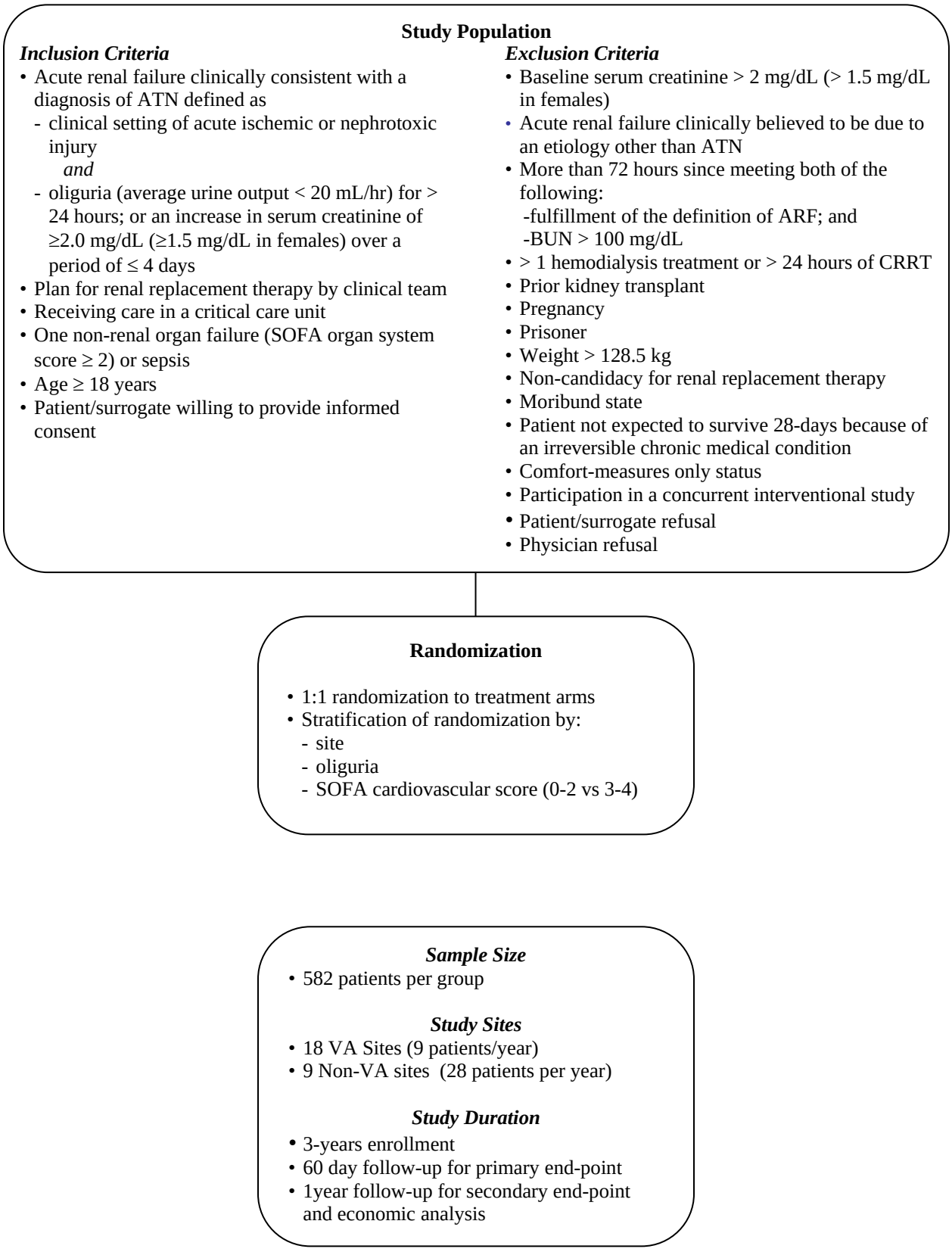

Figure 2: Overview of Study Design (continued)