Statistical Analysis Plan for a multi-centre randomised controlled trial: Nephro-protective effects of L-amino acids in critically ill patients

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BRIEF BACKGROUND

1.1 Overview:

Guided by the findings of a cluster randomised controlled trial, [1] we initiated and conducted a multi-centre, Phase II, randomised controlled trial (RCT) to determine if the provision of a continuous supplementary infusion of a standard mixture of L-amino acids protects the kidney from acute injury during critical illness.

1.2 Hypotheses to be tested:

In critically ill patients, who are at risk of developing acute kidney injury (AKI), does a continuous supplementary infusion of a standard mixture of L-amino acids prevent the onset, reduce the severity and enhance recovery from clinically significant renal dysfunction?

1.3 Eligibility criteria:

See **Appendix 1** for the complete list of study eligibility criteria, to be applied within the first two days of study ICU admission.

1.4 Randomisation:

Allocation concealment was maintained through the use of a central randomisation web site that was secure, encrypted and password protected.

The study web site was accessible 24 hours a day, seven days a week. This academic web site (http://www.EvidenceBased.net/NephroProtect) has been used to host numerous secure research projects.

The randomisation sequence was generated using SAS Version 9.2 with blocks of variable size and random seeds [2] to ensure allocation concealment could not be violated by guessing the allocation sequence at the end of each block. Randomisation was stratified within study site by APACHE II defined presence of Acute Renal Failure and Body Mass Index (BMI). Stratification variables and their thresholds were concealed from site investigators to further prevent anticipation of the allocation sequence.[3]

1.5 Study intervention:

If randomised to the intervention arm, the patient received a continuous infusion of a standard mixture of L-amino acids (Synthamin 17 Electrolyte Free, Baxter Healthcare, Australia) delivered at a rate to achieve a total daily protein intake of approximately 2.0 g/kg/day.

The initial infusion was begun at approximately 1 g/kg/day. If the patient was receiving any form of enteral or parenteral nutritional support, the infusion rate of the study L-amino acid intervention (study Synthamin 17 EF) was reduced such that the total protein intake from all sources (nutrition and study intervention) was approximately 2.0g/kg/day.

The study intervention was discontinued at discharge from the study ICU, or death, or when the patient's central venous catheter was removed.

Study nephroCALC web tool and Synthamin 17 EF infusion protocol

(https://Research.EvidenceBased.net/nephroCALC, see Appendix 2 for screen capture)

The nephroCALC study web tool calculated study Synthamin 17 EF infusion rates based on a patient's current protein intake from Enteral and Parenteral nutrition and the patient's weight. Protein intake calculations for overweight (BMI > 25) patients were based on their ideal body weight (ideal BMI set at 23).

The majority of patients commenced study Synthamin 17 EF at an infusion rate of 42 ml/h, which provided 100g protein per day.

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The protocol reduced the Synthamin 17 EF infusion to a lower rate **only** if total protein from EN, PN and study Synthamin 17 EF reached 2.5g/kg.

If total protein from EN, PN and study Synthamin 17 EF reached 2.5g/kg, the Protocol reduced the patient's study Synthamin 17 EF infusion rate such that a total protein intake of 2.0g/kg from EN, PN and study Synthamin 17 EF was achieved.

The nephroCALC study web tool was used to conduct all calculations. Results were printed or written on to a blank form to create a permanent record of calculations. It was the site investigator's responsibility to ensure that the appropriate study Synthamin 17 EF infusion rates, as calculated by the nephroCALC web tool, were effectively communicated to, and achieved by, the bedside health care team.

If a patient switched to a different brand of EN or a different type of PN, or if EN or PN was started or discontinued, the nephroCALC study web tool was used to calculate a new study Synthamin 17 EF infusion rate.

The nephroCALC study web tool was not password protected. It could be accessed by the bedside nurse on the weekend / at night if required.

1.6 Standard care:

Standard care in the patients randomised to the control arm consisted of a reasonable attempt to provide enteral or parenteral nutrition when the attending clinician judged the patient would tolerate feeding. The attending clinician selected the route, starting rate, metabolic targets, and protein goals based on current practice in their ICU.

1.7 Data collection and follow up:

Every randomised patient was followed up until hospital discharge or 90 days post-randomisation whichever was longer, unless death occurred first, as recommended by the UK Medical Research Council International Working Party for Clinical Trials in Patients with Sepsis and Septic Shock.[4] If patients remained in hospital on study Day 180, follow-up was censored and outcomes were recorded as per status at Day 180.

1.8 Summary of study outcomes:

The primary study outcome was defined as days of clinically significant renal dysfunction, adjusted for time at risk (ICU stay).

Secondary outcomes consisted of the following additional measures of renal function: Incidence of clinically significant renal dysfunction (proportion of patients per study arm); Days of Renal Replacement Therapy (RRT); Incidence of RRT (proportion of patients per study arm); Days of $eGFR_{CysC}$ < 15 mL/min/1.73 m^2; Days of $eGFR_{CysC}$ < 30 mL/min/1.73 m^2; Days of $eGFR_{CysC}$ < 60 mL/min/1.73 m^2; $eGFR_{CysC}$ values over time, difference between groups; Incidence of $eGFR_{CysC}$ < 15 mL/min/1.73 m^2 (proportion of patients per study arm); Incidence of $eGFR_{CysC}$ < 30 mL/min/1.73 m^2 (proportion of patients per study arm); Incidence of $eGFR_{CysC}$ < 60 mL/min/1.73 m^2 (proportion of patients per study arm); Days of $eGFR_{Creat}$ < 15 mL/min/1.73 m^2; Days of $eGFR_{Creat}$ < 30 mL/min/1.73 m^2; Days of $eGFR_{Creat}$ < 60 mL/min/1.73 m^2; $eGFR_{Creat}$ values over time, difference between groups; Incidence of $eGFR_{Creat}$ < 15 mL/min/1.73 m^2 (proportion of patients per study arm); Incidence of $eGFR_{Creat}$ < 30 mL/min/1.73 m^2 (proportion of patients per study arm); Incidence of $eGFR_{Creat}$ < 60 mL/min/1.73 m^2 (proportion of patients per study arm) and; continuing need for RRT at Study Day 90 (proportion of patients per study arm).

Tertiary patient oriented outcomes included: Vital status at Study Day 90; Zubrod/WHO Performance Status;[5] RAND-36 General Health Status Ver 1; and RAND-36 Physical Function scale Ver 1.[6]

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Tertiary disease oriented outcomes included: location of the patient on Day 90 follow-up (Rehabilitation ward, Acute care ward, ICU/HDU, Chronic care/Nursing home, Residential home, Hostel, Other); days of clinically significant organ dysfunction (reported by organ system);[7] ICU and hospital length of stay; vital status at hospital discharge; days of invasive mechanical ventilation; days of antibiotic usage; fluid intake; urine output; plus others.

Process measures were collected to describe the implementation of the study intervention (provision of supplementary protein). These process measures included: time from ICU admission to feeding start; time from study enrolment to feeding start; number of days of Supplementary Protein in patients allocated to receive the study intervention; mean nutrition support days per 10 patient days in patients receiving EN and or PN; mean nutrition support days per 10 patient days in patients receiving EN; mean nutrition support days per 10 patient days in patients receiving PN; percent of patients who were never fed; percent of patients fed within 24h of ICU admission; Mean energy (not including study Synthamin 17 EF) delivered in kcal/patient-day; Mean energy (including energy from study Synthamin 17 EF) delivered in kcal/patient-day; Mean total protein delivered in g/kg/patient-day; Mean energy delivered per patient for each of the first seven days of ICU stay; Mean protein delivered per patient for each of the first seven days of ICU stay.

STATISTICAL ANALYSIS

2.1 Safety and Data Monitoring Committee:

An independent Safety and Data Monitoring Committee (SDMC), comprising experts in clinical trials, biostatistics and intensive care was established. The committee reviewed information on all serious adverse events.

Using the Haybittle-Peto approach,[8;9] the SDMC was charged with informing the study management committee if there was a difference in serious adverse events between study groups that exceeded three standard deviations in magnitude.

2.2 Sample size and power:

The completed ANZ Nutrition Guidelines Trial demonstrated an overall reduction in the number of days of clinically significant renal dysfunction in all patients enrolled (1.54 vs. 2.12 renal dysfunction days per 10 patient•days, p=0.038).[1] The best estimate of potential treatment effect is obtained from the Poisson regression model submitted for publication in JAMA: the difference between 1.54 and 2.12 days is a reduction of 0.58 days of clinically significant renal dysfunction per patient per 10 ICU days. Unfortunately, the estimate of variability reported in the JAMA publication is unique to a cluster RCT. However, the variability that could be expected in an individual patient RCT can be calculated from the ANZ Nutrition Guidelines Trial database.

Although the Poisson distribution is distinct from the Normal distribution, Poisson regression is conducted in the logarithmic scale and the regression parameters are assumed to follow a Normal distribution in the logarithmic scale [10] hence standard sample size formulas for continuous outcomes can be used on the regression parameters.

In the logarithmic scale, the best estimate of the expected treatment effect is 0.54 [0.54=ln(0.58)] and the best estimate of the variance around this treatment effect is 3.31. Using standard formulae, [11] a trial of 474 patients would have 90% power to detect the expected treatment effect at the accepted two-sided significance threshold of 0.05.

2.3 Basic principles of analysis:

The primary conclusions of this project will be based on analyses conducted under the principle of intention to treat. All randomised patients will be analysed in the groups to which they were originally allocated to,

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regardless of whether they actually received the intended treatment or whether a protocol violation or protocol deviation occurred.

Patients who withdrew consent for use of their data will not be included in any analysis. Only the facts that they were enrolled into the trial and withdrew consent, and the original study group to which they were allocated, will be reported.

Two-sided 5% significance levels will be used to identify statistically significant results. A two-sided 10% significance level will be used to identify results that are trending towards statistical significance. All confidence intervals reported will be 95% confidence intervals.

Adjustments for multiplicity will not be undertaken because a hierarchy of outcomes has been stipulated [12] and because the conduct of an interim analysis using Haybittle-Peto stopping thresholds does not require adjustment of outcomes for multiplicity.[8;9] Furthermore, this is a Phase II trial with a goal of minimising Type II errors. The likelihood of Type I errors arising from this Phase II trial will be minimised by confirming key findings in a definitive Phase III trial.

2.4 Primary outcome:

The primary outcome for this clinical trial will be days of clinically significant renal dysfunction, defined according the validated global organ dysfunction scale known as the Brussels Table: serum creatinine greater than 168 μmol/L, screened whilst the patient remains in the study ICU.[7]

The Brussels Table is one of the most commonly used constructs for assessing clinically significant organ dysfunction in clinical trials conducted in critically ill patients. The Brussels Table was used to detect the improvement in clinically significant renal dysfunction observed in the ANZ Nutrition Guidelines Trial.[1]

2.5 Missing primary outcomes:

Missing primary outcomes (unknown serum creatinine values during study ICU stay) will be assumed to be missing at random (MAR) and thus will be 'ignored' in the primary analysis [13] however if greater than 1% of all primary outcomes that should be available for analysis are missing, the primary analysis will include imputed values.

If required, values will be imputed under the following assumptions: 1) imputation based on the average of immediate prior and immediate subsequent creatinine values; 2) last observation carried forward (or carried backwards in the case of missing Day 1 creatinine) and; 3) in the case of all days missing (Ex. very short stay patients), the patient-case will be excluded from analysis.[14,15] If imputation is required, results of the primary imputed analysis will take precedence over the primary MAR analysis, but will be interpreted in the context of the primary MAR analysis.

Information that is *unavailable* for analysis due to withdrawal of consent for data use will not be considered *missing* and therefore will not be included in the estimate of percent missing as described above nor will it be included in a simulation study.

2.6 Unadjusted analysis of primary outcome:

The unadjusted analysis of the effect of treatment with Supplementary Protein on the primary outcome (days of clinically significant renal dysfunction) will be assessed using Poisson regression. If the scaled deviance exceeds 1.4 units per degree of freedom, a conservative negative-binomial model will be employed instead of a Poisson model. Length of stay in the study ICU will be included as an offset term to account for time at risk.

The magnitude of the treatment effect will be reported as a rate difference between groups, with 95% confidence intervals.

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2.7 Distribution of baseline prognostic variables (aka Manuscript Table 1):

The following baseline prognostic variables, ascertained at time of study enrolment, will be reported by study group in Manuscript Table 1:

Age, Gender, BMI (as a continuous variable *and* categorised into percent underweight [BMI < 18] and not underweight [BMI ≥ 18]), APACHE II score, APACHE II defined presence of Acute Renal Failure, Source of admission to ICU (ED, OR, ward, ICU readmit, Other hospital), Surgical admission type (Elective, Emergency), Chronic Health States (Hepatic cirrhosis, Chronic dialysis, Respiratory Disease, CV Disease, Immunocompromised), APACHE III admission dx major category (Cardiovascular/vascular, Respiratory, Trauma, GI, Neuro, Sepsis, Metabolic, Haematological, Other surgical, Other medical), need for invasive mechanical ventilation, measures of organ dysfunction defined as per Brussels Table Scale and protein intake (gm/kg) from EN, PN and study Sythamin 17 EF support. Receipt of the following agents within 24 h prior to enrolment: a distal loop diuretic; acetazolamide; nephrotoxic agents and; nephrotoxic pigments. Recent history of: obstructive uropathy; oliguria and; massive transfusion. Pre-acute illness history of abnormal kidney function.

Continuous variables, which are expected to be Normally distributed, will be presented as Mean and Standard Deviation. Dichotomous variables will be presented as Numerator/Denominator and Percent.

Manuscript Table 1 will not present p-values however variables identified as meeting objective pre-established criteria for inclusion in a *covariate adjusted analysis* of the primary outcome will be marked with an asterix (*) or hash (#). The asterix (*) will denote variables that are shown to be strongly associated with outcome, which may confound even in the presence of minimal imbalance. The hash (#) will denote variables shown to have strong imbalance, which may confound even in the presence of a weaker association with outcome (See section 2.9 for complete details).

2.8 Missing baseline prognostic variables:

Exclusion of randomised patients with known outcomes from analysis, for any reason, contravenes the intention to treat principle.[16] Every effort should be made to minimise post-randomisation exclusions.[13]

By default, statistical software packages require complete information on all covariates for a patient case to be included in a covariate adjusted regression model. Any missing information from any covariate results in the exclusion of the entire patient case by the software package. Exclusion of incomplete cases with known outcomes reduces statistical efficiency and introduces bias into the estimate of treatment effectiveness.[17;18;19]

Missing baseline prognostic variables will be replaced with mean values calculated from the observed non-missing instances of that baseline prognostic variable.[20] The imputed means will be calculated using pooled data from both treatment arms. Imputed means will *not* be calculated within treatment arm using treatment arm-specific data *nor* will any post-randomisation information be incorporated into the calculation. Furthermore, replacement values for missing calculated constructs such as BMI and APACHE II score will be estimated using non-missing component-level information. For example, if one of the components of BMI is missing, such as height, overall mean height will be imputed and BMI will be calculated with the known weight and imputed mean height.

If a baseline prognostic variable requires imputation of missing values, the percent of cases that were originally missing will be reported.

2.9 Covariate adjusted analysis of primary outcome:

A *covariate adjusted analysis* of the effect of treatment on the primary outcome will be undertaken. An objective pre-specified algorithm will be used to select variables for inclusion in the covariate adjusted

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Poisson (or negative-binomial) regression model.[21] The primary purpose of the covariate adjusted analysis will be to remove bias from the estimate of the treatment effect on the primary outcome.

All prognostic variables reported in Manuscript Table 1 (see Section 2.7) will be eligible for inclusion in the covariate adjusted analysis. Variables that were stratified at randomisation (APACHE II defined presence of Acute Renal Failure, BMI) will also be eligible for inclusion in the covariate adjusted model.[21] Neither a *centre effect term* nor *any interaction terms* will be considered in the covariate adjusted model.[21]

Step 1: *Identification of prognostic variables with a strong association with outcome*
Prognostic variables shown to be strongly associated with outcome, even if not shown to be imbalanced between treatment groups, will be screened for inclusion in the covariate adjusted model as they may remove bias from the estimate of treatment effect.[21;22;23;24]

Univariate Poisson (or negative-binomial) regression analysis will be conducted to evaluate the relationship between each prognostic variable identified in Section 2.7 *and the study primary outcome*.

Prognostic variables with a Likelihood Ratio Test (LRT) p-value less than or equal to 0.15 will qualify for evaluation in the *maximum covariate adjusted model* (see Step 3).[25] Inferences will not be drawn from the interpretation of this univariate p-value, the p-value will simply be used to describe the *strength* of association between the prognostic variable and the primary outcome.[23]

Step 2: *Identification of prognostic variables with strong imbalance between treatment groups*
Prognostic variables shown to be strongly imbalanced between treatment groups, even if associations with outcome are shown to be weak, will be screened for inclusion in the covariate adjusted model as they may remove bias from the estimate of treatment effect.[21;22;23]

Univariate logistic regression analysis will be conducted to evaluate the relationship between each prognostic variable identified in Section 2.7 *and allocated treatment group*.

Prognostic variables with a LRT p-value less than or equal to 0.15 will qualify for evaluation in the *maximum covariate adjusted model* (see Step 3).[25] Inferences will not be drawn from the interpretation of this p-value, the p-value will simply be used to describe the *strength* of imbalance between treatment groups.[23]

We acknowledge that simulation studies demonstrate the addition of this step *may not* improve performance over 'predictor' detection alone (Step 1) however these simulations are not definitive.[24] 'Imbalance' detection *may* help preserve the face validity of the covariate adjusted results [26] and *may* remove bias from the estimate of treatment effect.[25;26]

Step 3: *Backwards stepwise elimination from the maximum model*
Parsimony must be embraced during the development of a covariate adjusted *Poisson* regression model because covariate adjustment may not always increase precision in the way that would be expected in a *least-squares* regression model for a continuous outcome.[21] Indeed, if a covariate does not reduce bias in the estimate of treatment effect, there may be no practical gains from its inclusion in a covariate adjusted *Poisson* regression model.[25]

All prognostic variables identified by Step 1 and Step 2 will be included in a *maximum covariate adjusted regression model.* The treatment group term (Protein Supplementation vs. standard care) will be forced to stay in the maximum model. The model outcome will be the study primary outcome.

If the maximum model demonstrates issues arising due to collinearity based on Eigenanalysis and Condition Number, collinearity will be addressed by standardizing and scaling of continuous variables before backwards stepwise elimination begins.[27]

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Step 3a: Prognostic variables will be eliminated from the maximum model, one variable at each step, if their multivariate LRT p-value is greater than 0.10.

Step 3b: From the subset of prognostic variables remaining after Step 3a, prognostic variables will be eliminated from the maximum model, one variable at each step, if their multivariate impact on bias in the estimate of the treatment effect is negligible.[28;29] A negligible impact will be defined as less than 5% change in the regression coefficient for the treatment effect after stepwise removal of the prognostic variable from the subset model.[24]

Step 4: *Final covariate adjusted model*
The *final* covariate adjusted model will contain all prognostic variables known to have a meaningful impact on bias in the estimate of the treatment effect as identified by the execution of Steps 1 to 3 (above). The complete *final* model will be presented as the *covariate adjusted model* in the primary paper.

The LRT p-value for the estimate of treatment effect from this model will be reported.

3.0 Estimated glomerular filtration rate (eGFR)

3.1 eGFR calculated serum cystatin C

Serum samples for cystatin C assay were obtained at baseline enrolment and while the patient remained in the study ICU on Study Day 1 and every second day for the first seven days followed by every third day up to Study Day 16.

eGFR will be calculated from cystatin C ($eGFR_{CysC}$) using the formula developed by Stevens *et al*: [30]

$$\text{Equation 2: } eGFR = 127.7 * CysC^{-1.17} * age^{-0.13} * (0.91 \text{ if female})$$

Note: *coefficients above are as originally reported by Stevens, assuming American units for CysC (mg/L).*

3.2 eGFR calculated from serum creatinine

eGFR will be calculated from creatinine ($eGFR_{Creat}$) using the CKD-EPI equations developed by Levey *et al*:[31]

	serum creatinine (μmol/L)	
Female	≤62	$eGFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62	$eGFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80	$eGFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80	$eGFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$

Note: *coefficients above are as originally reported by Levey, assuming American units for Scr (mg/L).*

4.0 Analysis of secondary outcomes: Additional measures of renal function

Incidence of clinically significant renal dysfunction (proportion of patients per study arm): assessed using an exact Pearson chi-square test with unconditional exact 95% confidence intervals around the risk difference (RD). No imputed values, MAR analysis only.

Days of Renal Replacement Therapy (RRT): assessed using Poisson regression. If the scaled deviance exceeds 1.4 units per degree of freedom, a conservative negative-binomial model will be employed instead. Length of stay in the study ICU will be included as an offset term to account for time at risk. The magnitude of the treatment effect will be reported as a rate difference between groups, with 95% confidence intervals. No imputed values, MAR analysis only.

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Incidence of RRT (proportion of patients per study arm): assessed using an exact Pearson chi-square test with unconditional exact 95% confidence intervals around the RD. No imputed values, MAR analysis only.

Days of $eGFR_{CysC}$ *< 15 mL/min/1.73* m^2: assessed using Poisson regression. If the scaled deviance exceeds 1.4 units per degree of freedom, a conservative negative-binomial model will be employed instead. Length of stay in the study ICU, up to Day 16, will be included as an offset term to account for time at risk. The magnitude of the treatment effect will be reported as a rate difference between groups, with 95% confidence intervals. Missing values will be assessed and imputed as per Section 2.5.

Days of $eGFR_{CysC}$ *< 30 mL/min/1.73* m^2: assessed using Poisson regression. If the scaled deviance exceeds 1.4 units per degree of freedom, a conservative negative-binomial model will be employed instead. Length of stay in the study ICU, up to Day 16, will be included as an offset term to account for time at risk. The magnitude of the treatment effect will be reported as a rate difference between groups, with 95% confidence intervals. Missing values will be assessed and imputed as per Section 2.5.

Days of $eGFR_{CysC}$ *< 60 mL/min/1.73* m^2: assessed using Poisson regression. If the scaled deviance exceeds 1.4 units per degree of freedom, a conservative negative-binomial model will be employed instead. Length of stay in the study ICU, up to Day 16, will be included as an offset term to account for time at risk. The magnitude of the treatment effect will be reported as a rate difference between groups, with 95% confidence intervals. Missing values will be assessed and imputed as per Section 2.5.

$eGFR_{CysC}$ *values over time, difference between groups*: assessed using a fully factorial ANOVA. The fully factorial ANOVA is a form of repeated measures analysis that does not require complete cases, thus patients are not excluded if any single value is missing. No imputed values, MAR analysis only.

Incidence of $eGFR_{CysC}$ *< 15 mL/min/1.73* m^2 *(proportion of patients per study arm):* assessed using an exact Pearson chi-square test with unconditional exact 95% confidence intervals around the RD. No imputed values, MAR analysis only.

Incidence of $eGFR_{CysC}$ *< 30 mL/min/1.73* m^2 *(proportion of patients per study arm):* assessed using an exact Pearson chi-square test with unconditional exact 95% confidence intervals around the RD. No imputed values, MAR analysis only.

Incidence of $eGFR_{CysC}$ *< 60 mL/min/1.73* m^2 *(proportion of patients per study arm):* assessed using an exact Pearson chi-square test with unconditional exact 95% confidence intervals around the RD. No imputed values, MAR analysis only.

Days of $eGFR_{Creat}$ *< 15 mL/min/1.73* m^2: assessed using Poisson regression. If the scaled deviance exceeds 1.4 units per degree of freedom, a conservative negative-binomial model will be employed instead. Length of stay in the study ICU will be included as an offset term to account for time at risk. The magnitude of the treatment effect will be reported as a rate difference between groups, with 95% confidence intervals. Missing values will be assessed and imputed as per Section 2.5.

Days of $eGFR_{Creat}$ *< 30 mL/min/1.73* m^2: assessed using Poisson regression. If the scaled deviance exceeds 1.4 units per degree of freedom, a conservative negative-binomial model will be employed instead. Length of stay in the study ICU will be included as an offset term to account for time at risk. The magnitude of the treatment effect will be reported as a rate difference between groups, with 95% confidence intervals. Missing values will be assessed and imputed as per Section 2.5.

Days of $eGFR_{Creat}$ *< 60 mL/min/1.73* m^2: assessed using Poisson regression. If the scaled deviance exceeds 1.4 units per degree of freedom, a conservative negative-binomial model will be employed instead. Length of stay in the study ICU will be included as an offset term to account for time at risk. The magnitude of the

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treatment effect will be reported as a rate difference between groups, with 95% confidence intervals. Missing values will be assessed and imputed as per Section 2.5.

$eGFR_{Creat}$ values over time, difference between groups: assessed using a fully factorial ANOVA. The fully factorial ANOVA is a form of repeated measures analysis that does not require complete cases, thus patients are not excluded if any single value is missing. No imputed values, MAR analysis only.

Incidence of $eGFR_{Creat}$ < 15 mL/min/1.73 m^2 (proportion of patients per study arm): assessed using an exact Pearson chi-square test with unconditional exact 95% confidence intervals around the RD. No imputed values, MAR analysis only.

Incidence of $eGFR_{Creat}$ < 30 mL/min/1.73 m^2 (proportion of patients per study arm): assessed using an exact Pearson chi-square test with unconditional exact 95% confidence intervals around the RD. No imputed values, MAR analysis only.

Incidence of $eGFR_{Creat}$ < 60 mL/min/1.73 m^2 (proportion of patients per study arm): assessed using an exact Pearson chi-square test with unconditional exact 95% confidence intervals around the RD. No imputed values, MAR analysis only.

Continuing need for RRT at Study Day 90 (proportion of patients per study arm): assessed using an exact Pearson chi-square test with unconditional exact 95% confidence intervals around the RD. No imputed values, MAR analysis only.

4.1 Covariate adjusted analysis of secondary outcomes

If the results of the covariate adjusted analysis of the primary outcome differ in any meaningful way from the results of the unadjusted analysis of the primary outcome with regards to statistical significance thresholds or estimation of the magnitude of treatment effect, unique covariate adjusted models will be developed for *each* secondary outcome listed in Section 4.0 using an objective pre-specified algorithm as detailed in Section 2.9.

5.0 Tertiary patient oriented outcomes: Establishing Minimal Important Differences:

Within the context of the interpretation of health-related quality of life (HRQoL) measures, a Minimal Important Difference (MID) is defined as a magnitude of change in (or difference between) HRQoL scores that is "consistent with real, as opposed to statistically significant, benefit."[32] We will therefore define our thresholds for MIDs for each HRQoL measure *a priori*.

In the situation where *statistically significant* results are reported *and* the magnitude of the differences between HRQoL measures is *greater than or equal to* the MID, the results will be interpreted as representing statistically significant findings that have a *clinically meaningful* impact on the patient's HRQoL.

If the results are found to be *statistically significant* and the magnitude of difference is *less than* the MID, the findings will be interpreted to be statistically significant only.

Because the *responsiveness* of an HRQoL instrument varies between patient populations and disease states, it is accepted that for any particular HRQoL instrument, the MID may also be unique to each patient population and disease state.[33] When the *responsiveness* of a specific HRQoL instrument has not been formally studied in a particular patient population or disease state, it is recommended that a formal method should be used to establish the population-disease specific MID using data collected from that particular population or disease state.[33]

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Responsiveness and MIDs for each of the three HRQoL scales used in this trial (Zubrod/WHO Performance Status; RAND-36 General Health Status; and the RAND-36 Physical Function scale) have not been reported for the patient population enrolled in the Nephro-Protective Trial. We will therefore use a formal analytic approach to establish MID thresholds for each HRQoL scale.[33]

Using the approach proposed by Juniper[34] and validated by Norman[32], we will define a MID as one half the Standard Deviation (SD) of the pooled results for that scale.[33] Furthermore, differences in the magnitude of 1 SD will be described as having a *moderate* impact on HRQoL and differences in excess of 1.5 SDs will be described as having a *large* effect on HRQoL.[34]

5.1 Scoring HRQoL measures:

The Zubrod/WHO Performance Status and RAND 36 Item Health Survey 1.0 domains will be scored on patients alive at Day 90 follow-up using the appropriate scale-specific standard scoring algorithms.[5;6]

At the time study instruments were selected for use in the Nephro-Protective Trial, it was recognised the RAND 36 Physical Function domain may not be a sensitive measure of differences between groups of bedbound patients due to a large percent of bedbound patients reporting physical function that results in a minimum score (known as 'flooring out'). To address this issue, we developed and pre-tested three additional physical function questions, worded in the style of the RAND 36, that are more appropriate to bedbound patients. These items asked the patient whether they were able to: Make themselves comfortable in bed; Eat or feed themselves and; Walk short distances, such as from the bed to a nearby chair.

Scores from the original 10 question RAND 36 Physical Function scale will take precedence over scores from the 13 question *extended* RAND 36 Physical Function scale unless the original RAND 36 Physical Function scores demonstrate a loss of responsiveness due to greater than 15%[35] of respondents reporting minimum scores (excessive flooring).

In the case of excessive flooring, scores from the *extended* RAND 36 Physical Function scale will take precedence over the original scale. The results of both the original and *extended* RAND 36 Physical Function scales will be reported.

5.2 Missing HRQoL outcomes:

Missing HRQoL outcomes will be assumed to be missing at random (MAR) and thus will be 'ignored' in analysis [13] however if greater than 1% of all HRQoL outcomes that should be available for analysis are missing, a sensitivity analysis will be undertaken in addition to the primary MAR analysis.

This sensitivity analysis for missing HRQoL outcomes will be limited to an evaluation of the results of regression model imputation using all available information.[15] Results of the primary MAR analysis will be interpreted in the context of this sensitivity analyses.

Information that is *unavailable* for analysis due to withdrawal of consent for data use or death before Day 90 will not be considered *missing* and therefore will not be included in the estimate of percent missing as described above nor will it be included in a simulation study of the HRQoL outcomes.

6.0 *A priori* defined subgroup analysis:

A priori identified subgroup analysis will be conducted on APACHE II defined Acute Renal Failure (present/absent) and BMI ≤ 18 at baseline.

Screening for differential subgroup treatment effects on the primary study outcome will be conducted using a formal test of interaction. The p-value for this interaction term will be obtained from an LRT.

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The Poisson regression model will contain a main effect term denoting the specific subgroup of interest, a main effect term for treatment group and a subgroup × treatment interaction term. If the two-sided LRT p-value for this test of the subgroup × treatment interaction term is less than 0.10, the presence of differential treatment effects within subgroups will be reported in the primary publication along with the LRT p-value for the interaction term.

Detailed subgroup analysis will be undertaken *only* within subgroups identified to have differential treatment responses by the screening process described above. Detailed subgroup analysis will adhere to the same analytic principles and plan outlined for the overall study results. Detailed subgroup analysis will include reassessment of the baseline distribution of prognostic variables within the subgroup of interest, development of a subgroup appropriate covariate adjusted model and reassessment of all study outcomes within the subgroup. The results of any detailed subgroup analysis will be reported in subsequent papers, to be submitted for publication soon after the submission of the primary publication.

The number of *a priori* subgroup analyses (**2**) will be reported in all publications. Due to the use of conservative tests of interaction to screen for the need to conduct detailed analysis within subgroups, no corrections to p-values will be undertaken for multiple-comparisons.

6.1 Exploratory, hypothesis generating subgroup analyses:

No hypothesis generating subgroup analyses, including efficacy subset type analyses,[13] will be undertaken for or reported in the primary publication.

However, the study protocol does report an intent to undertake exploratory analyses to determine if any demographic or physiological measures recorded at entry into the trial (Section 2.7) can identify patient groups most likely to benefit from treatment in order to inform the design of any subsequent clinical trials.

If any hypothesis generating subgroup analyses are reported in subsequent publications, they will be clearly identified as hypothesis generating when reported.

The number of *a priori* subgroup analyses will be reported in all publications along with the total number of any *hypothesis generating* subgroup analyses previously undertaken.

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Appendix 1: Detailed Study Inclusion and Exclusion Criteria

Inclusion Criteria

Patients will be considered ***eligible*** for the trial if ***all*** of the following *inclusion criteria* are met at the time of screening:

1) Is the patient currently on their First or Second calendar day of admission to the study ICU?

2) Is the patient expected to remain in the study ICU today and tomorrow?

3) Does the patient have a working central venous access line through which the study intervention could be delivered?

4) Is the patient able to tolerate at least 1L of fluid volume per day?
[The study intervention may involve the delivery of up to one litre of amino acids per day. This volume of amino acids can replace equivalent volumes from other fluids being received.]

5) Is the patient 18 years of age or older?

See next page for Exclusion Criteria.

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Exclusion Criteria

Patients will be considered ***ineligible*** for the trial if ***any*** of the following *exclusion criteria* are met at the time of screening: (Answer **NO** to all questions)

Note: The Exclusion criteria are continued over two pages:

1) Is the patient currently receiving an NSAID with specific emphasis on COX-2 inhibitors?

[*'Currently receiving'* means the patient will continue to receive the NSAID or COX-2 inhibitor during their ICU stay. If the patient does NOT plan to continue receiving one of these drugs daily, they may be enrolled: the COX-2 inhibitors Celecoxib, Paracoxib, Etoricoxib or > 160mg Aspirin or any dose of Ibuprofen, Naproxen, Piroxicam, Indomethacin, Meloxicam, Mefenamic Acid, Diclofenac, Prioxicam, Ketoprofen, Tiaprofenic Acid, Ketorolac.]

2) Is the patient currently enrolled into a clinical trial evaluating a nitric oxide (NO) inhibitor?

3) Is the patient currently receiving Acetazolamide, which is a diuretic that works on the proximal tubule?

4) Is the patient's current serum creatinine greater than the allowable age and gender adjusted maximum reported in the Maximum Creatinine Table? (see page 19)

5) Does the patient have severe Acute Kidney Injury, defined as:

Current serum creatinine (SCr) increased 3 times pre-acute illness value OR

SCr >350 μmol/L with recent increase greater than 44 μmol/L?

[**Note**: If pre-acute illness creatinine values are unknown, assume upper limit of normal: 90 μmol/L for females and 110 μmol/L for males.]

6) Is the patient currently receiving or scheduled for dialysis / renal replacement therapy?

7) Has the patient ever had a kidney transplant?

8) Is the patient expected to receive palliative care only and is not expected to survive ICU or hospital discharge?

9) Is the patient moribund and not expected to survive 24 hours?

10) Is the patient brain dead or suspected to be brain dead?

Continued on next page.....

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Exclusion Criteria *continued*

Patients will be considered ***ineligible*** for the trial if ***any*** of the following *exclusion criteria* are met at the time of screening: (Answer **NO** to all questions)

11) If the patient has been admitted to the study ICU directly from another ICU, is the total number of calendar days from other ICU admission until today greater than two calendar days?

12) Does the patient require treatment of a burn injury to greater than 20% of total body surface area?

13) Has the patient been taking Nardil (phenelzine) within the last 6 weeks?
[Nardil (phenelzine) is an uncommonly used anti-depressant. It may be used in people who are resistant to other treatment for major depression or anxiety disorders. Because of its unique side-effect profile, and explicit drug interactions (meperidine, epinephrine, norepinephrine), a history of Nardil (phenelzine) use is usually found clearly documented in the patient's charts.]

14) Has the patient previously been enrolled and randomised into this study?

15) Does the patient have a documented contraindication to the study intervention (IV amino acids), as listed on the TGA product licensing document?

Australian Therapeutic Goods Association Product Licensing Contraindications, Synthamin 17 EF:
(Answer **NO** to all questions)

15A. Is the patient known to be pregnant or currently breastfeeding?

15B. Does the patient have severe liver disease (Biopsy proven cirrhosis, or documented portal hypertension with a known past history of either upper GI bleeding attributed to portal hypertension or of hepatic failure leading to encephalopathy / coma)?

15C. Does the patient have a documented hypersensitivity (known allergy) to one or more of the included amino acids?
[Known allergies will be clearly documented in the Patient's Charts. See Product Details for complete list of Ingredients.]

15D. Does the patient have a documented inborn error of amino acid metabolism?
[Ex. Phenylketonuria (PKU), Maple Syrup Urine Disease. These disorders are actively screened for during childhood. If present, they will be clearly documented in the patient's charts and will likely be accompanied by strict directions to consult a Dietitian prior to providing nutritional support. Other less common inborn errors include: atypical phenylketonuria, hereditary tyrosinaemia, biotinidase deficiency, methylmalonic aciduria, glutaric acidemia, methylglutaconic acidemia.]

<end exclusion criteria>

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Maximum Creatinine Table

Age and Gender adjusted maximum allowable creatinine for enrolment.

See Exclusion Criteria 4.

Females										
Age (years)	*18*	*19*								
serum Creatinine (μMol/L)	284	282								
Age (years)	*20*	*21*	*22*	*23*	*24*	*25*	*26*	*27*	*28*	*29*
serum Creatinine (μMol/L)	279	277	274	272	270	268	266	265	263	261
Age (years)	*30*	*31*	*32*	*33*	*34*	*35*	*36*	*37*	*38*	*39*
serum Creatinine (μMol/L)	260	258	257	255	254	253	252	250	249	248
Age (years)	*40*	*41*	*42*	*43*	*44*	*45*	*46*	*47*	*48*	*49*
serum Creatinine (μMol/L)	247	246	245	244	243	242	241	240	239	238
Age (years)	*50*	*51*	*52*	*53*	*54*	*55*	*56*	*57*	*58*	*59*
serum Creatinine (μMol/L)	237	237	236	235	234	234	233	232	231	231
Age (years)	*60*	*61*	*62*	*63*	*64*	*65*	*66*	*67*	*68*	*69*
serum Creatinine (μMol/L)	230	229	229	228	227	227	226	226	225	224
Age (years)	*70*	*71*	*72*	*73*	*74*	*75*	*76*	*77*	*78*	*79*
serum Creatinine (μMol/L)	224	223	223	222	222	221	221	220	220	219
Age (years)	*80*	*81*	*82*	*83*	*84*	*85*	*86*	*87*	*88*	*89*
serum Creatinine (μMol/L)	219	218	218	217	217	216	216	215	215	215
Age (years)	*90*	*91*	*92*	*93*	*94*	*95*	*96*	*97*	*98*	*99*
serum Creatinine (μMol/L)	214	214	213	213	213	212	212	211	211	211
Age (years)	*100*	*101*	*102*	*103*	*104*	*105*	*106*	*107*	*108*	*>109*
serum Creatinine (μMol/L)	210	210	209	209	209	208	208	208	207	203

Males										
Age (years)	*18*	*19*								
serum Creatinine (μMol/L)	368	365								
Age (years)	*20*	*21*	*22*	*23*	*24*	*25*	*26*	*27*	*28*	*29*
serum Creatinine (μMol/L)	361	358	355	353	350	347	345	343	341	338
Age (years)	*30*	*31*	*32*	*33*	*34*	*35*	*36*	*37*	*38*	*39*
serum Creatinine (μMol/L)	336	335	333	331	329	327	326	324	323	321
Age (years)	*40*	*41*	*42*	*43*	*44*	*45*	*46*	*47*	*48*	*49*
serum Creatinine (μMol/L)	320	318	317	316	315	313	312	311	310	309
Age (years)	*50*	*51*	*52*	*53*	*54*	*55*	*56*	*57*	*58*	*59*
serum Creatinine (μMol/L)	308	306	305	304	303	302	301	301	300	299
Age (years)	*60*	*61*	*62*	*63*	*64*	*65*	*66*	*67*	*68*	*69*
serum Creatinine (μMol/L)	298	297	296	295	294	294	293	292	291	291
Age (years)	*70*	*71*	*72*	*73*	*74*	*75*	*76*	*77*	*78*	*79*
serum Creatinine (μMol/L)	290	289	288	288	287	286	286	285	284	284
Age (years)	*80*	*81*	*82*	*83*	*84*	*85*	*86*	*87*	*88*	*89*
serum Creatinine (μMol/L)	283	283	282	281	281	280	280	279	278	278
Age (years)	*90*	*91*	*92*	*93*	*94*	*95*	*96*	*97*	*98*	*99*
serum Creatinine (μMol/L)	277	277	276	276	275	275	274	274	273	273
Age (years)	*100*	*101*	*102*	*103*	*104*	*105*	*106*	*107*	*108*	*>109*
serum Creatinine (μMol/L)	272	272	271	271	270	270	269	269	269	264

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Appendix 2: https://research.EvidenceBased.net/NephroCALC / Synthamin 17 EF Infusion Protocol

Nephro-Protective Trial: Amino Acid Infusion Protocol

Date and Time: **Wednesday, 23 January 2013 6:27:06 AM**

Patient:

Weight: *kg* **Height:** *cm*

EN Name: **EN Bag Size:** *mLs*

EN Protein: *g/Bag* Calculated EN Protein content: *g/L*

EN gut protective rate: *High protein EN at low constant rate and patient also receiving PN*

PN Name: **PN Bag Size:** *mLs*

PN Nitrogen: *g/Bag* Calculated PN Protein content: *g/L*

Note: 1 g Nitrogen = 6.06 g Amino Acids, 1 g Amino Acids = 1 g Protein. To convert Protein to Nitrogen, divide Protein by 6.06.

*Study Synthamin 17 EF does **not** count towards protein or nitrogen intake from PN.*

Reset Form | Calculate Rates | Print

Begin infusion within 1 hour of randomisation.

- **Commence Synthamin 17 EF** at ml/hr continuously over **24 hrs** via a central venous catheter. *Note: Patient remains on this initial rate for entire ICU stay, unless threshold Nutrition Rate is exceeded.*
- This patient's **maximum** Synthamin 17 EF infusion rate is: **mls/h**.
- **Nutrition Rate** is calculated at the bedside as the sum of the current EN delivery rate *plus* PN infusion rate, expressed in mls/hr. Glucose alone, Study Syntamin 17 EF and Propofol do not count as PN.
- **IF** patients current Nutrition Rate **exceeds** the threshold Nutrition Rate, use the following table to *reduce* Synthamin 17 EF infusion rates:

Nutrition Rate exceeds:	ml/hr change Synthamin 17 EF to:	ml/hr
Nutrition Rate exceeds:	ml/hr change Synthamin 17 EF to:	ml/hr
Nutrition Rate exceeds:	ml/hr change Synthamin 17 EF to:	ml/hr
Nutrition Rate exceeds:	ml/hr change Synthamin 17 EF to:	ml/hr

- **IF** patient Nutrition Rate **decreases**, use table to ***increase*** Synthamin 17 EF rates.
- **IF** patient Nutrition Rate drops to **zero**, ***increase*** Synthamin 17 EF to **mls/h**.
- **IF** patients current type of **nutritional support is changed** (Ex. current Brand of EN or PN stopped/ new Brand added), print new Amino Acid Infusion Protocol Form using study web site: **https://research.evidencebased.net/NephroCalc**.
- **Recommend** routine clinical evaluation and laboratory measurement of glucose, serum proteins, kidney and liver function tests, and serum electrolytes, as clinically appropriate.

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BMI: Wt used for calcs: Protein level used for calcs:

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