Statistical Analysis Plan for a multi-centre randomised controlled trial: Management of Refeeding Syndrome in Critical Illness

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on behalf of the Refeeding Syndrome Trial Management Committee.

The Refeeding Syndrome Trial

A clinical trial endorsed by the Australasian Society for Parenteral and Enteral Nutrition (AuSPEN).

National Health and Medical Research Council Project Grant Number 632615

Australian and New Zealand Clinical Trials Registry Number 12609001043224

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DOI: http://dx.doi.org/10.4451/Refeeding_SAP

DOI: 10.4451/Refeeding_SAP
Title: **Statistical Analysis Plan for a multi-centre randomised controlled trial: Management of Refeeding Syndrome in Critical Illness.**
Edition: Version 1
Author/Contributor: Doig, Gordon S; Simpson, Fiona; Heighes, Philippa T;
Date of Publication: 29 May 2014 (First Draft), 20 June 2014 (Final Version)
Format: WEB
Size: 297x210
No. of Pages: 22
Publisher: EvidenceBased.net, Sydney, NSW, Australia.

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20 June 2014

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Version 1, 20 June 2014.
DOI: http://dx.doi.org/10.4451/Refeeding_SAP

BRIEF BACKGROUND

1.1 Overview:

Given equipoise established by a survey of current practice demonstrating that only 40-50% of critically ill patients with refeeding syndrome are managed with energy restriction by intensive care specialists in Australia and New Zealand, [1] we initiated and conducted a multi-centre randomised controlled trial (RCT) to evaluate the efficacy and effectiveness of restricting energy intake during the management of refeeding related hypophosphatemia in critically ill patients.

1.2 Hypotheses to be tested:

In critically ill patients with refeeding related hypophosphatemia under the care of an ICU specialist who plans to continue or increase nutrition support, does energy restriction affect the duration of critical illness, and other measures of morbidity, compared to standard care plans?

1.3 Eligibility criteria:

See **Appendix 1** for the complete list of study eligibility criteria, to be applied within 72 h of commencing nutrition support after admission to a study ICU.

Note: Study Inclusion Criteria 3 and 4 required the calculation of the patient's energy intake:

3) Has the patient received at least 500 kcals energy from nutrition support over the previous 24 h?

4) Is the patient's current total energy intake from nutrition support at least 30 kcals per hour?

> [*Nutrition support* was defined as enteral nutrition, parenteral nutrition or an intravenous infusion of any solution containing ≥ 10% glucose/dextrose. Energy (calories) from propofol or boluses of glucose/dextrose solutions did not count towards energy intake from *nutrition support*.]

The study web site provided a tool to allow consistent calculation of current energy intake at all sites. The *study nrgCalc tool* (https://research.EvidenceBased.net/nrgCalc, See **Appendix 2** for Screen Capture) was not password protected, to allow site researchers and other healthcare staff to access the tool after hours and on weekends if required.

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/Refeeding) 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 initial serum phosphate level and body mass index (BMI). Stratification variables and their thresholds were concealed from site investigators to further prevent anticipation of the allocation sequence. [2]

1.5 Blinding:

Because certain ICU-based infections are notoriously subjective to diagnose, an objective grading scheme based on infecting organism, site of infection and known impact on outcome, [3,4] was used to identify clinically important infectious complications, with key aspects of the diagnosis of certain infections (Ex. interpretation of chest x-rays for grading of the Clinical Pulmonary Infection Score [4]) ascertained in a blinded fashion.

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1.6 Study intervention:

If randomised to the intervention arm, the patient received nutrition support directed by the study **Caloric Management Protocol** (**Appendix 3a**).

The study **Caloric Management Protocol** required caloric intake to be decreased to 20 kcals/h for at least 2 days (48 h). If serum phosphate did not need to be replaced by the end of this 2 day period (defined by study protocol, **Appendix 3a**) caloric intake was gradually returned to normal by following the study **Gradual Return to Normal Intake Protocol** (**Appendix 3b**).

All study interventions and management protocols were discontinued when the patient was discharged from the study ICU.

1.7 Pragmatic Standard Care:

Standard care in the patients randomised to the control arm consisted of continuing or increasing nutrition support, as planned prior to study enrolment. The attending clinician selected the route, rate of increase and metabolic targets based on their current standard practice.

1.8 Serum Phosphate Replacement Protocol (Appendix 4):

Because different clinicians use different clinical triggers and prescribe different doses for phosphate replacement, potential confounding was reduced by the use of a protocol to guide phosphate replacement at all study sites in patients randomised to receive the study intervention (Caloric Management) ***and*** in patients randomised to receive Standard Care.

After a thorough review of all available evidence conducted independently by three members of the Management Committee, a previously published protocol known to be safe and efficacious was implemented in all study patients (**Appendix 4**). [5]

All study interventions and management protocols were discontinued when the patient was discharged from the study ICU.

1.9 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.

1.10 Summary of study outcomes:

The study primary outcome was *ICU free days*.

ICU free days is a conceptual extension of the composite outcome measure known as *ventilator free days (VFDs).* Schoenfeld *et al* proposed the construct referred to as VFDs in 2002 [6] and conducted simulation studies to evaluate the performance of VFDs. These studies demonstrated the use of VFDs as a primary outcome can improve statistical efficiency *if* the intervention under study results in a moderate reduction in duration of ventilation ***and*** a moderate reduction in mortality. However, these simulations also demonstrated the interrelationship between duration of ventilation, mortality and follow-up time is complex. [6] Therefore the primary outcome *ICU free days* will be interpreted in the context of the *direction and magnitude* of any effect on ICU length of stay, ICU mortality and time to ICU mortality.

Secondary outcomes consisted of the following: infectious complications; [3,4,7] days of systemic antibiotic treatment; measures of immune function and inflammation [monocyte count, Natural Killer (NK) cells, CD_4 and CD_8 cell marker status and Interleukin (IL)-6]; days of mechanical ventilation; days of respiratory failure; hormones associated with energy utilisation [adiponectin, leptin, insulin-like growth factor 1 (IGF-1), and

insulin]; exogenous insulin infusion requirements; serum glucose levels; daily dose of (oral and IV) phosphate supplementation received; days of moderate (<0.65 mmol/L) [8] and days of severe (<0.32 mmol/L) [8] hypophosphatemia; lowest daily serum potassium and phosphate levels; days of organ dysfunction by individual organ system; days of multiple (>2) organ dysfunction syndrome; sum total of number of organ systems failing per day; [7,9] days of renal replacement therapy; days of hypoalbuminaemia (<25g/L); pressure ulcer treatment days; witnessed pulmonary aspiration days; aspiration related pneumonitis; abnormal QT interval; and at sites able to undertake cardiac ultrasound, ejection fraction calculated from an apical 4-chamber or 2-chamber view.

Tertiary outcomes included: Physical Function and Quality of Life at Day 90, characterised using the Zubrod / Eastern Cooperative Oncology Group (ECOG) / WHO Performance Status Scale [10] and the public domain version of the SF-36 questionnaire; [11] vital status at hospital discharge and at Day 90 and; location of the patient at Day 90 follow-up (Rehabilitation ward, Acute care ward, ICU/HDU, Chronic care/Nursing home, Residential home, Hostel, Other).

Process measures were collected to describe the implementation of the study intervention whilst in the study ICU. These measures included: energy from nutrition support delivered per day; protein delivered per day; receipt of high-energy or high-protein oral supplements; daily thiamine dose; provision of other vitamins/minerals and trace elements plus other detailed measures of nutritional support provided whilst in the study ICU. [7]

Estimates of marginal differences in major measures of acute care hospital resource consumption and patient outcomes generated by this trial will be combined with published costs of care to generate an economic simulation to investigate the cost-implications of the study intervention.

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, [12,13] 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:

Sample size estimates for the Refeeding Syndrome Trial were based on data available from an NHMRC funded clinical trial, the Early PN Trial. [7] At time of sample size estimation for the Refeeding Syndrome Trial, complete data was available on 209 ICU patients who had expressed refeeding related hypophosphatemia in the Early PN Trial. Patients who were managed with caloric restriction had a significantly shorter ICU stay (RR=0.43, p<0.001) and significantly more ICU free days (RR=1.19, p<0.001). This shorter ICU stay translated to an absolute increase of 8.5 ICU free days (95% CI 5.6 to 11.4 days) over the 60 day follow-up period of the Early PN Trial.

Under conservative assumptions, the estimate of expected treatment effect was decreased from 8.5 days to 6.4 days (a 25% reduction). Using standard sample size formula, it was estimated a 336 patient clinical trial would have 90% power to detect a 6.4 day difference in ICU free days (SD=18.1 days). A trial of 336 patients was also expected to have 84% power to detect a 5.6 day difference, which represented the lower 95% confidence boundary of the original estimated treatment effect.

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DOI: http://dx.doi.org/10.4451/Refeeding_SAP

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, regardless of whether a subsequent protocol violation or protocol deviation occurred.

It is accepted that an overly rigid application of the principle of intention to treat may increase the chance of a Type II error in an analysis of *efficacy* (as opposed to effectiveness). [14;15] To minimise Type II errors in an analysis of *efficacy*, authoritative sources have proposed that minor *modifications* to an intention to treat analysis are appropriate. Bias may be avoided and random error may be minimised by exclusion of the following patient groups from the primary *modified* intention to treat analysis: **1)** Patients who were *mistakenly enrolled* and stand no chance of benefit; and **2)** Patients who were *prematurely enrolled* resulting in failure to deliver the allocated intervention. [15]

The primary *modified* intention to treat analysis for *efficacy* will therefore exclude patients who were enrolled by *obvious mistake* who stand no chance of benefit and will exclude patients who were *enrolled prematurely*, before senior clinician's treatment plans were understood. An understanding of senior clinician's treatment plans at time of enrolment was an explicit component of the eligibility criteria (Inclusion Criteria 5), as it was expected that conflicts between treatment plans and allocated treatment group may result in early discontinuation of the allocated treatment (Ex. Senior clinician plans to reduce energy intake after learning of hypophosphatemia, but patient already enrolled and allocated to maintain or increase energy intake by study web site).

The decision to exclude patients from the modified intention to treat analysis of *efficacy* based on *mistaken enrolment* and *premature enrolment* will be made by an adjudication committee blinded to study group and patient outcome.

An (unmodified) intention to treat analysis will be conducted, with results reported to support inferences regarding *effectiveness*.

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.

A two-sided 5% significance level 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 [16] and because the conduct of an interim analysis using Haybittle-Peto stopping thresholds does not require adjustment of outcomes for multiplicity. [12,13]

2.4 Primary outcome:

The primary outcome for this clinical trial will be *ICU free days*, defined as the number of days spent alive discharged from ICU after enrolment into the trial, with a follow-up time of 60 days. If vital status at Day 60 is unknown, known follow-up time will be used to calculate ICU free days (Ex. hospital discharge status and date, if discharge is recorded prior to Day 60).

Schoenfeld *et al's* original simulation studies demonstrated a relationship between effective power of VFDs and follow-up time. [6] We have confirmed this relationship with cursory simulations using data from previously conducted NHMRC funded clinical trials: as follow-up time increases from 28 days to 60 days to 90 days, the magnitude of the variability (SD) around the estimate of any treatment effect on ICU free days increases and the statistical efficiency of ICU free days changes.

Since data with a 60 day follow-up period was used to calculate ICU free days to support the original sample size estimates for the Refeeding Syndrome Trial, to maintain statistical efficiency, a 60 day follow-up period will be used to calculate ICU free days for the primary outcome of the Refeeding Syndrome Trial.

2.5 Missing primary outcomes:

Missing primary outcomes (ICU free days) will be assumed to be missing at random (MAR) and thus will be 'ignored' in the primary analysis [17] unless greater than 5% of all primary outcomes that should be available for analysis are missing, in which case the primary analysis will include imputed values.

If required, values will be imputed under the following assumptions: **Model 1, Best Case:** If it is known the patient was discharged from ICU alive, group average ICU free days will be imputed, discounted for known time spent in ICU: Imputed ICU free days = group average ICU free days - (group average ICU stay – known ICU stay); **Model 2, Worst Case:** If known discharged alive from ICU, zero ICU free days will be imputed.

In the case of all information regarding ICU discharge status missing (Ex. hospital chart lost, hospital administrative data lost), the patient-case will be excluded from analysis. [18,19]

If imputation is required, results of the imputed analyses 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 the study Caloric Management Protocol on the primary outcome (ICU free days) 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.

The magnitude of the treatment effect will be reported as an absolute difference (days) between groups, with 95% confidence intervals.

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; Subjective Global Assessment of Fat Loss; Subjective Global Assessment of Muscle Wasting; APACHE II score; 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, Diabetes); Type of Nutrition Support (EN, PN or IV infusion of ≥10% glucose solution) provided at time of enrolment; Hours of Nutritional Support provided in ICU prior to enrolment; Total energy intake from Nutrition Support commenced after ICU until time of enrolment; Energy intake from Nutrition Support at time of enrolment; Presence of a semi-permanent (surgically placed) feeding tube; Current history of high alcohol intake; Receipt of loop diuretic over 24 h prior to enrolment; Long term steroid use; Serum phosphate at time of enrolment; Lowest serum albumin over 24 h prior to enrolment; Lowest blood glucose over 24 h prior to enrolment; Highest blood glucose over 24 h prior to enrolment; Maximum insulin dose rate over 24 h prior to enrolment; Invasive mechanical ventilation at time of enrolment; Pneumonia at time of enrolment (CPIS probable and confirmed); APACHE III ICU admission diagnosis major category (Cardiovascular/vascular, Respiratory, Trauma, GI, Neuro, Sepsis, Metabolic, Haematological, Other surgical, Other medical); phosphate replacement provided (IV and Oral) over 24 h prior to enrolment; Time in ICU prior to study enrolment; Time in hospital prior to study enrolment.

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.

2.8 Missing baseline prognostic variables:

Exclusion of randomised patients with known outcomes from analysis may contravene the intention to treat principle. [20] Every effort should be made to minimise post-randomisation exclusions. [17]

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 effect. [21,22,23]

Missing baseline prognostic variables will be replaced with mean (or median if not a continuous distribution) values calculated from the observed non-missing instances of that baseline prognostic variable. [24] The imputed values 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 Poisson (or negative-binomial) regression model. [25] 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 (initial serum phosphate and BMI) will also be eligible for inclusion in the covariate adjusted model. [25] Neither a *centre effect term* nor *any interaction terms* will be considered in the covariate adjusted model. [25]

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. [25,26,27,28]

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). [29] 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. [27]

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. [25,26,27]

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). [29] 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. [27]

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. [28] 'Imbalance' detection *may* help preserve the face validity of the covariate adjusted results [30] and *may* remove bias from the estimate of treatment effect. [29,30]

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. [25] 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. [29]

All prognostic variables identified by Step 1 and Step 2 will be included in a *maximum covariate adjusted regression model.* The treatment group term (Caloric Management Protocol 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: **1)** if variables are found to be exact linear combinations of each other (Ex. Variable A: Source of ICU admission, admitted from Operating Room and Variable B: Type of Surgery, Elective vs. Emergency) collinearity will be reduced by eliminating the component of one variable contributing the least amount of information (Ex. Replace A with B); **2)** if required, continuous variables will be standardized and scaled and **3)** if required, one pair of a highly correlated set of variables (Ex. SBP vs MAP) may be eliminated, such that minimal information is lost. [31] Formal Backwards Stepwise elimination will begin only after collinearity has been adequately addressed.

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. [32,33] A negligible impact will be defined as less than 5% change in the regression coefficient of the treatment effect after stepwise removal of the prognostic variable from the subset model. [28]

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.

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, the primary conclusions of the study will be based on the results of the covariate adjusted analysis.

2.10 Covariate adjusted analysis of other 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 and tertiary outcome using an objective pre-specified algorithm as detailed in Section 2.9.

2.11 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." [34] 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. [35] 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. [35]

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 Refeeding Syndrome Trial. We will therefore use a formal analytic approach to establish MID thresholds for each HRQoL scale. [35]

Using the approach proposed by Juniper [36] and validated by Norman [34], we will define a MID as one half the Standard Deviation (SD) of the pooled results for that scale. [35] 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. [36]

2.12 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. [10,11]

At the time study instruments were selected for use in the Refeeding Syndrome 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% [37] 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.

2.13 Missing HRQoL outcomes:

Missing HRQoL outcomes will be assumed to be missing at random (MAR) and thus will be 'ignored' in analysis [17] unless greater than 5% of all HRQoL outcomes that should be available for analysis are missing. In the presence of excessive missing HRQoL outcomes, 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. [19] 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.

2.14 *A priori* defined subgroup analysis:

A priori identified subgroup analysis will be conducted based on the following baseline variables: **1)** Severity of hypophosphatemia (≤50th vs. > 50th percentile); **2)** SGA Physical Assessment of muscle and fat (No evidence of wasting vs. Evidence of wasting [Severe, Moderate or Mild]); **3)** Energy intake (≤ 50th vs. > 50th percentile); **4)** Blood glucose (≤ 50th vs. > 50th percentile); **5)** Insulin dose rate (≤ 50th vs. > 50th percentile); **6)** Timing of onset of hypophosphatemia (≤ 50th vs. > 50th percentile for hours after initiation of Nutrition Support in ICU until study enrolment).

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.

The Poisson [or negative-binomial] 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.

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The number of *a priori* subgroup analyses (**6**) 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.

2.15 Exploratory, hypothesis generating subgroup analyses:

No hypothesis generating subgroup analyses 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 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

The onset of Refeeding Syndrome was diagnosed according to the criteria of Marik and Bedigian:[38] serum phosphate drop of more than 0.16 mmol/L from a previous reading to below 0.65 mmol/L within 72 hours of the onset of nutritional support.

Inclusion Criteria

Patients will be considered ***eligible*** for the trial if ***all*** of the following *inclusion criteria* are met at the time of screening:
(Answer **YES** to all questions)

1) Within the past 72 hours, has the patient commenced nutrition support for the first time during this current stay in the study ICU?

[Nutritional support is defined as enteral nutrition, parenteral nutrition or an intravenous infusion of any solution containing ≥ 10% glucose/dextrose.]

2) Within the past 12 hours, has the patient's serum phosphate dropped to below 0.65 mmol/L AND this drop was greater than a 0.16 mmol/L decrease from any previous phosphate value?

[Any previous phosphate value obtained within the past 72 hours that was collected during this current study ICU admission may be used.]

3) Has the patient received at least 500kcals energy from nutrition support over the previous 24 h?

[Nutritional support is defined as enteral nutrition, parenteral nutrition or an intravenous infusion of any solution containing≥ 10% glucose/dextrose. Energy (calories) from propofol or boluses of glucose/dextrose solutions do not count towards energy intake.]

4) Is the patient's current total energy intake from nutrition support at least 30 kcals per hour?

[Nutritional support is defined as enteral nutrition, parenteral nutrition or an intravenous infusion of any solution containing≥ 10% glucose/dextrose. Energy (calories) from propofol or boluses of glucose/dextrose solutions do not count towards energy intake.]

5) Does the ICU specialist presently caring for the patient plan to continue, or increase, the current rate of nutrition support?

[Specialist does not currently plan to reduce or stop energy intake as part of this patient's standard care plan.]

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

7) Does the patient have a working central venous access line through which an electrolyte infusion could be delivered?

See next page for Exclusion Criteria.

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)

1) Was the patient actively receiving enteral nutrition or parenteral nutrition at another location (outside of the study ICU) up to 6 hours prior to being admitted to the study ICU?

[IV glucose/dextrose provided outside the ICU does **not** exclude the patient from enrollment.]

2) Has the patient received an intravenous phosphate infusion since meeting Inclusion Criteria 1 during this current ICU stay that was commenced more than **2 hours** ago?

[A phosphate infusion started **within the past** 2 hours is OK. Please consider any electrolyte replacement infusion that contained more than 5 mmol of phosphate. Patients who receive phosphate prior to the commencement of nutritional support (Inc Crit 1) are not excluded.]

3) Is the patient expected to be discharged from the study ICU today or tomorrow?

4) Was the patient admitted to the study ICU after a parathyroidectomy, performed during this hospital stay?

5) Has the patient received recent active treatment for **hyper**phosphatemia that may be associated with the onset of this current **hypo**phosphataemic event?

[Common treatments for **hyper**phosphataemia include dialysis/RRT or the use of phosphate binders such as: calcium containing binders (calcium carbonate, calcium citrate), newer binders that don't contain aluminium or calcium (Sevelamar *(Renegal*) and Ranthanum Carbonate *(Fosrenol)* or Aluminium containing binders (generally not used anymore due to risks of aluminium absorption).]

6) Has the patient received treatment for diabetic ketoacidosis during this current ICU admission?

7) Does the patient currently require treatment for hyperosmolar non-ketotic coma?

8) Is the patient currently receiving, or scheduled to receive, dialysis/renal replacement therapy?

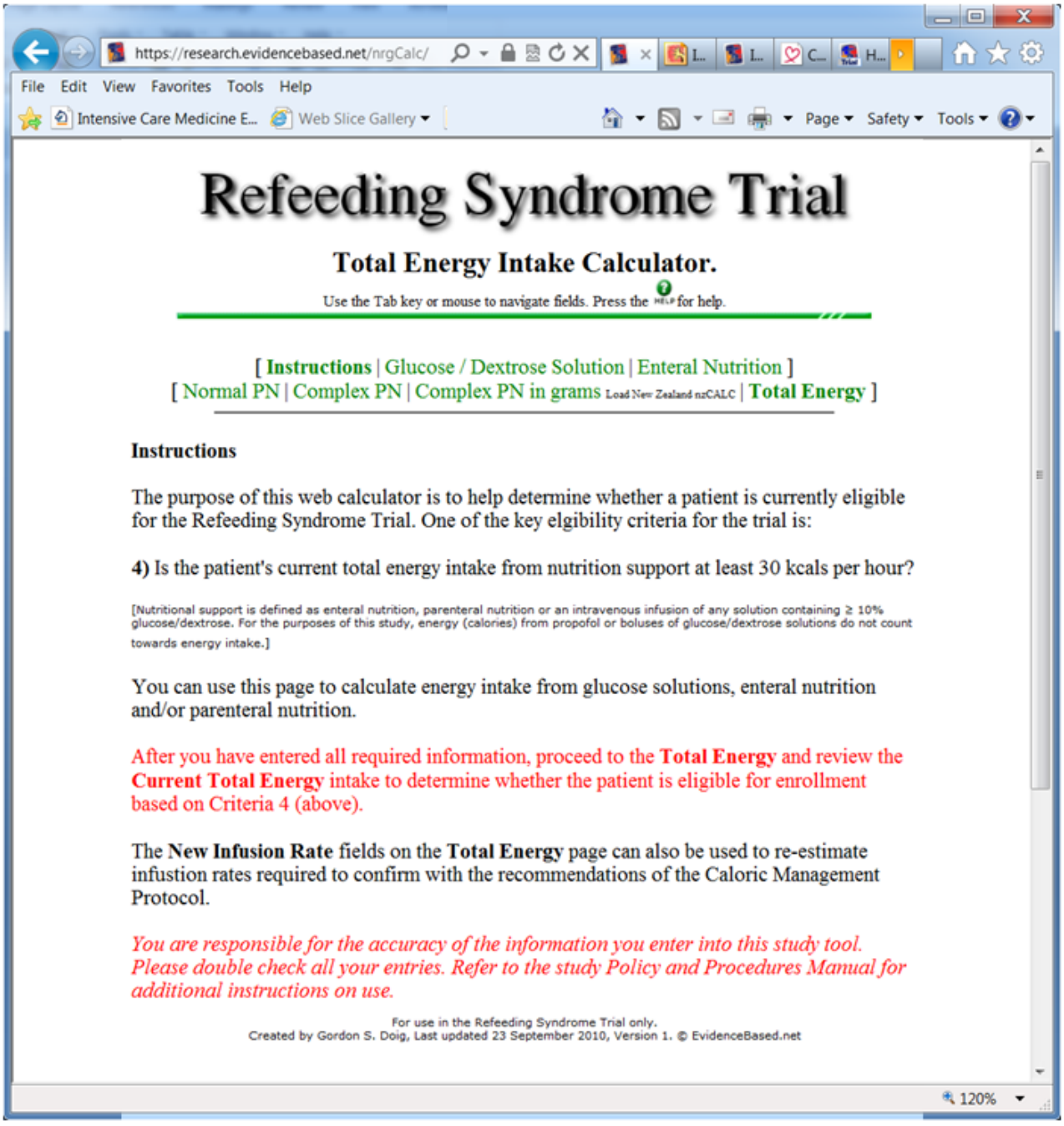
9) Is the patient expected to receive palliative care only and is not expected to survive ICU or hospital discharge?

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

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

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

Appendix 2: Study Energy Intake Calculation Tool (https://research.EvidenceBased.net/nrgCalc)



Appendix 3a: Caloric Management Protocol

Caloric Management Protocol Day 1 (first 24 h of energy management)

- ***Reduce*** current nutrition support to **20 kcals/hr.**
  Use the study web site (httpS://Research.EvidenceBased.Net/nrgCALC/) to calculate the energy content of the patient's current nutrition support (EN, PN plus any intravenous infusion containing ≥10% dextrose/glucose) in kcals per ml and re-calculate the patient's nutrition support rate to **reduce energy intake to 20 kcals / hr.**
- **Replace** phosphate deficit in accordance to study Phosphate Replacement Protocol.
- **Strongly recommend** daily administration of at least 100mg Thiamine IV.
- **Strongly recommend** daily administration of other B-group vitamins, and a balanced Multivitamin and Trace Element supplement, as clinically appropriate.
- **Recommend** frequent monitoring and supplementation of low levels of electrolytes such as potassium, magnesium, and others, as clinically appropriate.

Caloric Management Protocol Day 2 (second 24 h of energy management)

- ***Continue*** current nutrition support at **20 kcals/hr.**
- **Replace** phosphate deficit in accordance to study Phosphate Replacement Protocol.
- **Strongly recommend** daily administration of at least 100mg Thiamine IV.
- **Strongly recommend** daily administration of other B-group vitamins, and a balanced Multivitamin and Trace Element supplement, as clinically appropriate.
- **Recommend** frequent monitoring and supplementation of low levels of electrolytes such as potassium, magnesium, and others, as clinically appropriate.

At beginning of Day 3, plus additional days (next 24 h of energy management):

If most recent serum phosphate value does not rise above 0.71 mmol/L, replace phosphates as per Phosphate Protocol and continue Caloric Management as per Protocol Day 2 (above).

If most recent serum phosphate value rises above 0.71 mmol/L, initiate Day 1 of Gradual return to normal intake Protocol (see next page).

Note: *Whilst patients are on the study Caloric Management Protocol, energy targets* **must not** *be exceeded. If targets are met with EN, PN and IV glucose ≥ 10% concentration),* ***oral consumption of high-energy / high-protein oral supplements*** *(Resource, Ensure, Sustagen etc), which may contain upwards of 2.0 kcal/ml,* ***may lead to Protocol targets being exceeded.*** *Use supplements with care. Patients should be monitored closely.* ***Total energy intake should be managed such that the Protocol set targets are not exceeded.***

Version 1, 20 June 2014.
DOI: http://dx.doi.org/10.4451/Refeeding_SAP

Appendix 3b: Gradual Return to Normal Intake Protocol:

Calculate patient's eventual full-normal caloric goal using local hospital methods.

Gradual return to normal intake, Protocol Day 1 (first 24 h of energy increase)

- **Increase** nutrition support to **40 kcals/hr.**
  Use the study web site (httpS://Research.EvidenceBased.Net/nrgCALC/) to calculate the energy content of the patient's current nutrition support (EN, PN plus any intravenous infusion containing ≥10% dextrose/glucose) in kcals per ml and re-calculate the patient's nutritional support rate to **increase energy intake to 40 kcals / hr.**
- **Strongly recommend** frequent monitoring of **phosphate**.
  If the patient's phosphate drops to 0.71 mmol/L or lower, replace phosphate as per Phosphate Replacement Protocol and revert to Caloric Management Protocol Day 1.
- **Recommend** daily administration of at least 100mg Thiamine IV.
- **Recommend** daily administration of other B-group vitamins, and a balanced Multivitamin and Trace Element supplement, as clinically appropriate.
- **Recommend** frequent monitoring and supplementation of low levels of electrolytes such as potassium, and magnesium, as clinically appropriate.

Gradual return to normal intake, Protocol Day 2 (second 24 h of increase)

- **Increase** nutrition support to **60 kcals/hr, or 80% of goal *whichever is lower*.**
  *Use the study web site (httpS://Research.EvidenceBased.Net/nrgCALC/) to calculate the energy content of the patient's current nutrition support (EN, PN plus any intravenous infusion containing ≥ 10% dextrose/glucose) in kcals per ml and re-calculate the patient's nutritional support rate to **increase energy intake to 60 kcals / hr or 80% of goal, whichever is lower**.*
- **Strongly recommend** frequent monitoring of **phosphate**.
  If the patient's phosphate drops to 0.71 mmol/L or lower, replace phosphate as per Phosphate Replacement Protocol and revert to Caloric Management Protocol Day 1.
- **Recommend** daily administration of at least 100mg Thiamine IV.
- **Recommend** daily administration of other B-group vitamins, and a balanced Multivitamin and Trace Element supplement, as clinically appropriate.
- **Recommend** frequent monitoring and supplementation of low levels of electrolytes such as potassium, and magnesium, as clinically appropriate.

Additional Days, until return to full normal intake is achieved

- **Increase** nutrition support to **80% of goal rate *OR*** if 80% has already been achieved, **increase to full goal rate,** as clinically appropriate.
- **Strongly recommend** frequent monitoring of **phosphate**.
  If the patient's phosphate drops to 0.71 mmol/L or lower, replace phosphate as per Phosphate Replacement Protocol and revert to Caloric Management Protocol Day 1.
- **Recommend** daily administration of at least 100mg Thiamine IV.
- **Recommend** daily administration of other B-group vitamins, and a balanced Multivitamin and Trace Element supplement, as clinically appropriate.
- **Recommend** frequent monitoring and supplementation of low levels of electrolytes such as potassium, and magnesium, as clinically appropriate.

Appendix 4: Phosphate Replacement Protocol: Phosphate dosing table.

	Patient weight			
Serum Phosphate	*40 - 60kg*	*61 - 80kg*	*81 - 120kg*	*> 120kg*
0.71 to 0.55 mmol/L	*10 mmol Phosphate IV* over 6 hours*	*15 mmol Phosphate IV* over 6 hours*	*20 mmol Phosphate IV* over 6 hours*	*25 mmol Phosphate IV* over 6 hours*
0.54 to 0.32 mmol/L	*20 mmol Phosphate IV* over 6 hours*	*30 mmol Phosphate IV* over 6 hours*	*40 mmol Phosphate IV* over 6 hours*	*50 mmol Phosphate IV* over 6 hours*
below 0.32 mmol/L	*30 mmol Phosphate IV* over 6 hours*	*40 mmol Phosphate IV* over 6 hours*	*50 mmol Phosphate IV* over 6 hours*	*60 mmol Phosphate IV* over 6 hours*

*If **potassium is > 4.0 mmol/L, use sodium phosphate** [#]; If potassium < 4.0 mmol/L, use of potassium phosphate may also be acceptable [##].*

***** Rate may be increased, up to a maximum of 14.5 mmol/hr, at the discretion of local physician most responsible for the patient.

[#] Sodium phosphate solutions available in Australia contain a small quantity of potassium. For example, *DBL Sodium Phosphate and Potassium Phosphate Concentrated Injection (Hospira)* contains potassium ions in a final concentration of 0.13 mmol/ml. *This small quantity of potassium is safe in all patients*.

[##] Potassium phosphate may be used to correct both hypokalaemia and hypophosphataemia, but when larger doses of phosphate are required, potassium phosphate may provide excessive potassium. Consult the local physician most responsible for patient if you have concerns regarding use of potassium phosphate. We ***recommend*** use of sodium phosphate solutions for *all* patients, with hypokalaemia treated independently with an infusion of KCl. Refer to local protocols for the replacement of K.

Follow established local protocols and procedures to determine the appropriate time to re-asses patient's serum phosphate values post-infusion. However we ***strongly recommend*** that serum phosphate values should be checked at approximately 12 hours and 24 hours after the initiation of the phosphate infusion.

Additional phosphate infusions should be provided if serum phosphate drops to 0.71mmol/L or below. Dose additional phosphate infusions according to the above phosphate dosing table.

We **strongly recommend** that all **standard care** patients should receive at least **100mg Thiamine IV** each day they receive a phosphate infusion.

We **strongly recommend** the use of cautionary clinical judgment when prescribing an ORAL dose of phosphate soon after an IV dose is administered, especially when serum phosphate values are not available.

IV: intravenous

Note: Patients with hypomagnesaemia may also require infusion of $MgSO_4$ or $MgCl_2$. Refer to local protocols for the replacement of Mg, or any other electrolytes, in these patients.

From: Taylor BE, Huey WY, Buchman TG, *et al.* Treatment of hypophosphatemia using a protocol based on patient weight and serum phosphorus level in a surgical intensive care unit. *J Am Coll Surg* 2004;198:198-204.

DOI: http://dx.doi.org/10.4451/Refeeding_SAP

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Version 1, 20 June 2014.
DOI: http://dx.doi.org/10.4451/Refeeding_SAP