

**Management of refeeding syndrome in critical illness:  
An Australasian Society of Parenteral and Enteral Nutrition (AuSPEN)  
endorsed multi-centre clinical trial**

**NHMRC Application ID: 632615**

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### Summary

We intend to conduct a multi-centre, randomised controlled trial (RCT) to evaluate the efficacy and effectiveness of restricting energy intake during the management of refeeding related hypophosphataemia in critically ill patients.

Although physiological experiments and observational studies support the restriction of energy intake during the treatment of refeeding related hypophosphataemia in non-critically ill patients, a survey of current practice and preliminary data from an ongoing clinical trial reveal that only 40-50% of critically ill patients with refeeding syndrome are managed with energy restriction in Australian intensive care units (ICUs) <sup>1</sup>. ICU specialists question the necessity and benefits of energy restriction during management of refeeding syndrome because there is evidence that hypocaloric feeding during critical illness results in an 'energy deficit' that is associated with worse outcomes <sup>2</sup>. Evidence from a focussed RCT conducted in critically ill patients with refeeding syndrome is required to inform and guide practice.

**There are no RCTs conducted in critically ill patients, or other patient groups, evaluating the efficacy or effectiveness of restricting energy intake during the management of refeeding related hypophosphataemia** <sup>3,4,5</sup>.

If the treatment benefits of energy restriction identified in our preliminary work are confirmed by this planned trial, these results will change practice on a National and International scale. Appropriate management of refeeding syndrome in critically ill patients could save the Australian health care system more than \$58 million dollars per year.

The expertise, infrastructure, patient population, and particular practice characteristics exist in Australia to conduct this trial. These features make it uniquely possible to complete such a study successfully at the highest possible scientific standard within a relatively short period of time.

### Hypothesis to be tested

In critically ill patients with refeeding related hypophosphataemia under the care of an ICU specialist who would not normally restrict energy intake during the management of refeeding syndrome, does energy restriction affect the duration of critical illness, and other measures of morbidity, compared to standard care?

### Background

The refeeding syndrome is characterised by a host of metabolic disturbances that occur as a result of the rapid reinstatement of nutritional support in patients who are starved or severely malnourished. The syndrome was first recognised in repatriated allied prisoners of war who were chronically and severely malnourished, and was often fatal <sup>3,5</sup>. Today it is widely accepted that the refeeding syndrome can occur in apparently well nourished patients after only a short period of fasting <sup>6,7</sup>.

After a period of fasting as brief as 48 hours <sup>7</sup>, a rapid recommencement of nutritional support can lead to a surge in insulin release and a decrease in glucagon secretion with a metabolic shift towards anabolism <sup>4</sup>. This primary insulin surge results in rapid intracellular uptake of glucose, which draws phosphate, water and other electrolytes from the extracellular space <sup>8</sup>. If extracellular electrolyte levels are low, this rapid intracellular shift of electrolytes and fluid can give rise to respiratory failure, cardiac failure, delirium, rhabdomyolysis, haemolytic anaemia, seizures, coma and even death <sup>7,9,10,11</sup>.

Although the refeeding syndrome can result in hypokalaemia, rapid depletion of thiamine and hypomagnesaemia <sup>5</sup>, the hallmark clinical sign is serum hypophosphataemia <sup>8</sup>. Even moderate serum hypophosphataemia can lead to the depletion of phosphorylated intermediates and compounds such as adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (2,3-DPG) in red and white blood cells. This reduction in 2,3-DPG results in impaired red cell membrane deformability, reduced red cell life span, impaired oxygen transfer, diminished white cell intracellular killing and

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reduced generation of superoxide radicals during phagocytosis<sup>11</sup>. The relationship between refeeding associate hypophosphataemia, impaired diaphragmatic contractility<sup>10</sup> and respiratory failure with a need for prolonged mechanical ventilation<sup>7</sup> is well established. Likewise, many studies have documented an association between hypophosphataemia and subsequent infectious complications<sup>12,13</sup>, including sepsis<sup>9</sup>.

*Incidence*

Decreased food intake is one of the most common signs of illness, injury, or inflammation. In response to critical illness, trauma or surgery, the immune system produces and releases numerous pro- and anti-inflammatory cytokines that govern the body's reaction to injury<sup>14</sup>. These cytokines also act on the central nervous system to control food intake and energy homeostasis<sup>15,16</sup> and their release is associated with a reduction in the orexigenic hormone ghrelin<sup>17</sup> and an increase in the anorexogenic hormone leptin<sup>15</sup>. It is not yet clear whether circulating leptin and ghrelin levels are directly influenced by the release of inflammatory cytokines, however the resultant appetite suppression and reduced energy intake characteristic of early critical illness or injury places ICU patients at high risk of refeeding syndrome.

In their seminal work published in 1996, Marik and Bedigian followed 62 patients who were admitted to a mixed medical surgical ICU and had a documented history of no nutritional intake for at least 48 hours. Based on objective criteria, 34% (21/62) of these patients developed refeeding related hypophosphataemia<sup>7</sup>. We recently completed a retrospective observational study of consecutive critically ill patients admitted to an Australian ICU over a four year period and, using accepted criteria<sup>7</sup>, we found that 17% (496/2,915) of all patients expressed refeeding syndrome<sup>18</sup>.

*Treatment*

The correction of electrolyte and fluid imbalances is accepted as the first step in the appropriate treatment of refeeding syndrome<sup>3,5,6,19</sup>. Small clinical trials have been conducted to investigate optimal strategies for phosphate replacement in critically ill patient populations. These trials have investigated the safety and efficacy of replacement doses based on pre-supplementation serum phosphorus levels<sup>20</sup> and patient weight<sup>21</sup> along with delivery rates<sup>22</sup>. Although clinical trials are available to guide phosphate replacement, it is universally recognised that no randomised clinical trials have been conducted in patients with refeeding syndrome to evaluate the role of nutritional support<sup>3,4,5</sup>.

In order to *prevent* the onset of refeeding syndrome in high risk patients, authoritative guidelines recommend that nutritional support should be introduced at less than 50% of a patient's energy requirements and gradually increased to meet energy requirements over two to three days<sup>19</sup>. Unfortunately, explicit recommendations regarding optimal nutritional intake during the *treatment* of refeeding syndrome are not made<sup>19</sup>. Other authors have attributed the inability to make definitive recommendations for energy intake during the treatment of refeeding syndrome to the complete lack of evidence from clinical trials<sup>3</sup> and outcome studies<sup>4</sup>.

There are no internationally validated guidelines for the nutritional treatment of refeeding syndrome<sup>5</sup>. In the face of this lack of evidence, some experts recommend that "feeding can be continued" during electrolyte replacement for refeeding syndrome<sup>3</sup> however others are more cautious and recommend that intake should be reduced to less than 50% of intake prior to when signs developed<sup>6</sup> or to as little as 10kcal/kg/day<sup>5</sup>.

*Current awareness and treatment in Australia*

We (CI-A and CI-B) conducted a series of site visits to ICUs throughout Australia and New Zealand in preparation for a large-scale clinical trial of parenteral nutrition ([Early PN Trial, NHMRC Project Grant ID 402643](#)). Structured interviews were conducted with specialists from 33 ICUs in order to determine the site's ability to participate in the Early PN Trial. One focus of this process was to obtain information on the local incidence and treatment of refeeding syndrome.

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Twenty-one percent of interviewed intensive care specialists reported '*never*' encountering refeeding syndrome. Sixty-three percent reported they encountered it '*rarely*', and 15.2% reported '*often*'. Of the '*never*' respondents, when asked if they ever saw serum phosphorus drop after the onset of feeding in their critically ill patients, they responded '*frequently*'.

When asked how they usually treat refeeding syndrome, 51.5% of responding ICU specialists indicated they would replace serum phosphorus (and other electrolytes) as required but would not reduce energy intake, whereas the remaining 48.5% indicated they would replace electrolytes *and* reduce energy intake<sup>1</sup>. Data generated from the currently ongoing Early PN Trial confirms these self reported practice patterns.

Daily information on serum phosphorus levels has been collected on all patients enrolled into the Early PN Trial since 20 December 2007. In preparation for this grant submission, an exploratory analysis was undertaken to evaluate the treatment of, and outcomes associated with, patients who developed refeeding syndrome. At the time of this exploratory analysis, validated data was available on 112 patients who had completed the trial. Randomised treatment groups were masked and no analysis of the primary treatment groups was undertaken.

*Fifty-three percent (60/112) of the Early PN Trial patients developed refeeding related hypophosphataemia.* The median time to onset was 1.27 days after ICU admission (range 0 to 6 days). The average blood glucose level at onset was 9.3 mmol/L and 29% of patients were hyperglycaemic (> 10 mmol/L) at onset of hypophosphataemia.

Compared to patients with normal serum phosphorus levels, patients with refeeding related hypophosphataemia developed significantly more respiratory failure (3.8 extra days of respiratory failure,  $p=0.004$ ) and required a longer duration of mechanical ventilation (3.9 extra days of ventilation,  $p=0.004$ ). They also required more antibiotics (3.8 extra days of antibiotics,  $p=0.003$ ) and had a significantly longer duration of ICU stay (4.6 extra ICU days,  $p=0.002$ ). Furthermore, increasing duration of hypophosphataemia was significantly associated with a need for more antibiotics ( $p=0.0319$ ), a longer duration of ventilation ( $p=0.0275$ ) and a longer ICU stay ( $p=0.0156$ ).

Fifty-eight percent (35/60) of patients with refeeding hypophosphataemia had normal nutritional support continued during their hypophosphataemia while 41% (25/60) were managed with restricted energy intake (< 600 kcal/day). Physiological studies suggest that infusion of glucose during phosphate replacement increases the rate at which phosphorus migrates from the plasma to the intracellular pool by a factor of three<sup>23</sup>. Failure to reduce energy intake during the treatment of refeeding syndrome may prolong plasma hypophosphataemia and increase the risk of adverse sequelae.

Patients who received continued normal nutritional support during refeeding associated hypophosphataemia experienced a significantly longer duration of hypophosphataemia (2.1 vs. 1.5 days,  $p=0.02$ ) and had significantly lower serum phosphate levels after the onset of refeeding syndrome (0.46 vs. 0.56 mmol/L,  $p=0.0003$ ).

On average, patients treated with restricted nutritional intake demonstrated a trend towards a shorter duration of ICU stay (3.4 days less,  $p=0.13$ ), a shorter duration of mechanical ventilation (3.0 days less,  $p=0.18$ ) and less antibiotic treatment (2.1 days less,  $p=0.28$ ).

Our preliminary information demonstrates that refeeding syndrome is under-recognised by Australian intensive care specialists and that patients stand to benefit from improved treatment. The under-diagnosis and under-treatment of refeeding syndrome has been reported elsewhere<sup>3</sup>.

**Economic consequences**

Refeeding syndrome is a major unrecognised problem in Australian ICUs<sup>1</sup>. Up to 17% of all patients admitted to an Australian ICU may express refeeding hypophosphataemia<sup>18</sup>. With over

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60,000 patients admitted to ICUs in Australia each year<sup>24</sup> this represents 10,200 cases of refeeding syndrome per annum.

Surveys of current practice<sup>1</sup> and data from ongoing clinical trials reveal that only 40-50% of critically ill patients with refeeding syndrome hypophosphataemia are managed by reducing energy intake. Data from ongoing clinical trials demonstrate that patients who receive conservative nutritional support may have a 3.4 day shorter duration of critical illness.

The most recent prospective 'ground up' costing study conducted in Australian public hospitals estimates the average daily cost of ICU care at \$3,396 (2008 AUD)<sup>25</sup>. An average reduction of 3.4 days per patient for 50% of the 10,200 annual cases each year represents a saving of 17,340 ICU days, worth \$58 million per year.

This estimate of \$58 million savings to the system is conservative because it does not include savings as a result of an expected reduction in the duration of mechanical ventilation or an expected reduction in the need for antibiotics. It is likely that acuity of care *and* duration of stay will be reduced.

**Research Plan**

The proposed study is a multi-centre, single-blinded, open label, randomised, controlled trial of restricted energy intake versus standard care.

**Aim**

The primary aim of this study is to compare the effects of two approaches to nutritional management on the duration and severity of critical illness in ICU patients who express refeeding syndrome.

The effects of *restricted energy intake* will be compared to *continued normal energy goals* with regards to their impact on patient's length of ICU stay, duration of mechanical ventilation, duration of hypophosphataemia, severity of hypophosphataemia, immune function, infectious complications, need for anti-infective therapy, cardiac dysfunction, various hormone levels, physical function and quality of life at 90 days post randomisation, overall survival and other clinically relevant outcomes.

This study will also provide an opportunity to investigate novel risk factors that may be able to predict the severity of refeeding syndrome and response to treatment.

**Sample size and power**

Data from our ongoing clinical trial ([Early PN Trial, NHMRC Project Grant ID 402643](#)) provides estimates of expected treatment benefits attributable to energy restriction. Defined using the criteria of Marik and Bedigian<sup>7</sup>, patients who developed refeeding related hypophosphataemia and received continued normal nutritional support experienced a significantly longer duration of hypophosphataemia ( $2.1 \pm 1.19$  vs.  $1.5 \pm 0.72$  days,  $p=0.02$ ) and developed significantly lower serum phosphate levels after onset of refeeding ( $0.46 \pm 0.13$  vs.  $0.56 \pm 0.07$  mmol/L,  $p=0.0003$ ).

After the onset of refeeding hypophosphataemia, patients who received continued normal nutritional support also required a longer duration of mechanical ventilation (RR=3.7,  $p<0.001$ ) needed intensive care for a longer period of time (RR=2.32,  $p<0.001$ ) and received antibiotics more often (RR=2.2,  $p<0.001$ ). Note that these differences in duration of hypophosphataemia, antibiotic use, mechanical ventilation and ICU stay were observed and compared *after* the onset of refeeding hypophosphataemia. The primary outcome, *ICU free days*, was significantly increased (RR=1.19,  $p<0.001$ ) in patients receiving restricted caloric intake, which translates to an absolute increase of 8.5 additional *ICU free days* (95% CI 5.6 to 11.4 days).

Using standard sample size formula<sup>26</sup>, with conservative discounting by 25% to account for the possibility the full effect may not be achieved in a clinical trial ( $0.75 * 8.4$  days = 6.4 days), a 336 patient clinical trial will have 90% power to detect a 6.4 day difference in *ICU free days* (SD=18.1 days). A trial of this size would also have 95% power to detect a significant reduction in the

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duration of hypophosphataemia, 90% power to detect a significant reduction in duration of ventilation and 85% power to detect a significant reduction in the need for antibiotics.

**Recruitment feasibility**

Recruitment rates were estimated using an extensive database containing daily serum phosphorus values collected on 2,915 patients admitted to one of the participating ICUs over a four year period<sup>18</sup>. This study reveals that 17% of all ICU admissions may develop hypophosphataemia associated with the onset of feeding during the first week of ICU stay.

The seven ICUs participating in this planned clinical trial admit over 2,500 patients each year. Given that 17% of all ICU admissions may develop refeeding hypophosphataemia, up to 425 potentially eligible patients could be identified each year. Not all participating ICUs will be able to provide routine weekend coverage for recruitment thus 305 patients will be eligible during weekdays.

Based on the study eligibility criteria and unique aspects of this patient population, it is reasonable up to assume 40% of potentially eligible patients may not be recruited. We therefore estimate that 23 months will be required to screen and enrol 348 truly eligible patients into the trial at seven participating ICUs.

Successful recruitment and conduct of the 7,000 patient Saline vs. Albumin Fluid Evaluation trial<sup>27</sup>, the 21,000 patient Medical Early Response Intervention Trial<sup>28</sup>, and the 1,500 patient ANZ Evidence-based Nutrition Guidelines Trial<sup>29</sup> demonstrate the ability of the current Chief Investigators to complete projects of this duration and scope.

**Patient eligibility criteria**

The onset of refeeding syndrome will be diagnosed according to the criteria of Marik and Bedigian<sup>7</sup>: a serum phosphorus 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.

To validate the requirement for a 0.16 mmol/L change, we re-calculated the Reference Change Value (RCV)<sup>30</sup> for serum phosphorus. Given the published coefficient of biological variation and the observed analytical variation in our laboratory, the RCV for our lab is 20.2%, which equates to a 0.16 mmol/L change. The requirement of 0.16 mmol/L change compensates for analytical variation and normal diurnal variation.

**Appendix 1** presents the complete list of eligibility criteria.

**Consent**

Informed consent will be obtained from the patient, or their legal surrogate, whenever possible. For critically ill patients who are not able to provide consent due to the severity of their illness or the use of sedative medications in their treatment (the majority), or if the legal surrogate cannot be contacted at time of study eligibility, an explanatory statement will be provided to the patient or their legal surrogate at the earliest opportunity. Such information will always be provided to the patient, when and if they regain consciousness and are able to make an informed decision concerning continued participation in the study. The randomised treatment may be withdrawn at any time at the discretion of the patient or their legal surrogate.

The use of delayed consent is in keeping with NHMRC Guidelines and precedent has been established in previous studies conducted by the Chief Investigators ([Early PN Trial, NHMRC Project Grant ID 402643](#)). Delayed consent will only be employed where allowed by State Law.

**Randomisation**

Allocation concealment will be maintained through the use of a central randomisation web site that is secure, encrypted and password protected. The web site is hosted by a redundant cluster of enterprise-level servers located in a secure University of Sydney machine room. The web site will be accessible 24 hours a day, seven days a week. It has hosted numerous secure research projects, including NHMRC funded clinical trials ([Early PN Trial, NHMRC Project Grant ID 402643](#),

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<http://icu-10.med.usyd.edu.au/EarlyPN>) and US Food and Drug Administration Phase II licensing trials (Protocol F1K-MC-EVAA, drotrecogin alpha (activated), Eli Lilly and Company).

Within study centre, randomisation will be stratified on: 1) severity of refeeding syndrome and; 2) nutritional status. Blocks of variable size and a random seed will be used to ensure allocation concealment cannot be violated by deciphering near the end of each block<sup>31</sup>. To further protect from deciphering, block size and strata thresholds will not be revealed to site investigators<sup>31</sup>.

**Study treatments***Study intervention:*

If randomised to the intervention arm, the patient will receive protocol-directed and energy restricted nutritional support during the treatment of refeeding syndrome. The complete treatment protocol is presented in **Appendix 2**.

*Standard care:*

If randomised to standard care, the patient will receive continuation of the usual nutritional support plan previously initiated by the ICU specialist most responsible for the patient's care.

**Cessation of either study treatment**

If at any time during the trial the treating ICU physician deems that it is in the patient's best interest due to safety issues then, at the discretion of the treating physician, the study treatment (intervention or standard care) can be withdrawn.

All patients withdrawn from the allocated treatment arm will be followed up according to the study protocol and analysed according to the intention to treat principle.

**Safety concerns**

All serious adverse events potentially attributable to either study treatment arm will be reported to the study coordinating centre, and local HREC, in a timely fashion.

**Phosphate replacement**

To control for the possibility of a confounding effect due to physician directed phosphate replacement, or sub-optimal phosphate replacement protocols, phosphate replacement will be standardised in both the intervention and standard care arms of the trial.

Phosphate replacement will be guided by the protocol evaluated in the clinical trial conducted by Taylor *et al*<sup>21</sup>, infused over a six hour period (**Appendix 3**). French and Bellomo have demonstrated that phosphate infusions of up to 14.5 mmol per hour are safe in ICU patients<sup>32</sup>.

**Thiamine**

To control for a possible confounding effect of differential thiamine supplementation between groups, all enrolled patients will receive a standardised dose of thiamine.

**Ancillary treatments**

Other aspects of patient management are unaffected by study procedures and the treating clinician will be free to provide whatever care is deemed appropriate and necessary.

**Data collection and follow up**

Every randomised patient will be followed up until either hospital discharge or 90 days post-randomisation, whichever is longer, unless death occurs first, as recommended by the UK Medical Research Council International Working Party for Clinical Trials in Patients with Sepsis and Septic Shock<sup>33</sup>.

Because it is known that excessive protocol violations may mask treatment effectiveness<sup>34</sup>, training procedures and data collection instruments have been developed to maximise protocol adherence and reduce data errors<sup>35</sup>. Protocol violations will be further reduced by conducting a formal run-in phase that provides performance feedback on major aspects of study conduct to each site prior to site initiation<sup>36</sup>. Study conduct, protocol adherence and data quality will be progressively improved throughout the trial via serial site monitoring visits<sup>37</sup>.

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Information recorded on all patients at study entry will include demographic and physiological variables routinely considered necessary to demonstrate baseline balance in a population of critically ill patients,<sup>27,28,29</sup> along with measures of nutritional status appropriate to a critically ill patient population<sup>38</sup>. During follow-up in the ICU, information routinely considered necessary to characterise the severity of ongoing critical illness, organ dysfunction, need for organ-specific support and other ICU treatments will be recorded<sup>27,28,29</sup>.

Because of the focus of this particular trial, detailed information on the type and amount of nutritional support and phosphate replacement received on each day of study will be collected. In addition to detailed measures of infectious complications, measures of immune function will be obtained, echocardiography will be conducted and hormones associated with refeeding syndrome will be profiled at baseline and during the study.

Although the relationship between immune function and fasting has been studied<sup>39</sup>, and hypophosphataemia is accepted to be associated with modified immune function<sup>11</sup> and an increase in infectious complications<sup>9,12,13</sup>, there is scant evidence relating changes in immune function to subsequent infectious complications in critically ill patients with refeeding syndrome. We will collect baseline and serial measures of immune function (monocyte count, NK, CD<sub>4</sub> and CD<sub>8</sub> cell marker status) in all patients. Changes in immune function will be related to subsequent infectious complications, documented using an objective grading scheme<sup>40</sup>.

Although it is widely accepted that expression of the refeeding syndrome can be accompanied by cardiac dysfunction, no documented reports quantify or describe the extent of dysfunction to be expected. We will conduct follow-up echocardiography studies in all patients.

With the discovery of appetite-modulating and metabolic hormones such as ghrelin, adiponectin and leptin, interest has been generated into their roles in the refeeding syndrome<sup>41</sup> and in insulin resistance (IR)<sup>42</sup>. IR occurs commonly in critically-ill patients<sup>43</sup> and it is not clear whether these patients are at a modified risk of refeeding syndrome or complications arising from refeeding syndrome. It has been recommended that high-insulin stress-related IR needs further study in the context of the refeeding syndrome in the critically ill<sup>4</sup>. We will collect baseline and serial measurements of ghrelin, adiponectin, leptin, insulin-like growth factor (IGF-1), and IL-6 in order to explore their interrelationship with the expression of IR in the context of the refeeding syndrome.

**Outcomes**

The primary outcome for this clinical trial will be ICU-free survival time, which is a quality of life adjusted survival construct.

Efficacy will be assessed using laboratory and clinical measures of the duration / severity of the expression of refeeding syndrome. These measures will include the amount of phosphate supplementation required, days of moderate / severe hypophosphataemia post-randomisation and minimum serum phosphorus levels.

Secondary clinical outcomes will include: duration of ICU and hospital stay, duration of ventilation; echocardiographic measures of cardiac dysfunction; measures of white cell function; number and severity of infectious complications; need for antibiotics; other organ system dysfunctions; and requirement for organ-specific support.

Physical Function and Quality of Life at day 90 will be characterised using the Zubrod / Eastern Cooperative Oncology Group (ECOG) / WHO Performance Status Scale<sup>44</sup> and the public domain version of the SF-36 questionnaire. Vital status will be recorded at day 90 and assessed.

Estimates of resource consumption and outcome benefits generated by this trial will be combined with published costs of treatment to generate an economic simulation to investigate the cost-effectiveness of the study intervention.



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### Blinding

Because ICU-based infections are notoriously difficult to define, an objective grading scheme, based on infecting organism, site of infection and known impact on outcome<sup>40</sup>, will be used to identify clinically important infectious complications. This grading scheme will be applied by a blinded adjudication committee. The potential influence of an ascertainment bias on this outcome can be investigated by obtaining the total number of culture requests at each specific site of infection.

### Analysis of results

The primary findings of this project will be based on analyses conducted under the principle of intention to treat (ITT). All patients enrolled and randomised into the trial will be accounted for and analysed. Results will be reported according to the Consolidated Standards of Reporting Trials statement<sup>45</sup>.

The primary outcome, ICU free days, will be analysed using a Poisson model, controlling for stratification at randomisation<sup>29</sup>. A power analysis simulation demonstrates a Poisson model will have 95% power to detect a difference of 5.6 days between groups<sup>46</sup> and will not be subject to false positive errors due to long tailed length of stay distributions.

All other outcomes based on count data (i.e. number of ventilated days, days of clinically significant organ dysfunction, infection rates etc) will be analysed using a Poisson model. Where appropriate, an offset term will be used to account for time at risk<sup>29</sup>. Normally distributed continuous variables will be analysed using t-tests or linear regression and dichotomous variables will be analysed using a chi-square test, Fishers Exact test or logistic regression, as appropriate.

All baseline variables with a p-value less than 0.05 will be considered to be in imbalance. The primary outcome will be re-assessed using multivariate regression analysis, accounting for this imbalance and stratification at randomisation.

An efficacy subset analysis will be conducted including only appropriately enrolled patients (met all eligibility and no exclusion criteria). The conclusions of the efficacy subset analysis will not take precedence over the conclusions of the ITT analysis. They will only be interpreted in the context of the ITT analysis.

A priori identified subgroup analysis will be conducted on patients determined to have severe refeeding syndrome and those who were malnourished and at baseline by investigating the significance of a treatment x subgroup interaction term.

An exploratory analysis will be undertaken to determine if any demographic or physiological measures recorded at entry into the trial can predict the severity of subsequent refeeding syndrome or response to treatment.

### Safety and Data Monitoring Committee

An independent Safety and Data Monitoring Committee (SDMC), comprising experts in clinical trials, biostatistics, nutrition and intensive care will be established. The committee will independently review all major serious adverse events blinded to study treatment.

Using the Haybittle-Peto approach<sup>47</sup> the SDMC will be charged with informing the study management committee if there emerges a difference in serious adverse events between study groups that exceeds three standard deviations in magnitude. If such a difference occurs, the SDMC will be empowered to conduct a blinded interim analysis on the primary outcome to ensure patient safety. If a difference in the primary outcome exceeds three standard deviations, the SDMC is empowered to stop the trial.

### Research timeframe and milestones

HREC submissions will begin at lead centres in November 2009 and study personnel will be recruited early 2010. Study instruments and processes will be refined and participating centre agreements will be finalised throughout 2010. The study start-up meeting will be held before the

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end of 2010 with the run-in phase and site initiation to occur early 2011. Recruitment is expected to run 23 months. Target sample size will be achieved by first quarter 2013, with database lock to occur 6 months thereafter. The final results paper will be submitted before the end of 2013.

**Organisation and collaboration**

This project has been endorsed by the Research Committee and full Council of the Australasian Society of Parenteral and Enteral Nutrition (AuSPEN) and will be conducted and overseen by a study steering committee comprising the chief and associate investigators listed on this application. The coordinating centre for the project will be located at the Northern Clinical School, University of Sydney, Royal North Shore Hospital.

The members of the study steering committee have extensive experience in the conduct of large-scale multi-centred, collaborative research in the intensive care setting.

The steering committee's previous collaborative experience and dedication to high-quality research will ensure that the trial is completed in a timely fashion and with methodological rigour.

Endorsement by AuSPEN ensures the results of the trial are accepted by the clinical community.

As of the date of submission, the following hospitals and investigators have formally expressed interest in conducting this study:

**Institution**

**Investigator**

- |                                      |                 |
|--------------------------------------|-----------------|
| 1. Royal North Shore Hospital, NSW   | Gordon Doig     |
| 2. Royal Prince Alfred Hospital, NSW | Ian Caterson    |
| 3. The Alfred, VIC                   | Andrew Davies   |
| 4. Nepean Hospital, NSW              | Ian Seppelt     |
| 5. Austin Health, VIC                | Rinaldo Bellomo |
| 6. John Hunter Hospital, NSW         | Peter Harrigan  |
| 7. St. Vincent's Hospital, NSW       | Priya Nair      |

**Publications and presentations**

The main reports from the study will be published by the steering committee, with credit assigned to the collaborating investigators.

Presentations of the study findings will be made at regional, national and international meetings concerned with the nutritional management of patients in intensive care.

The steering committee is fully dedicated to the successful transfer and translation of any meaningful results of this trial into clinical practice throughout Australia.

**Expected outcomes and clinical significance**

This study will provide landmark evidence concerning a clinically important question relevant to critically ill patients treated in the Australian intensive care setting. This evidence will have direct bearing on decisions about the care of a significant number of critically ill patients admitted to intensive care units throughout Australia.

This study is of great clinical and scientific importance. No clinical trials have been conducted in refeeding syndrome to inform and guide its management in the critically ill. More appropriate management has the potential to save up to \$58 million per year in health care costs.

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A/Prof Gordon S. Doig completed his Research Fellowship in Critical Care Medicine (WJ Sibbald, University of Western Ontario, London, Canada) in 1996 and his PhD in Epidemiology and Biostatistics (JM Robertson, University of Western Ontario, London, Canada) in 1999. He received the US Society of Critical Care Medicine's In-Training Fellow Award for his work in sepsis in 1996 and was awarded the Foundation Visitor's Medal from the ANZ Faculty of Intensive Care in 1998 for his contributions to evidence-based critical care. In 1999 he was invited to China as a Short Term Consultant for the WHO and in 2000, he was the Year 2000 Royal Perth Hospital Visiting Professor. In 2001 he was recruited from Canada to the Royal North Shore Hospital, Sydney.

GSD has been a Chief Investigator on 45 grants totalling over \$19 million dollars, many of which were awarded by Major National and National-level funding agencies. He currently manages an active funding base of over \$2 million. He was a member of the management committee of the 7,000 patient NHMRC funded Saline vs. Albumin Fluid Evaluation (SAFE) study, which was published in the NEJM and was also a member of the management committee of the 21,000 patient NHMRC funded Medical Early Response Intervention Trial (MERIT), which has been published in the Lancet. Currently, he is CI-A on a 32 hospital NHMRC funded clinical trial evaluating the impact of early nutritional support on outcomes from critical illness.

GSD is an Associate Editor for the peer-review methodological journal *Trials* and reviews more than 30 submissions a year for *JAMA*, *BMJ* and ten other leading specialty journals. He has reviewed Project Grant submissions for the NHMRC Large Scale Clinical Trials Grant Review Panel, served as an external reviewer for other NHMRC Panels and reviewed grants for the Canadian Institutes of Health Research. He is the Chief Editor of the Evidence-based Decision Making in Critical Care Medicine web site ([www.EvidenceBased.net](http://www.EvidenceBased.net)), which has been ranked as one of the top five evidence-based medicine resources in the world by the American Thoracic Society.

GSD has published 43 primary research papers in leading specialty and general journals, 60 review papers, 3 research books, and 15 book chapters. Based on 72 citations listed in the ISI Web of Science, his h-index is 20 with an average citations per article of 27.5. He has published six papers that have been cited more than 100 times.

GSD has delivered 13 invited plenary sessions, 81 invited talks and has organised and conducted 20 workshops at International and National level meetings. He has been invited to deliver Grand Rounds 8 times in hospitals other than the one in which he works.

In 2001, GSD developed an 18-hour course on evidence-based medicine. He teaches this course to the intensive care Senior Registrars at two hospitals in NSW. This course is currently the only formal course in EBM delivered to critical care trainees in Australia and New Zealand. He also regularly teaches EBM to medical students at the University of Sydney.

He is currently the primary Supervisor of three PhD students.

GSD's track record of involvement in successful collaborative research projects leading to key publications clearly indicates that he is capable of successfully managing and completing a trial of the scope proposed in this submission.

Fiona Simpson is a Senior Research Fellow in the Intensive Care Department of Royal North Shore Hospital. In 2006 she was invited by the President of the Australasian Society of Parenteral and Enteral Nutrition (AuSPEN) to join the AuSPEN Council, a body which strives to be the principal scientific society for all health professional, academics and industry scientists involved in Clinical Nutrition in Australasia. She has been endorsed by her peers to represent her National professional association, the Dietitians Association of Australia (DAA), on four separate National projects: the Clinical Guidelines for Acute Stroke Management, the Clinical Guidelines for Stroke Rehabilitation and Recovery, The National Stroke Coalition and the Novartis Dysphagia Working Party. In 2008 she was acknowledged by the Department of Health as a recognised expert in her field at an advanced level of clinical expertise, practice and research, being awarded the highest grade of Clinical Specialist in the Expertise stream.

Fiona is well qualified to help lead a clinical trial of this size due to her formal training and past experience. She has recently completed the requirements for the Graduate Certificate in Clinical Epidemiology at Sydney University, and in 2003 she co-chaired the development of Bi-National (Australian and New Zealand) Evidence-Based Guidelines for feeding critically ill patients. She was a Chief Investigator on the consequent 27-hospital Nutrition Guidelines Trial that evaluated the impact of the Evidence-Based feeding guidelines on patient outcome. The results of the 1118 patient trial have recently been published in the Journal of the American Medical Association. Fiona is a current Chief Investigator on the NH&MRC Early Parenteral Nutrition versus Standard Care trial.

Fiona was an Invited Expert and Advisory Working Group Member on two NH&MRC endorsed National Stroke Foundation Guidelines, being the only dietitian invited to participate in the guideline development project. She was responsible for identifying, appraising and helping compile the nutrition sections of the guideline and liaising with the DAA to ensure that the guidelines were suitable for DAA endorsement. These guidelines have changed practice and improved processes of care across Australia for those with Stroke.

Fiona currently reviews for the methodological journal *Trials*, and has reviewed for a disciplinary specific journal. In addition to the above achievements, Fiona has delivered 17 invited talks at International, National, Regional and Local level meetings. She has also conducted six invited workshops.

Professor Caterson is an acknowledged international expert on obesity, its management and the metabolic disease it produces, and on diet and eating. In addition he has extensive experience with animal models of obesity and techniques for investigating insulin resistance in small animals and has published widely in this field.

Having established the first Obesity Service in Australia, he has been involved in trials of obesity management for many years and has published widely on this area. He has expertise in trial design, eating and activity interventions and in many aspects of research into obesity management and obesity complications. He is involved in studies of interventions for disease prevention and the epidemiology and assessment of obesity. A particular current clinical interest is the definition and impact of obesity in Asia.

He was a member of the working party of the NH&MRC on the Prevention of Overweight and Obesity, the Implementation Committee of that report, and chaired the National Obesity prevention group. He was a keynote speaker at both the NSW and Queensland Parliamentary Summits on Obesity. He has been president of both the Australian Diabetes Society and the Australasian Society for the Study of Obesity. Internationally he is a member of the steering group of the International Obesity Task Force, was a Vice-President of the International Association for the Study of Obesity, has been and is on the scientific program committee for international conferences and was co-chair of the 10<sup>th</sup> International Congress on Obesity held in Sydney in 2006. He is a Technical Adviser for WHO on obesity. He is an adviser to governments on Diabetes and Obesity. He is the immediate past-president of the Asia Oceania Association for the Study of Obesity. He is Foundation Director of the Institute of Obesity Nutrition and Exercise at the University of Sydney.

Other than published journal articles, he has published 7 books or book chapters since 2004, and is an editor of Clinical Obesity 3rd Edition (to be published this year). He has contributed 8 reviews to various journals and has written (with others) 7 reports for WHO or governments. In the last 5 years he has been invited to speak overseas on 26 occasions. He has spoken at the Dunn School of Nutrition at Cambridge, the Hotel-Dieu, University of Paris, University of Leeds, for the Chinese Nutrition Society, for WHO and for the Working Group on Obesity in China (Department of Public Health), in Singapore, Malaysia, Hong Kong and Tokyo, and plenary lectures at the 9th International Congress of Obesity and a has given 8 plenary lectures at various international obesity society meetings in the last 5 years. Within Australia he has given a further 36 invited lectures in that period. In addition to NHMRC funding and funding from the NHF he has received funding from the NSW Department of Health, the Commonwealth Department of Health & Aging and various other research funding agencies and industry bodies.

Dr Andrew Davies is Deputy Director of the Intensive Care Unit (ICU) and Head of Trauma Intensive Care at the Alfred Hospital, Melbourne.

AD developed a strong clinical research program after winning the prestigious Matt Spence Medal in 1995 (the Best Young Investigator Award at the Annual Australian and New Zealand Scientific Meeting on Intensive Care). Since 1995 he has been a key participant in the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG) and for the past 5 years he served as the President of Australasian Society of Parenteral and Enteral Nutrition (AuSPEN). During his tenure, he led the set up of major new initiatives including research grant funding, guideline development policy and collaborative links with equivalent nutrition societies in the USA and Europe. He is currently Chair of the Research Committee for AuSPEN.

His main achievements with the ANZICS CTG and AuSPEN have been in the initiation of multi-disciplinary, collaborative, multi-centre clinical research projects to study the effects of nutrition on critical illness. As a result of these efforts, he has published 7 investigator-initiated RCTs in high impact journals.

AD is an Associate Editor of the Journal *Clinical Nutrition* and is an Editorial Board member for the *Journal of Parenteral and Enteral Nutrition*. He reviews manuscripts for several other nutrition and critical care journals.

He has delivered 30 invited presentations at International meetings and 20 invited presentations at National meetings. This includes the following conferences with large international attendances: International Symposium of Intensive Care and Emergency Medicine (Belgium, 2006 & 2008), Society of Critical Care Medicine (USA, 2009), European Society of Parenteral and Enteral Nutrition (2005 & 2007) and Clinical Nutrition Week (USA, 2009).

AD is the instigator and Chief Investigator of a current 180 patient multi-centre RCT comparing small bowel and gastric feeding in critical illness which is within 10 patients of completion. He has also been or is currently a member of the management committees of 4 large RCTs in the areas of both nutrition and critical illness. Three of these were funded by the NH&MRC including the 7000 patient SAFE study comparing saline and albumin for fluid resuscitation (published in the *New England Journal of Medicine*). In all AD has now published 31 peer-reviewed manuscripts, 8 book chapters and 36 abstracts.

He reviews grants for several Australasian funding organisations and has been a member of the Human Research Ethics Committee at the Alfred Hospital since 2005. He has been a conference organising committee member for 6 national conferences (5 of which he chaired the Abstract and Poster Judging Committees) and was recently the AuSPEN Chair for the highly successful Asia Pacific Critical Care 2008 Congress in Sydney.



Professor Anthony McLean is currently the Professor and Head of the Department of Intensive Care Medicine at Nepean Hospital and the Head of the Discipline of Intensive Care Medicine at Sydney University. He is a past President of the Australian and New Zealand Intensive Care Society (ANZICS). Having introduced the first training courses for echocardiography in Intensive Care in Australia in the 1990s, he is internationally recognised for such educational activity and receives numerous invitations from around the world to deliver courses. He is the Director of the Cardiovascular Ultrasound Laboratory which performs over 6,000 echocardiographic and vascular ultrasound studies per annum and is also responsible for an active and productive critical care research team.

Professor A S McLean began his research career when undertaking a B Sc (Hons) at Massey University, completing this with 1<sup>st</sup> class honours in 1971. He received the university prize for his research work on the 'Taxonomic classification of native rhizobia'. He subsequently transferred to medicine completing his medical degree at Otago University in 1977. Research activities were undertaken in addition to his routine medical studies. One of these studies was published in the prestigious neurological journal 'Brain'. He then undertook postgraduate medical training in Sydney Australia in 1985. He was appointed Head of the Intensive Care Medicine at Nepean Hospital in 1986. From a virtually non existent ICU in a semi rural hospital he has contributed both to the development of the hospital itself into a major tertiary referral hospital, in addition to overseeing the growth of the Department of Intensive Care Medicine into one of the most research active departments in the country.

Research undertaken at the Nepean Department of Intensive Care Medicine range from involvement in major multicentre trials to laboratory based molecular biology work. There is a strong emphasis on translating laboratory work to clinical care of a patient. Nepean has been involved in most of the major ANZICS Clinical Trials Group trials, including Dopamine in Renal Failure, SAFE, DECRA, RENAL to name a few. These trials have been supported with many millions of dollars from the NHMRC and other funding bodies. In addition, research has focused on two other predominant areas. The first is in cardiac function in the critically ill patient, including diagnosis, evaluation and treatment. Numerous publications in peer review journals have resulted in work on the use of echocardiography in such patients, the management of Acute Decompensating Heart Failure, the role of B-Type Natriuretic Peptide in the diagnosis and prognosis in critically ill patients, and the role of levosimendon in acute heart failure.

The second focus has been on the application of genetics in the diagnosis of patients with sepsis. Genetic microarray analysis have been used to identify a number of marker genes in the diagnosis of septic patients. This work continues with an emphasis on translating information obtained from genetic microarray studies and applying it to rapid bedside testing PCR studies. Once again this work has resulted in a number of papers in high quality peer review journals. Funding for local studies has come from the Nepean Medical Research Foundation (total to date \$125,000), the Nepean Critical Care Research Fund (approximately \$250,000) in addition to smaller grants from other bodies. Professor A S McLean is currently the supervisor for four PhD students.

Professor McLean runs numerous courses throughout the world every year on the application of echocardiography in the critically ill patient. Over the past two years the Rapid Assessment by Cardiac Echo (RACE), an introductory course, has been in strong demand by Emergency Physicians, Intensivists and Anaesthetists. As an example in the period of February - April 2009, courses will be run in New Zealand, India, Belgium, the Netherlands and the Czech Republic.

Professor A S Mclean is actively involved in drafting training guidelines for Intensivists undertaking echocardiography in Australia and internationally.

**CI-A A/Prof Gordon Doig**

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**PROGRESS REPORT # 402643**

Grant Type: NH&MRC Project Grant  
NHMRC Application ID: 402643  
Administering Institution: The University of Sydney  
Chief Investigator A: A/Prof Gordon S Doig  
Project Title: Early parenteral nutrition vs. standard care in the critically ill patient: A level I randomised controlled trial.  
Year Funding Commenced: 2006

Study is actively recruiting patients at target rate (10-12 pts per week) from 32 hospitals throughout Australia and New Zealand. Current total recruitment is 635 patients. *A priori* planned interim analysis will be conducted after outcomes are obtained on patient 710. Study is anticipated to complete recruitment on time.

**Publications arising to date:**

Doig GS, Simpson F and Sweetman EA. Evidence-based nutrition support in the intensive care unit: An update on reported trial quality. *Current Opinion in Clinical Nutrition and Metabolic Care* (in press).

Doig GS and Simpson F. General Treatment Concepts: Parenteral Nutrition. In: Critical Care Nephrology, 2<sup>nd</sup> Edition. Bellomo, Ronco and Kellum Eds. Elsevier, Philadelphia 2009.

Simpson F and Doig GS. Parenteral vs. enteral nutrition in the critically ill patient: A meta-analysis of trials using the intention to treat principle. *Intensive Care Med* 2005;31(1):12-23.

**Abstracts arising to date:**

Sweetman EA, Doig GS, Simpson F and Heighes PT. Multi-centre clinical trial site monitoring visits focus on data accuracy and miss important opportunities to improve trial conduct: Results of a survey of experienced research coordinators (RCs). The American Thoracic Society International Conference, San Diego, 15-20 May 2009.

Simpson F, Doig GS, Sweetman EA and Heighes PT. Refeeding syndrome (RS) is under recognized and may be inappropriately managed in the Intensive Care Unit (ICU): Results of a multicentre survey. The American Thoracic Society International Conference, San Diego, 15-20 May 2009.

Doig GS, Simpson F and Sweetman EA. Use of a formal study run-in phase to reduce recruitment errors in a multi-centre randomised controlled trial: Is quality better than quantity? Asia Pacific Critical Care 2008 Congress, Sydney, 30<sup>th</sup> October – 2<sup>nd</sup> November, 2008.

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Doig GS and Simpson F. Improving the reliability of web-based randomisation using encrypted allocation information embedded into data elements. 3<sup>rd</sup> International Clinical Trails Symposium, Sydney, 23-26 September 2007.

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**Title:** Testing the protein leverage hypothesis in humans

**Chief Investigators:** S Simpson, A Conigrave, I Caterson, J Brand-Miller

**Period of Support: 2007-2009**

The objective of this study is to test the protein leverage hypothesis in humans by manipulating the protein to energy ratio of the diet for 4 consecutive days on 3 occasions while allowing subjects to eat *ad libitum*. In 2007 we successfully designed 3 versions (10%, 15% and 25% protein) of a 4 day menu, matching energy density, variety and palatability as closely as possible. Since pleasantness may influence amount eaten, a selection of foods from each menu has been tested by a group of volunteers to ensure there is limited difference in the pleasantness between the 10, 15 and 25% versions of each menu. These studies indicated that there is no difference in the overall pleasantness between each menu and this work is ready for submission as a methodological paper. All study protocols including recruitment, accommodation, blood and urine analysis, appetite questionnaires, body composition measurement and continuous glucose monitoring protocols are being implemented. Recruitment for the study has been in progress since the end of 2007 and a total of 12 female and three lean male volunteers will have completed by the end of February 2009. It is planned that recruitment and progression of the trial will continue throughout 2009 and into 2010, with a focus on lean and obese male and obese female subjects. The data on a cohort of 12-14 lean females will provide the subject of the first major data paper and a poster at the European Obesity Congress in May 2009. Results thus far are strongly supportive of the predictions of the protein leverage hypothesis.

We have also continued to work with other groups internationally to run parallel human diet trials, at MRC Human Nutrition Research in Cambridge (Dr Susan Jebb), through the London School of Hygiene and Tropical Medicine in The Gambia (Professor Andrew Prentice), and through the Liggins Institute in Auckland and Jamaica (Peter Gluckman and Terrence Forrester). Finally, we have been involved with a test of the protein-leverage hypothesis in wild primates (Felton et al., 2009) and mice (Sorensen et al., 2008).

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  $\geq 10\%$  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 500kcal 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  $\geq 10\%$  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 kcal per hour?**

[Nutritional support is defined as enteral nutrition, parenteral nutrition or an intravenous infusion of any solution containing  $\geq 10\%$  glucose/dextrose. Energy (calories) from propofol 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?**

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 **hyperphosphatemia** that may be associated with the onset of this current **hypophosphataemic** event?

[Common treatments for **hyperphosphataemia** 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?

**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.html>) to calculate the energy content of the patient's current nutrition support (EN, PN plus any intravenous infusion containing  $\geq 10\%$  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 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 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).

**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.html>) to calculate the energy content of the patient's current nutrition support (EN, PN plus any intravenous infusion containing  $\geq 10\%$  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 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.html>) to calculate the energy content of the patient's current nutrition support (EN, PN plus any intravenous infusion containing  $\geq 10\%$  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 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 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.

**Phosphate protocol: Phosphate dosing table.**

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

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

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

<sup>#</sup> 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.*

<sup>##</sup> 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** 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<sub>4</sub> or MgCl<sub>2</sub>. Refer to local protocols for the replacement of Mg, or any other electrolytes, in these patients.