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Statistical Analysis Plan for a multi-centre randomised controlled trial: Early parenteral nutrition vs. standard care in patients not expected to be fed within 24 h of ICU admission.

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The Early PN Trial

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BRIEF BACKGROUND

1.1 Overview:

Guided by the results of a published meta-analysis of randomised controlled trials,¹ we initiated and conducted a multi-centre clinical trial of early parenteral nutrition (PN) in critically ill patients who were not expected to be fed for at least 24 hours after intensive care unit (ICU) admission.

1.2 Hypotheses to be tested:

In critically ill patients who are not expected to receive nutritional support within 24 hours of ICU admission, the provision of early PN (within 24 hours of ICU admission) alters 60-day landmark mortality, and associated measures of quality of life, physical function and morbidity, compared to standard care.

1.3 Eligibility criteria:

See **Appendix 1** for the complete list of study eligibility criteria, to be applied within 24 hours of ICU admission.

1.4 Randomisation:

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

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

The randomisation sequence was generated using SAS Version 9.1 with blocks of variable size and random seeds² 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 Age and Body Mass Index (BMI). Stratification variables and their thresholds were concealed from site investigators to further prevent anticipation of the allocation sequence.³

1.5 Study intervention:

If randomised to the intervention arm, the patient received standard PN (Kabiven G19%, Fresenius Kabi Australia Pty Limited, Pymble NSW 2073). PN starting rates and daily rate increases were defined by study protocols (**Appendix 2**, PN Protocol A and **Appendix 3**, PN Protocol B). Calculated target metabolic needs were usually achieved on study Day 3.

Target metabolic needs were calculated at time of randomisation by the study web site using the Harris-Benedict equation.⁴ The Harris-Benedict equation on the web site defaulted to the 'bed rest' *activity factor* but allowed the selection of appropriate *stress factors* from a drop down menu.⁵ See **Table 1** for the complete Harris-Benedict equations and adjustment factors used.

The Harris-Benedict calculations were capped to an upper limit of 35 kcal/kg/day. The *total* caloric content (including protein calories) of the study PN was used to calculate actual PN infusion rates needed to meet the calculated target metabolic needs.

Metabolic needs for obese patients, defined as a BMI ≥ 30 , were calculated based on ideal body weight (BMI = 21).

The study web site automatically calculated metabolic needs for malnourished patients (BMI < 17) using a Malnourished (high risk of refeeding syndrome) *stress factor* of 0.85 and assigned them to a protocol designed for patients at high risk of developing refeeding syndrome (**Appendix 3**, Protocol B). If a study site investigator determined that a patient was malnourished at study entry based on criteria other than BMI < 17, they were able to select the Malnourished (high risk of refeeding syndrome) *stress factor* of 0.85 at time of randomisation. If the Malnourished patient was randomly allocated to the intervention arm (Early PN), the study web site automatically indicated they should be managed using PN Protocol B.

Both PN Protocol A and PN Protocol B reminded clinicians to consider enteral or oral nutrition support on study Day 3, if clinically appropriate. In addition, if the patient tolerated 475 kcals/day of enteral nutrition (EN) or any oral calories, the Protocol indicated the current bag of study PN was to be finished at the current rate and no new PN bags were hung.

EN starting rates, daily increases and metabolic targets for EN were set using the participating site's standard techniques.

1.6 Standard care:

Standard care in the patients randomised to the control arm of the study consisted of a reasonable attempt to provide EN or oral nutrition when the attending clinician judged the patient able to tolerate feeding. If the clinician determined that a reasonable attempt at the provision of EN or oral nutrition was not in the patient's best interest, or if efforts at providing EN failed, then at the clinician's discretion, PN was provided.

The attending clinician selected the route, starting rate, metabolic targets, measures of tolerance and composition of feeds to be used in standard care patients based on current practice in *their* ICU.

1.7 Glycaemic control:

To reflect the application of current practice standards in Australia and New Zealand, PN Protocol A and PN Protocol B recommended an insulin infusion if blood glucose levels exceeded 10 mmol/L to achieve peak glucose levels less than 10mmol/L. Tighter glycaemic control was allowed if the treating clinician determined that it was indicated.

1.8 Data collection and follow up:

Every randomised patient was followed up until hospital discharge or 60 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.⁶ If patients remained in hospital on study Day 180, follow-up was censored and outcomes were recorded as per status at Day 180.

1.9 Summary of study outcomes:

The primary study outcome was defined as all-cause landmark mortality, obtained 60 days post-randomisation.

Secondary patient oriented outcomes included: Zubrod/WHO Performance Status;⁷ RAND-36 General Health Status Ver 1; and RAND-36 Physical Function scale Ver 1.⁸

Tertiary disease oriented outcomes included: location of the patient on Day 60 follow-up (Rehabilitation ward, Acute care ward, ICU/HDU, Chronic care/Nursing home, Residential home, Hostel, Other); days of clinically significant organ dysfunction (reported by organ system);⁹ clinically significant infectious complications (reported by type of infection);¹⁰ ICU and hospital length of stay; vital status at hospital discharge; days of invasive mechanical ventilation; days of renal replacement therapy; duration and severity of pressure ulcers; days of antibiotic usage; plus others.

Process measures were collected to describe the implementation of the study intervention (provision of Early PN). These process measures included: time from ICU admission to feeding start; time from study enrolment to feeding start; time from enrollment to EN commenced in patients initially receiving EN; time from enrollment to PN commenced in patients initially receiving PN; number of days Early PN patients received the study intervention; mean nutrition support days per 10 patient days in patients receiving EN and or PN; mean nutrition support days per 10 patient days in patients receiving EN; mean nutrition support days per 10 patient days in patients receiving PN; mean nutrition support days per 10 patient days during which nutrition goals were met; percent of patients who were never fed; percent of patients fed within 24h of ICU admission; Mean energy delivered (all patients) in kcal/patient-day; Mean protein delivered (all patients) in g/patient-day; Mean energy delivered from EN (patients receiving EN); Mean energy delivered from PN (patients receiving PN); Mean energy delivered per patient for each of the first seven days of ICU stay; proportion of patients receiving EN and/or PN for each of the first seven days of ICU stay; proportion of patients receiving EN for each of the first seven days of ICU stay; proportion of patients receiving PN for each of the first seven days of ICU stay.

1.10 Blinding:

Objective interpretation of the chest x-ray is essential to the diagnosis of pneumonia using the Clinical Pulmonary Infection Score.¹¹ Because interpretation of the chest x-ray by the attending intensive care clinician may have been biased by the knowledge of a patient's assigned treatment group, the presence of new or worsening infiltrates on chest x-ray were ascertained from the hospital radiologist's official written report. In all participating ICUs, hospital radiologists reviewed chest x-rays unaware of the patient's assigned study treatment group.

Any adjudication of data recorded on case report forms required to ascertain whether a clinically significant infection was present will be undertaken blinded to intervention group.

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 and conducted a blinded interim analysis at study mid-recruitment.

Using the Haybittle-Peto approach,^{12;13} the SDMC was charged with informing the study management committee if there was a difference in outcomes or serious adverse events between study groups that exceeded three standard deviations in magnitude.

The SDMC met on 9th October 2009 after enrollment of 719 patients and determined that the stopping rules were not met and that the trial should continue.

2.2 Sample size and power:

Conservative estimates obtained from the sensitivity analysis of the published meta-analysis¹ on this topic suggested a relative risk (RR) of 0.54 (95% CI 0.34 to 0.86) could be expected from the early use of PN. Data from the control arm of a 27 hospital cluster randomised trial conducted in target participating sites¹⁴ was used to identify potentially eligible patients and estimate expected baseline mortality. The 354 patients identified in this database as potentially eligible had a baseline mortality rate of 29.7%.

Since meta-analyses of Level II trials may over-estimate treatment effects observed in subsequent Level I trials,¹⁵ it was considered reasonable to be conservative in expectations of benefit. Based on simulation studies and discussions with experts, the magnitude of the expected treatment effect was deflated by 45%. This yielded an expected RR of 0.74 which, at the estimated baseline mortality of 29.7%, translated to a 7.7% absolute risk difference (ARD).

Using standard formulas,¹⁶ with 90% power to detect a 7.7% ARD, and assuming 29.7% baseline mortality, 1,470 patients would need to be enrolled and randomised. A trial of this size (N=1,470) also provided 80% power to detect an ARD of 6.7% and, in the worst case scenario, if the trial yielded a treatment effect as low as 4.5% ARD, the overall findings were still expected to be statistically significant at the traditional two-sided p-value threshold of 0.05.

2.3 Basic principles of analysis:

The primary conclusions of this project will be based on analyses conducted under the principle of intention to treat. All randomised patients will be analysed in the groups to which they were originally allocated to, regardless of whether they actually received the intended treatment or whether a protocol violation or protocol deviation occurred.

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

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

Adjustments for multiplicity will not be undertaken because a hierarchy of outcomes has been stipulated¹⁷ and because the conduct of one interim analysis using Haybittle-Peto stopping thresholds does not require adjustment of outcomes for multiplicity.^{12;13}

2.4 Primary outcome:

The primary study outcome is defined as patient vital status (alive/dead) to be determined on the 60th calendar day post-enrollment.

2.5 Missing primary outcomes:

Missing primary outcomes (Day 60 vital status) will be assumed to be missing at random (MAR) and thus will be 'ignored' in the primary analysis¹⁸ however if greater than 1% of all primary outcomes that should be available for analysis are missing, a sensitivity analysis will be undertaken in addition to the primary MAR analysis.

This sensitivity analysis will include an evaluation of the results of models developed under the assumptions of: 1) last observation carried forward; 2) worst extreme case imputation and; 3) regression model imputation using all available information.^{19,20} Results of the primary MAR analysis will be interpreted in the context of these sensitivity analyses.

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 Early PN on the primary outcome will be assessed using an exact Pearson chi-square test. This test will not be adjusted for continuity.

The magnitude of the treatment effect will be reported as an odds ratio with exact precision-based 95% confidence intervals and a risk difference with exact test-based 95% confidence intervals.

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

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

Age, Gender, BMI (as a continuous variable *and* categorised into underweight [BMI < 18.5] and obese [BMI ≥ 30]), 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, Insulin treated Type I or II diabetes), APACHE III admission dx major category (Cardiovascular/vascular, Respiratory, Trauma, GI, Neuro, Sepsis, Metabolic, Haematological, Other surgical, Other medical).

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

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

2.8 Missing baseline prognostic variables:

Exclusion of randomised patients with known outcomes from analysis, for any reason, contravenes the intention to treat principle.²¹ Every effort should be made to minimise post-randomisation exclusions.¹⁸

By default, statistical software packages require complete information on all covariates for a patient case to be included in a covariate adjusted regression model. Any missing information

from any covariate results in the exclusion of the entire patient case by the software package. Exclusion of incomplete cases with known outcomes reduces statistical efficiency and introduces bias into the estimate of treatment effectiveness.^{22;23;24}

Missing baseline prognostic variables will be replaced with mean values calculated from the observed non-missing instances of that baseline prognostic variable.²⁵ The imputed means will be calculated using pooled data from both treatment arms. Imputed means will *not* be calculated within treatment arm using treatment arm-specific data *nor* will any post-randomisation information be incorporated into the calculation. Furthermore, replacement values for missing calculated constructs such as BMI and APACHE II score will be estimated using non-missing component-level information. For example, if one of the components of BMI is missing, such as height, overall mean height will be imputed and BMI will be calculated with the known weight and imputed mean height.

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

2.9 Covariate adjusted analysis of primary outcome:

A *covariate adjusted analysis* of the effect of treatment with Early PN on the primary outcome will be undertaken. An objective pre-specified algorithm will be used to select variables for inclusion in the covariate adjusted logistic regression model.²⁶ 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 (Age and BMI) will also be eligible for inclusion in the covariate adjusted model.²⁶ Neither a *centre effect term* nor *any interaction terms* will be considered in the covariate adjusted model.²⁶

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.^{26;27;28;29}

Univariate logistic 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).³⁰ 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.²⁸

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.^{26;27;28}

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).³⁰ 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.²⁸

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.²⁹ ‘Imbalance’ detection *may* help preserve the face validity of the covariate adjusted results³¹ and *may* remove bias from the estimate of treatment effect.^{30;31}

Step 3: Backwards stepwise elimination from the maximum model

Parsimony must be embraced during the development of a covariate adjusted *logistic* regression model because covariate adjustment does not always increase precision in the way that would be expected in a *least-squares* regression model for a continuous outcome.²⁶ 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 *logistic* regression model.³⁰

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

If the maximum model demonstrates issues arising due to collinearity based on Eigenanalysis and Condition Number, collinearity will be addressed by standardizing and scaling of continuous variables before backwards stepwise elimination begins.³²

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.^{33;34} A negligible impact will be defined as less than 5% change in the regression coefficient for the treatment effect after stepwise removal of the prognostic variable from the subset model.²⁹

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. The covariate adjusted Odds Ratio (OR) for treatment effect, along with the appropriate 95% confidence interval (CI), will be reported. Using the method of Bender, a covariate adjusted Average Risk Difference (ARD) for the effect of treatment, and appropriate 95% CI, will also be presented.³⁵

3.0 Secondary 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.”³⁶ 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.³⁷ 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.³⁷

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 Early PN Trial. We will therefore use a formal analytic approach to establish MID thresholds for each HRQoL scale.³⁷

Using the approach proposed by Juniper³⁸ and validated by Norman³⁶, we will define a MID as one half the Standard Deviation (SD) of the pooled results for that scale.³⁷ 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.³⁸

3.1 Scoring HRQoL measures:

The Zubrod/WHO Performance Status and RAND 36 Item Health Survey 1.0 domains will be scored on patients alive at Day 60 follow-up using the appropriate scale-specific standard scoring algorithms.^{7;8}

At the time study instruments were selected for use in the Early PN 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%³⁹ 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.

3.2 Missing HRQoL outcomes:

Missing HRQoL outcomes will be assumed to be missing at random (MAR) and thus will be 'ignored' in analysis¹⁸ however if greater than 1% of all HRQoL outcomes that should be available for analysis are missing, a sensitivity analysis will be undertaken in addition to the primary MAR analysis.

This sensitivity analysis for missing HRQoL outcomes will be limited to an evaluation of the results of regression model imputation using all available information.²⁰ 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 60 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.

4.0 A priori defined subgroup analyses:

A priori identified subgroup analysis will be conducted on the following baseline characteristics:

- 1) underweight (BMI < 18.5 kg/m²) at baseline;
- 2) obese (BMI ≥ 30 kg/m²) at baseline;
- 3) elderly (Age > 70 years) at baseline;
- 4) insulin treated diabetes (Type I or II) at baseline.

Screening for differential subgroup treatment effects on the primary study outcome (Day 60 vital status) will be conducted using a formal test of interaction obtained from a logistic regression model. The p-value for this interaction term will be obtained from a LRT.

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

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

The number of *a priori* subgroup analyses (4) 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.

5.0 *Post hoc* hypothesis generating subgroup analyses:

No *post hoc* hypothesis generating subgroup analysis, including efficacy subset type analyses,¹⁸ will be undertaken for or reported in the primary publication.

If any *post hoc* hypothesis generating subgroup analyses are undertaken for subsequent publications, they will be clearly identified as hypothesis generating when reported.

The number of *a priori* subgroup analyses (4) will be reported in all publications along with the total number of any *post hoc* subgroup analyses undertaken.

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Table 1. Harris-Benedict equations and adjustment factors used by study web site

For males:

Target metabolic needs (kcal/day) = (66.5 + (13.75 × Wt) + (5.003 × Ht) - (6.775 × Age)) × adjustment factor

For females:

Target metabolic needs (kcal/day) = (655.1 + (9.563 × Wt) + (1.85 × Ht) - (4.676 × Age)) × adjustment factor

Wt = weight in Kg

Ht = height in cm

Age = Age in years

Adjustment Factors (most severe was selected).

Other, not listed below <value="1.2">

- Any other problem, not listed below.

Infection, mild <value="1.3">

- Ex. mild skin, line or surgical wound infection. Local redness, heat and swelling but no systemic signs.

Operation, minor <value="1.3">

- Any surgical procedure that does not require general anaesthesia or respiratory support.

Operation, major <value="1.35">

- Any surgical procedure that **does** require general anaesthesia or respiratory support.

Infection, peritonitis (non-septic) <value="1.35">

- Peritonitis based on visual inspection or culture. Patient does not have systemic signs of sepsis.

Cancer <value="1.35">

- Patient is known to have an active tumour. May or may not be undergoing active or palliative treatment.

Trauma, single fracture (skeletal) <value="1.4">

- Patient has trauma resulting in a single skeletal fracture of any bone except long bones.

Infection, moderate <value="1.45">

- Infections that would normally require ICU admission for treatment. Ex. Community acquired pneumonia, Ventilator Associated Pneumonia.

Trauma, single long-bone fracture <value="1.45">

- Trauma with a fracture to a long bone (femur, humerus, tibia, fibula, radius and ulna).

Trauma, multiple fractures <value="1.5">

- Trauma with multiple fractures to any bones, including at least one long bone.

Trauma, blunt with or without fractures <value="1.6">

- Blunt trauma, such as a motor vehicle crash and fall from height. Includes Penetrating trauma.

Infection, severe <value="1.65">

- Any infection, or suspected infection, that expresses itself systemically as sepsis.

Burns, less than or equal to 20% TBSA <value="1.7">

- Chemical or thermal burns to less than 20% of total body surface area.

Malnourished (high risk of refeeding syndrome) <value="0.85">

- Body mass index of less than 17 or history and physical exam consistent with malnourishment or high risk of malnourishment. Based on clinical grounds decided by attending clinician.

Appendix 1: Study Inclusion and Exclusion Criteria

Inclusion Criteria (All YES answers for enrolment)

1. Is the patient expected to remain in ICU today and tomorrow?
2. Is the patient 18 years of age or older?
3. Has the patient been admitted to the study ICU less than 24 hours?
4. Does the patient have a central venous access line through which parenteral nutrition could be delivered?
5. Is this patient **not** expected to receive enteral, parenteral or oral nutrition today or tomorrow?

Exclusion Criteria (All NO answers for enrolment, YES to any for exclusion)

1. Known pregnancy or currently breastfeeding.
2. Has the patient previously been enrolled and randomised into this study?
3. Is the patient to receive palliative care only and is not expected to survive ICU or hospital discharge?
4. Was the patient admitted to this, or another, ICU during this current hospitalisation?
5. Was the patient admitted to the study ICU directly from another ICU?
6. Is the patient moribund and not expected to survive 24 hours?
7. Is the patient brain dead or suspected to be brain dead?
8. Are there long term contraindications to enteral or oral nutrition such that the patient would normally be supported with parenteral nutrition (Ex. Home TPN patient)?
9. Does the patient require treatment of thermal injury to greater than 20% of total body surface area?
10. Is the primary reason for admission to the ICU for the treatment of a condition that requires timely nutritional support (Ex. Anorexia nervosa.)?
11. Body weight < 35 Kg
12. Height < 140 cm (Demi armspan < 59 cm)
13. Is there a contraindication to treatment with Kabiven G19%?

NB - see next page for contraindications to Kabiven G19% based on TGA licensing indications.

Contraindications to Kabiven G19% based on TGA Licensing Indications.

- c1. Known hypersensitivity to egg or soya protein or to any of the ingredients of the study PN (for full ingredients see Product Information, MIMS TGA Document Appendix 1).
- c2. Severe hyperlipidaemia (Documented serum total cholesterol >7mmol/L and/or triglycerides >3 mmol/L).
- c3. Severe liver insufficiency (Biopsy proven cirrhosis, or documented portal hypertension with a known past history of either upper GI bleeding attributed to portal hypertension or of hepatic failure leading to encephalopathy / coma.)
- c4. Severe blood coagulation disorders (Documented INR > 3.0 not due to coumarin therapy, platelet count <15,000).
- c5. Inborn errors of amino acid metabolism (Ex. PKU etc)
- c6. Severe renal insufficiency without access to haemofiltration or dialysis.
- c7. Acute shock as defined by arterial systolic blood pressure \leq 90mmHg or mean arterial pressure \leq 70mmHg despite adequate fluid resuscitation (i.e. following rapid infusion of \geq 500mL crystalloid or 200mL colloid solution and /or PAOP \geq 12mmHg, CVP \geq 8mmHg) **or** increasing need for noradrenaline / adrenaline / dopamine to maintain blood pressure where the infusion rate has **increased by more than 50%** over the previous hour **to greater than 0.6mg/hour (10 mcg/min)** norad / adrenaline or **30mg** dopamine.

*Patients are **not excluded** if their initial shock responds to fluid therapy or if the catecholamine infusion rate has not increased by more than 50% over the previous one hour period or if the current infusion rate is less than 0.6mg norad / adrenaline per hour .*

- c8. Hyperglycaemia (blood sugar > 10 mmol/L) that currently requires the administration of more than 6 units of insulin/hour **at the time of enrolment.**
- c9. Pathologically elevated serum levels of any of the electrolytes included in Kabiven G19% **at the time of enrolment. Documented** Sodium >155 mmol/L, potassium > 6.2 mmol/L, magnesium > 2.0 mmol/L, ionised calcium > 1.5 mmol/L, phosphate >2.0 mmol/L, chloride > 120 mmol/L.

The patient may become eligible if these pathologically elevated electrolyte levels can be corrected within 24 hours of admission to the study ICU.

- c10. General contraindications of infusion therapy: acute pulmonary oedema, hyperhydration, decompensated cardiac insufficiency and hypotonic dehydration

The patient may become eligible if these general contraindications to fluid therapy can be corrected within 24 hours of admission to the study ICU.

- c11. Haemophagocytic syndrome
- c12. Severe trauma with acute shock (see **Exclusion Criteria c7** for definition of acute shock).
- c13. Diabetes mellitus with ketoacidosis or non-ketotic hyperosmolar state.
- c14. Acute myocardial infarction with acute shock (see **Exclusion Criteria c7** for definition of acute shock) or pulmonary oedema.
- c15. (Metabolic acidosis or severe sepsis) with acute shock (see Exclusion Criteria c7 for definition of acute shock. Use Bone Criteria for definition of Severe Sepsis).
- c16. Coma (GCS \leq 8) in association with hyperosmolarity of the blood (\geq 320mOs/kg) from any cause.

Appendix 2: PN Protocol A

Study PN Protocol A: **ALL PATIENTS EXCEPT MALNOURISHED PATIENTS**

Feeding Day 1 (first 24 hours of PN)

- Commence Kabiven G19% at **60ml/hr** (or goal rate, whichever is lower).
- **Consider** trace element, mineral and vitamin needs as clinically appropriate.

Feeding Day 2 (second 24 hours of PN)

- Increase Kabiven G19% to **80ml/hr** (or goal rate, whichever is lower).
- **Consider** trace element, mineral and vitamin needs as clinically appropriate.

Feeding Day 3 (next 24 hours)

- Increase Kabiven G19% to **goal rate**, as appropriate.
- **Consider** trace element, mineral and vitamin needs, as clinically appropriate.
- **Recommend** trialing enteral/oral nutrition, if clinically appropriate.
- Once the patient tolerates ≥ 475 kcal/day EN, complete remainder of 24 hour Kabiven infusion and do not hang another bag.
- If patient tolerates any oral caloric intake from food, complete remainder of 24 hour Kabiven infusion and do not hang another bag.

Feeding Day 4 (next 24 hours) plus all additional days after Day 4

- **May switch** to parenteral nutrition solution tailored to patient's specific clinical needs. Goals not to exceed 25–35 kcal/kg and 1.0–1.5 g protein/kg.
- **Consider** long term needs regarding trace element, mineral and vitamins as clinically appropriate.
- **Recommend** trialing enteral/oral nutrition, if clinically appropriate.
- Once the patient tolerates ≥ 475 kcal/day EN, complete remainder of 24 hour Kabiven infusion and do not hang another bag.
- If patient tolerates any oral caloric intake from food, complete remainder of 24 hour Kabiven infusion and do not hang another bag.

INSULIN / GLUCOSE PROTOCOL: Early PN Patients

If glucose levels exceed **10 mmol/L** an insulin infusion should be commenced and titrated to achieve peak serum glucose levels of **< 10 mmol/L**. Frequent monitoring of the patient's blood glucose should be initiated as per your ICU's usual practice for patients receiving an insulin infusion.

If insulin infusion is required at ≥ 6 **units/hr** to maintain glucose target:

- Reduce Kabiven G19% to 40ml/hr for 24 hours.
- At the end of 24 hours, if insulin needs are reduced below 6 units/hr, increase Kabiven G19% to 80mls (or original goal rate, whichever is lower) for 24 hours.
- At the end of this second 24 hour period, if insulin needs remain below 6 units/hr, increase Kabiven G19% to goal rate.
- If insulin requirements exceed 6 units/hr at any time during the above process, reduce PN to previously tolerated rate, or 40 mls/hr (whichever is higher), for 24 hours. Begin increasing rate every 24 hours as above, if tolerated.

Appendix 3: PN Protocol B

Study PN Protocol B: **MALNOURISHED PATIENTS (Ex. BMI \leq 17):**

Feeding Day 1 (first 24 h of PN)

- Commence Kabiven G19% at **40ml/hr** (or goal rate, whichever lower).
- **Strongly recommend** administering 100mg thiamine, commencing at least 30 minutes prior to initiation of Kabiven G19% infusion, as clinically indicated as per product licensing indications.
- **Recommend** daily administration of other vitamins, minerals and trace elements, as clinically appropriate.

Feeding Day 2 (second 24 hours of PN)

- Increase Kabiven G19% to **60ml/hr** (or goal rate, whichever is lower).
- **Recommend** daily administration of vitamins, minerals and trace elements, as clinically appropriate.

Feeding Day 3 (next 24 hours)

- Increase Kabiven G19% to **goal rate**, as appropriate.
- **Recommend** daily administration of vitamins, minerals and trace elements, as clinically appropriate.
- **Recommend** trialing enteral/oral nutrition, if clinically appropriate.
- Once the patient tolerates \geq 475 kcal/day EN, complete remainder of 24 hour Kabiven infusion and do not hang another bag.
- If patient tolerates any oral caloric intake from food, complete remainder of 24 hour Kabiven infusion and do not hang another bag.

Feeding Day 4 (next 24 hours) *plus all additional days after Day 4*

- **May switch** to parenteral nutrition solution tailored to patient's specific clinical needs. Goals not to exceed 25–35 kcal/kg and 1.0–1.5 g protein/kg.
- **Strongly recommend** addressing long term needs regarding trace elements, minerals and vitamins as clinically appropriate.
- **Recommend** trialing enteral/oral nutrition, if clinically appropriate.
- Once the patient tolerates \geq 475 kcal/day EN, complete remainder of 24 hour Kabiven infusion and do not hang another bag.
- If patient tolerates any oral caloric intake from food, complete remainder of 24 hour Kabiven infusion and do not hang another bag.

INSULIN / GLUCOSE PROTOCOL: Early PN Patients

If glucose levels exceed **10 mmol/L** an insulin infusion should be commenced and titrated to achieve peak serum glucose levels of **< 10 mmol/L**. Frequent monitoring of the patient's blood glucose should be initiated as per your ICU's usual practice for patients receiving an insulin infusion.

If insulin infusion is required at \geq **6 units/hr** to maintain glucose target:

- Reduce Kabiven G19% to 40ml/hr for 24 hours.
- At the end of 24 hours, if insulin needs are reduced below 6 units/hr, increase Kabiven G19% to 80mls (or original goal rate, whichever is lower) for 24 hours.
- At the end of this second 24 hour period, if insulin needs remain below 6 units/hr, increase Kabiven G19% to goal rate.
- If insulin requirements exceed 6 units/hr at any time during the above process, reduce PN to previously tolerated rate, or 40 mls/hr (whichever is higher), for 24 hours. Begin increasing rate every 24 hours as above, if tolerated.