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| **protocol** |
| IGNITe ImprovinG Nutrition Intake after Trauma |
| Version Number: 1.0  Date:16/10/2019 |
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| **Statement of Compliance**  This document is a protocol for a research project. This study will be conducted in compliance with all stipulations of this protocol, the conditions of the ethics committee approval, the NHMRC *National Statement on Ethical Conduct in Human Research (2007) – Updated 2018*, and the NHMRC and Universities Australia *Australian Code for the Responsible Conduct of Research (2018)*. If the project is a clinical trial, it will comply withthe *Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95)*. |

**STUDY INVESTIGATORS**

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| Principal Investigator: | Name: Prof Andrea Marshall  Institution: Gold Coast Hospital and Health Service  Department: Nursing and Midwifery Education and Research  Address: Gold Coast University Hospital, 1 Hospital Blvd, Southport, 4215  Tel. +61 7 5687 3235  Email: a.marshall@griffith.edu.au  Role in Study: Marshall will lead the study, supervise research assistants who will be responsible for screening, recruiting and consenting participants. She will also provide research training to novice researchers commensurate with their individual learning goals. |
| Co-Investigator: | Name: Prof Martin Eduard Wullschleger  Institution: Gold Coast Hospital and Health Service  Department: Trauma Services  Address: Gold Coast University Hospital, 1 Hospital Blvd, Southport, 4215  Tel: +61 7 5687 0231  Email: Martin.Wullschleger@health.qld.gov.au  Role in Study: Wullschleger will provide clinical leadership in the specialty and day-to-day support of clinician researchers and research assistants who are screening, recruiting and consenting participants. He will have some oversight of ongoing data collection and will influence intervention adherence. |
| Co-Investigator: | Name: Ms Lisa Mahoney  Institution: Gold Coast Hospital and Health Service  Department: Nutrition and Dietetics/Allied Health  Address: Gold Coast University Hospital, 1 Hospital Blvd, Southport, 4215  Tel:+61 7 5687 3019  Email: Lisa.Mahoney@health.qld.gov.au  Role in Study: Mahoney will be responsible for helping to identify potentially eligible patients and for enacting aspects of the intervention prior to ward transfer. She will work with Rose to promote intervention fidelity and adherence throughout the study. As able, Mahoney will contribute to data analysis and interpretation. |
| Co-Investigator: | Name: Dr Shelley Roberts  Institution: Gold Coast Hospital and Health Service/Griffith University  Department: Allied Health  Address: Gold Coast University Hospital, 1 Hospital Blvd, Southport, 4215  Tel:+61 7 5687 3041  Email: Shelley.Roberts@health.qld.gov.au  Role in Study: Roberts will support Mahoney and Rose in undertaking their research roles and will support Marshall in providing research training to novice researchers. She will assist with intervention implementation and will, with Marshall and Wullschlegger, support clinicians and research assistants with study operations including data collection. Roberts will assist with both quantitative and qualitative data analysis and with formal dissemination of research through publication. |
| Co-Investigator: | Name: Ms Natalie Rose  Institution: Gold Coast Hospital and Health Service  Department: Nutrition and Dietetics Department  Address: Gold Coast University Hospital, 1 Hospital Blvd, Southport, 4215  Tel: +61 7 5687 3688  Email: Natalie.Rose@health.qld.gov.au  Role in Study: Rose will be responsible for enacting aspects of the intervention after transfer to the ward. She will work with Mahoney to promote intervention fidelity and adherence throughout the study. As able, Rose will contribute to data analysis and interpretation. |
| Associate Investigator: | Name: Dr Angelly Martinez  Institution: Gold Coast Hospital and Health Service  Department: Intensive Care Unit  Address: Gold Coast University Hospital, 1 Hospital Blvd, Southport, 4215  Tel: +61 7 5687 5705  Email: Angelly.Martinez@health.qld.gov.au  Role in Study: Martinez will assist with identification of potential participants and will support Mahoney with intervention implementation in the ICU. |
| Associate Investigator: | Name: Dr Bhavik Patel  Institution: Gold Coast Hospital and Health Service  Department: Trauma Services  Address: Gold Coast University Hospital, 1 Hospital Blvd, Southport, 4215  Tel: +61 7 5687 0231  Email: Bhavik.Patel@ health.qld.gov.au  Role in Study: use of ultrasound equipment. |
| Co-Investigator: | Name: Ms Elizabeth Wake  Institution: Gold Coast Hospital and Health Service  Department: Trauma Services  Address: Gold Coast University Hospital, 1 Hospital Blvd, Southport, 4215  Tel: +61 7 5687 4149  Email: Elizabeth.Wake@health.qld.gov.au  Role in Study: Wake will assist with identification of potential participants and will assist Marshall and Roberts with supervising research assistants. She will, as able, contribute to data analysis and development of publications. |
| Co-Investigator: | Name: Prof Daren Heyland  Institution: Queen’s University  Department: Clinical Evaluation Research Unit  Address: 76 Stuart Street, Kingston, ON, Canada  Tel: +1 403 915 5573  Email: [dhk2@queensu.ca](mailto:dhk2@queensu.ca)  Role in study: Heyland has provided methodological input into the study design and will assist with data analysis and manuscript development. |
| Research Assistant:  Julie Barker | Name: Ms Julie Barker  **Institution:** Gold Coast Hospital and Health Service  **Department:** Nursing and Midwifery Education and Research Unit  **Address:** E 2 020, Gold Coast University Hospital, Southport, QLD 4215  **Tel:** 56873253  Email: [Julie.Barker2@health.qld.gov.au](mailto:Julie.Barker2@health.qld.gov.au)  Role in Study: Research Assistant |
| Research Assistant:  Cheryl Rapier | Name: Mrs Cheryl Rapier  **Institution:** Gold Coast Hospital and Health Service  **Department:** Integrated and Ambulatory Care Services  **Address:** E 2 020, Gold Coast University Hospital, Southport, QLD 4215  **Tel:** 56873603  Email: cheryl.rapier@health.qld.gov.au  Role in Study: Research Assistant |

**STUDY SYNOPSIS**

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| Title: | ImprovinG Nutrition Intake after Trauma (IGNITe) |
| Short Title: | Improving Nutrition after Trauma |
| Study Sites: | Gold Coast University Hospital (GCUH) |
| Study Aims/Objectives/Hypothesis: | Aim: To evaluate the feasibility of a randomised controlled trial of critically injured patients with nutrition risk factors where intervention group patients receive a higher dose (≥2.2 grams/kg/day) of protein/amino acid administration in ICU and a high protein oral nutrition supplement (ONS) on the ward; control patients receive ≤1.2 gram/kg/day of protein in the ICU and ONS on the ward as prescribed at the discretion of the treating team.  Secondary aim: To contribute ICU data to the EFFORT trial which, is a large, multicenter, pragmatic, registry-based, patient randomised, clinical trial of 4000 nutritionally high-risk critically ill patients. In this study the administration of lower dose of protein/amino acids (≤1.2g/kg/day) will be compared with the administration of a higher dose of protein/amino acids (≥2.2g/kg/day) to nutritionally high-risk critically ill patients to determine if higher protein administration is associated with greater muscle mass, improved survival and a quicker rate of recovery**.**  Hypothesis: We hypothesise that the trial will be feasible as judged by enrolment rates, intervention fidelity and protocol compliance. |
| Study Design: | A pilot, phase II, open-label, randomised, clinical trial. |
| Study Outcome Measures: | Study feasibility is the primary outcome: we define feasibility as the ability to deliver higher dose of protein to patients in the intervention group (intervention fidelity), recruit 75% of eligible patients, and collect outcome data at specified timepoints.  As we are contributing data to the EFFORT trial, secondary outcomes for our study (will include: 60-day mortality, time to discharge alive from hospital, muscle quality and quantity measured by quadriceps ultrasound, and functional status (physical recovery). |
| Study Population | All patients >18 years of age admitted to ICU with a diagnosis of trauma who are nutritionally at risk as defined as:   1. Mechanically ventilated for 48 hours from screening 2. Low (≤25) or High BMI (≥35) 3. Moderate to severe malnutrition (as defined by local assessments). We will document the means by which sites are making this determination and capture the elements of the assessment (history of weight loss, history of reduced oral intake, etc.). 4. Frailty (Clinical Frailty Scale 5 or more from proxy) 5. Sarcopenia- (SARC-F score of 4 or more from proxy) 6. From point of screening, projected duration of mechanical ventilation >4 days |
| Number of participants: | 40 |
| Translation to Clinical Practice: | The results of this study will help inform clinical practice where recommendations for protein prescription varies from 1.2g/kg/day to 2.5g/kg/day.  Feasibility assessment is a core feature of this study which will lay the foundation for future collaborative work. Evaluation of study feasibility will provide additional data to demonstrate that a larger scale study can be done and will inform streamlining of study processes. |
| Key Ethical and Safety Considerations | Ethical approval will be sought from GCHHS hospital HREC prior to recruitment. The trial will be registered, and the protocol developed according to the SPIRIT Guidelines.  Informed consent includes:   * Participants will be provided written and verbal explanations of project by trained RA. * Consent will be obtained prior to randomisation and arm of study cannot be changed once randomised. * Participation is voluntary, and participants may choose to withdraw from the study at any time.   Privacy and confidentiality:   * All collected data will be protected in line with NHMRC guidelines to ensure participant privacy and confidentiality * Data will be re-identifiable * Obtaining data which relates to nutrition adequacy in ICU and the ward will follow established quality audit processes previously employed in this health service. Consistent with undertaking local audits we are requesting a waiver of consent for this data.   Safety/Risk considerations:   * There is no anticipated physical harm or discomfort to participants. * The ranges of protein prescribed are within the standard of care, the protein supplementation used is approved and currently used in practice, and there is significant equipoise amongst clinicians as to the best practice. If for a given patient, equipoise does not exist, the patient will be excluded from participation. |

## Glossary of Abbreviations, Terms, and Acronyms

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| Abbreviation, Term, Acronym | Definition (using lay language) |
| ICU | Intensive Care Unit |
| LOS | Length of stay |
| EN | Enteral nutrition |
| PN | Parenteral nutrition |
| SDM | Significant decision maker |
| MST | Malnutrition Screening Tool |
| HCP | Health care professional |
| RA | Research assistant |
| ONS | Oral nutritional supplements |
| RCT | Randomised control trial |

## Background

Trauma is a major contributor to morbidity and mortality; the average mortality rate for trauma patients is reported to be 11.1%, representing over 2,000 deaths annually 1. Injuries, including trauma, account for 5.3% of hospital admissions 2 however the costs of treatment place a substantial burden on the health care system. Over a decade ago the estimated cost of injuries cost to the Queensland (QLD) economy was estimated to be $2.6 billion annually; this does not account for the social impact injuries have on patients and their families such as time away from work, decreased productivity and requirements for caring 3. The cost of treating trauma patients is high due to the treatments required and, with critical injury, is further exacerbated by intensive care admission, need for respiratory support and prolonged length of stay (LOS) 4. Reducing health care expenditures and creating more efficient use of health resources is therefore a national health priority area 5. As a result, researchers have invested considerable time in finding ways of reducing LOS and complications associated with trauma while also looking for strategies to enhance recovery.

Specifically, the provision of adequate energy and protein to this population has been shown to improve wound healing, time to mobilisation and long-term functional recovery; decrease the risks of infection, pressure injuries and muscle wasting; and contribute to shorter hospital LOS 6. The provision of adequate nutrition also helps to prevent the development or progression of malnutrition, which may delay recovery from critical injury 7-9. Emerging evidence suggests that exogenous protein/amino acid supplementation has the potential to favourably impact protein balance and improve the recovery of critically ill patients. After a careful review of the published evidence, experts concluded that critically ill patients should receive up to 2.0-2.5 grams/kg/day of protein and receiving at least 80% of the protein that is prescribed is associated with optimal outcomes.10,11

The 2014 International Nutrition Survey (INS) described clinical practice in 187 ICUs around the world involving almost 4000 patients. These survey data clearly demonstrated that ICU patients worldwide are receiving nowhere near current protein recommendations.12 On average, patients were prescribed 94 grams of protein per day or approximately 1.3 grams/kg/day (interquartile range, 1.0-1.5 grams/kg/day, overall range, 0.5-3.8 grams/kg/day). Even within a site, tremendous variability in the protein prescription was observed. Median prescription within a site was 1.2 gram/kg/day but the range went from 0.86 to 2.6. Overall, patients from these participating ICUs received approximately 55% of prescribed protein requirements. Protein delivery was low with the majority of protein delivered coming from enteral nutrition (EN) formulas (82.5%), an additional 11.5% coming from parenteral amino acid sources and very little coming from enteral protein supplements (5.9%) or intravenous (IV) amino acids alone without IV glucose and/or lipids (13 patients, 0.1%). Of note, parenteral nutrition (PN) was used in only 14.2% of included patients, enteral protein supplements were used in only 21.0% of patients, and only 7 sites used a feeding protocol that optimised the delivery of EN (i.e., PEP uP Protocol).

Statistical analysis of the same INS database, as well as other existing nutritional databases, revealed a relationship between increased nutrition intake (either 30 grams/day more of protein and/or 1000 more calories per day) and improved clinical outcomes. For example, it has been shown that for an additional 30 grams of protein per day or 1000 calories per day, critically ill or injured patients have reduced infectious complications, shorter duration of mechanical ventilation, and reduced mortality.11,13,14 Admittedly, the clinical inference we can make from these observational data is weak. But in the absence of stronger evidence from randomised trials, it is sufficient to inform clinical practice.

Some of the most exciting recent developments in the world of critical care nutrition are the emerging evidences that our nutritional practices may actually impact the physical recovery of critically ill or injured patients. A recent study found that IV amino acids in ICU patients improved protein balance and stimulated an anabolic response.15 This suggests that our nutritional strategies may be used to preserve muscle mass and muscle function although data supporting this assertion is just accumulating. For example, Heyland and colleagues conducted a long-term follow up study of patients enrolled in a randomised trial and documented their physical function using the Short-form 36 health status measure at 3 and 6 months.16 They demonstrated that for every 25% increase in nutritional intake, surviving patients had a higher physical function or better physical recovery that was statistically significant at 3 months. At 6 months, the improvements with better nutritional intake were still present and clinically important but lost statistical significance.

In another recent analysis using the same INS data, it was demonstrated that meeting protein requirements seems to be more important than meeting caloric requirements. When caloric intake was controlled for, a significant reduction in associated mortality when more than 80% of protein requirements are delivered compared to less than 80% (Odds Ratio [OR] for 60-day mortality, 0.68 and 95% Confidence Intervals [CI]: 0.50, 0.91) was observed. In contrast, when protein administration was controlled for, there was no incremental effect of increased caloric administration (OR 0.89; 95% CI 0.71, 1.12). Whilst the inference is weak from this statistical modelling, it is consistent with other observational studies that show an association between protein optimisation and survival, but a negative or absent effect of caloric intake.17,18 It is important to note that not all observational studies report similar findings. In an elegant cohort study that carefully examined muscle outcomes using imaging techniques, Puthucheary and colleagues concluded that increased protein delivery was associated with increased muscle wasting19 while others showed an association with increased protein intake and lower likelihood of early ICU discharge.20 Whilst these observations are hypothesis-generating analyses, they are significant in that they suggest a significant harm associated with increased protein and further contribute to the uncertainty about the role of protein in critical illness.

Delivering adequate nutrition, including adequate amounts of both energy and protein to critically injured patients, may be challenging during the initial phase of critical injury and subsequently during recovery after ICU discharge.21. Research reporting on the nutritional intakes of critically ill trauma patients throughout their recovery trajectory is limited. Previous studies have either investigated nutritional intakes of general patients within the intensive care unit or the nutritional intakes of patients at the ward level. Currently only one study has followed patients with traumatic brain injuries (one subset of trauma patients) from the ICU to the ward, showing that nutritional deficits occur throughout hospitalisation, but are greater at the ward level.22 Further, another study that followed critically ill patients after extubation showed that oral intakes were inadequate and were not sufficient to meet patients' nutritional requirements.23 Additionally, both studies only provided limited information regarding the factors that contribute to poor oral intakes among this vulnerable patient group at the ward level. Nutritional deficits experienced by these patients may be a result of either patient related factors such as poor appetite, or organisational factors such as mealtime interruptions or inadequate nutrition prescription. While previous studies have investigated these factors, they have been conducted in general patient populations and have not explored factors that may be specific to trauma patients. Further, organisational related factors, which may be identified through quantitative (e.g. direct observation of meal times) and/or qualitative (e.g. interviews with hospital staff) studies have not been explored in detail.

As the first step in improving patient outcomes, our group has undertaken an evaluation of nutrition intakes in critically injured trauma patients admitted to the Gold Coast University Hospital (GCUH) trauma service, during and following recovery from critical illness. Our data demonstrate that critically injured patients admitted to GCUH have suboptimal nutrition intake, with reduced intake of both energy and protein. During admission to the intensive care unit (ICU) and when patients were receiving artificial (enteral) nutrition, adequacy of energy (29%) and protein (38%) were below the recommended 80% of requirements. Fewer than half of all trauma patients admitted to ICU had adequate protein or energy intake during the first 10 days of ICU admission. The percentage of protein and energy requirements met during the first week following ICU discharge reached 60% of requirements. On the ward the main patient-related factors included poor appetite, dislike of food and nutrition impacting symptoms. Organisational factors included unnecessary meal interruptions, no meal being delivered and missing the meal because of being off the ward. In our preliminary data we have also demonstrated that half of critically injured patients had a Subjective Global Assessment (SGA) score of B or C, which means that these patients were moderately (30%) to severely (20%) malnourished).

Optimising nutrition intake amongst trauma patients is important for preventing complications and improving functional recovery.21 Additionally, the provision of adequate nutrition (achieving ≥75% of estimated requirements) has been shown to reduce health care costs in this patient population.24 Reduced nutrition intake contributes to the development of hospital-acquired malnutrition, which affects 5,400 patients each year in Australia who require an extra 21.3 days in hospital and cost the health service an additional $44,176 for each admission.25 Clearly there is an urgent need to enhance nutrition intake in this group of nutritionally at-risk patients. Strategies to improve nutrition intake should address identified barriers to nutrition intake, which can be at the patient, practitioner or organisational level. Our plan is to work within an interdisciplinary (surgery, nursing, dietetics), and interorganisational (Bond and Griffith) team to develop and implement strategies to improve nutrition intakes in this at-risk group. Using a strong research framework and working with experienced clinicians who are novice researchers we will be strengthening partnerships and building research capacity within Gold Coast Health.

## Study Objectives

**Aim**:

To evaluate the feasibility and acceptability of a randomised controlled trial of critically injured patients with nutrition risk factors who receive either a higher dose (≥2.2 grams/kg/day) of protein/amino acid administration in ICU and a high protein ONS on the ward compared to patients prescribed ≤1.2 grams/kg/day in the ICU with ONS prescribed on the ward at the discretion of the treating team.

Secondary aim: To contribute ICU data to the EFFORT trial which, is a large, multicenter, pragmatic, registry-based, patient randomised, clinical trial of 4000 nutritionally high-risk critically ill patients (CTRN NCT03160547). In this study the administration of lower dose of protein/amino acids (≤1.2g/kg/day) will be compared with the administration of a higher dose of protein/amino acids (≥2.2g/kg/day) to nutritionally high-risk critically ill patients to determine if higher protein administration is associated with greater muscle mass, improved survival and a quicker rate of recovery**.**

**Hypothesis**: We hypothesise that the trial will be feasible as judged by enrolment and retention rates, intervention fidelity.

## Methods

### Methodological Approach

We propose a pilot, phase II, single centre, open-label, RCT involving two groups.

### Study Sites/Settings

This study will commence in the ICU of the Gold Coast University Hospital and continue on the hospital ward to which the patient is admitted after ICU discharge.

### Study Population

We plan to enrol 40 critically injured mechanically ventilated adult patients (≥18 years old) expected to remain mechanically ventilated for an additional 48 hours from screening and have one or more of the following risk factors that make them at high nutritional risk:

1. Low (≤25) or High BMI (≥35)
2. Moderate to severe malnutrition (as defined by local assessments). We will document the means by which sites are making this determination and capture the elements of the assessment (history of weight loss, history of reduced oral intake, etc.).
3. Frailty (Clinical Frailty Scale 5 or more from proxy)
4. Sarcopenia- (SARC-F score of 4 or more from proxy)
5. From point of screening, projected duration of mechanical ventilation >4 days

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| **Table 1. Inclusion and Exclusion Criteria for Study Entry** | | |
| Inclusion Criteria | Exclusion Criteria | Rationale for Exclusion |
| 1. ≥18 years old 2. Nutritionally ‘high-risk” (meeting one of above criteria) 3. Requiring mechanical ventilation with expected total duration of mechanical ventilation >48 hours from point of screening | 1. >96 continuous hours of mechanical ventilation before screening | Intervention is likely most effective when delivered early |
| 1. Expected death or withdrawal of life-sustaining treatments within 7 days from screening | Patients unlikely to receive benefit |
| 1. Pregnant | Unknown effects on foetus |
| 1. The responsible clinician feels that the patient either needs low or high protein | Uncertainty doesn’t exist; patient safety issues |
| 1. Patient requires parenteral nutrition only and site does not have products to reach the high protein dose group. | Site will be unable to reach high protein dose prescription. |
| 1. Not ambulating independently prior to illness that lead to ICU admission (use of gait aid permitted) | Unable to perform outcome assessments |
| 1. Lower extremity injury or impairments that prevents them walking prior to hospital discharge (e.g. amputation, knee/hip injury) | Unable to perform outcome assessments |
| 1. Pre-existing cognitive impairment or language barrier that prohibits outcomes assessment | Unable to perform outcome assessments |
| 1. Pre-existing primary severe systemic neuromuscular disease resulting in severe weakness pre-ICU (e.g., Guillain Barre | Unable to perform outcome assessments |
| 1. Intracranial or spinal process affecting motor function | Unable to perform outcome assessments |
| 1. Patients in hospital >5 days prior to ICU admission | Most of muscle atrophy and weakness occurs at the onset of bedrest and patients with prolonged illness prior to enrolment may not respond to interventions |
| 12. Not expected to stay ≥4 days after enrolment | To permit adequate exposures to the proposed intervention |

### Recruitment/ Selection

**Screening:**

Patients admitted to the ICU with a traumatic injury will be identified through screening of daily ICU admissions by a RA with screening occurring within 96 hours of admission to the ICU. Once eligible participants are identified, the RA will liaise with the treating intensivist and ICU dietitian to confirm the suitability of the potential participant(s).

**Recruitment and consent:**

*Waiver of informed consent for ICU component of study*:

ICU is a complex environment with patients meeting the inclusion criteria unlikely to be able to provide informed consent because they are mechanically ventilated, sedated and may have injuries which impact cognition.

This RCT will be testing two practices within the range of usual or standard care. Currently, protein prescriptions for critically ill patients range from 0.5-3.8 g/kg/d and current clinical practice guidelines recommend 1.2-2.5 g/kg/day. There is an insufficient evidentiary basis to establish which level of protein administration is right for which patient population. Some have argued that until one level of protein administration is proven to be beneficial, randomisation is the most ethical approach that will provide the correct answer sooner compared to allowing current practice, with tremendous variability and uncertainty, to continue. We will take usual practices and create 2 groups randomising eligible patients to a lower prescription (≤1.2 g/kg/d) or to a higher prescribed protein prescription (≥2.2 g/kg/d). The remainder of care provided to eligible patients will be at the discretion of ICU providers.

To ensure adequate safety of trial participants, our study has the following features:

* No modifications to usual ICU care other than fixing the dose of protein intake (by randomisation), from the wide range of existing doses in current practice.
* Because of patient’s individual characteristics, if a clinician believes the patients must receive either high or low protein, they will be excluded from the trial.
* No experimental products will be tested.
* Credentialed clinicians with expertise in directing the feeding of critically ill patients will monitor and provide usual nutritional care.
* No tissue or blood specimens will be collected for the RCT.
* Although data collection for the purposes of medical records will be prospective, for the purposes of this trial, data collection will be retrospective and abstracted from the medical record (no contact with patient or family for the purposes of this trial will be required). Please note, dietitians, as part of their standard of care will be attempting to contact families to obtain nutrition risk factor information from proxies.
* Trained ICU clinicians and research assistants will enter de-identified data into a secure, password-protected web site using a study identification code.
* A unique patient ID number will be assigned to patients. No direct patient identifiers will be disclosed to the registry site or in any publications or presentation

We consider this trial to be low risk and impractical for clinicians to obtain fully informed consent and thus, are applying for a waiver of informed consent. This request is consistent with the evolution of modern medicine where clinical research is embedded into “learning health care systems”, a system designed to improve the effectiveness and safety of health care by creating a system that “continuously learns to be better”. The learning comes through research. This creates a tension between moral imperatives. Some authors have developed an ethical framework for evaluating the ethics of research activities embedded within health care systems26 and concluded, along with others,27 that, in some pragmatic, comparative-effectiveness RCTs, the fact of randomization need not be disclosed to patients and no express informed consent is required.28,29 These investigators argued that this approach is unnecessarily prohibitive and, in some situations, exposes vulnerable patients to unnecessary risks. By maintaining the status quo, unproven and potentially inferior interventions continue to be delivered due to a lack of better alternative. In this trial, we simply aim to replace the clinician variability in practice with a randomisation schema.

Given the safety characteristics of this trial described above, this trial presents no greater risk than typical management of feeding in ICU patients today. The ranges of protein prescribed are within the standard of care, the protein supplementation used is approved and currently used in practice, and there is significant equipoise amongst clinicians as to the best practice. If for a given patient, equipoise does not exist, the patient will be excluded from participation. It is important to point out that data collected for this study will mirror data collected for the International Nutrition Survey, a multicenter, multinational quality improvement collaborative, which has been granted a waiver of consent for more than a decade for >250 ICUs across the US and >500 ICUs worldwide. Data are all collected from standard hospital records and there are no study-specific procedures EXCEPT the randomisation function explained above. Simply adding a randomisation function to these patients in which equipoise exists does not increase risk and is consistent with ‘minimal risk.’ Certainly, there is precedent in the critical care literature that other such registry trials30-32 conducted in critically ill patients using existing datasets and cluster RCTs of other nutrition interventions33-35 have been granted a waiver of informed consent.

The other reason to justify a waiver of informed consent is that protein administration is time sensitive. In order to be most effective, protein administration needs to occur as soon as possible after initiation of mechanical ventilation. To be consistent with clinical practice guidelines, there should be no delays from the time the patient is assessed to when nutrition therapy is initiated. Delays in initiating optimal protein therapy may result in sub-optimal patient outcomes. Requiring informed consent will mean the trial is impractical as not all patients will have families available to discuss the matter within the time frame for enrollment (within 96 hours of admission to ICU). Lack of family availability may result in a very select and biased patient population enrolled, which will severely limit the generalisability of what is meant to be a ‘real practice, pragmatic study.’ With all enrolled patients, we aim to contact family members, where and when available, to advise them regarding the fact that their family member is enrolled in a clinical trial and provide them with an information sheet. If at that point, they refuse to have their family member involved in the trial, they will be withdrawn.

*Consent to continue:*

The components of the intervention delivered on the ward, and the primary and secondary outcome data collected from patients will require informed consent to continue, as these measures are beyond the scope of usual or standard care. We will seek written informed consent from the patient, or in the case where a patient does not have mental capacity to consent (which may occur in patients with traumatic injury), we will seek written informed consent from the family member to continue participation in the study.

**Randomisation and allocation concealment:**

Patients will be screened, evaluated, and randomised into this trial within 96 hours of admission to the ICU. Randomisation will occur through a web-based system at the Clinical Evaluation Research Unit (<http://www.ceru.ca/>) at Kingston General Hospital. The system will confirm eligibility prior to allowing randomisation. The system will then provide the site representative with the treatment assignment (either low dose protein group or high dose protein group) along with a reminder of the caloric targets to be used in this trial. The randomisation system, which has proven reliable in several prior RCTs, has a robust audit trail, and will maintain concealment of future allocations.

The randomisation system will use a computer-generated randomisation schedule to allocate patients 1:1 to either low dose or high dose protein by the method of permuted blocks of random undisclosed size within strata.

### Risk Mitigation Procedures

This study presents no greater risk than typical management of feeding in ICU patients today. The ranges of protein prescribed are within the standard of care, the protein supplementation used is approved and currently used in practice, and there is significant equipoise amongst clinicians as to the best practice. If for a given patient, equipoise does not exist, the patient will be excluded from participation.

Primary aim data: outcome data will be collected from screening logs, patient medical charts, and through meal audits, which have no foreseeable risks to the patient. For acceptability interviews, the highest risk we foresee is inconvenience for participants, and participants can withdraw from the interview at any time.

Secondary aim data: outcome data collected will include:

* 1. Ultrasounds: There are no risks associated with the ultrasound as it is a safe, non-invasive type of imaging.
  2. 6-minute walk test: The tests used are low risk test. This will be performed by a trained healthcare professional, with the ability to assess and maintain patient safety during testing.
  3. Strength tests of upper and lower body (i.e. Medical Research Council sum-score evaluated via standardised “manual muscle testing’, battery to measure balance, walking speed, and rising from a chair, functional Status Score for ICU, and functional independence measure (see later in protocol for more detail of these tests): The tests used are low risk test. This will be performed by a trained healthcare professional, with the ability to assess and maintain patient safety during testing.
  4. Hand-grip strength: The hand grip strength test is a low risk test. This will be performed by a trained healthcare professional, with the ability to assess and maintain patient safety during testing.

For the phone call interview as 6-months, the highest risk we foresee is inconvenience for participants, and participants can withdraw from the interview at any time.

### Participant Withdrawal Procedures

With all enrolled patients, we aim to contact family members, where and when available, to advise them regarding the fact that their family member is enrolled in a clinical trial and provide them with an information sheet. If at that point, they refuse to have their family member involved in the trial, they will be withdrawn.

Once on the ward, patients and/or family members will be approached to consent to continue participation in the study providing them with the opportunity to withdraw from the study. Participants will be able to withdraw their consent at any time throughout the study by contacting the research team or GCHHS HREC department.

### Study Procedure

Currently, protein prescriptions for critically ill patients range from 0.5-3.8 g/kg/d. There is an insufficient evidentiary basis to establish which level of protein administration is right for which patient population. We will take usual practices and create two groups randomising eligible patients to a lower prescription (≤1.2 g/kg/d) or to a higher prescribed protein intake (≥2.2 g/kg/d). In both groups, targets will be set using pre-ICU dry actual weight. For patients with BMI >30, ideal body weight based on a BMI of 25 will be used. For the higher protein group, we will use Nutrison Protein Intense (Nutricia; 10g protein/100ml) which provides a higher protein to energy ratio in line with current guidelines. Alternatively, we could use Nutrison Protein Plus Multifibre (Nutricia; 6.3g/100ml) or Isosource 2.0 (8.4g/100ml; Nestlé Health Science) supplemented with Beneprotein powder (85.7g/100ml; Nestlé Health Science) to bring the protein provision up to 2.2g/kg. Once on the ward, protein supplementation will continue by providing high protein ONS (Resource 2.0; Nestlé Health Science) which will provide an additional 19.7g of protein in one 237ml supplement (an additional 40g of protein per day). In the event that flavour fatigue occurs, alternative protein supplementation will be prescribed using higher protein food supplements such as Up n Go Protein Energize (Sanitarium; 16.8g per serve), Quest Protein bars (Quest Nutrition; 21g protein), Chobani Fit high protein yoghurt (Chobani; 15 g).

Although this trial is not about caloric dose, we want to encourage participating clinicians to be conservative in meeting energy targets and avoid overfeeding. Caloric goals should be the same in both groups. We will endorse the guidelines for energy targets set forth by American Society of Parenteral and Enteral Nutrition/ Society of Critical Care Medicine, especially as it pertains to the obese patient.6 For non-obese patients, we suggest that their caloric prescription be around 20-25 kcal/kg/day using a simple weight based formula. If the site chooses to use more sophisticated equations or indirect calorimetry, that is permissible. For obese patients, if indirect calorimetry is used, the goal of the nutritional prescription should be to provide energy not to exceed 65%–70% of measured requirements. If indirect calorimetry is unavailable or not used, consistent with the published guidelines, we suggest using the weight-based equation 11–14 kcal/kg actual body weight per day for patients with BMI in the range of 30–50 and 22–25 kcal/kg ideal body weight per day for patients with BMI >50.

In both groups, targets will be achieved through any combination of enteral nutrition (high protein content in high group if available), protein supplements, and parenteral nutrition or amino acids only (as clinically available). The only difference between the two groups is the protein targets that are set. Similar efforts should be used in both groups to achieve at least 80% of these targets. The remainder of care provided to eligible patients will be at the discretion of ICU providers.

**Data Collection**

Data will be collected to allow for study feasibility to be assessed. Specifically, we will consider:

1. The enrolment, consent and retention rate. We expect the majority of eligible patients will be enrolled in this study during the ICU component of the study but will track enrolment rates to identify any eligible patients who were missed and reasons they were not enrolled. For consent rates we will judge the current study protocol feasible if >75% of eligible patients and/or families of eligible patients consent to continue once on the ward. For retention rates, the study will be considered feasible if we are able to collect 6-month outcome data for >75% of patients enrolled.
2. Compliance with the intervention. We will collect data regarding the delivery of protein and amino acid administration in ICU to determine whether 2.2g/kg/day are delivered to patients in the intervention group. This will include calculation of protein received from enteral or parenteral nutrition plus any protein supplements. When the patient is discharged to the ward, we will monitor prescription, delivery and consumption of oral nutrition supplements in the intervention group to assess compliance with the study intervention. We will also collect consumption of ONS in the control group (both product and protein consumed) for the control group to assess the degree of treatment differentiation.
3. Acceptability: We will also collect data, including qualitative interviews prior to hospital discharge, to enable assessment of intervention and study feasibility. Qualitative interviews with patients and/or family members and health professionals will be guided by the Theoretical Domains Framework to identify factors influencing intervention implementation (including its acceptability to patients and/or family members and staff). Qualitative data will be collected from a sub-sample of participants (patients, health professionals) in the intervention group to assess intervention acceptability, feasibility and to identify what factors helped or hindered intervention adherence. Based on previous work we anticipate achieving data saturation after interviewing 10 patients and/or family members and 10 health professionals.
4. Compliance with outcome assessment at hospital discharge. We will collect data regarding the ability to complete in-hospital outcome assessments which include: i) including quadriceps ultrasound at baseline (within 24 hours of randomisation, 10 days post randomisation and just prior to hospital discharge); ii) 6-minute walk test at hospital discharge; iii) Medical Research Council sum-score evaluated via standardised “manual muscle testing’ with each of 12 muscle groups assessed using a 6-point MRC scale; iv) quadriceps force, via hand-held dynamometry for both lower extremities; v) distal strength measured via isometric hand grip strength via a hydraulic hand dynamometer; vi) Short Physical Performance Battery to measure balance, walking speed, and rising from a chair; vii) Functional Status Score for ICU; viii) Functional Independence Measure.
5. Compliance with outcome assessment 6 months after discharge (by telephone). We will collect data regarding the ability to complete post-discharge outcome assessments which include: i) Health related quality of life (QOL) will be measured using SF-36 version 2 (SF-36 v2) and EQ-5D-5L; ii) Physical function status will be measured using the Katz activities of daily living and Lawton’s Instrumental ADL scales; iii) Mental and cognitive function will be measured using the Hospital Anxiety and Depression Scale, the Impact of Events-R scale and MoCA-BLIND screening questionnaires as part of the recommended Core Outcome Measurement Set for evaluating post discharge-outcomes in acute respiratory failure survivors.

We have adopted the data collection procedures which have been used within the International Nutrition Survey for a number of years. Data will be entered into a secure web-based data (REDCap, server located at Queen’s University) collection tool to capture all relevant de-identified data. Site characteristics will also be recorded in this system including characteristics of the hospital and ICU plus general aspects of nutrition practice (e.g. use of feeding protocol or algorithms). For randomised patients, data will be abstracted from the medical record. These data points include: admission category (surgical vs. medical), diagnosis, comorbidities, sex, age, height, weight, baseline APACHE II score, SOFA score. In addition, we will extract data on the nutrition care provided such as: nutrition prescription (protein and calories), recent weight loss or food intake changes, type of nutrition, received, amount of nutrition received (protein and calories), blood sugar levels, insulin total units/day, lowest phosphate level, highest triglycerides, urea and creatinine, use of pro-kinetics, and use of supplements. This daily data will be extracted for 12 days except protein intake, which will continue for duration of ICU stay (maximum of 28 days) or until death or transition to oral feeds. Finally, duration of mechanical ventilation, length of ICU and hospital stay, ICU readmissions, and hospital mortality will also be recorded.

We will collect baseline ultrasound (US) measures (within 24 hours of randomisation, 10 days post randomisation – if the patient is still in hospital, and just prior to hospital discharge). In the event that hospital discharge is prior to day 10, the day 10 measure will not be done. To ensure standardisation and quality in the measures, we have created high quality training materials and will have US films sent centrally to abstract all measurements. In the first 10 patients enrolled in the US sub-study, participating sites will conduct a run-in phase where their submitted data will be evaluated for quality and reliability (both intra and inter-rater reliability) to ensure subsequent measures are of high quality. Nutritional and clinical data for these patients will be included in the parent EFFORT trial but the US measures may be omitted if quality is poor. The de-identified ultrasound images will be stored encrypted on servers in Germany by the European market leader for data protection-certified long-term archiving of medical data, HealthDataSpace.

We will also collect data specific to secondary outcomes that would be used in a future effectiveness trial. In developing our evaluation framework, we followed the recommendations of a recent expert consensus statement.36 The primary outcome for a future effectiveness trial will be the walking distance achieved during a 6-minute walk test (6MWT) measured at hospital discharge. Implementation of the test will be based upon the 2014 ATS standards, with adaptation, as needed, for the in-patient setting and ICU survivor population.37 The 6MWT is a reliable, valid, responsive measure of physical function38 for survivors of acute respiratory failure.

Secondary measures for a future effectiveness trial will include:

1. 60-day mortality: data extracted from patients’ medical chart
2. Time to discharge alive from hospital: data extracted from patients’ medical chart
3. Nutritional adequacy, hospital mortality, readmission to ICU and hospital, and duration of mechanical ventilation, ICU stay, and hospital stay: data extracted from patients’ medical chart.
4. Overall strength using Medical Research Council (MRC) sum-score evaluated via standardized “manual muscle testing” with each of 12 muscle groups assessed using a 6-point MRC scale39 and summed to a total score (range: 0-60).40 41-46
5. Quadriceps force, via hand-held dynamometry (HHD)47, 48 for of both lower extremities. Each will be scored by, averaging the results of three trials.49, 50
6. Distal strength measured via isometric hand grip strength via a hydraulic hand dynamometer performed bilaterally as per American Society of Hand Therapist guidelines51 and evaluated using normal values.52
7. Short Physical Performance Battery (SPPB)whichmeasures balance, walking speed, and rising from a chair53-59
8. Functional Status Score for ICU (FSS-ICU), which is a 5-item, 35-point assessment of bed mobility, transfers, and ambulation.designed for ICU patients.60-63 and was designed and validated specifically in ICU patients evaluated 8-point Functional Independence Measure (FIM) response scale used throughout rehabilitation assessments,64-67 and is responsive to change during recovery for ICU patients. 60, 62, 63, 68, 69.
9. Lastly, outcomes after hospital discharge will be assessed via 6-month phone-based follow-up. Health related quality of life (QOL) will be measured using SF-36 version 2 (SF-36 v2) and EQ-5D-5L. The SF-36 is valid and reliable across a variety of patient groups, including ICU survivors.70, 71 The EQ-5D-5L is included, in addition to SF-36 v2, because it is suitable for patients with inattention and fatigue,72, 73 recommended for use in ICU survivors.74, 75 Physical functional status will be measured using Katz activities of daily living (ADL)76 and Lawton’s Instrumental ADL (IADL)77 scales, as well as return to baseline work/activity and living location. Mental and cognitive function will be measured, in addition, using the HADS, IES-R and MoCA-BLIND screening questionnaires as part the recommended Core Outcome Measurement Set for evaluating post-discharge outcomes in acute respiratory failure survivors.75 In order to improve retention, a call will be made to participants at 3 months to update contact information and act as a reminder of upcoming follow-up assessments to be completed at the 6-month time point.

### Outcome Measures

Primary outcomes of the Phase II study relate to study feasibility. Feasibility will be assessed against the following criteria:

* + - >75% of patients approached agree to participate (in the outcomes measurement aspect of the study recruitment)
    - >75% of patients assigned to the intervention group will receive at least 2.2g/kg/day of protein as prescribed
    - >75% of outcome measures are able to be collected from patients who survive to hospital discharge
    - >75% of patients are able to complete outcome measures at 6-months via the phone-based follow up.

### Data Storage and Confidentiality

Participant data will be protected in line with national ethical standards to ensure privacy and confidentiality always by ensuring:

Collected data will be accessible by the named investigators only. De-identified data may be accessed by a statistician not currently named in this application.

Screening logs will contain participant IDs, logs will be kept on password protected computers. Files linking the patient with the study number will be stored separately from the data.

Data will be re­identifiable to allow follow up of participants on the ward and 6-months after hospital discharge. Data will be collected using an assigned study number on paper-based case report forms.

Information collected will be re identifiable but will be reported and entered into REDCap in a de-identified manner. Ultrasounds will be de-identified before they are shared. The ultrasounds will be shared via HealthDataSpace, an innovative service of Telepaxx Medical Data GmbH and Digithurst Bildverarbeitungssysteme GmbH & Co. KG. With over 13 billion health records, Telepaxx is the European leader in cloud-based archiving, storage and transmission of medical images and privacy-seal information. All medical images and findings are stored encrypted on servers in Germany by the European market leader for data protection-certified long-term archiving of medical data. HealthDataSpace is certified with a total of two privacy seals.

Research data gathered from the results of the study may be published, however identifying data will not be used.

Data will be stored in locked filing cabinets at Gold Coast University Hospital. Electronic data pertaining uploaded to RedCAP (server located at Queen’s University), a secure web application for building and managing online research databases

Upon completion of the project, the data will be stored for a minimum of 5 years following publication to allow for appropriate peer review as suggested by current NHMRC (12) guidelines, the data contributing to the EFFORT trial will be kept for 10 years in line with Canadian policy. After this period the data will be shredded and destroyed, and files will be deleted from computers.

### Data Analysis and Statistical Considerations

The feasibility outcomes (enrolment and consent rate, and compliance with outcome assessments) will be described by group as rates with 95% confidence intervals. As part of the screening procedures we will collect data on factors influencing recruitment and retention rates.

Intervention compliance (another feasibility outcome) will be determined by calculating the amount of protein consumed by the patient in ICU and again once the patient is on the ward. Prior to analysis, missing values will be described for all variables; all missing data and improbable values checked against source data. Nutritional adequacy at hospital discharge will be compared between the two groups using the rank-based Mann-Whitney U test, as we expect data to not be normally distributed. Secondary continuous outcomes will be analysed as described above. Categorical secondary outcomes will be analysed using Fisher’s exact tests. If >5% of outcome data are missing, multiple imputation will be used for the primary analysis and a ‘missing not at random’ sensitivity analysis will be performed using the tipping point approach of the pattern mixture model with multiple imputation.

Acceptability outcomes will be used to assess intervention acceptability, feasibility and to identify what factors helped or hindered adherence to intervention components. Qualitative data will be analysed using content analysis with an inductive approach.

We will provide secondary outcome data to the EFFORT trial where the data will be analysed following the procedures outlined for the cohort of patients in the EFFORT OUTCOMES substudy (Clinical trials.gov ID #NCT03160547).

**Sample size and duration**:

Given the main objective of the study related to feasibility, acceptability and intervention compliance we feel a sample size of 20 per group will allow us to assess these endpoints with reasonable precision and is consistent with the sample size of other Phase II studies. Based on the number of critically injured patients admitted to GCUH ICU each year (approx. 180 per year) we anticipate recruitment to take 2 years, with an anticipated consent rate of 50%.

### Translation to Changes in Clinical Practice

This project evaluates a tailored, multifaceted nutrition intervention designed to improve nutrition intakes for patients recovering from critical injury at GCH. Clinicians are integral to this work with the ICU and trauma dietitian’s principal investigators on this study. Involving clinicians in all phases of the project means the intervention will likely be acceptable, effective and sustained in practice. This is expected to improve nutrition care provided by staff, nutrition delivery by foodservices, and nutrition intakes among patients.

Feasibility assessment is a core feature of this study which will lay the foundation for future collaborative work. Our learning from this study will position us well to lead a future multisite study evaluating the intervention in different health services. Locally, the benefit of our learning from this study will help improve systems and processes and to identify strategies which may help improve protein and energy intakes and patient outcomes.

Findings from our work will be communicated to the Trauma Service, Nutrition and Dietetics Department and Food and Nutrition committee at GCH. Consumers (patients) will provide important data to this study which will help inform sustainability of the intervention and any potential modifications or enhancements. Our learnings from this study will inform refinement of local guidelines. There currently exists a nutrition support guideline for providing nutrition to critically ill and injured patients and a guideline for nutrition support for trauma patients is currently in development (evaluated in the usual care group in this study). Refinement of both internal documents based on data from our study will enhance current practice and policy at GCH.

### Timeline

* October 2019 HREC and governance application submitted
* August-December 2019 Study start-up and training
* January 2020 – October 2021 – trial recruitment period
* October 2021- December 2021 – analysis and publication; dissemination of findings.

### Funding and Resources

Funding organization: Gold Coast Health and Gold Coast Hospital Foundation Research Grant Scheme. The project underwent peer review during this process.

Amount: $100 000

Approved: 31/10/2018. The funding is for 2 years, ceasing 31/12/2020. Because of delays in study start up, a request to extend this grant by a further 12 months has been requested (until December 2021).

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