

# BMJ Open Study protocol for a randomised controlled trial investigating two different refeeding formulations to improve safety and efficacy of hospital management of adolescent and young adults admitted with anorexia nervosa

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## ABSTRACT

**Introduction** Providing effective nutritional rehabilitation to patients hospitalised with anorexia nervosa (AN) is challenging, partly due to conservative recommendations that advocate feeding patients at low energy intakes. An ‘underfeeding syndrome’ can develop when patients are not provided with adequate nutrition during treatment, whereby malnourished patients fail to restore weight in a timely matter, and even lose weight. Of particular concern, the reintroduction of carbohydrate in a starved patient can increase the risk of developing electrolyte, metabolic and organ dysfunction. The proposed trial assesses the efficacy and safety of a lower carbohydrate enteral formula (28% carbohydrate) against a standard enteral formula (54% carbohydrate), in adolescent and young adult patients (aged 15–25 years), hospitalised with AN.

**Methods and analysis** The study employs a double-blind randomised controlled trial design. At admission to hospital, malnourished adolescent and young adults with AN will be randomly allocated to commence feeding on a standard enteral feeding formula (1.5 kcal/mL, 54% carbohydrate) or a lower carbohydrate isocaloric enteral feeding formula (1.5 kcal/mL, 28% carbohydrate). Assessments of nutritional intake, weight and biochemistry (phosphate, magnesium, potassium) will be conducted at baseline and during the first 3 weeks of hospital admission. The primary outcome measure will be incidence of hypophosphatemia. Secondary outcomes include weight gain, oedema, other electrolyte distortion, length of hospital admission, admission to the Intensive Care Unit (ICU) and number of days to reach medical stability, using defined parameters.

**Ethics and dissemination** The protocol was approved by the Western Sydney Local Health District Human Research Ethics Committee and institutional research governance approvals were granted. Written informed consent will be sought prior to study enrolment. Study findings will be widely disseminated through peer-reviewed publications and conference presentations.

## Strengths and limitations of this study

- In terms of comparing the two feeding formulas, use of a double-blinded randomised controlled trial design will control for bias, thereby enhancing the reliability of the study findings.
- By employing the participant group hospitalised young people with anorexia nervosa (AN), the study addresses the urgent need to identify effective treatments to reduce length of hospital stay and in the longer term prevent chronicity.
- To the authors knowledge, this is the first study comparing a standard enteral feeding formula against a lower carbohydrate formula in patients with AN.

**Trial registration number** Australian New Zealand Clinical Trials Registry (ACTRN12617000342314); Pre-results.

## INTRODUCTION

Patients hospitalised with anorexia nervosa (AN) require (1) acute management, (2) restoration of positive caloric balance and (3) nutritional rehabilitation to reverse the medical complications of malnutrition, such as dehydration, bradycardia, hypotension, hypothermia, neutropenia, hypertransaminemia, amenorrhoea and impairments in growth and bone health.<sup>1</sup>

Malnourished patients, such as those with AN, are considered at high risk for the development of refeeding syndrome during nutritional rehabilitation. Refeeding syndrome lacks a consistent definition in the literature; however, it is generally described as severe electrolyte disturbances (in particular phosphate) leading to clinical deterioration and



possible sudden cardiac death, and can occur when a starved person undergoes nutrition repletion.<sup>2</sup>

During starvation, the body is in a catabolic state and shifts from carbohydrate to fat and protein utilisation. This results in an altered insulin response and increased glucagon secretion.<sup>3</sup> When the body undergoes nutrition repletion, the change from catabolic to anabolic metabolism results in switching back from fat utilisation to carbohydrate utilisation. This process results in lower serum levels of phosphate. Changes with refeeding can progress to clinical symptoms, including acute circulatory fluid overload, respiratory failure and cardiac failure, and result in death. Hypophosphatemia, in particular, is seen as the precursor to the development of refeeding syndrome.<sup>3</sup>

Consensus-based guidelines for providing nutritional rehabilitation to patients with AN vary; however, most guidelines advocate feeding patients slowly to prevent refeeding complications, such as refeeding syndrome. For example, the UK-based guidelines recommend initial feeding rates as low as 10 kcal/kg/day for at risk patients and 5 kcal/kg/day for extreme cases (body mass index (BMI) <14 kg/m<sup>2</sup>),<sup>4</sup> the American-based guidelines recommend feeding at a slightly higher rate of 30–40 kcal/kg/day (1000–1600 kcal/day)<sup>5</sup> and Australian-based guidelines advocate a starting rate of 6000 kJ/day (1435 kcal/day).<sup>6</sup>

Irrespective of which guidelines are employed, slow feeding results in poor weight gain, and typically initial weight loss in an already malnourished patient group.<sup>7</sup> Under current guidelines, the rate of feed is not increased if a patient displays electrolyte derangement.<sup>4</sup> This often results in ‘underfeeding syndrome’, whereby patients do not reach adequate energy intakes to restore weight in a timely manner, which in turn potentially delays correction of medical instability, prolongs hospital stay and increases the associated costs of hospital treatment.<sup>8</sup> Of concern, strict adherence to guidelines has not prevented the occurrence of refeeding syndrome in a variety of clinical areas, including AN. This calls into question the validity of these conservative guidelines,<sup>9–11</sup> and points to a need for them to be re-evaluated and potentially revised.

A growing body of evidence is now challenging the ‘start low, go slow’ approach advocated in conservative guidelines. A systematic review by Garber *et al* included 27 studies investigating approaches to refeeding patients with AN.<sup>12</sup> The authors concluded that higher caloric refeeding had not been associated with increased risk for the development of refeeding syndrome under close medical monitoring and electrolytes correction.<sup>12</sup> There was insufficient evidence to change the current standard of care for refeeding severely malnourished inpatients, defined as BMI <15 kg/m<sup>2</sup> in adults and <70% of median BMI in adolescents.<sup>12–14</sup> However, at present, consensus is lacking around what is considered the current standard of care.

The UK-based National Institute for Clinical Excellence guidelines recommending starting ‘at risk’ patients

on 5–10 kcal/kg/day were originally published more than a decade ago, and the updated version in 2017 has continued to recommend the same approach of slowly introducing nutrition.<sup>4</sup> The Management of Really Sick Patients with Anorexia Nervosa report for refeeding has recommended more frequent assessment (at least 12 hourly) so that energy provision can be increased in the absence of refeeding syndrome, in order to minimise the risk of ‘underfeeding syndrome’.<sup>13</sup>

While new evidence supports more aggressive feeding in adolescent patients with AN, less robust evidence exists for adult patients with AN.<sup>12</sup> More recent recommendations have been published stating inpatient refeeding protocols for adolescent patients can be ‘more aggressive than previously recommended’, however these lack specific recommendations for the initial caloric prescription.<sup>14</sup> Some authors have recommended starting caloric intakes as high as 35–45 kcal/kg/day (Cape Town Metropole Paediatric Interest Group<sup>15</sup>) to 60 kcal/kg/day (Afzal *et al*<sup>16</sup>) in adolescents with AN, 1600 kcal/day in adults with AN.<sup>17</sup> Adult patients with AN have been safely started on caloric intakes of 1200–1500 kcal/day, without the occurrence of refeeding syndrome, even in populations with a BMI <12 kg/m<sup>2</sup>.<sup>18 19</sup>

Of particular concern is the reintroduction of carbohydrate in a starved patient, which is postulated to lead to a surge in insulin and result in electrolyte derangement and increase the risk of developing refeeding complications.<sup>20</sup> While the literature suggests strategies to avoid refeeding complications such as continuous delivery of nutrients (eg, nasogastric feeding) with less than 40% of energy from carbohydrate,<sup>3</sup> this has not been formally tested. Furthermore, standard enteral formula usually contain >50% energy from carbohydrate.<sup>21</sup> Not all studies demonstrating the safety of higher energy intakes (initiating ≥1200 kcal/day) have specified the macronutrient composition provided to patients during treatment.<sup>18 19 22–24</sup> Studies that have specified the macronutrient content have ranged from 1200 to 1764 kcal/day and 40%–60% carbohydrate in oral meal-based programmes<sup>8 25–28</sup> and 1617–2400 kcal/day and 44%–50% carbohydrate in programmes utilising nasogastric feeding.<sup>29 30</sup>

The current trial aims to test the efficacy and safety of a lower carbohydrate enteral formula (less than 40% carbohydrate) against a standard enteral formula (54% carbohydrate), in adolescent and young adult patients (aged 15–25 years), hospitalised with AN.

Our working hypothesis is that carbohydrate ingested during a starving state increases the risk of hypophosphatemia, via a process whereby a surge of insulin following carbohydrate ingestion causes an intracellular shift of glucose, fluid and electrolytes. Hence, it is predicted that malnourished patients with AN who are provided with a low carbohydrate enteral formula will have lower rates of hypophosphatemia compared with malnourished patients with AN provided with a standard higher carbohydrate enteral formula.

Secondary predictions are that, relative to patients on a standard enteral formula, patients provided with a lower carbohydrate formula may reach feeding target rates sooner due to less electrolyte derangement, which can delay the increase in the rate of feeds. This will affect total energy intake, rate of weight gain, number of days to reach medical stability and length of hospital stay (LOS).

## METHODS AND ANALYSIS

### Study design

This study will use a double-blind randomised controlled design. Adolescent and young adult participants will be randomised into two groups (Standard Feed vs Lower Carbohydrate Feed), using a computer-generated sequence placed into opaque envelopes, stratified by gender. This trial protocol was prepared based on the SPIRIT 2013 statement (online supplemental file 1).<sup>31</sup>

### Recruitment

Participants will be recruited at two public hospitals in NSW with specialised inpatient eating disorder treatment services. Participants will be invited to participate at the commencement of their inpatient treatment, and will be approached once the treating team has decided the patient requires nasogastric feeding. The assessment for the requirement of nasogastric feeding will be made by the treating medical officer based on clinical need and will be made independent to the study. Written informed consent (online supplemental file 2) will be obtained from all participants and will be obtained from guardians if under 18 years of age.

### Participants

This study will recruit patients (aged 15–25 years) hospitalised with AN (assessed by the supervising medical officer using DSM-5 criteria),<sup>32</sup> and requiring nasogastric feeding for nutritional rehabilitation.

Exclusion criteria will include patients that have transferred from another facility, where they have already received nasogastric feeding and/or prophylactic phosphate replacement.

### Enteral feed content

The standard and trial enteral feed were products of Abbott Nutrition, and the nutrient breakdown is described in [table 1](#).

### Treatment

The flowsheet of the treatment protocol is described in [figure 1](#).

### Supplementation

Participants will receive a daily multivitamin. Participants will not receive prophylactic phosphate supplementation if serum phosphate levels are  $>1.0$  mmol/L. Participants will receive 1 g phosphate supplementation prior to commencing nasogastric feeds if baseline serum phosphate level is  $\leq 1.0$  mmol/L, and will be provided

**Table 1** Nutrient breakdown of standard and trial enteral feed (per 1000 mL)

Feed	Standard 1.5 kcal/mL formula	Lower carbohydrate 1.5 kcal/mL formula
Energy (kcal)	1500	1500
Carbohydrate (g)	204 (54% energy)	106 (28% energy)
Fat (g)	49 (29% energy)	93 (56% energy)
Protein (g)	63 (17% energy)	63 (17% energy)
Fibre (g)	0	0
Na (mg)	1400	1310
Potassium (mg)	1650	1960
Calcium (mg)	1000	1050
Phosphorus (mg)	1000	1050
Magnesium (mg)	310	422
Iron (mg)	22	19
Zinc (mg)	19	24
Manganese (mg)	5.0	5.5
Folic acid ( $\mu$ g)	400	840
Vitamin B <sub>12</sub> ( $\mu$ g)	4	13
Thiamine (mg)	2.6	3.2
Osmolality (mOsm/kg H <sub>2</sub> O)	510	475

with phosphate supplementation if serum phosphate levels are  $\leq 1.0$  mmol/L during nutritional rehabilitation. Participants will not receive prophylactic magnesium or potassium supplementation; however, electrolytes will be monitored closely and supplementation will be provided if clinically indicated.

### Assessments

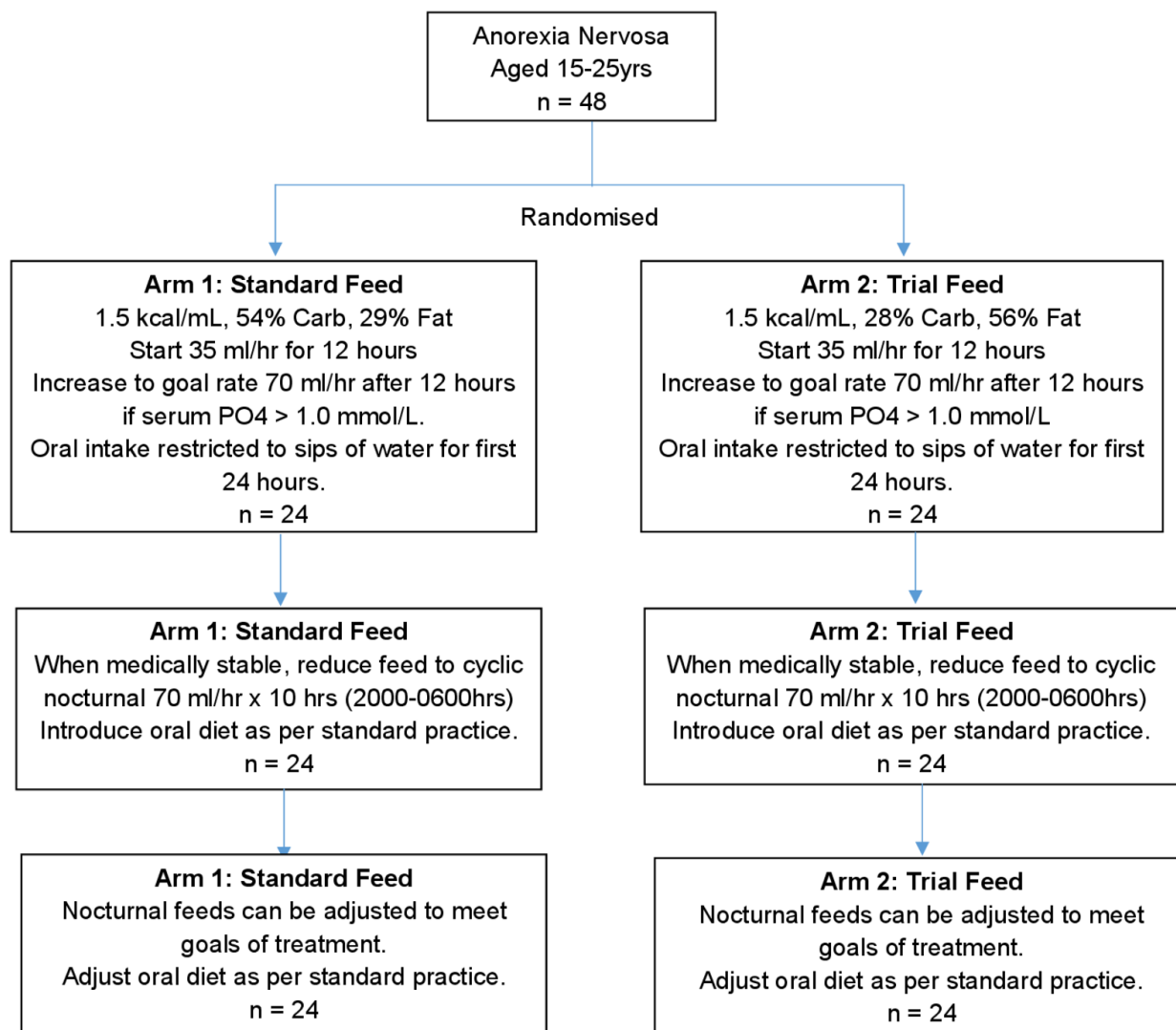
Assessments of primary and secondary outcomes will be conducted during the first 3 weeks of hospital admission. Participation will cease on discharge.

### Diagnosis of AN

Diagnosis based on clinical assessment by the supervising medical officer, using DSM-5 criteria.<sup>32</sup>

### Nutrition assessment

An accredited, practising dietitian will complete a nutrition assessment using the validated nutrition assessment tool, the Subjective Global Assessment (SGA).<sup>33</sup> The assessment examines known prognostic indicators of nutritional status, such as change in weight, change in oral intake, gastrointestinal symptoms, change in functional capacity and the presence of muscle wasting and loss of subcutaneous fat stores. The nutritional status of participants will be scored as an SGA rating A (well nourished), B (mildly/moderately malnourished) or C (severely malnourished).<sup>33</sup> In addition, nutritional status will be assessed in patients using percentage median BMI (%mBMI), defined as 80%–90% mBMI (mild



**Figure 1** Flowchart of treatment protocol.

malnutrition), 70%–79% mBMI (moderate malnutrition) or <70 %mBMI (severe malnutrition).<sup>14</sup>

Anthropometric measures will be taken at baseline by a trained accredited practicing dietitian and will include: height using a wall mounted stadiometer, skinfold measurement using callipers (Holtain, Crymych, UK) and non-dominant hand-grip strength using a dynamometer (Jamar, Sammons Preston Roylan, Bolingbrook, Illinois, USA), with technique recommended in practice. Standard percentile ranges for participant's sex and age will be used for comparison of skinfold measurement.<sup>34 35</sup> Percentage of normal grip strength will be compared with normative data using z scores.<sup>36</sup> Body mass will be recorded from routine weight checks, minimum 3 days/week, using the ward scales recorded to the nearest 0.1 kg, and BMI will be calculated using the initial measured height.

#### Blood tests

Electrolytes (sodium, phosphate, magnesium, potassium) will be measured at baseline, 6–8 hours after starting feeds, then daily for the first week and at least weekly in week 2 and week 3. Thiamine and liver function tests will

be monitored at baseline and weekly during the first 3 weeks of admission. Blood glucose levels will be measured at baseline and at least two times per day during the first week and at least weekly in week 2 and week 3.

#### Dietary intake

The nutritional intake of participants will be assessed by an accredited practising dietitian, using recorded food charts, standardised meal plans and recorded administered enteral feed volumes. Participants on oral intake will have three main meals and three mid meals supervised by nursing staff as per routine care. The macronutrient content of oral diet will also be monitored and reported. Patients on nocturnal nasogastric feeds will receive feeds over 10 hours (20:00–06:00).

#### Medical record review

Participant medical records will be reviewed to generate the following information: standard demographics, LOS, outcomes from daily medical monitoring, presence of peripheral oedema, electrolyte replacement, admission to ICU, days required to reach medical stability, defined

as heart rate >50 beats per minute, temperature >35.5°C, blood pressure >80/50 mm Hg and postural hypotension <20 mm. Routine nursing monitoring will include heart rate, blood pressure, respiratory rate and blood glucose levels.

### Sample size

The target sample size for this trial will be 48. This power calculation was calculated using a dichotomous endpoint two independent study sample, incidence of 45% hypophosphatemia in the standard feed arm<sup>27</sup> and 10% hypophosphatemia in the trial feed arm, 48 patients (24 in each arm) would have 80% power, alpha 0.05. The power calculation was based on reported findings from a meal-based programme<sup>27</sup> providing an initial energy intake and macronutrient composition comparable with the standard feed arm of this trial. Studies utilising nasogastric feeding could not be used in the power analysis due to the lack of reported macronutrient composition<sup>19 23</sup> or the provision of prophylactic phosphate supplementation from commencement of treatment.<sup>29 30</sup>

### Outcome measures

The primary outcome measure will be the incidence of hypophosphatemia.

Secondary outcome measures will be the change in weight, LOS, hypoglycaemia, development of peripheral oedema, serum thiamine (vitamin B<sub>1</sub>), prescribed electrolyte replacement, admission to ICU, days required to reach medical stability, defined as heart rate >50 beats per minute, temperature >35.5°C, blood pressure >80/50 mm Hg and postural hypotension <20 mm.

### Statistical analysis

Continuous outcomes will be assessed for normality and if normally distributed, the two treatment groups will be compared using repeated measures analysis of variance for variables with multiple time point measures (eg, change in weight over time) or independent t-tests for single measures (eg, LOS). Binary outcomes will be compared using a  $\chi^2$  test. An interim analysis will be completed at midpoint.

### Auditing

A coordinating study investigator will conduct regular site visits during recruitment to ensure the protocol is being followed. As per conditions of ethics approval, the human research ethics committee (HREC) is able to conduct independent audits as required.

### Reporting of adverse events

Adverse events will be reported to the Australia New Zealand Clinical Trials Registry and the Western Sydney Local Health District HREC. Unblinding will occur at request of the treating medical team in the event of an adverse reaction (eg, allergic reaction).

### Patient and public involvement

Patients or the public were not involved in the design or conduct plans of our research. Once the trial has been published, we intend to disseminate the main results to trial participants and will seek patient and public involvement in the development of an appropriate method of dissemination.

### DISCUSSION

This study addresses the challenges of providing effective nutritional rehabilitation to adolescent and young adult patients hospitalised with AN, and will provide key evidence-based outcomes to inform changes to current consensus-based guidelines.

It is anticipated that the results of this trial will: (1) be translatable widely into clinical settings, (2) make a significant contribution to dietetic clinical practice, (3) inform the medical management of adolescent and young adult patients with AN, (4) inform the clinical practice of dietitians working with eating disordered patients, (5) improve the nutritional care and health of patients hospitalised with AN and (6) reduce LOS and associated costs.

### Ethics and dissemination

This study protocol has received ethical approval from the Western Sydney Local Health District HREC. Approval has also been received from the Western Sydney Local Health District Research Governance and Sydney Local Health District Research Governance.

Participants will receive nutritional rehabilitation similar to what they would receive as part of standard care, with exception to the possibility of being randomised to receive an isocaloric enteral formula with a different macronutrient composition. As part of routine care, participants will receive close monitoring of electrolytes, and replacement if required, as well as adjustments to caloric intake required to promote adequate weight gain.

Study findings will be widely disseminated through peer-reviewed publications and conference presentation.

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**Contributors** Development of the manuscript was led by EP. Funding was secured by EP, VF, MK, FW, SC and EF. The study design was developed by EP, VF, MK and FW and further refined by LG, GA, SC, MH, CW, EF and JR. Sample size calculation was determined by VF. Ethics approval and amendments were obtained by EP, VF and MK, with assistance from MH and CW. The trial will be coordinated by EP. All authors approved the final version of the manuscript.

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**Competing interests** None declared.

**Patient and public involvement** Patients or the public were not involved in the design or conduct plans of our research. Once the trial has been published, we intend to disseminate the main results to trial participants and will seek patient and public involvement in the development of an appropriate method of dissemination.

**Patient consent for publication** Not required.

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