

The effect of augmented administration of enteral protein to critically ill adults on clinical outcomes:
a cluster randomised, cross-sectional double cross-over clinical trial



TARGET Protein Trial

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The Australian New Zealand Intensive Care Foundation
Nutricia Australia

Endorsement

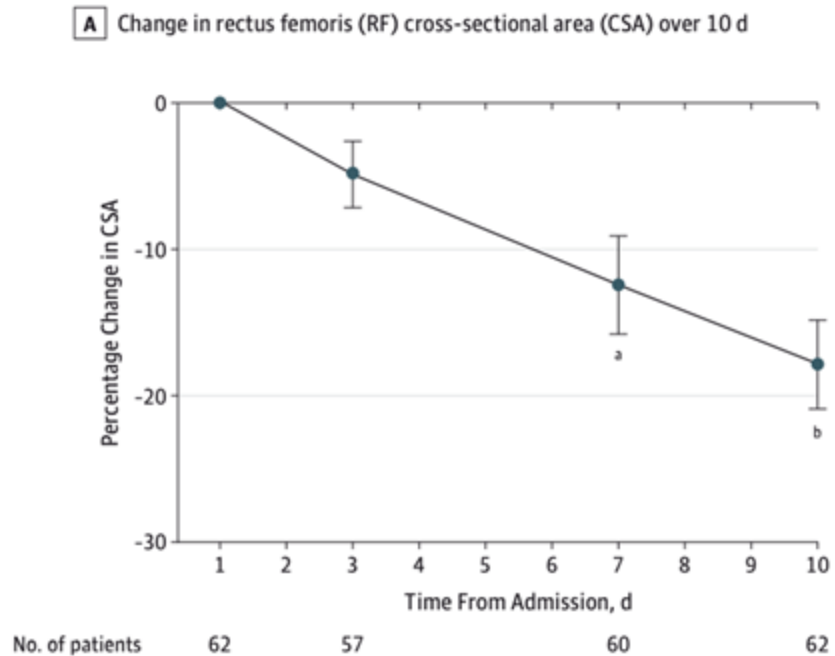
Australia and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group

Coordinating Centre

Royal Adelaide Hospital

Muscle loss is common

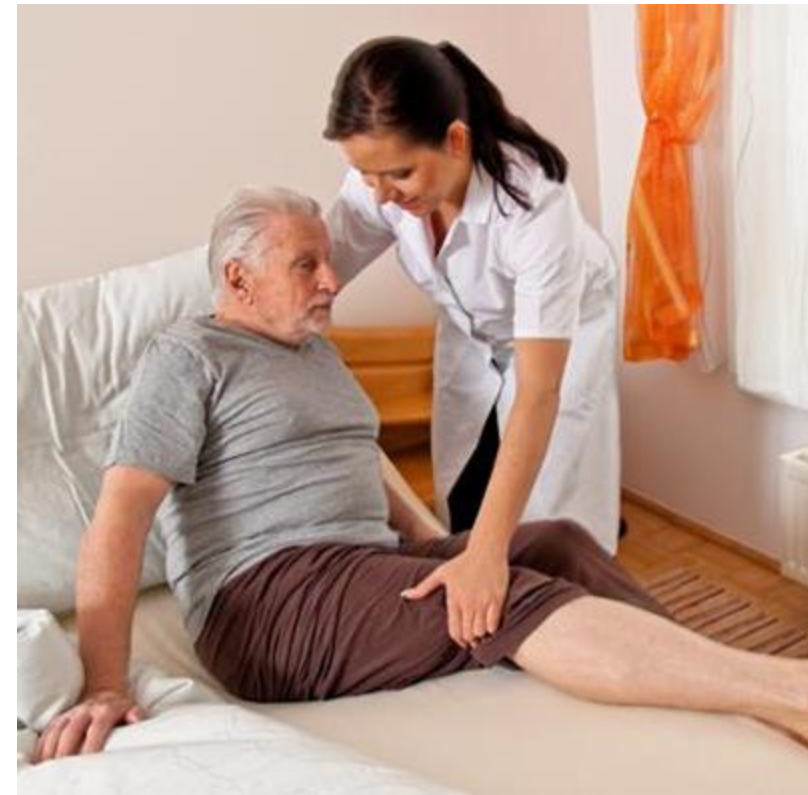
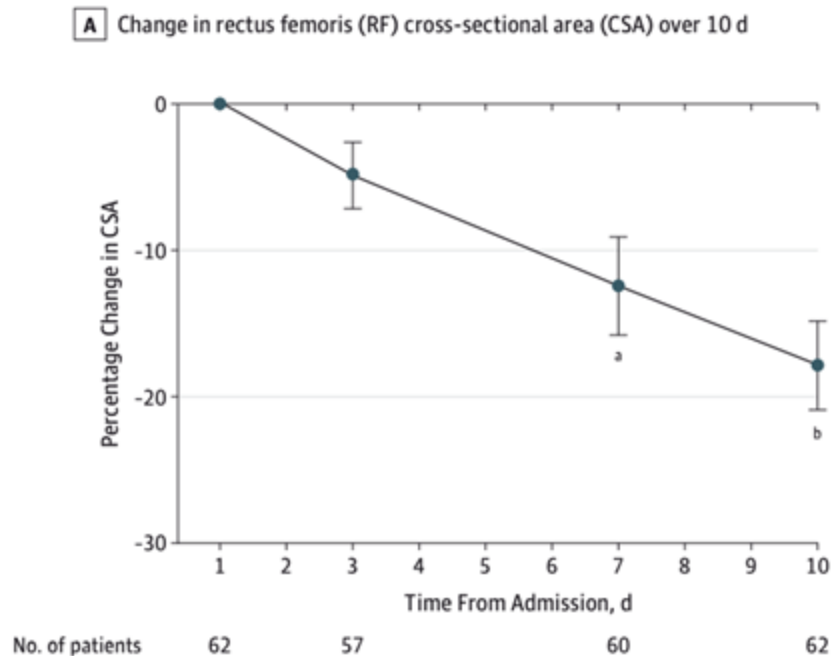
Up to 20% muscle mass in
10 days in MV patients



Muscle loss is common

Up to 20% muscle mass in 10 days in MV patients

Muscle wasting is a major driver of ICU acquired weakness, impacting recovery



Dietary protein stimulates muscle protein synthesis

- ~55% of dietary protein-derived amino acids become available in the circulation
- ~20% of that is taken up in skeletal muscle tissue



Critical Care International Nutrition Guidelines

DOI: 10.1002/jpen.2267

CLINICAL GUIDELINES



Guidelines for the provision of nutrition support therapy in the adult critically ill patient: The American Society for Parenteral and Enteral Nutrition

Charlene Compher PhD, RD¹  | Angela L. Bingham PharmD^{2,3}  | Michele McCall MSc, RD⁴ | Jayshil Patel MD⁵  | Todd W. Rice MD, MSc⁶  | Carol Braunschweig PhD⁷  | Liam McKeever PhD, RDN⁷ 

American:
1.2 – 2.0 g/kg/day

Clinical Nutrition 42 (2023) 1671–1689



Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: <http://www.elsevier.com/locate/clnu>



ESPEN Guideline

ESPEN practical and partially revised guideline: Clinical nutrition in the intensive care unit

Pierre Singer^{a,*}, Annika Reintam Blaser^{b,c}, Mette M. Berger^d, Philip C. Calder^e, Michael Casaer^f, Michael Hiesmayr^g, Konstantin Mayer^h, Juan Carlos Montejo-Gonzalezⁱ, Claude Pichard^j, Jean-Charles Preiser^k, Wojciech Szczeklik^l, Arthur R.H. van Zanten^m, Stephan C. Bischoffⁿ



European:
1.3 g/kg/day

Health: 0.75 g/kg/day

Expert opinion/very low quality of evidence

American:

GRADE recommendation: There was no difference in clinical outcomes in the relatively limited data. Because of a paucity of trials with high-quality evidence, we cannot make a new recommendation at this time beyond the 2016 guideline suggestion for 1.2–2.0 g/kg/day.

**Strength of GRADE
recommendation: Weak**

European:

**25) During critical illness, 1.3 g/kg protein equivalents per day can be delivered progressively.
(R22, updated, Grade 0, strong consensus, 92%)**

Increased use of higher protein formula



Research paper

Nutrition practices in Australia and New Zealand in response to evolving evidence: Results of three point-prevalence audits

L.S. Chapple, PhD, APD ^{a,b,c,d,*}, A. Neuts, MD ^{a,e}, S.N. O'Connor, MNSc, RN ^{a,b,c}, P. Williams, BN, RN ^{b,c,d,f}, S. Hurford, PG Dip Clinical Research, RN ^g, P.J. Young, PhD, MBChB ^{d,g,h,i}, N.E. Hammond, PhD, RN ^{j,k}, S. Knowles, PhD, RN ^j, M.J. Chapman, PhD, BMBS ^{a,b,c,d}, S. Peake, PhD, BMBS ^{b,c,d,f}, On behalf of the TARGET Investigators, The George Institute for Global Health and the Australian and New Zealand Intensive Care Society Clinical Trials Group

- 65 ICUs, >1600 patients
- Greater prescription of higher protein formulae from 2018 to 2020

Protein delivery in mechanically ventilated adults in Australia and New Zealand: current practice

Tejaswini Arunachala Murthy, Rinaldo Bellomo, Marianne J Chapman, Adam M Deane, Suzie Ferrie, Mark E Finnis, Sally Hurford, Stephanie N O'Connor, Sandra L Peake, Matthew J Summers, Patricia J Williams, Paul J Young, and Lee-anne S Chapple; for the TARGET Protein Management Committee

- Prospective observational study to quantify current protein delivery
- 120 critically ill patients
- 5 ICUs in Australia / New Zealand
- Mean protein prescription: 1.46 g/kg IBW/day
- Mean protein delivery: 0.88 g/kg IBW/day



TARGET Protein Feasibility

Original Communication

aspen | LEADING THE SCIENCE AND
PRACTICE OF CLINICAL NUTRITION
American Society for Parenteral and Enteral Nutrition

Use of a High-Protein Enteral Nutrition Formula to Increase Protein Delivery to Critically Ill Patients: A Randomized, Blinded, Parallel-Group, Feasibility Trial

Journal of Parenteral and Enteral
Nutrition
Volume 45 Number 4
May 2021 699–709
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Parenteral and Enteral Nutrition
DOI: 10.1002/jpen.2059
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WILEY

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Stephanie N. O'Connor, MNSc^{1,2}; Sandra L. Peake, PhD^{2,6,10};
Emma J. Ridley, PhD⁶ ; Paul J. Young, PhD⁹; Patricia J. Williams, BNP^{2,6,10};
Adam M. Deane, PhD⁵ ; and for the TARGET Investigator Collaborative and the
ANZICS Clinical Trials Group¹

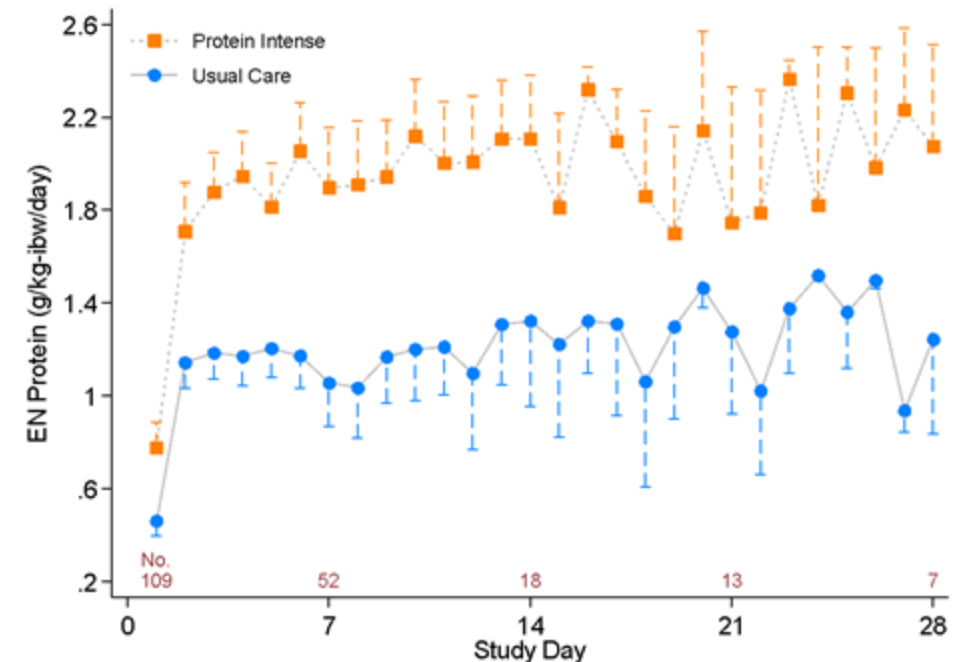


TARGET Protein Feasibility: Primary outcome

Difference in mean (SD) protein delivered from trial EN:

- Augmented protein: 1.52 (0.52) g/kg IBW/day
- Usual care protein: 0.99 (0.27) g/kg IBW/day

Doses representative of usual care (≤ 1.0 g/kg/day) and international recommendations (1.2-2.0 g /kg/day)



Delivered similar amounts of calories

TARGET Protein Feasibility

- Providing a very high protein formula (100 g/L) can achieve protein doses within international recommendations
- A definitive RCT is required before benefit or harm can be demonstrated





TARGET Protein Trial



ELSEVIER

Contents lists available at [ScienceDirect](#)

Critical Care and Resuscitation

journal homepage: www.elsevier.com/locate/ccrj



Original Article

Study protocol for TARGET protein: The effect of augmented administration of enteral protein to critically ill adults on clinical outcomes: A cluster randomised, cross-sectional, double cross-over, clinical trial

Matthew J. Summers, MDiet ^{a, b, *}, Lee-anne S. Chapple, MNutDiet, PhD ^{a, b, c, f},
Rinaldo Bellomo, MBBS, MD ^{d, e, f, o}, Marianne J. Chapman, MBBS, PhD ^{a, b, c, f}, Suzie Ferrie,
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Sandra L. Peake, MBBS, PhD ^{b, f, l}, Jeffrey J. Presneill, MBBS, PhD ^{f, n, o}, Emma J. Ridley,
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MBChB, PhD ^{e, j, p}, Sophie Zaloumis, PhD ^q, Adam M. Deane, MBBS, PhD ^{n, o}, on behalf of
the TARGET Protein Investigators and the Australian and New Zealand Intensive Care
Society Clinical Trials Group

METHODOLOGY

Open Access



TARGET Protein: the effect of augmented administration of enteral protein to critically ill adults on clinical outcomes—statistical analysis plan for a cluster randomized, cross-sectional, double cross-over, clinical trial

Sophie Zaloumis^{1,2}, Matthew J. Summers^{3,4} , Jeffrey J. Presneill^{5,6,7}, Rinaldo Bellomo^{5,6,8}, Lee-anne S. Chapple^{3,4,5,9}, Marianne J. Chapman^{3,4,5,9}, Adam M. Deane^{4,6,7}, Suzie Ferrie^{10,11}, Craig French¹², Sally Hurford¹³, Nima Kakho¹⁴, Matthew J. Maiden^{6,7}, Stephanie N. O'Connor^{3,4}, Sandra L. Peake^{4,5,15}, Emma J. Ridley^{5,16}, An Tran-Duy^{2,17}, Patricia J. Williams^{4,5,15}, Paul J. Young^{6,13,18}, Amalia Karahalios^{1,2*} and on behalf of the TARGET Protein Investigators, the Australian, New Zealand Intensive Care Society Clinical Trials Group

Objective

To determine if augmenting dietary protein to critically ill adult patients when compared to usual care will increase the number of days alive and out of hospital censored at day 90

METHODS

Study design

- Cluster randomised, cross-sectional, double cross-over, registry-embedded, pragmatic clinical trial

		Cluster Period 1	Cluster Period 2	Cluster Period 3	Cluster Period 4
Randomisation	Group 1 (4 ICUs)	Intervention (Augmented dietary protein)	Control (Usual dietary protein)	Intervention (Augmented dietary protein)	Control (Usual dietary protein)
	Group 2 (4 ICUs)	Control (Usual dietary protein)	Intervention (Augmented dietary protein)	Control (Usual dietary protein)	Intervention (Augmented dietary protein)
Time		Month 1 to 3	Month 4 to 6	Month 7 to 9	Month 10 to 12

Sites

8 sites:

- Austin Hospital, Vic
- Royal Adelaide Hospital, SA
- Royal Melbourne Hospital, Vic
- Royal Prince Alfred Hospital, NSW
- Sunshine Hospital, Vic
- The Queen Elizabeth Hospital, SA
- University Hospital Geelong, Vic
- Wellington Regional Hospital, NZ



Trial participants

Inclusion criteria:

All patients aged ≥ 16 years of age were eligible if they were:

- About to commence enteral nutrition on their index admission to ICU, or
- Prescribed enteral nutrition for the first time in ICU during a subsequent ICU admission in the index hospital admission

Exclusion criteria:

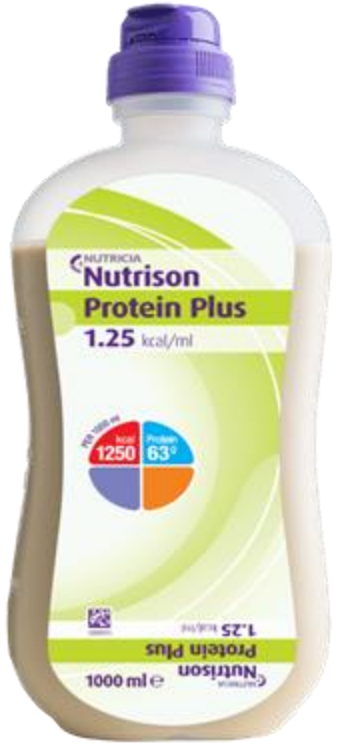
- The treating clinician considered the trial formula to be contraindicated
- The patient had received greater than 12 hours of non-trial enteral formula
- The patient had previously participated in TARGET Protein Trial

Ethical considerations

- Approved by Central Adelaide Local Health Network Human Research Ethics Committee
- Consent model:
 - Full waiver for consent (Australian sites)
 - Initial waiver and consent to continue (New Zealand sites)
- Trial registration at ANZCTR: ACTRN12621001484831



Intervention



Protein Plus
Calories: 1.25kcal/ml
Protein: 63g/L

- During each cluster the whole ICU used as their standard formula (open label) either:
 - Usual care: Nutrison Protein Plus (Protein: 63g/L)
 - Augmented protein intervention: Nutrison Protein Intense (Protein: 100g/L)



Protein Intense
Calories: 1.26kcal/ml
Protein: 100g/L

Study procedures

- Following the treating clinician's decision to commence EN, the participant received the trial EN formula to which the ICU was randomised in that period
- All other aspects of nutrition management (feeding regimen, goal feed rate, management) according to individual site practice
- Trial EN was delivered when clinically indicated up to 90 days, or until the patient was discharged from ICU or died

Data collection

- Screening data – all patients that commenced EN in ICU
- Baseline patient characteristics and outcome data
 - Data collected as a part of the Australian New Zealand Intensive Care Society Adult Patient Database (ANZICS APD)
- Daily data:
 - Volume of trial EN delivered: Day 1-5, Day 10, Day 20, Day 30, Day 90
 - Biochemistry data (Urea, Albumin, Phosphate, BGL): Day 1, 5, 10
- Primary outcome:
 - Last known patient status
 - Data linkage to the National Death Index for mortality

Trial compliance

Trial enteral formula delivery audit

- Conducted every 6 weeks:
 - Mid-cluster
 - At cluster changeover
 - At trial completion
- Checked actual type of enteral formula at the bedside on audit day
- Compared to trial EN assigned

Adverse Events and Serious Adverse Events

Adverse events:

- Any untoward medical occurrence
- Collected from commencement of trial EN until 48 hours post-cessation

Serious adverse events:

- Any event that results in death or is life-threatening
- Mesenteric ischaemia and abdominal compartment syndrome
- Reported up to day 90 post-trial enrolment

Primary outcome

Number of days free of the index hospital and
alive at day 90



Secondary outcomes

1. Days free of the index hospital and alive at day 90 in survivors
2. Alive at day 90
3. Duration of invasive ventilation (hours)
4. Duration of admission to ICU (days)
5. Duration of admission to hospital (days)
6. Tracheostomy during index hospitalisation
7. New RRT commenced during index ICU admission after EN commencement
8. Discharge destination

Sample size calculation

- 8 ICUs enrolling ~80 patients per 3-month period, 2560 patients gives 90% power ($\alpha = 0.05$) to find a mean difference of one day for the primary outcome
- Recruitment goal increased by 15% to allow for likely skewed distribution of data, ~3000 patients should provide 90% power
- Assumptions:
 - SD for primary outcome 11.3 days (from TARGET Calories)
 - Exchangeable correlation structure
 - Coefficient of variation for cluster size = 0.5
 - Intraclass correlation = 0.02
- Four clusters, recruiting ≥ 60 patients per cluster period, provides $>80\%$ power to detect a two-day difference in the primary outcome

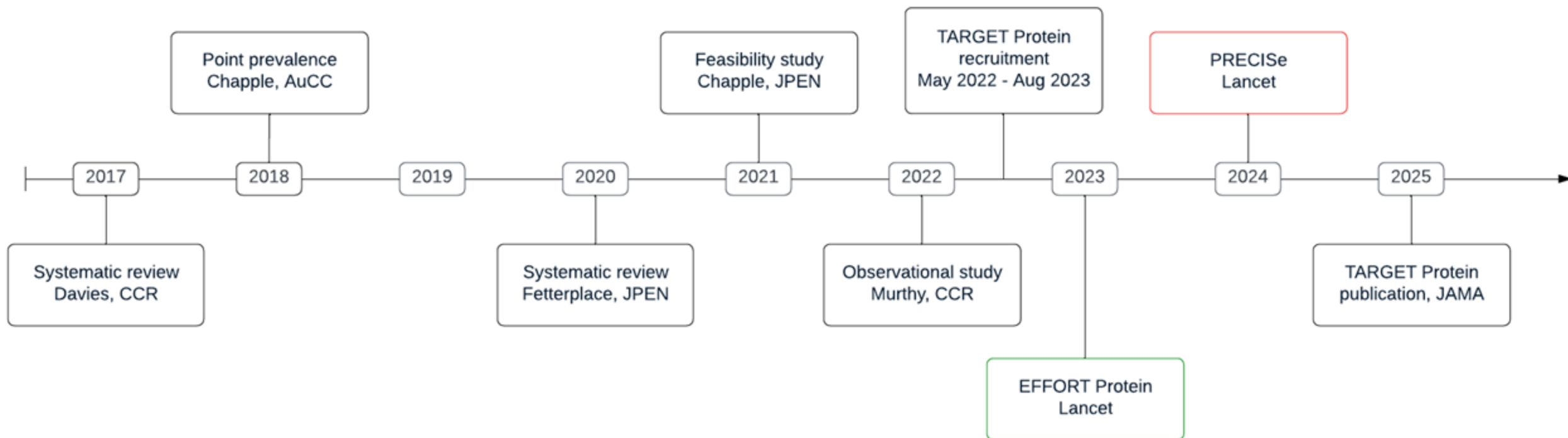
Analysis – Primary outcome

Number of days free of the index hospital and alive at day 90

- Quantile mixed effects model fitted to compare the median (0.5 quantile) response between groups
 - Fixed effects: Treatment group, period (1-4), delayed start (Group 1 vs Group 2)
 - Random effect: ICU; assumed to be normally distributed
- Effect of treatment comparisons presented as a difference in medians (95% CI)

Sub-group Analyses – Primary outcome

- All sub-group analyses assessed heterogeneity of treatment effect for each of the below conditions:
 1. Mechanical ventilation (no/yes)
 2. Aged ≥ 70 years vs <70 years
 3. BMI $\geq 35\text{kg/m}^2$ vs $<35\text{ kg/m}^2$
 4. AKI prior to trial EN commencement (no/yes)
- Assessment of credibility for heterogeneity of treatment effect was conducted using ICEMAN in RCTs

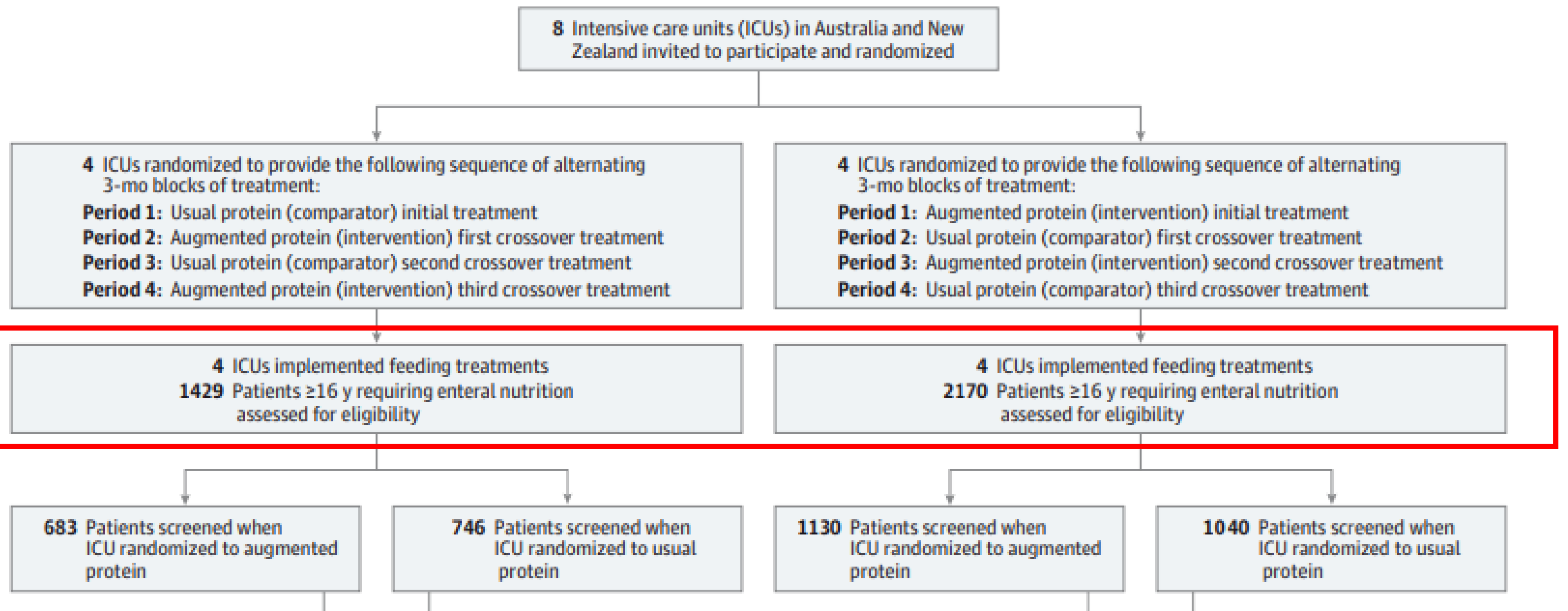




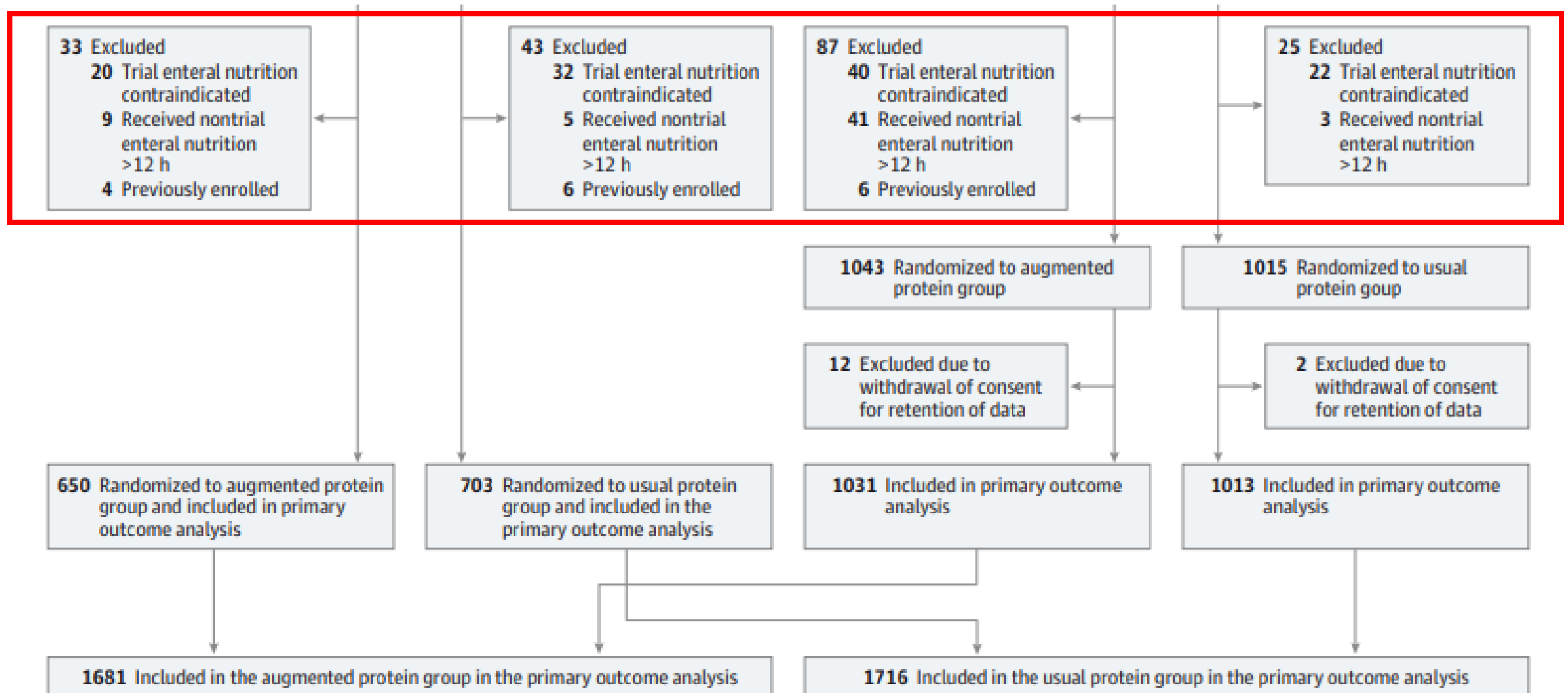
RESULTS

Enrolment

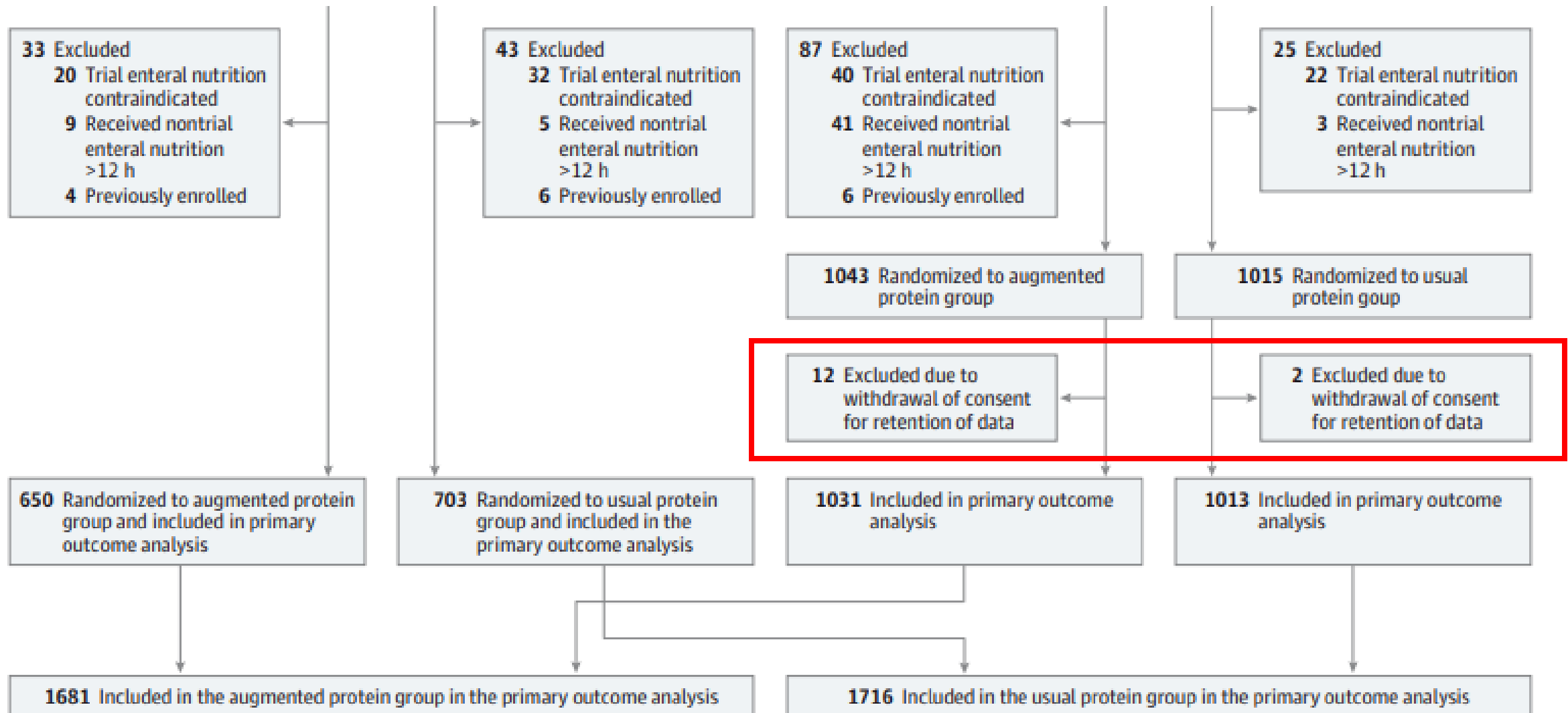
Participants enrolled between 23 May 2022 to 23 August 2023



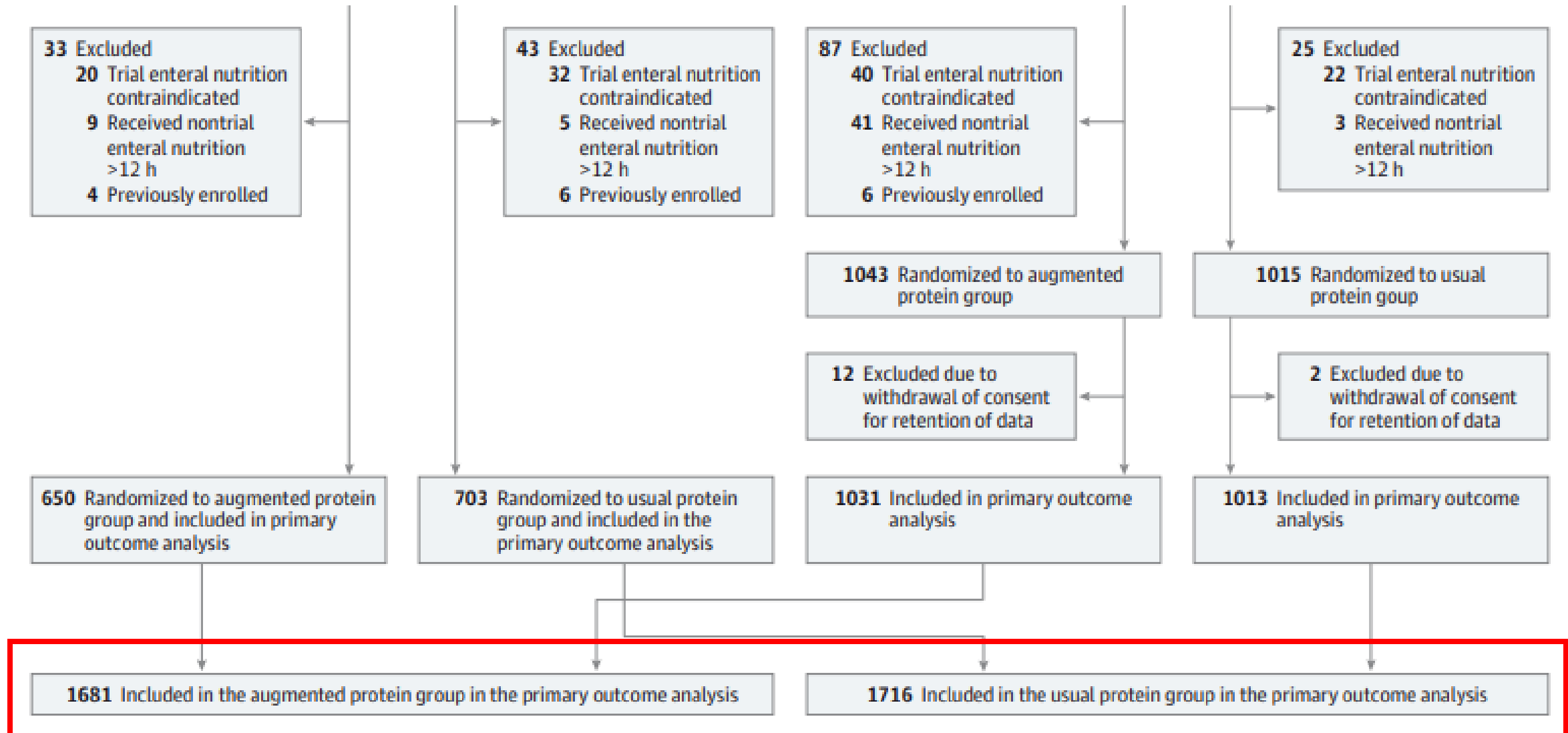
Enrolment



Enrolment



Enrolment



Baseline characteristics

	Augmented Protein (n = 1681)	Usual Protein (n = 1716)
Male Sex [n (%)]	1,070 (64%)	1,087 (63%)
Age, years	61 (48, 70)	61 (48,71)
APACHE II score at ICU admission	19 (15, 24)	19 (14,25)
Weight, kg	80 (68, 94)	80 (67, 97)
Body Mass Index ⁺ , kg/m ²	28 (24, 33)	28 (24, 32)
Ideal body weight ⁺ , kg	66 (57, 73)	66 (57,73)

*Data are median (IQR) unless otherwise stated

⁺ data from n=2,618

Baseline characteristics

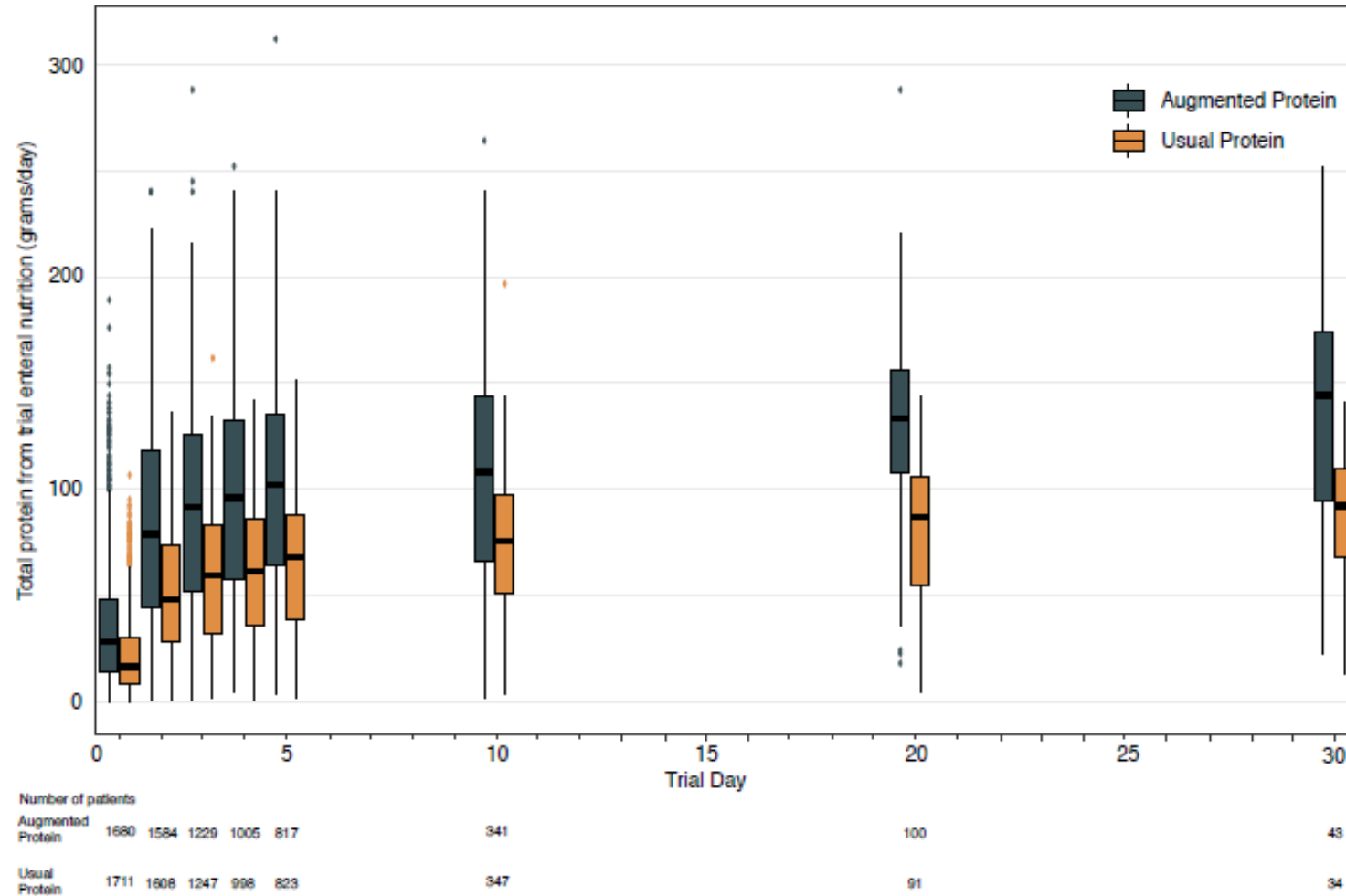
	Augmented Protein (n = 1681)	Usual Protein (n = 1716)
ICU admission [n]		
Non-Surgical (Medical)	1,068 (64%)	1,100 (64%)
Emergency Surgical	379 (23%)	361 (21%)
Elective Surgical	234 (14%)	255 (15%)
ICU admission diagnosis category [n]		
Neurological	374 (22%)	350 (20%)
Respiratory	325 (19%)	360 (21%)
Cardiovascular	300 (18%)	310 (18%)
Trauma	204 (12%)	209 (12%)
Gastrointestinal	168 (10%)	190 (11%)
Other	162 (10%)	163 (9%)
Sepsis	148 (9%)	134 (8%)
Invasive ventilation at trial EN commencement[n]	1,385 (82%)	1,355 (80%)

Trial nutrition delivery

Measure, Median (IQR)	Augmented Protein (n = 1681)	Usual Protein (n = 1716)
Time from ICU admission to trial enteral formula commencement, hours	19 (9, 38)	19 (10, 40)
Duration of trial nutrition, hours	87 (36, 187)	84 (34, 182)

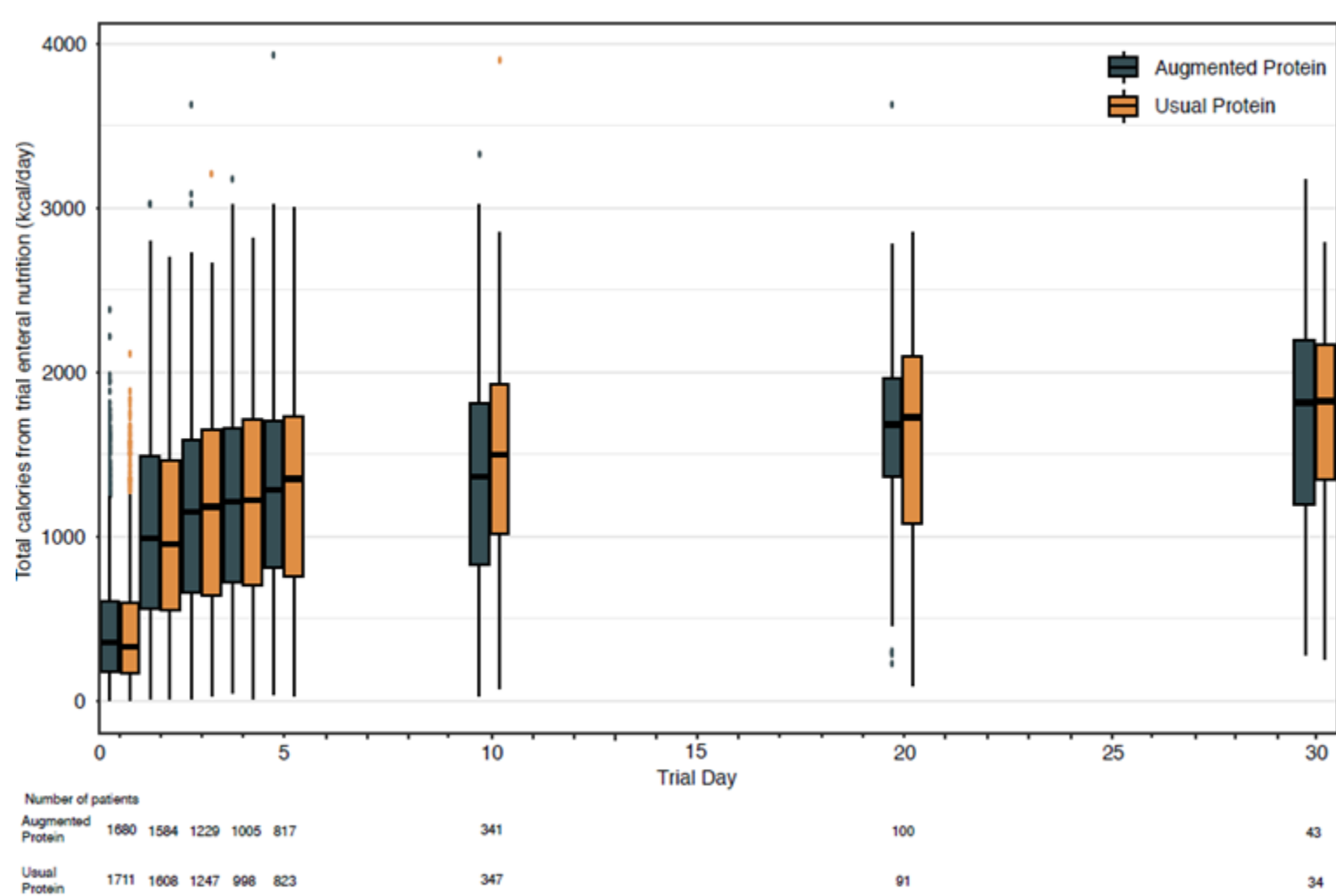
Trial nutrition delivery

Protein (g/day)



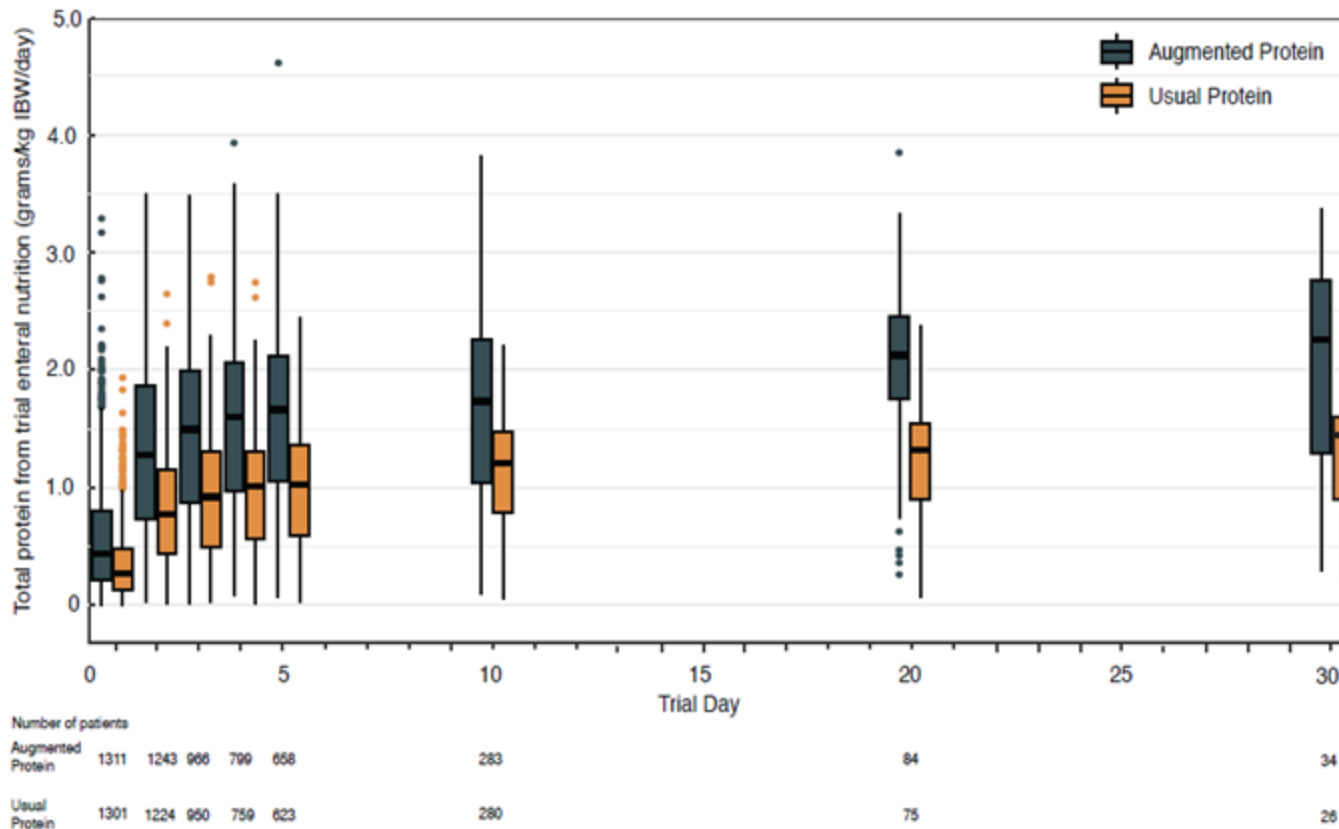
Trial nutrition delivery

Energy (kcal/day)



Trial nutrition delivery

Protein (g/kg IBW/day)



Augmented Protein:
1.33 (0.88, 1.78) g/kg IBW/day

Usual Protein:
0.84 (0.49, 1.11) g/kg IBW/day

*Excluding day 1

Protocol deviations

Protocol deviations	Augmented Protein (n = 1681)	Usual Protein (n = 1716)
Clinical decision	92 (5.5%)	64 (3.7%)
Error on subsequent EN administration	34 (2.0%)	17 (1.0%)
Error at initial commencement of EN	11 (0.7%)	10 (0.6%)

Trial compliance

	Audit Period			
	Mid-cluster	Cluster crossover	Trial completion	Total
Audit EN Type, n (%)				
Correct trial EN	188 (64)	153 (68)	35 (67)	376 (66%)
Alternate trial EN	0 (0)	2 (0.9)	2 (3.8)	4 (0.7%)
Other EN	15 (5.1)	5 (2.2)	1 (1.9)	21 (3.7%)
Not receiving EN (fasted, no longer required, etc.)	88 (30)	64 (29)	14 (27)	166 (29%)
Missing audit EN	1 (0.3)	0 (0)	0 (0)	1 (0.2%)
Total	292 (100)	224 (100)	52 (100)	568 (100%)

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Total	292 (100)	224 (100)	52 (100)	568 (100%)

Adverse/Serious Adverse Events

- 4 adverse events
 - 3 in augmented protein group – 1 x elevated urea, 2 x Bacillus Cereus infection
 - 1 in usual protein group – 1 x Campylobacter infection
- 2 serious adverse events
 - 1 in augmented protein group - Bacillus Cereus infection
 - 1 in usual protein group - Mesenteric Ischaemia



PRIMARY OUTCOME

Number of days free of the index hospital and alive at day 90

Primary outcome

Number of days free of the index hospital and alive at day 90

Analysis model	Augmented Protein (n=1681)	Usual Protein (n=1716)	Median Difference (95% CI)	p-value	Intraclass correlation coefficient
Quantile mixed model	62 (0.0, 77)	64 (0.0, 77)	-1.97 (-7.24, 3.30)	0.464	0.004



0

Augmented protein = 62

Usual protein = 64



90



More free days = better outcome

Primary outcome

Number of days free of the index hospital and alive at day 90

Analysis model	Augmented Protein (n=1681)	Usual Protein (n=1716)	Median Difference (95% CI)	p-value	Intraclass correlation coefficient
Quantile mixed model	62 (0.0, 77)	64 (0.0, 77)	-1.97 (-7.24, 3.30)	0.464	0.004



0

Augmented protein = 62

Usual protein = 64



90



More hospital-free days = better outcome



SECONDARY OUTCOMES

Secondary outcomes

Outcome	Augmented Protein (n = 1681)	Usual Protein (n = 1716)	Effect estimate (95% CI)	p-value
Days free of the index hospital at day 90 in survivors	72 (57, 80)	72 (59, 80)	Median Difference: 0.01 (-1.94, 1.96)	0.995

Secondary outcomes

Outcome	Augmented Protein (n = 1681)	Usual Protein (n = 1716)	Effect estimate (95% CI)	p-value
Days free of the index hospital at day 90 in survivors	72 (57, 80)	72 (59, 80)	Median Difference: 0.01 (-1.94, 1.96)	0.995
Alive at day 90, n (%)	1221 (72.6)	1269 (74.0)	Risk Ratio: 0.99 (0.95, 1.03)	0.47

Secondary outcomes

Outcome	Augmented Protein (n = 1681)	Usual Protein (n = 1716)	Effect estimate (95% CI)	p-value
Days free of the index hospital at day 90 in survivors	72 (57, 80)	72 (59, 80)	Median Difference: 0.01 (-1.94, 1.96)	0.995
Alive at day 90, n (%)	1221 (72.6)	1269 (74.0)	Risk Ratio: 0.99 (0.95, 1.03)	0.47
Duration of invasive ventilation, hours	84.0 (35.0, 178.9)	78.0 (33.2, 161.0)	Mean Difference: 6.8 (-3.0, 16.5)	0.17

Secondary outcomes

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Duration of invasive ventilation, hours	84.0 (35.0, 178.9)	78.0 (33.2, 161.0)	Mean Difference: 6.8 (-3.0, 16.5)	0.17
Duration of admission to ICU, days	6.6 (3.1, 18.0)	6.2 (3.0, 15.0)	Hazard Ratio: 0.93 (0.88, 1.00)	0.04

Secondary outcomes

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Duration of invasive ventilation, hours	84.0 (35.0, 178.9)	78.0 (33.2, 161.0)	Mean Difference: 6.8 (-3.0, 16.5)	0.17
Duration of admission to ICU, days	6.6 (3.1, 18.0)	6.2 (3.0, 15.0)	Hazard Ratio: 0.93 (0.88, 1.00)	0.04
Duration of admission to hospital, days	21.4 (10.2, 80.0)	21.1 (10.1, 68.9)	Hazard Ratio: 0.96 (0.90, 1.02)	0.15

Secondary outcomes

Outcome	Augmented Protein (n = 1681)	Usual Protein (n = 1716)	Effect estimate (95% CI)	p-value
Days free of the index hospital at day 90 in survivors	72 (57, 80)	72 (59, 80)	Median Difference: 0.01 (-1.94, 1.96)	0.995
Alive at day 90, n (%)	1221 (72.6)	1269 (74.0)	Risk Ratio: 0.99 (0.95, 1.03)	0.47
Duration of invasive ventilation, hours	84.0 (35.0, 178.9)	78.0 (33.2, 161.0)	Mean Difference: 6.8 (-3.0, 16.5)	0.17
Duration of admission to ICU, days	6.6 (3.1, 18.0)	6.2 (3.0, 15.0)	Hazard Ratio: 0.93 (0.88, 1.00)	0.04
Duration of admission to hospital, days	21.4 (10.2, 80.0)	21.1 (10.1, 68.9)	Hazard Ratio: 0.96 (0.90, 1.02)	0.15
Tracheostomy during index hospitalization, n (%)	134/1681 (8.0)	121/1716 (7.1)	Risk Ratio: 1.15 (0.66, 2.01)	0.57

Secondary outcomes

Outcome	Augmented Protein (n = 1681)	Usual Protein (n = 1716)	Effect estimate (95% CI)	p-value
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Tracheostomy during index hospitalization, n (%)	134/1681 (8.0)	121/1716 (7.1)	Risk Ratio: 1.15 (0.66, 2.01)	0.57
New renal replacement therapy, n (%)	122/1681 (7.3)	127/1716 (7.4)	Risk Ratio: 0.97 (0.81, 1.16)	0.69

Secondary outcomes

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New kidney replacement therapy, n (%)	122/1681 (7.3)	127/1716 (7.4)	Risk Ratio: 0.97 (0.81, 1.16)	0.69

Secondary outcomes

Discharge destination

Discharge destination, n (%)	Augmented Protein (n = 1681)	Usual Protein (n = 1716)
Died	378/1681 (23%)	380/1716 (22%)
Home	634/1681 (38%)	723/1716 (42%)
Other Hospital ICU	27/1681 (2%)	23/1716 (1%)
Other Acute Hospital	321/1681 (19%)	306/1716 (18%)
Rehabilitation	244/1681 (15%)	215/1716 (13%)
Long Term Care	61/1681 (4%)	49/1716 (3%)

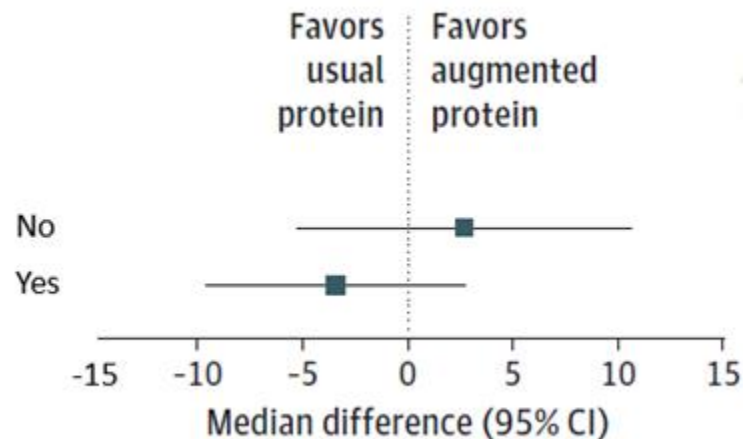


SUB-GROUP ANALYSES

Sub-Group Analysis for Primary Outcome

Mechanical Ventilation

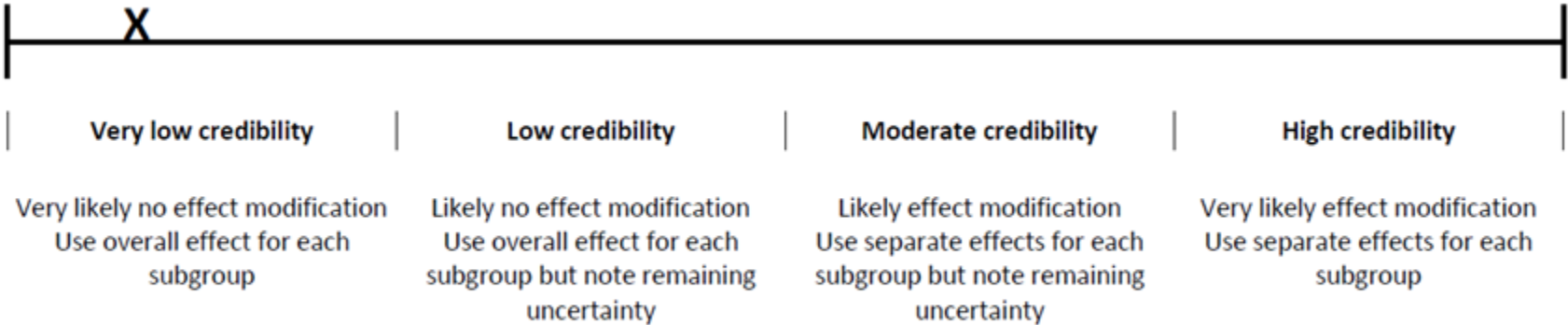
	Augmented Protein		Usual Protein		Effect estimate (95% CI)	Interaction p-value
	No. of patients	Median (IQR)	No. of patients	Median (IQR)		
No	296	69 (46, 81)	361	67 (34, 77)	2.7 (-5.2, 10.6)	0.023
Yes	1,385	60 (0, 76)	1,355	63 (0, 77)	-3.4 (-9.6, 2.8)	



Sub-Group Analysis for Primary Outcome

Mechanical Ventilation

	Augmented Protein		Usual Protein		Effect estimate (95% CI)	Interaction p-value
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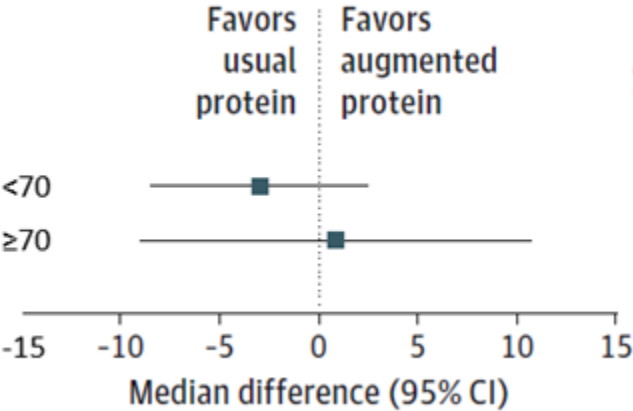
Very low credibility

Comment: Deemed very low credibility of effect modification

Sub-Group Analysis for Primary Outcome

Aged ≥ 70 years

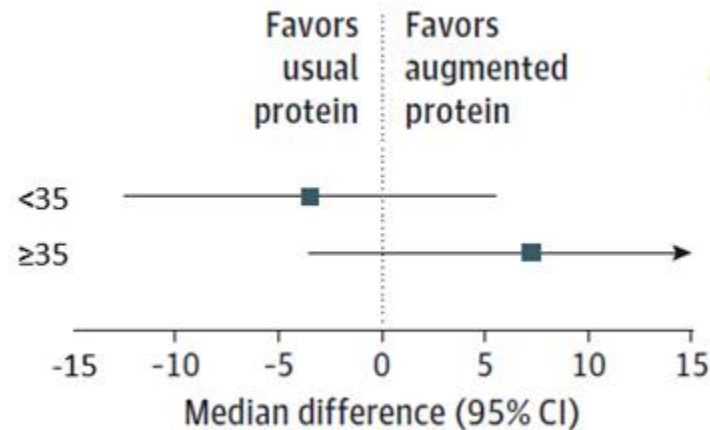
	Augmented Protein		Usual Protein		Effect estimate (95% CI)	Interaction p-value
	No. of patients	Median (IQR)	No. of patients	Median (IQR)		
<70 years	1,231	65 (0-78)	1,211	67 (24-79)	-3.0 (-8.5, 2.5)	0.106
≥ 70 years	450	54 (0-75)	505	51 (0-73)	0.9 (-9.0, 10.7)	



Sub-Group Analysis for Primary Outcome

BMI $\geq 35\text{kg/m}^2$

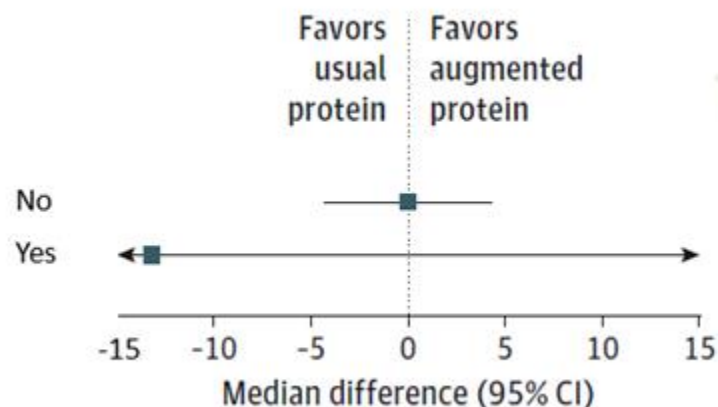
	Augmented Protein		Usual Protein		Effect estimate (95% CI)	Interaction p-value
	No. of patients	Median (IQR)	No. of patients	Median (IQR)		
<35 kg/m ²	1,066	62 (0-76)	1,074	65 (0-77)	-3.5 (-12.4, 5.5)	0.468
≥35 kg/m ²	222	66 (9-77)	206	60 (0-76)	7.23 (-3.6, 18.0)	



Sub-Group Analysis for Primary Outcome

AKI prior to trial EN commencement
(Defined as new RRT between hospital admission and EN commencement)

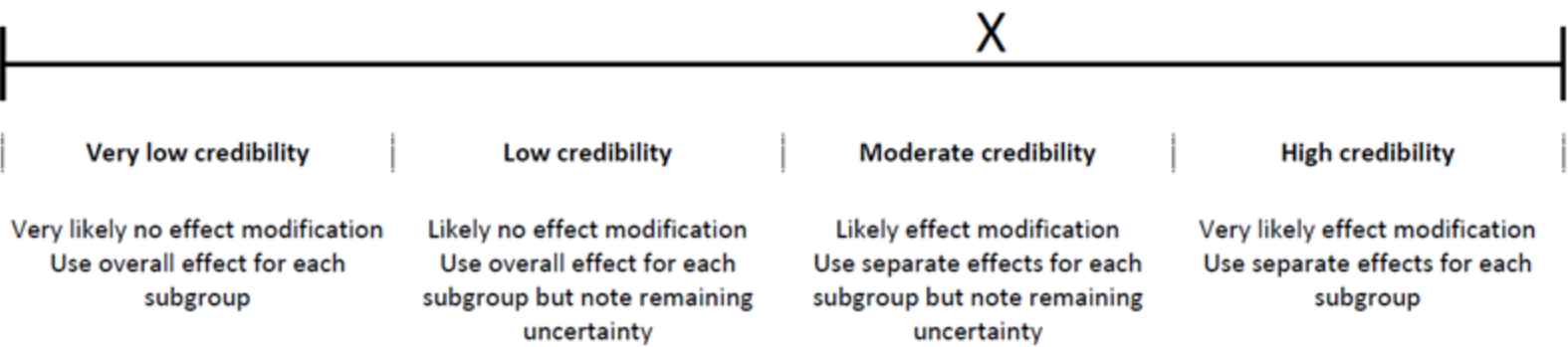
Augmented Protein			Usual Protein		Effect estimate (95% CI)	Interaction p-value
	No. of patients	Median (IQR)	No. of patients	Median (IQR)		
No	1,559	65 (0-78)	1,597	65 (0-78)	0.0 (-4.3, 4.3)	<0.001
Yes	122	15 (0-60)	119	24 (0-64)	-13.2 (-50.0, 23.6)	



Sub-Group Analysis for Primary Outcome

AKI prior to trial EN commencement
(Defined as new RRT between hospital admission and EN commencement)

Augmented Protein			Usual Protein		Effect estimate (95% CI)	Interaction p-value
	No. of patients	Median (IQR)	No. of patients	Median (IQR)		
No	1,559	65 (0-78)	1,597	65 (0-78)	0.0 (-4.3, 4.3)	<0.001
Yes	122	15 (0-60)	119	24 (0-64)	-13.2 (-50.0, 23.6)	



Moderate credibility

Comment:
Deemed moderate credibility of effect modification

Summary

- Augmenting protein delivery did not increase the primary outcome of days alive and free of the index hospital at day 90
- Point estimates did not identify any signal of improvement with augmented protein for any secondary outcome
- Assessment for heterogeneity of effect favoured usual protein group for sub-groups of patients:
 - Receiving mechanical ventilation at baseline (very low credibility)
 - With AKI at baseline (moderate credibility)
 - Both variables which predispose patients to longer duration of EN

Interpretation



The effect of higher protein dosing in critically ill patients with high nutritional risk (EFFORT Protein): an international, multicentre, pragmatic, registry-based randomised trial

Daren K Heyland, Jayshil Patel, Charlene Compher, Todd W Rice, Danielle E Bear, Zheng-Yii Lee, Victoria C Gonzalez, Kevin O'Reilly, Raquel Regala, Courtney Wedemire, Miguelbana-Estrada, Christian Stoppe, Luis Ortiz-Ribes, Xuran Jiang, Andrew G Day, on behalf of the EFFORT Protein Trial team

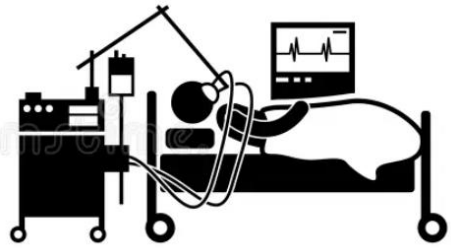


Effect of high versus standard protein provision on functional recovery in people with critical illness (PRECISE): an investigator-initiated, double-blinded, multicentre, parallel-group, randomised controlled trial in Belgium and the Netherlands

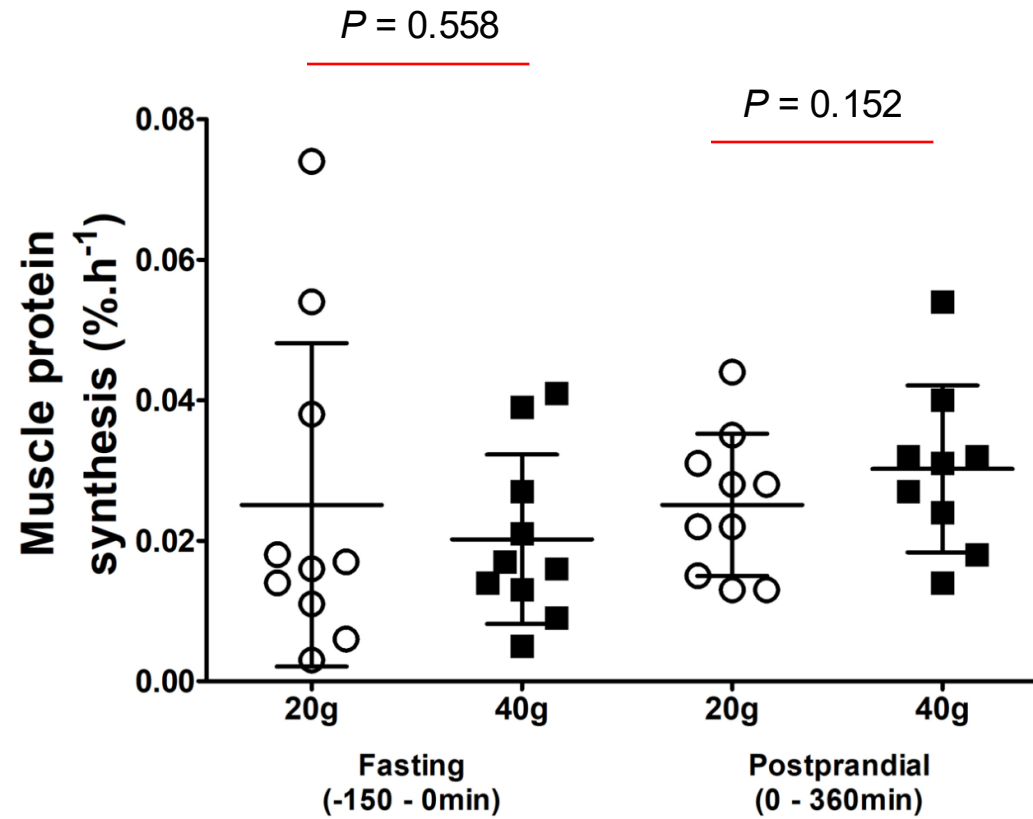
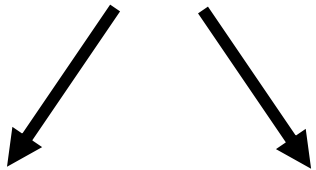
Julia L M Bels, Steven Thiessen, Rob J J van Gassel, Albertus Beishuizen, Ashley De Bie Dekker, Vincent Fraipont, Stoffel Lamote, Didier Ledoux, Clarissa Scheeren, Elisabeth De Waale, Arthur R H van Zanten, Laura Bormans-Russell, Bas C T van Bussel, Marlies M J Dictus, Tom Fiver, Ingeborg Harks, Iwan C C van der Horst, Joop Jonckheer, Hugues Marechal, Paul B Massion, Ingrid Meex, Michelle C Paulus, Martin Rinkel, Susanne van Santen, Katrien Tartaglia, Adam M Deane, Frieda Demuydt, Zudin Puthucherry, Lilian C M Vloet, Peter J M Weijs, Sander M J van Kuijk, Marcel C G van de Poll, Dieter Mesotten*, on behalf of the PRECISE study team†

- TARGET Protein is the 3rd recently completed multi-centre trial on protein dose, with similar results
- EFFORT Protein: Point estimate suggested augmented protein delayed time to discharge alive from the hospital, albeit with wide CIs
- PRECISE: Point estimate suggested being discharged alive during 180 days after randomisation (tertiary outcome) was less likely with augmented protein, with wide CI

Why these results?



20 ICU patients



- Higher protein increased post-prandial plasma amino acid availability
- But did not further increase post-prandial muscle protein synthesis rates in critical illness

Interpretation

- Patients exhibit an inability to use plasma amino acids for muscle protein synthesis
- Higher protein doses create more amino acids not utilised for muscle protein synthesis
- Potential increase in harmful by-products such as urea
- Protein dose may suppress autophagy

Conclusion

- In critically ill patients, augmented enteral protein delivery did not increase days free of the index hospital and alive at day 90 compared to usual protein
- These data do not support augmenting enteral protein early during critical illness

Implications for everyday practice in the ICU

For patients who are genuinely critically ill:

- aim for 1.3g protein/kg/day, avoiding aggressive strategies in the first few days
- monitor actual delivery (patients get much less than they are prescribed)
- caution with patients who have an acute kidney injury if not being dialysed
- monitor for signs of impaired nutrient utilisation

Summers MJ, Chapple LS, Karahalios A, et al; for the TARGET Protein Investigators and for the Australian and New Zealand Intensive Care Society Clinical Trials Group

Augmented Enteral Protein During Critical Illness

The TARGET Protein Randomized Clinical Trial

Published online June 11, 2025

Critical Care Reviews 2025

Available at jama.com



Scan to read the article

Thank you

Additional slides

Analysis – Secondary outcomes

Outcome	Statistical analysis method
Days free of the index hospital and alive at day 90 in survivors	Same approach as for primary outcome
Alive at day 90 Incidence of tracheostomy insertion Incidence of renal replacement therapy	Estimated using GEEs with log link function, exchangeable working correlation matrix, and small sample bias corrected standard errors using ICU as clustering unit
Duration of invasive ventilation (hours) Duration of admission to ICU (days) Duration of admission to hospital (days)	Cox regression with covariate adjustment for period and delayed start, stratified by ICU and robust standard errors Patients dying prior to discharge (or extubation) censored at their time of death
Discharge destination	Descriptive analysis; frequency presented by allocated treatment sequence and observation period

Trial nutrition delivery

Parenteral nutrition and protein supplementation delivered

	Augmented Protein (n = 1681)	Usual Protein (n = 1716)
Parenteral nutrition administered at any stage during ICU admission	115/1681 (6.8%)	120/1716 (7.0%)
Protein supplement administered at any stage during ICU admission	12/1681 (0.7%)	10/1716 (0.6%)

Discussion

- We showed there was a heterogeneity of treatment effect according to presence of new kidney failure
- Consistent with the subgroup analysis of EFFORT Protein (albeit with differing definitions of acute kidney injury) and also a recent meta-analysis

Protein trials

Author, year	Population	Intervention	Control	Primary outcome
EFFORT Protein, 2023, Lancet	1301 MV adult pts at nutritional risk	≥ 2.2 g/kg/d	≤ 1.2 g/kg/d	No diff in time-to-discharge-alive
PRECISE, 2024, Lancet	935 MV adult pts	2.0 g/kg/d	1.3 g/kg/d	Worse EQ-5D-5L health utility score with intervention (mean diff -0.05; 95% CI -0.10, -0.01; P=0.031)



The effect of higher protein dosing in critically ill patients with high nutritional risk (EFFORT Protein): an international, multicentre, pragmatic, registry-based randomised trial

Daren K Heyland, Jayshil Patel, Charlene Compher, Todd W Rice, Danielle E Bear, Zheng-Yii Lee, Victoria C González, Kevin O'Reilly, Racquel Regala, Courtney Wedemire, Miguel Ibarra-Estrada, Christian Stoppe, Luis Ortiz-Reyes, Xuran Jiang, Andrew G Day, on behalf of the EFFORT Protein Trial team

Summary

Lancet 2023; 401: 568–76

Published Online

January 25, 2023

[https://doi.org/10.1016/](https://doi.org/10.1016/S0140-6736(22)02469-2)

S0140-6736(22)02469-2

Background On the basis of low-quality evidence, international critical care nutrition guidelines recommend a wide range of protein doses. The effect of delivering high-dose protein during critical illness is unknown. We aimed to test the hypothesis that a higher dose of protein provided to critically ill patients would improve their clinical outcomes.

Methods This international, investigator-initiated, pragmatic, registry-based, single-blinded, randomised trial was

STUDY DESIGN

Pragmatic, investigator-initiated, registry-based, single-blinded randomised trial in 85 ICUs in 15 countries

POPULATION

Adults within 96h of ICU adm, expected to be MV for ≥ 48 h, at nutritional risk

AIM

To determine whether higher dose protein in MV adults at high nutrition risk will reduce the time-to-discharge-alive from hospital when compared to usual protein dose

Usual-dose protein
(≤ 1.2 g/kg/d)

Using EN or PN, IV amino
acids, or protein
supplements

High-dose protein
(≥ 2.2 g/kg/d)

RESULTS

- 1301 pts recruited (645 high vs 656 usual)
- Achieved 1.6 vs 0.9 g/kg/d
- No difference in time-to-discharge-alive (primary outcome)
- Higher protein associated with worse outcomes in pts with AKI and high SOFA score (≥ 9)



Effect of high versus standard protein provision on functional recovery in people with critical illness (PRECISE): an investigator-initiated, double-blinded, multicentre, parallel-group, randomised controlled trial in Belgium and the Netherlands

Julia L M Bels, Steven Thiessen, Rob J J van Gassel, Albertus Beishuizen, Ashley De Bie Dekker, Vincent Fraipont, Stoffel Lamote, Didier Ledoux, Clarissa Scheeren, Elisabeth De Waele, Arthur R H van Zanten, Laura Bormans-Russell, Bas C T van Bussel, Marlies M J Dictus, Tom Fivez, Ingeborg Harks, Iwan C C van der Horst, Joop Jonckheer, Hugues Marechal, Paul B Massion, Ingrid Meex, Michelle C Paulus, Martin Rinket, Susanne van Santen, Katrien Tartaglia, Adam M Deane, Frieda Demuydt, Zudin Puthuchear, Lilian C M Vloet, Peter J M Weijs, Sander M J van Kuijk, Marcel C G van de Poll, Dieter Mesotten*, on behalf of the PRECISE study team†*

Lancet 2024; 404: 659–69

STUDY DESIGN

Investigator-initiated, double-blinded, multicentre, parallel-group, RCT in 10 ICUs from 2 counties

POPULATION

Adults with unplanned ICU adm, IMV initiated within 24hrs of ICU, and expected IMV of ≥ 3 d

AIM

To assess whether higher enteral protein provision would improve health-related quality of life and functional outcomes in IMV critically ill patients compared with standard enteral protein provision

Standard dose protein
(1.3 g/kg/d)

Using two isocaloric EN
formulae

Higher dose protein
(2.0 g/kg/d)

RESULTS

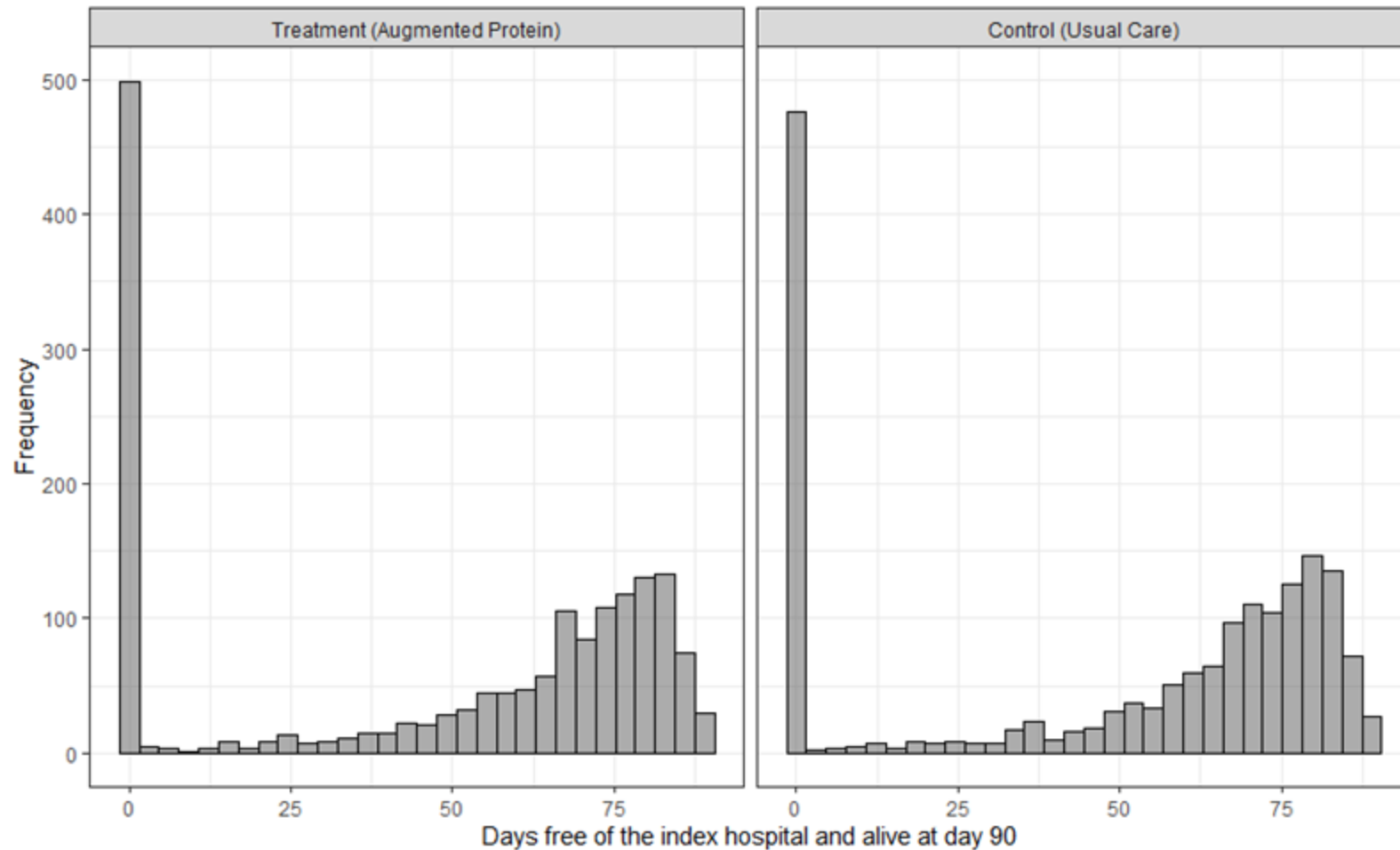
- 935 pts recruited (470 higher vs 465 standard)
- Achieved 1.87 (0.96-2.00) vs 1.19 (0.63-1.26) g/kg/day
- Primary outcome: Worse EQ-5D-5L health utility score during 180d in higher than standard protein group (mean diff -0.05 (95% CI -0.10 to -0.01; $p=0.031$)
- No impact on muscle-related outcomes, or in patients with AKI on ICU admission
- Post-hoc showed longer time to discharge alive with high protein

Biochemistry

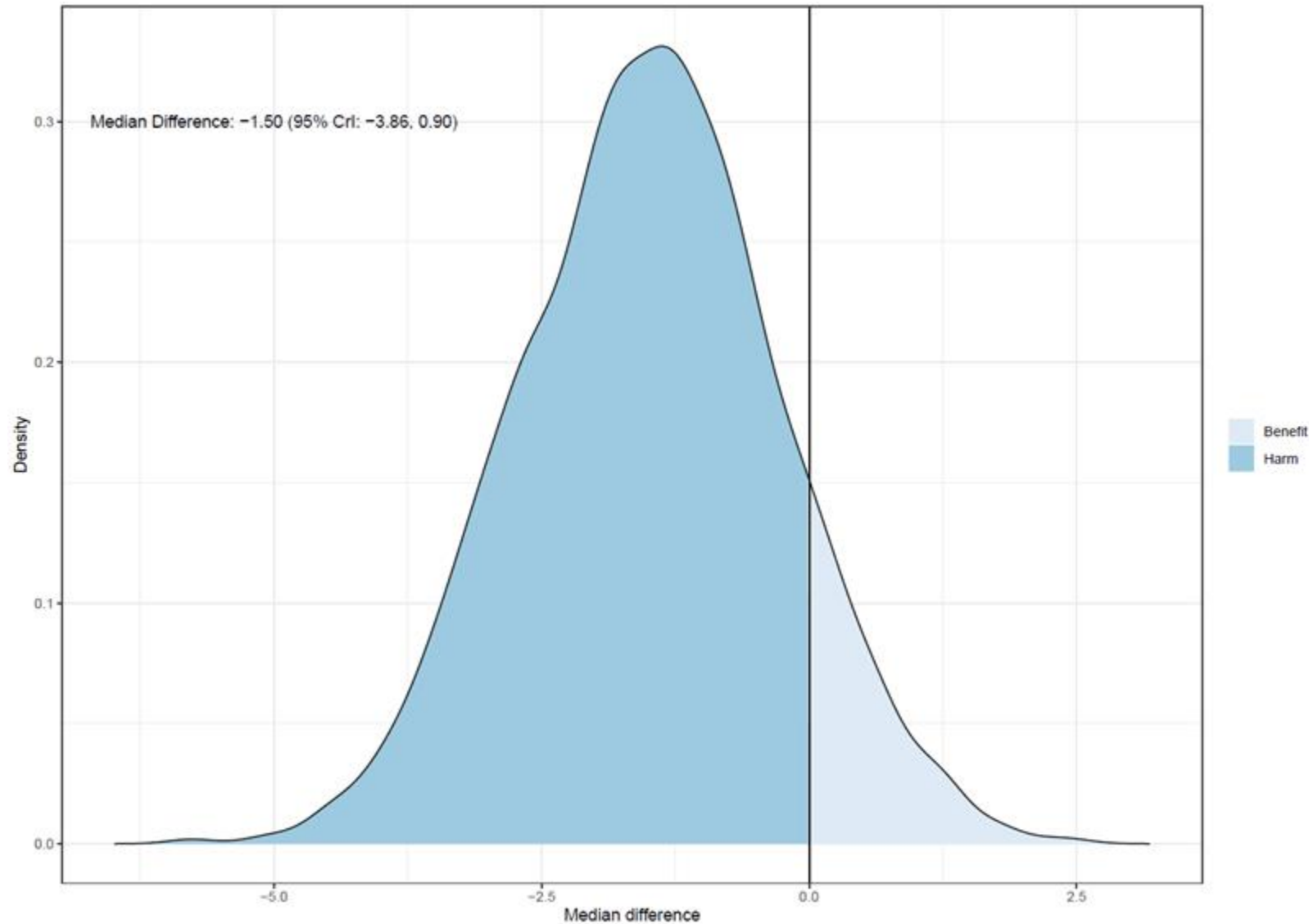
Measure	Augmented Protein (n = 1681)	Usual Protein (n = 1716)
Blood urea, mmol/l		
Day 1	7.3 (4.8, 12.4); n = 1583	7.5 (4.8, 11.8); n = 1663
Day 5	10.3 (6.8, 16.2); n = 1003	8.4 (5.5, 13.8); n = 985
Day 10	13.0 (8.2, 18.8); n = 439	10.6 (7.1, 15.4); n = 417
Serum albumin, g/l		
Day 1	29.0 (24.0, 33.0); n = 1577	28.0 (24.0, 33.0); n = 1622
Day 5	24.0 (21.0, 27.2); n = 1000	24.0 (21.0, 27.0); n = 979
Day 10	24.0 (21.0, 28.8); n = 438	23.0 (20.0, 28.0); n = 417
Serum phosphate, mmol/l		
Day 1	1.2 (0.9, 1.5); n = 1552	1.2 (0.9, 1.5); n = 1642
Day 5	1.0 (0.9, 1.2); n = 995	1.1 (0.9, 1.3); n = 971
Day 10	1.1 (1.0, 1.4); n = 433	1.2 (1.0, 1.4); n = 408
Blood glucose, mmol/l		
Day 1	7.7 (6.4, 9.6); n = 1662	7.8 (6.4, 9.7); n = 1704
Day 5	7.5 (6.4, 9.1); n = 993	7.8 (6.5, 9.9); n = 992
Day 10	7.5 (6.4, 9.0); n = 442	8.1 (6.8, 10.0); n = 430

Primary outcome

Number of days free of the index hospital and alive at day 90



Bayesian Quantile Mixed Model Analysis



NUTRISON PROTEIN PLUS

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NUTRITION INFORMATION		Per 100ml	Per 1000ml
Energy	kcal	125	1250
	kJ	525	5250
Protein	g	63 (20% E)	63
Casein	g	16	16
Whey	g	2.2	22
Soy	g	1.3	13
Pea	g	1.3	13
Carbohydrate	g	142 (45% E)	142
Sugars	g	0.9	9
as Lactose	g	<0.025	<0.25
Fat	g	4.9 (35% E)	49
Saturates	g	1.3	13
- of which MCT	g	0.7	7
Monounsaturates	g	2.7	27
Polyunsaturates	g	0.9	9
DHA	mg	20.4	204
EPA	mg	30	300
ω6 / ω3 ratio		2.7:1	2.7:1
Fibre	g	<0.1	<1
Water	ml	81	810
Minerals		Per 100ml	Per 1000ml
Sodium	mg	111	1110
	mmol	4.8	48
Potassium	mg	168	1680
	mmol	4.3	43
Calcium	mg	90	900
Phosphorus	mg	90	900
Magnesium	mg	28	280
Chloride	mg	80	800
Ca:P ratio		1:1	1:1

¹ In accordance with Australia New Zealand Food Standards Code - Standard 2.02

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NUTRISON PROTEIN INTENSE

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NUTRITION INFORMATION		Per 100ml	Per 500ml
Energy	kcal	126	630
	kJ	528	2640
Protein	g	10 (32%E)	50
Casein	g	2.5	12.5
Whey	g	3.5	17.5
Soy	g	2	10
Pea	g	2	10
Carbohydrate	g	104 (33%E)	52
Sugars	g	0.8	4
as Lactose	g	<0.025	<0.125
Fat	g	4.9 (35%E)	24.5
Saturates	g	1.3	6.5
of which MCT ¹	mg	694	3470
Monounsaturates	g	2.6	13
Polyunsaturates	g	0.96	4.8
DHA	mg	20.6	103
EPA	mg	30.1	150.5
ω6 / ω3 ratio		2.9:1	2.9:1
Fibre	g	0.09	0.45
Water	ml	81	405
Minerals		Per 100ml	Per 500ml
Sodium	mg	116	580
	mmol	5.05	25.25
Potassium	mg	218	1090
	mmol	5.57	27.85
Calcium	mg	75	375
Phosphorus	mg	81.9	409.5
Magnesium	mg	22	110
Chloride	mg	96.4	482
Ca:P ratio		1:1	1:1

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¹ In accordance with Australia New Zealand Food Standards Code - Standard 2.02

² Medium-chain triglycerides

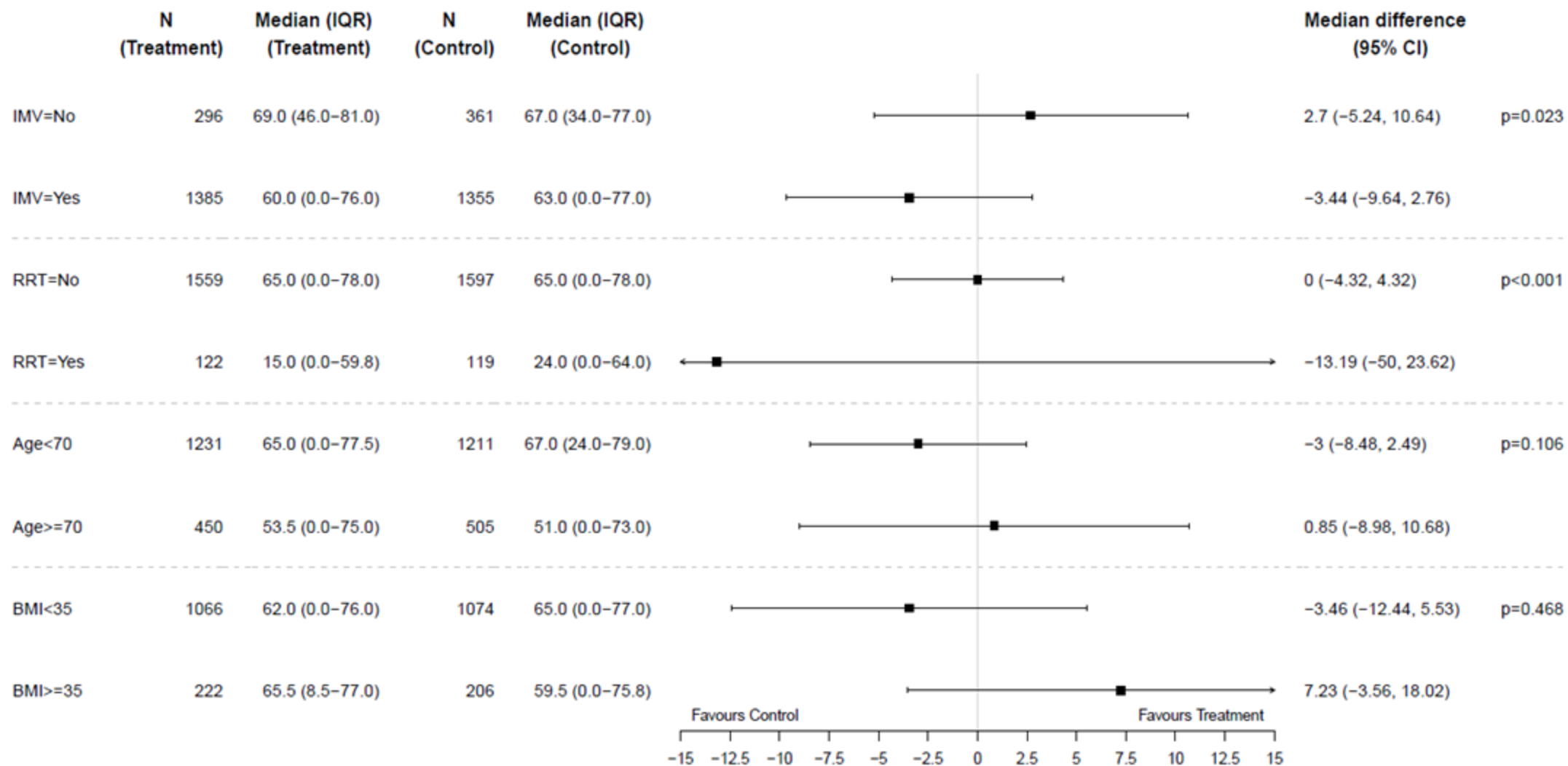
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Forest Plot of Sub-Group Analysis



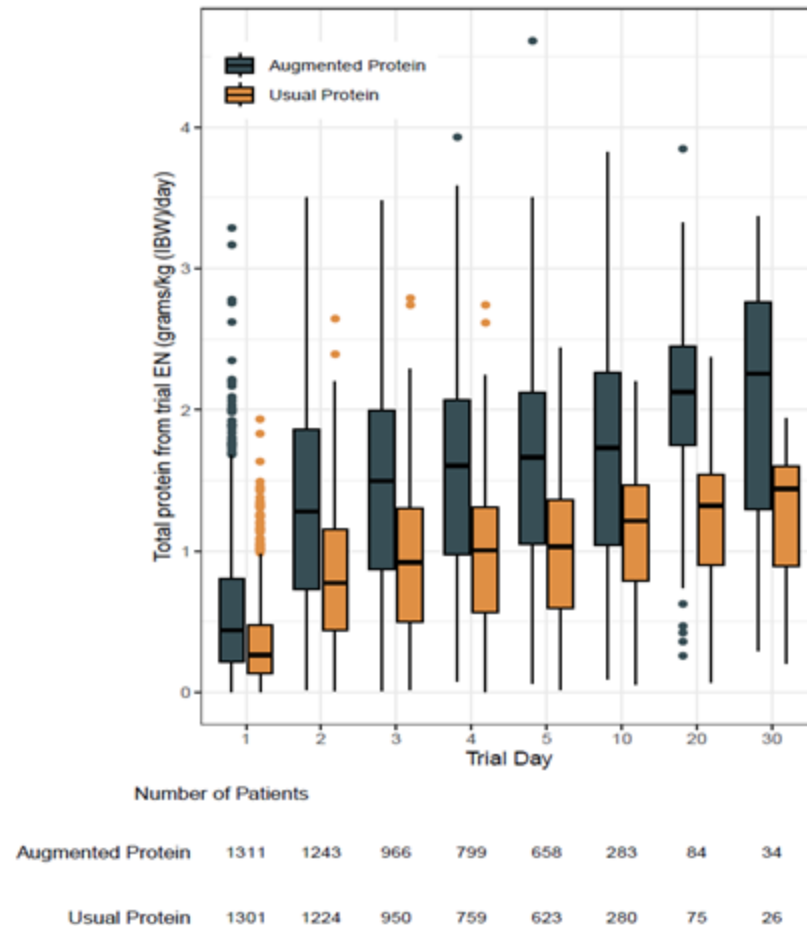
Enrolment Per Site

Royal Melbourne Hospital - 913 (26.9%)
Royal Adelaide Hospital – 660 (19.4%)
Royal Prince Alfred Hospital - 625 (18.4%)
Austin Hospital - 394 (11.6%)
Wellington Regional Hospital - 260 (7.7%)
Sunshine Hospital - 246 (7.2%)
University Hospital Geelong - 236 (6.9%)
The Queen Elizabeth Hospital - 63 (1.9%)



Trial nutrition delivery

Protein (g/kg IBW/day) - including day of enrollment

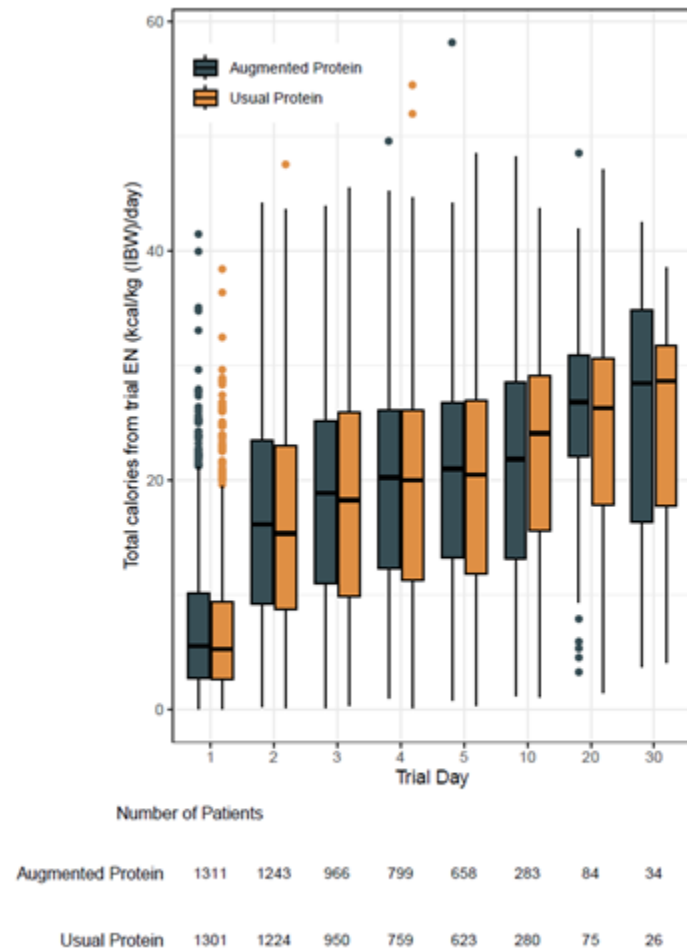


Augmented Protein: 1.12 (0.71, 1.53)
g/kg IBW/day

Usual Protein: 0.69 (0.40, 0.95) g/kg
IBW/day

Trial nutrition delivery

Calories (Kcal/kg IBW/day) - including day of enrollment

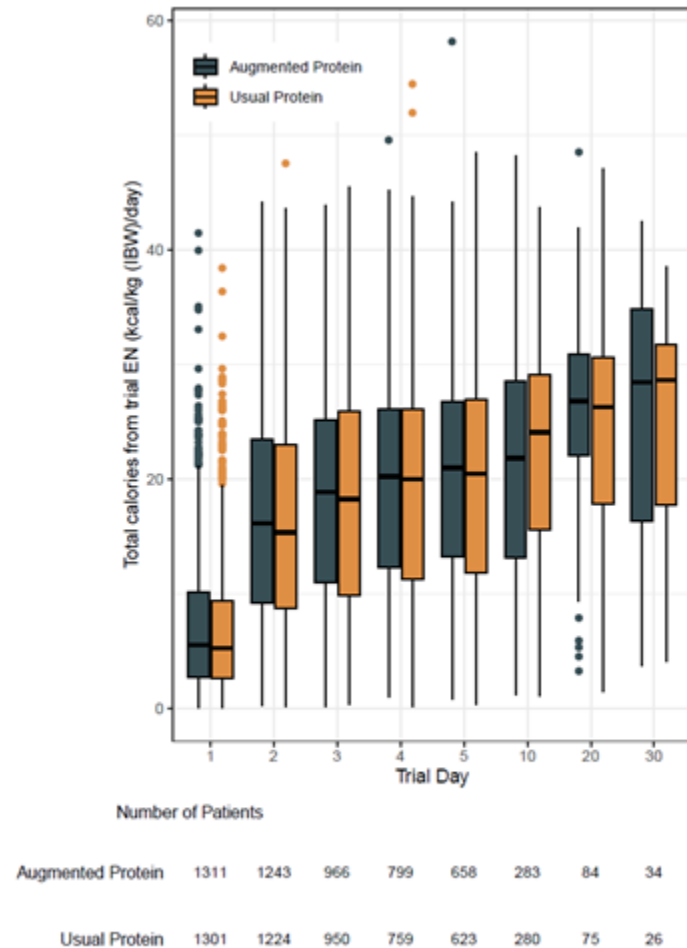


Augmented Protein: 14 (9, 19) kcal/kg
IBW/day

Usual Protein: 14 (8, 19) kcal/kg
IBW/day

Trial nutrition delivery

Calories (Kcal/kg IBW/day) - excluding day of enrollment



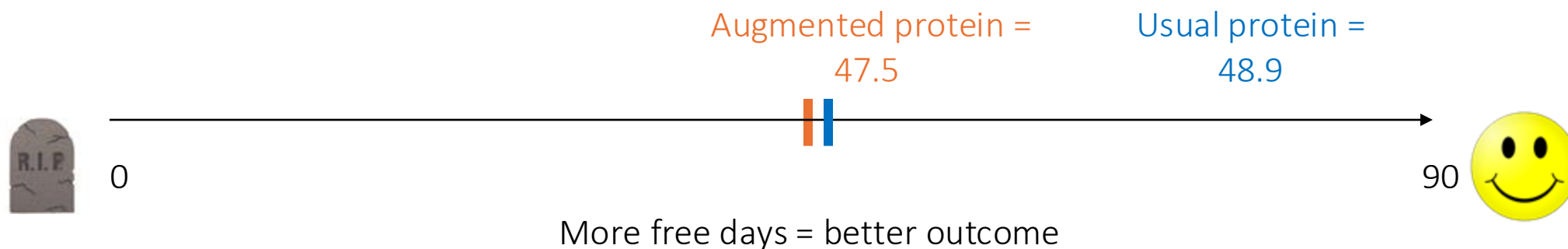
Augmented Protein: 17 (11, 22)
kcal/kg IBW/day

Usual Protein: 17 (10, 22) kcal/kg
IBW/day

Primary outcome - Linear Mixed Model

Number of days free of the index hospital and alive at day 90

Outcome - Median (IQR)			Augmented Protein (n=1681)	Usual Protein (n=1716)	Intraclass correlation coefficient	Effect estimate (95% CI)	p-value
Primary outcome	Number of days free of the index hospital and alive at day 90	Linear mixed model	47.5 (34.0)	48.9 (33.5)	<0.001	Median Difference: -1.26 (-3.59, 1.06)	0.29



Primary outcome - Bayesian model

Number of days free of the index hospital and alive at day 90

Outcome - Median (IQR)			Augmented Protein (n=1681)	Usual Protein (n=1716)	Intraclass correlation coefficient	Effect estimate (95% CI)	p-value
Primary outcome	Number of days free of the index hospital and alive at day 90	Bayesian quantile mixed model	62 (0.0, 77)	64 (0.0, 77)	0.0023	Median Difference: -1.50 (-3.86, 0.90)	NA



0

Augmented protein = 62

Usual protein = 64



90



More free days = better outcome

Primary outcome - Sensitivity analyses

Number of days free of the index hospital and alive at day 90

Primary outcome (Sensitivity analyses)	Augmented Protein (n = 1681)	Usual Protein (n = 1716)	Effect estimate (95% CI)	p-value	Intra-cluster correlation coefficient
Excluding patients known to have received non-trial enteral formula ⁵	64 (0, 78)	65.0 (0, 78)	Median Difference: -0.97 (-6.04, 4.10)	0.71	0.009
Excluding patients admitted for palliative care or organ donation ⁶	63.0 (0, 77)	64.0 (0, 77)	Median Difference: -1.12 (-7.17, 4.93)	0.72	0.007

⁵234 participants excluded (144 in augmented protein group and 90 in usual protein group). Treatment effect estimated using primary analysis model (quantile mixed model).

⁶27 participants excluded (17 in augmented protein group and 10 in usual protein group). Treatment effect estimated using primary analysis model (quantile mixed model).

Sub-Group Analysis for Primary Outcome

Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) in RCTs

- 95% CI crossed zero for mechanical ventilation and AKI
- An assessment of credibility for heterogeneity of treatment effect was conducted using ICEMAN
- Moderate credibility that the signal of harm for those with AKI at baseline is true
- Very low credibility that mechanical ventilation is an effect modifier

Appendix 5 (as supplied by the authors): Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials

- Quick instructions**
- Synonyms for effect modification include subgroup effect, interaction, and moderation
 - The instrument applies to a single proposed effect modification at a time; complete one form per each outcome, time-point, effect measure, and effect modifier
 - Response options on the left indicate definitely or probably reduced, response options on the right probably or definitely increased credibility
 - Completely unclear goes under probably reduced credibility
 - It is helpful to provide a supporting comment or quotation under each question
 - Whether an effect modification is patient-important is not part of the credibility assessment
 - The manual provides more detailed instructions and examples

Preliminary considerations

Study reference(s): **TARGET Protein - heterogeneity of effect in patients with acute kidney failure**

If available, protocol reference(s):

State a single outcome and, if applicable, time-point of interest (e.g. mortality at 1 year follow-up): **Days free of hospital and alive at day 90**

State a single effect measure of interest (e.g. relative or absolute risk difference): **Median (95% confidence intervals)**

State a single potential effect modifier of interest (e.g. age or comorbidity): **Renal failure**

Was the potential effect modifier measured before randomisation? **[*] yes, continue** [] no, stop here, refer to manual for further instructions

Credibility assessment

1: Was the direction of the effect modification correctly hypothesized a priori?

[] Definitely no	[] Probably no or unclear	[*] Probably yes	[] Definitely yes
Clearly post-hoc or results inconsistent with hypothesized direction or biologically very implausible	Vague hypothesis or hypothesized direction unclear	No prior protocol available but unequivocal statement of a priori hypothesis with correct direction of effect modification	Prior protocol available and includes correct specification of direction of effect modification, e.g. based on a biologic rationale
Comment: During conduct of TARGET Protein, the EFFORT Protein trial was published. Added renal failure as subgroup. Hypothesized that outcomes were in those with kidney failure who received augmented protein			

2: Was the effect modification supported by prior evidence?

[] Inconsistent with prior evidence	[] Little or no support or unclear	[] Some support	[*] Strong support
Prior evidence suggested a different direction of effect modification	No prior evidence or consistent with weak or very indirect prior evidence (e.g. animal study at high risk of bias) or unclear	Consistent with more limited or indirect prior evidence (e.g. large observational study, non-significant effect modification in prior RCT, or different population)	Consistent with strong prior evidence directly applicable to the clinical scenario (e.g. significant effect modification in related RCT)
Comment: Yes, see above (EFFORT Protein)			

3: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? (consider irrespective of number of effect modifiers)

[] Chance a very likely explanation	[] Chance a likely explanation or unclear	[] Chance may not explain	[*] Chance unlikely explanation
interaction p-value >0.05	interaction p-value ≤0.05 and >0.01, or no test of interaction reported and not computable	interaction p-value ≤0.01 and >0.005	interaction p-value ≤0.005
Comment: P<0.001			

4: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?

[] Definitely no	[] Probably no or unclear	[*] Probably yes	[] Definitely yes
Explicitly exploratory analysis or large number of effect modifiers tested (e.g. greater than 10) and multiplicity not considered in analysis	No mention of number or 4-10 effect modifiers tested and number not considered in analysis	No protocol available but unequivocal statement of 3 or fewer effect modifiers tested	Protocol available and 3 or fewer effect modifiers tested or number considered in analysis
Comment: Four effect modifiers tested			

AKI

5: If the effect modifier is a continuous variable, were arbitrary cut points avoided? [*] not applicable: not continuous

[] Definitely no	[] Probably no or unclear	[] Probably yes	[] Definitely yes
Analysis based on exploratory cut point (e.g. picking cut point associated with highest interaction p-value)	Analysis based on cut point(s) of unclear origin	Analysis based on pre-specified cut points, e.g. suggested by prior RCT	Analysis based on the full continuum, e.g. assuming a linear or logarithmic relationship
Comment:			

6 Optional: Are there any additional considerations that may increase or decrease credibility? (manual section 2.6)

[*] yes, probably decrease [] yes, probably increase

Comment: **Difference in definition with commencement of new renal replacement therapy prior to commencing study used for TARGET Protein. Also small numbers in the cohort (augmented protein=122, usual protein=119 and wide 95% CI [-50.00, +23.61] days**

7: How would you rate the overall credibility of the proposed effect modification?

The overall rating should be driven by the items that decrease credibility. The following provides a sensible strategy:

- All responses definitely or probably reduced credibility or unclear → very low
- Two or more responses definitely reduced credibility → maximum usually low even if all other responses satisfy credibility criteria
- One response definitely reduced credibility → maximum usually moderate even if all other responses satisfy credibility criteria
- Two responses probably reduced credibility → maximum usually moderate even if all other responses satisfy credibility criteria
- No response options definitely or probably reduced credibility → high very likely

Place a mark on the continuous line (e.g. hit "x" in electronic version)

X			
Very low credibility	Low credibility	Moderate credibility	High credibility
Very likely no effect modification Use overall effect for each subgroup	Little no effect modification Use overall effect for each subgroup but note remaining uncertainty	Likely effect modification Use separate effects for each subgroup but note remaining uncertainty	Very likely effect modification Use separate effects for each subgroup
Comment: Decreased moderate credibility of effect modification			

Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials

Quick instructions

- Synonyms for effect modification include subgroup effect, interaction, and moderation
- The instrument applies to a single proposed effect modification at a time; complete one form per each outcome, time-point, effect measure, and effect modifier
- Response options on the left indicate definitely or probably reduced, response options on the right probably or definitely increased credibility
- Completely unclear goes under probably reduced credibility
- It is helpful to provide a supporting comment or quotation under each question
- Whether an effect modification is patient-important is not part of the credibility assessment
- The manual provides more detailed instructions and examples

Preliminary considerations

Study reference(s): **TARGET Probes - heterogeneity of effect in patients receiving mechanical ventilation**

If available, protocol reference(s):

State a single outcome and, if applicable, time-point of interest [e.g. mortality at 1 year follow-up]: **Days free of hospital and alive at day 90**

State a single effect measure of interest (e.g. relative or absolute risk difference): **Median (95 % confidence intervals)**

State a single potential effect modifier of interest [e.g. age or comorbidity]: **Mechanical ventilation**

Was the potential effect modifier measured before randomization? ☒ **yes, continue** ☐ **no, stop here, refer to manual for further instructions**

Credibility assessment

1: Was the direction of the effect modification correctly hypothesized a priori?

☒ Definitely no	☐ Probably no or unclear	☐ Probably yes	☐ Definitely yes
Clearly post-hoc or results inconsistent with hypothesized direction or biologically very implausible	Vague hypothesis or hypothesized direction unclear	No prior protocol available but unequivocal statement of a priori hypothesis with correct direction of effect modification	Prior protocol available and includes correct specification of direction of effect modification, e.g. based on a biologic rationale

Comment: **Hypothesized greater benefit to be observed in those receiving mechanical ventilation at baseline**

2: Was the effect modification supported by prior evidence?

☐ Inconsistent with prior evidence	☒ Little or no support or discordance suggested a different direction of effect modification	☐ Some support	☐ Strong support
	No prior evidence or consistent with weak or very indirect prior evidence (e.g. animal study at high risk of bias) or unclear	Consistent with more limited or indirect prior evidence (e.g. large observational study, non-significant effect modification in prior RCT, or different population)	Consistent with strong prior evidence directly applicable to the clinical scenario (e.g. significant effect modification in related RCT)

Comment: **No existing data to support**

3: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? (consider irrespective of number of effect modifiers)

☐ Chance a very likely explanation	☒ Chance a likely explanation or unclear	☐ Chance may not explain	☐ Chance an unlikely explanation
Interaction p-value >0.05	Interaction p-value ≤0.05 and >0.01, or no test of interaction reported and not computable	Interaction p-value ≤0.01 and >0.005	Interaction p-value ≤0.005

Comment: **P=0.023**

4: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?

☐ Definitely no	☐ Probably no or unclear	☒ Probably yes	☐ Definitely yes
Explicitly exploratory analysis or large number of effect modifiers tested (e.g. greater than 10) and multiplicity not considered in analysis	No mention of number or 4-10 effect modifiers tested and number not considered in analysis	No protocol available but unequivocal statement of 3 or fewer effect modifiers tested	Protocol available and 3 or fewer effect modifiers tested or number considered in analysis

Comment: **Four effect modifiers tested.**

IMV

5: If the effect modifier is a continuous variable, were arbitrary cut points avoided? ☒ **not applicable: not continuous**

☐ Definitely no	☐ Probably no or unclear	☐ Probably yes	☐ Definitely yes
Analysis based on exploratory cut point (e.g. picking cut point associated with highest interaction p-value)	Analysis based on cut point(s) of unclear origin	Analysis based on pre-specified cut points, e.g. suggested by prior RCT	Analysis based on the full continuum, e.g. assuming a linear or logarithmic relationship

Comment:

6 Optional: Are there any additional considerations that may increase or decrease credibility? (manual section 2.6)

☐ yes, probably decrease ☐ yes, probably increase

Comment: **Not applicable**

7: How would you rate the overall credibility of the proposed effect modification?

The overall rating should be driven by the items that decrease credibility. The following provides a sensible strategy:

- All responses definitely or probably reduced credibility or unclear → very low
- Two or more responses definitely reduced credibility → maximum usually low even if all other responses satisfy credibility criteria
- One response definitely reduced credibility → maximum usually moderate even if all other responses satisfy credibility criteria
- Two responses probably reduced credibility → maximum usually moderate even if all other responses satisfy credibility criteria
- No response options definitely or probably reduced credibility → high very likely

Place a mark on the continuous line (e.g. hit "x" in electronic version)

