

1 **Refeeding risks in patients requiring intravenous nutrition support: results of a**
2 **two-centre, prospective, double-blind, randomised controlled trial**

3 Tim Ambrose^{1,4,7}, Aminda De Silva^{1,7}, Mani Naghibi^{2,5}, John Saunders^{2,6}, Trevor R Smith², Ruth L
4 Coleman³, Mike Stroud²

6 ¹Department of Gastroenterology, Royal Berkshire NHS Foundation Trust, Royal Berkshire Hospi-
7 tal, London Road, Reading RG1 5AN, United Kingdom

8 ²Department of Gastroenterology, University Hospital Southampton NHS Foundation Trust, South-
9 ampton, Southampton General Hospital, Tremona Road, Southampton, Hampshire SO16 6YD,
10 United Kingdom

11 ³Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Old Road, Oxford
12 OX3 7LJ, United Kingdom

13 ⁴Present address: Department of Gastroenterology, Oxford University Hospitals NHS Foundation
14 Trust, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, United Kingdom

15 ⁵Present address: Department of Gastroenterology, London Northwest Healthcare NHS Trust, St
16 Mark's Hospital, Watford Road, Harrow, Middlesex HA1 3UJ, United Kingdom

17 ⁶Present address: Department of Gastroenterology, Royal United Hospitals Bath NHS Foundation
18 Trust, Combe Park, Bath BA1 3NG, United Kingdom

19 ⁷Joint first authors

21 **Corresponding author**

22 Dr Mike Stroud, Department of Gastroenterology, University Hospital Southampton NHS Founda-
23 tion Trust, Southampton, Southampton General Hospital, Tremona Road, Southampton, Hampshire
24 SO16 6YD

25 Email: mas1@soton.ac.uk

26 Contact telephone: +44 (0)7745 937772

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28

29 **Abstract**

30 **Background/Aims**

31 Refeeding syndrome can result following excessive feeding of malnourished patients. The syndrome
32 remains poorly defined but encompasses a range of adverse effects including electrolyte shifts, hy-
33 perglycaemia and other less well-defined phenomena. There are additional risks of underfeeding mal-
34 nourished individuals. Studies of refeeding syndrome have generally focussed on critical care envi-
35 ronments or patients with anorexia nervosa. Here we have conducted a two-centre, prospective, dou-
36 ble-blind, randomised controlled trial amongst all patients referred to hospital nutrition support teams
37 for intravenous nutrition support. We sought to determine whether electrolyte and other abnormalities
38 suggestive of refeeding syndrome risk varied depending on initial rate of intravenous feeding.

39
40 **Methods**

41 Patients at moderate or high risk of refeeding syndrome, as defined by United Kingdom National
42 Institute of Health and Care Excellence guidelines, were screened for inclusion. Patients were ran-
43 domised to receive either high (30kcal/kg/day, 0.25gN/kg/day) or low (15kcal/day, 0.125gN/kg/day)
44 rate feeding for the first 48 hours prior to escalation to standard parenteral nutrition regimens. The
45 primary outcome was rates of potential refeeding risks within the first 7 days as defined by electrolyte
46 imbalance or hyperglycaemia requiring insulin. Secondary outcomes included effects on QTc inter-
47 val, infections and length of hospital stay. Statistical analysis was performed with χ^2 or Wilcoxon
48 rank sum tests and all analysis was intention-to-treat. Problems with study recruitment led to prema-
49 ture termination of the trial. Registered on the EU Clinical Trials Register (EudraCT number 2007-
50 005547-17).

51
52 **Results**

53 534 patients were screened and 104 randomised to either high or low rate feeding based on risk of
54 refeeding syndrome. Seven patients were withdrawn prior to collection of baseline demographics and

55 were excluded from analysis. 48 patients were analysed for the primary outcome with potential
56 refeeding risks identified in 46%. No differences in risks were seen between high and low rate feeding
57 ($p>0.99$) or high and moderate risk feeding ($p=0.68$). There were no differences in QTc abnormalities,
58 infection rates, or hospital length of stay between groups.

59

60 **Conclusions**

61 In this randomised trial of rates of refeeding risk, in patients pre-stratified as being at high or moderate
62 risk, we found no evidence of increased refeeding related disturbances in those commenced on high
63 rate feeding compared to low rate. No differences were seen in secondary endpoints including cardiac
64 rhythm analysis, infections or length of stay. Our study reflects real world experience of patients
65 referred for nutrition support and highlights challenges encountered when conducting clinical nutri-
66 tion research.

67

68 **Keywords**

69 Refeeding syndrome

70 Parenteral nutrition

71 Malnutrition

72 Hypophosphataemia

73 Clinical trial

74

75 **Abbreviations**

76 BMI – Body Mass Index

77 CTIMP – Clinical Trials of Investigational Medicinal Products

78 CV – Coefficient of variance

79 ECG - Electrocardiogram

80 IF – Intestinal failure

81 IVN – Intravenous nutrition

82 K - Potassium

83 LLN – Lower limit of normal

84 Mg - Magnesium

85 MUST – Malnutrition Universal Screening Tool

86 NICE – National Institute of Health and Care Excellence

87 NIHR – National Institute of Health Research

88 NST – Nutrition support team

89 PN – Parenteral nutrition

90 PO₄ - Phosphate

91 QTc – Corrected QT interval

92 RFS – Refeeding syndrome

93 UK – United Kingdom

94 **Introduction**

95 Refeeding syndrome (RFS) traditionally refers to the deleterious effects of feeding malnourished in-
96 dividuals particularly on serum electrolyte concentrations. Historical studies of starvation helped to
97 identify the adverse consequences that can result from overzealous feeding of the malnourished¹, now
98 referred to as RFS. ‘War famine oedema’ was well-documented^{2,3}, particularly in those involved in
99 the Great Wars, but it was the comprehensive studies of malnutrition in Japanese prisoners of war⁴,
100 and the landmark Minnesota starvation trials^{5,6}, that characterised these changes more fully. It is
101 known from critical care that adequate, but not excessive, glucose control is important for out-
102 comes^{7,8}. Hyperglycaemia associated with feeding is recognised and may reflect not only excess ca-
103 loric delivery exceeding glucose oxidation rate but also be a marker of underlying infection. The
104 extent to which this affects outcome is not yet clear. Other clinically relevant refeeding phenomena,
105 such as effects on cognitive function, are more challenging to measure.

106
107 Malnutrition is associated with fundamental changes in physiology resulting in reduced organ func-
108 tion, abnormal shifts of sodium and water to intracellular compartments, and loss of intracellular
109 electrolytes to extracellular compartments with consequent urinary losses, and total body deficiency⁹.
110 The provision of nutrition to these individuals, especially at high levels, will lead to a rise in serum
111 insulin levels and a return of normal cellular function, which in turn may precipitate a rapid reversal
112 of the starvation induced electrolyte changes with consequent oedema, hypophosphataemia, hypoka-
113 laemia, and hypomagnesaemia^{9,10}. In extreme cases, life threatening cardiac dysfunction may occur
114 and even death¹¹. It may also be undesirable to underfeed malnourished individuals as their condition
115 may deteriorate further with organ dysfunction, poor wound healing and increased rates of infection.

116
117 Hospital patients at risk of malnutrition may be managed through oral, enteral or parenteral strategies
118 and RFS poses a potential risk to all these patients. The current United Kingdom (UK) National In-
119 stitute for Health and Care Excellence (NICE) guidelines for nutrition support¹² classify the risk of

120 RFS in malnourished patients as moderate or high (Table 1) but no studies were identified to enable
121 either true risk stratification or firm recommendations on the best level of feeding in these groups.
122 The guidelines therefore recommend that patients at *any* risk of RFS should receive low level feed
123 for the first few days but a UK survey conducted in 2008 showed disparities in agreement with the
124 guidelines¹³ with 39% feeling that the guidance was appropriate whilst 36% felt it was too cautious.
125 Concern was highlighted that the guidelines were an obstacle to adequate nutrition especially given
126 that many respondents stated they had never seen a case of RFS despite always starting feeding at
127 100%. The incidence of indicators of refeeding risks amongst internal medicine patients identified as
128 ‘at risk’ was only 14% in a recent study¹⁴ and was only 2% in all patients commenced on nutritional
129 support in another hospital¹⁵. Recently it has been shown that the presence of indicators of refeeding
130 risk is associated with increased mortality and longer length of stay in malnourished hospital inpa-
131 tients¹⁶ but the incidence of abnormalities in these indicators amongst patients referred to hospital
132 Nutrition Support Teams (NST) for intravenous nutrition (IVN) support is not known.
133
134 The aim of this two-centre, prospective, double blind, randomised controlled trial was to determine
135 whether initiation of feeding at 100% estimated requirements compared to 50% estimated require-
136 ments increased electrolyte/fluid disturbance, feeding-induced hyperglycaemia or other potential
137 clinical problems in patients at moderate or high risk of refeeding syndrome as classified by the NICE
138 guidelines. The trial was designed to reflect patients who are referred to NSTs for ward-based care
139 rather than just the critically ill.

140

141 **Methods**

142

143 Trial design

144 Two-centre, prospective, double-blind, randomised controlled trial comparing 100% versus 50%
145 feeding in patients referred for IVN support and at risk of RFS. The trial was conducted at University
146 Hospitals Southampton and Royal Berkshire Hospital, Reading.

147

148 Inclusion/Exclusion criteria

149 *Original inclusion criterion*

150 All adults at moderate or high risk of refeeding syndrome who required Parenteral Nutrition (PN).

151

152 *Original exclusion criteria*

- 153 a) Patients at very high risk of refeeding syndrome (BMI <14kg/m²; or 2 or more of the NICE
154 criteria – BMI <16kg/m², recent weight loss >15% within 6 months, no nutritional intake >10
155 days)
- 156 b) Levels of K, Mg, PO₄ below lower limit of normal range for the local laboratory prior to
157 feeding
- 158 c) Patients with oral nutritional intake
- 159 d) Patients needing specialised individual PN regimens.
- 160 e) Intensive care patients who often cannot consent and may receive variable levels of additional
161 enteral tube feeding
- 162 f) Patients >80kg (excluding oedema (see Supplementary Methods for details)) giving an esti-
163 mated energy requirement >2400kcal/day
- 164 g) Patients with pre-existing diabetes mellitus
- 165 h) Patients unable to give informed consent

166

167 *Revisions to criteria (as of December 2011, explanation in 'Study Problems' below)*

168 c) Inclusion of patients with small amounts of oral intake (less than 300 kcal per day) – Original-
169 nally we excluded patients who had been taking any form of oral nutrition. As the trial pro-
170 gressed it was observed that a significant number of patients who required PN were having
171 very small amounts of oral nutrition at levels that were not felt to either mitigate or exacerbate
172 refeeding risks.

173 f) Inclusion of patients 80-100kg (excluding oedema) – Due to increasing levels of obesity in
174 the population more than 10% of patients originally screened were unable to be included in
175 the trial. Therefore the exclusion threshold for weight was increased to >100kg assuming that
176 much of the additional weight would be largely adipose tissue which has different metabolic
177 requirements to lean tissue and would be unlikely to affect the validity of application of the
178 trial results. Patients between 80-100kg were treated at a maximum 2400kcal/day in keeping
179 with our clinical practice.

180 h) Inclusion of patients unable to consent to treatment – Clinical practice which follows both
181 high and low initial rates of feeding are routinely recommended by different expert groups
182 and widely established. We therefore felt it appropriate to include patients who were unable
183 to consent since they had potentially as much to gain as other patient groups. This included
184 individuals with post-operative confusion due to sepsis and/or side effects of analgesia, e.g.
185 morphine, or anaesthetic agents.

186

187 *Withdrawal criteria*

188 Patients were withdrawn from the trial at any stage if PN was no longer appropriate, the clinical
189 condition necessitated switching to a specialised regimen, or at their request.

190

191 Treatment

192 Patients were stratified into moderate or high risk of refeeding syndrome and subsequently random-
193 ised with concealed allocation to receive either high or low level/rate PN for the first 48 hours.

194

195 1) High – 30kcal/kg/day (including protein), 0.25gN/kg/day

196 2) Low – 15kcal/kg/day (including protein), 0.125gN/kg/day

197

198 Both groups received equal concentrations of electrolytes, trace elements and micronutrients. After
199 48 hours all patients received standard PN regimens providing 30kcal/kg/day in accordance with
200 standard practice for the two centres. Further specific details of the composition of the trial PN, to-
201 gether with vitamin, mineral and trace element concentrations is given in Supplementary Methods.

202

203 Outcome measures

204 *Primary outcome*

205 A fall below the lower limit of normal of the local laboratory of K, Mg, PO₄ within 7 days of ran-
206 domisation, or a rise in blood glucose (>11mmol/l) requiring insulin. Normal ranges were taken to
207 be:

208

209 K 3.5-5.3 mmol/l

210 Mg 0.7-1.0 mmol/l

211 PO₄ 0.8-1.5 mmol/l

212

213 *Secondary outcomes*

214 1) A requirement for infusions of K, Mg, PO₄, or insulin within 7 days of randomisation

215 2) Fluid overload as assessed by clinical oedema score (see Supplementary Methods)

216 3) Abnormal corrected QT (QTc) interval on electrocardiogram (ECG) – calculated using Ba-
217 zett's formula (QT interval/ $\sqrt{\text{RR interval}}$) with a normal QTc \leq 440ms.

218 4) Infections in the first 7 days of feeding. Infections were classified as suspected or confirmed,
219 the latter usually being applied only in the presence of positive cultures or definitive clinical
220 judgement for infection.

221 5) Length of stay
222

223 Study problems

224 1) Recruitment at Southampton was delayed unexpectedly by Clinical Trials of Investigational
225 Medicinal Products (CTIMP) until October 2010 resulting in 6 months lost recruitment time.

226 2) Recruitment at Reading was delayed until April 2011 by CTIMP and local Research & De-
227 velopment resulting in 12 months lost recruitment time.

228 3) In the period between the development of the study protocol and commencement of study
229 recruitment, significant changes in surgical practice had occurred particularly an increase in
230 laparoscopic interventions for gastrointestinal patients and the introduction of guidance re-
231 stricting intravenous fluid administration after surgery. These changes resulted in a significant
232 fall in PN referrals for prolonged post-operative intestinal failure related to ileus, the indica-
233 tion which had provided most of the cohort in the pilot trials, of approximately 66%.

234 4) More patients declined trial participation than anticipated from pilot studies. This was in part
235 due to higher standards of research governance and documentation relating to consent and
236 patient information.

237 5) More patients were excluded than anticipated due to weight >80kg or inability to give consent.

238 6) These difficulties resulted in major revisions in inclusion and exclusion criteria (listed above)
239 and an application for an unfunded extension to the trial which was not granted until Novem-
240 ber 2012. During this time, problems with PN manufacturing halted supply of trial PN from
241 July-September 2012. Recruitment was suspended at both sites during this time period. Re-
242 cruitment reopened at both sites in February 2013.

243

244 Power calculation

245 At the time of protocol development, all patients in our institutions received PN according to NICE
246 guidelines at 50% of requirements for the first 48 hours. There were no data available to indicate
247 likely electrolyte changes were these patients to have received feeding at 100% of requirements in
248 the first 48 hours. In a retrospective review of 50 patients receiving feed at 50% of requirements we
249 did not identify any electrolyte reductions necessitating replacement. However, we estimated that 5%
250 of patients in this group and an additional 15% in the 100% feeding group would sustain a fall in
251 electrolyte values (K, Mg, PO₄) during the trial necessitating replacement. A sample size of 101 in
252 each feeding group (50% versus 100%) was determined with 90% power to detect the difference
253 between a proportion of 5% falling below the LLN in the 50% feeding group and a proportion of 20%
254 falling below the LLN in the 100% feeding group, with a 5% two-sided significance level. Thus a
255 total of 230 patients (approximately 58 in each of the four arms) were required to allow for 10% loss
256 to follow up. Formal statistical advice on power calculations was given from the Research Develop-
257 ment & Support Unit, University Hospitals Southampton. Based on similar pilot studies of approxi-
258 mately 60 patients conducted prior to protocol development and funding application, we estimated
259 that >10 patients per month could be recruited to reach the target of 230 patients over 24 months.
260 Difficulties with recruitment are described above in ‘Study Problems’.

261

262 Randomisation and blinding

263 Each centre was allocated a number (Southampton 01, Reading 02) and a randomisation list created
264 manually by the Pharmacy Department at University Hospitals Southampton from blocks of four
265 using four counters in a pot. Each block contained two of each arm, every block was individually
266 drawn and no blocks were copied. Separate randomisation lists were drawn up for each centre and
267 for high and moderate risk patients.

268

269 Patients were enrolled by a member of the clinical trials team. After consent was granted, patients
270 were stratified into high or moderate risk using the NICE criteria. A blinded, trial-specific, prescrip-
271 tion was sent to pharmacy outlining the risk of refeeding syndrome, and then the patients were ran-
272 domised 1:1 using the previously generated lists by a member of the local pharmacy department. The
273 next available randomisation number in the indicated subgroup was allocated to the patient. Every
274 bag of PN was provided with identical labels regardless of the intervention the patient received. Trial
275 PN was manufactured by the Bath Aseptics Unit (Bath, UK).

276
277 Blinding was assured for medical/nursing teams, the patients, and members of the clinical trials team.
278 The only unblinded staff were from pharmacy.

279 280 Ethics and trial registration

281 Ethics was granted by NHS Research Ethics Committee (REC) 09/H0504/78 and the trial registered
282 on the EU Clinical Trials Register (EudraCT number 2007-005547-17). All changes to the original
283 protocol were submitted as amendments and approved by the REC.

284 285 Statistical analysis

286 The primary and secondary analyses were performed on all patients without the outcome of interest
287 at baseline with categorical variables analysed using χ^2 and continuous variables using Wilcoxon
288 rank sum tests. All analyses were performed in R (R Core Team (2017). R: A language and envi-
289 ronment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL
290 <https://www.R-project.org/>).

291
292 In order to calculate a significant change within the normal ranges of electrolytes, the total coeffi-
293 cient of variance (CV) of both biological and analytical variation was calculated:

294

295 $\text{Total CV(\%)} = (\sqrt{(\text{analytical variation(\%)}^2 + \text{biological variation(\%)}^2)})$

296 *Biological variation: K 4.6%, Mg 3.6%, PO₄ 8.2%*

297 *Analytical variation (Southampton): K 1.5%, Mg 2.4%, PO₄ 2.2%*

298 *Analytical variation (Reading): K 1.6%, Mg 2.3%, PO₄ 7.2%*

299

300 Then, for each paired value the standard deviation, s, was calculated using the highest of paired pa-
301 tient values (z) as the ‘mean’:

302

303 $s(\text{mmol/l}) = (\text{total CV(\%)} \times z(\text{mmol/l}))/100$

304

305 For two results to be significantly different (at $p < 0.05$) they had to be at least 2.8 standard devia-
306 tions apart from z:

307

308 $A(\%) = (2.8 \times s \times 100)/z$

309

310 Finally the difference between two measurements (e.g. day 1 and day 2) was calculated as a per-
311 centage of the higher of the two values: (B(%)). If $B > A$ then this was viewed as a significant differ-
312 ence in electrolyte values.

313 **Results**

314 Patients were enrolled between April 2010 and August 2013 at the two hospital sites with data rec-
315 orded for 7 days or until discharge/death, unless they met the withdrawal criteria. Data collected up
316 to the point of withdrawal were analysed and all analyses were performed as intention-to-treat. Due
317 to ongoing poor levels of recruitment the trial was terminated early in August 2013 after discussion
318 with the funding body as target recruitment could not be achieved in fewer than 40 months and was
319 not financially viable.

320

321 **Baseline demographics**

322 The flow of patients through the trial is shown in Figure 1 with baseline patient demographics in
323 Table 2. Although 104 patients were risk stratified, 7 patients were withdrawn before randomisation
324 (without collection of demographics and baseline data) and so are excluded from any further analysis,
325 leaving 97 patients analysed. Reasons for withdrawal were: repeat bloods on day of randomisation
326 demonstrated PO₄ below lower limit of normal (n=1), insufficient trial PN available (n=1), unresolv-
327 able query over PN prescription (n=1), consultant decision (n=1), no central venous access (n=2),
328 review of oral intake deemed too great to merit PN (n=1). Baseline values for K, Mg, PO₄ and diabetes
329 requiring insulin are shown in Table 3. There were no significant differences between the groups at
330 baseline.

331

332 **Primary outcome**

333 Of the 97 patients recruited to the study, 34 (35%) either had levels of K, Mg, or PO₄ below the lower
334 limit of normal or a blood glucose >11mmol/l and requiring insulin on day 0 (38% vs 32% in the low
335 versus high rate feeding arms respectively). This was due to changes in parameters between the day
336 of randomisation and the day of commencing PN. These patients were therefore excluded from the
337 analysis for primary outcome. 48 patients had complete datasets for all baseline parameters for the
338 primary outcome.

339
340 Of these, 22 (46%) met the primary outcome but there was no difference based on rate of feeding
341 (Table 4). The primary outcome occurred in 11 of the 24 patients (45.8%) in the high rate group and
342 11 of the 24 patients (45.8%) in the low rate group. The relative risk (RR) of the primary outcome
343 occurring in the high vs. low group was 1.00 (95% confidence interval [CI] 0.54-1.85, $p>0.99$). Sim-
344 ilarly there was no difference between high and moderate risk patients on incidence of refeeding
345 syndrome by rate of feeding (low rate feeding: moderate risk 6/12, high risk 5/12; high rate feeding:
346 moderate risk 4/10, high risk 7/14 ($p=0.68$)).

347
348 **Secondary outcomes**

349 As this was a trial of ward-based patients, the majority received supplemental electrolytes either
350 orally or intravenously in addition to the PN at the discretion of the clinical team. This being the case
351 it is not possible to draw conclusions on rates of refeeding between the groups based on a requirement
352 for infusions of electrolytes within 7 days. Therefore we sought to analyse a significant fall in elec-
353 trolyte values between consecutive samples even if this remained within the normal range. Further-
354 more, interpretation of clinical oedema scores is impeded by inaccurate documentation, supplemental
355 intravenous sodium in addition to prescribed PN, and comorbidities such as heart failure and ne-
356 phrotic syndrome which could not be controlled for.

357
358 Individual patient data were analysed for significant reductions in electrolyte concentration but re-
359 maining within the normal range. 3/97 (3%) patients had missing data at baseline or no subsequent
360 measures. Of the 94 patients with data, there was a nominal reduction within the normal range in K,
361 Mg, or PO_4 in 4/46 (9%) and 8/48 (17%) of the low vs high rate feeding groups respectively with RR
362 1.92 (95% CI 0.62-5.93, $p=0.36$).

363

364 Of the 89 patients not on insulin at baseline and who had subsequent glucose measurements through
365 the trial, 4/89 (4%) developed a glucose >11mmol/l and requiring insulin but this did not vary by rate
366 of feeding. This endpoint occurred in 2 of 43 (5%) and 2 of 46 (4%) in the high and low groups
367 respectively, with RR 0.94 (95% CI 0.14-6.38, p>0.99) (Table 5). The denominators for secondary
368 endpoint analysis are different to those for primary endpoint analysis as the endpoints are mutually
369 exclusive.

370

371 53 patients had normal QTc intervals at baseline. Of these, there were 25 abnormal QTc measurements
372 in 15 patients during the study. There were no differences between rates of feeding with abnormal
373 QTc intervals occurring in 8/29 (28%) and 7/24 (29%) in the high and low groups respectively with
374 RR 0.95 (95% CI 0.40-2.24, p=0.90). (Figure 2).

375

376 18 patients developed evidence of infection within the first 7 days of feeding with a total of 22 sepa-
377 rate episodes (Tables 6 and 7) - 10/50 (20%) and 8/47 (17%) in the high and low groups respectively
378 with RR 1.15 (95% CI 0.49-2.69, p=0.75). There was no effect either related to rate of feeding or risk
379 of refeeding on infection episodes although the overall numbers are too small to confirm this through
380 statistical hypothesis testing.

381

382 No differences were seen in length of hospital stay (30 vs 26 days, p=0.31).

383

384 **Adverse events**

385 One patient died of aspiration pneumonia during the trial, one patient had a prolonged hospital stay
386 with slow neurological recovery following extubation, and one patient died following a post-surgical
387 cardiac arrest. None of these were related to the trial PN.

388

389 Discussion

390 In this trial we sought to investigate whether intravenous feeding initiated at 100% versus 50% of
391 requirements would result in higher rates of indicators of refeeding as defined by levels of K, Mg, or
392 PO₄ below the lower limit of normal, or feeding-related hyperglycaemia defined as a rise in glucose
393 >11mmol/l requiring insulin. Unfortunately in conducting the study we met several limitations that
394 prevented recruitment meeting our pre-specified power calculation. These limitations are detailed
395 above and reflect the challenges of undertaking clinical nutrition research in situations where trial
396 participants have diverse conditions and diverse needs. In light of this, the results should be inter-
397 preted with a degree of caution. We believe, however, that our cohort is likely to be representative of
398 the majority of patients requiring IVN support in the UK and hence that our results are a reflection of
399 the real world. A third of our patients met the inclusion criteria on the day of screening and random-
400 isation but by the first day of the trial when PN started, had electrolytes outside the normal range.
401 Furthermore only half of those patients recruited had data available for the analysis of the primary
402 endpoint, and gaps in data acquisition existed for components of secondary endpoint analysis. For
403 instance, whilst the protocol specified daily blood tests, this may not have occurred for diverse, yet
404 valid, reasons such as patient refusal on the day, inability to locate a vessel for venepuncture, or lack
405 of availability of the patient (e.g. away from ward space undergoing diagnostics). Again, whilst re-
406 grettable in terms of study recruitment, this reflects the issues faced by all NSTs undertaking clinical
407 nutrition research. A change of inclusion criteria midway through the trial certainly enhanced recruit-
408 ment but could furthermore call into question the validity of these results.

409
410 Bearing in mind the limitations above, our results do not suggest there is a differing incidence of
411 indicators of RFS, feeding-induced hyperglycaemia, or other less well-defined potentially deleterious
412 effects of early higher level feeding between individuals at either moderate or high risk of refeeding
413 problems as defined by the NICE guidelines when feeding is commenced at 100% versus 50% of
414 estimated requirements for the first 48 hours. Furthermore we found no differences induced by the

415 higher vs. lower feeding rates on falls in electrolytes concentrations within the normal range, QTc
416 intervals, lengths of stay, or infection rates. Although two patients in the higher feeding rate groups
417 died during the study, neither were related to the trial PN, and the study overall was not designed to
418 detect an effect on mortality between feeding rates.

419
420 Interestingly, however, the rates of abnormalities in RFS indicators in our study (46%) are higher than
421 some other published rates^{14,15}. Whilst this may be due to small numbers, this could also be explained
422 by variations in definitions, with other trials using hypophosphataemia alone as the marker of RFS
423 risk rather than incorporating K, Mg or glucose (as a measure of feeding-induced hyperglycaemia).
424 The issue of needing a consistent and adequate definition for RFS has been highlighted in a recent
425 systematic review¹⁷ where incidence rates varied from 0-80% depending on the population studied
426 and the definition used. A recent consensus statement⁹ provides some guidance on defining refeeding
427 syndrome and this may help standardise future studies.

428
429 A notable weakness of our study is that we excluded all individuals at highest risk of RFS and our
430 results should not be extrapolated to this group. It is therefore not possible to advocate full rate feeding
431 in all patients at the point of commencing IVN support. Future research should address the optimal
432 rate of feeding in patients at highest risk of RFS.

433
434 The key strength to our study is that, to our knowledge, this is the first randomised-controlled trial
435 assessing rate of feeding and potential risk of refeeding syndrome in all-comers referred to the NST
436 for IVN support. Studies to date on refeeding have largely been conducted in the environment of
437 critical care units where not only can variables be more easily controlled, but also the magnitude of
438 inflammation and catabolism on top of malnutrition may be greater. Despite the ability to better con-
439 trol variables, conflicting results have been reported. Patients with head injury requiring mechanical
440 ventilation had a similar neurological outcome at 6 months regardless of rate of feeding¹⁸. Infection

441 rates and other major complications were lower in the enhanced rate feeding group. A subsequent
442 study demonstrated that permissive underfeeding of 60-70% may be associated with lower hospital
443 mortality, but not 28-day all cause mortality, in the critically ill¹⁹. Underfeeding achieved through
444 restricting non-protein calories, but not protein calories, does not associate with lower 90-day mor-
445 tality in critically ill patients²⁰. Post-operative infections in critical care are not altered based on low
446 or standard rate of feeding²¹ and similarly we did not identify a clear effect of rate of feeding on
447 incidence of infections. Trophic enteral feed administered to mechanically ventilated patients with
448 acute lung injury does not result in worsened outcomes versus full rate feed^{22,23} but these patients
449 were not clearly malnourished at the point of entry to the trial and so it is difficult to extrapolate this
450 to patients at highest risk of refeeding syndrome. A recent multicentre study of just under 4000 pa-
451 tients undergoing mechanical ventilation reported no mortality benefit of energy dense enteral feed
452 (1.5kcal/ml) over routine feeding (1kcal/ml)²⁴.

453
454 In patients receiving enteral nutrition at a level insufficient to meet demands, later initiation of sup-
455 plemental parenteral nutrition is associated with faster recovery and fewer complications²⁵ suggesting
456 that early caloric restriction, particularly in the critically ill is of benefit. A subsequent randomised
457 controlled trial demonstrated the caloric restriction to 20kcal/h, in patients who developed hypophos-
458 phataemia and another sign of refeeding syndrome within 72h of commencing nutritional support,
459 was associated with a reduction in mortality rates and major infections^{26,27}. Additionally, in another
460 study 36.8% of critically ill, mechanically ventilated patients developed hypophosphataemia and
461 those fed at 50% target rate had improved 6 month outcomes²⁸. Whilst the patients in the first study
462 had multiple markers of refeeding syndrome, refeeding syndrome in the second study was defined by
463 hypophosphataemia alone. This electrolyte disturbance is common in critically ill patients and may
464 not associate with adverse outcomes²⁹ and so reducing early calorie intake on the basis of this param-
465 eter alone may not be necessary. Whilst consensus exists for feeding rate in the critically ill³⁰, it is
466 apparent that there is not yet consensus for the impact of hypophosphataemia alone on outcomes in

467 this cohort. There is a clinical trial of refeeding syndrome in elderly patients underway (ClinicalTri-
468 als.gov identifier: NCT03141489) comparing high versus low calorie enteral tube feeding.

469
470 Aside from this study, very few studies have been performed outside of critical care. Refeeding of
471 adolescents with anorexia nervosa at 1200kcal/day versus 500kcal/day resulted in improved weight
472 gain but no other adverse effect, including on QTc interval, with higher rate³¹. The absence of adverse
473 effects reported by this group is consistent with the results of our study. A significant challenge of
474 research into refeeding syndrome remains a lack of a clear definition which is prognostically relevant.
475 In the study described above, within 48h of feeding commencing, 28% of high calorie and 11% of
476 low calorie developed hypophosphataemia but in the absence of other electrolyte abnormality. It is
477 possible that a reliance on PO₄ to diagnose refeeding syndrome is overcautious and puts patients at
478 risk of inadvertent nutritional restriction. A recent retrospective study showed no association between
479 hypophosphataemia in refeeding syndrome and length of stay³².

480
481 Accepting the limitations of this study, the data do not support the need to commence intravenous
482 feeding at lower rates in non-critical care patients at moderate or high risk of RFS as defined by the
483 NICE guidelines. It is important to recognise that the results may be different with the inclusion of
484 patients deemed to be at very high risk of RFS and so our conclusions cannot be extrapolated to this
485 group. Furthermore we have not studied the effects of rates of oral or enteral feeding on indicators of
486 RFS and it is likely that patients requiring IVN support represent a different and inherently more
487 complex group to feed. There is an urgent need not only to adequately define RFS and other compli-
488 cations of refeeding but also to evaluate whether we should be underfeeding, feeding-at-requirement,
489 or overfeeding our malnourished patients at highest risk.

490
491

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496

497

498 **Statement of Authorship**

499 TA – Investigation, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review &
500 Editing

501 ANdS – Conceptualization, Methodology, Project Administration, Supervision, Investigation, Writ-
502 ing – Review & Editing, Funding Acquisition

503 MN – Investigation, Writing – Review & Editing

504 JS – Investigation, Writing – Review & Editing

505 TS – Investigation, Writing – Review & Editing

506 RC – Formal Analysis, Writing – Review & Editing

507 MS – Conceptualization, Methodology, Project Administration, Supervision, Investigation, Writing
508 – Review & Editing, Funding Acquisition

509

510 All authors approved the final manuscript

511

512

513 **Conflict of Interest Statement and Funding sources**

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517

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601

602

603 **Figure 1**

604 **Flowchart showing the number of patients at each stage of the trial.** Decisions to stop PN be-

605 fore the end of the trial were based on clinical judgement at the time unless the patient had died or

606 was discharged.

607 *Other includes no doctors available to sign the prescription (n=13), trial PN not available (n=20),

608 no useable venous catheter (n=23), already receiving PN at time of referral (n=28), PN not indi-

609 cated (n=14), low risk of refeeding (n=6), clinician decision not to recruit (n=3), referred too late to

610 be entered into trial (n=4), terminally ill (n=2), pregnant (n=1), immunocompromised (n=1), re-

611 quired too many calories (n=1), too young (n=1), only receiving 1 day PN (n=1), inappropriate to

612 approach (n=1), awaiting surgery (n=1), ongoing litigation against recruiting hospital (n=1), trans-

613 ferred to another hospital (n=1), no trial documents available at time of screening (n=1), not speci-

614 fied (n=83).

615 **Both patients withdrawn after collection of demographics: unsafe central venous access before

616 receiving any intervention (n=1), missed one day of trial PN (n=1).

617 ICU = Intensive Care Unit; (H)PN = (home) parenteral nutrition.

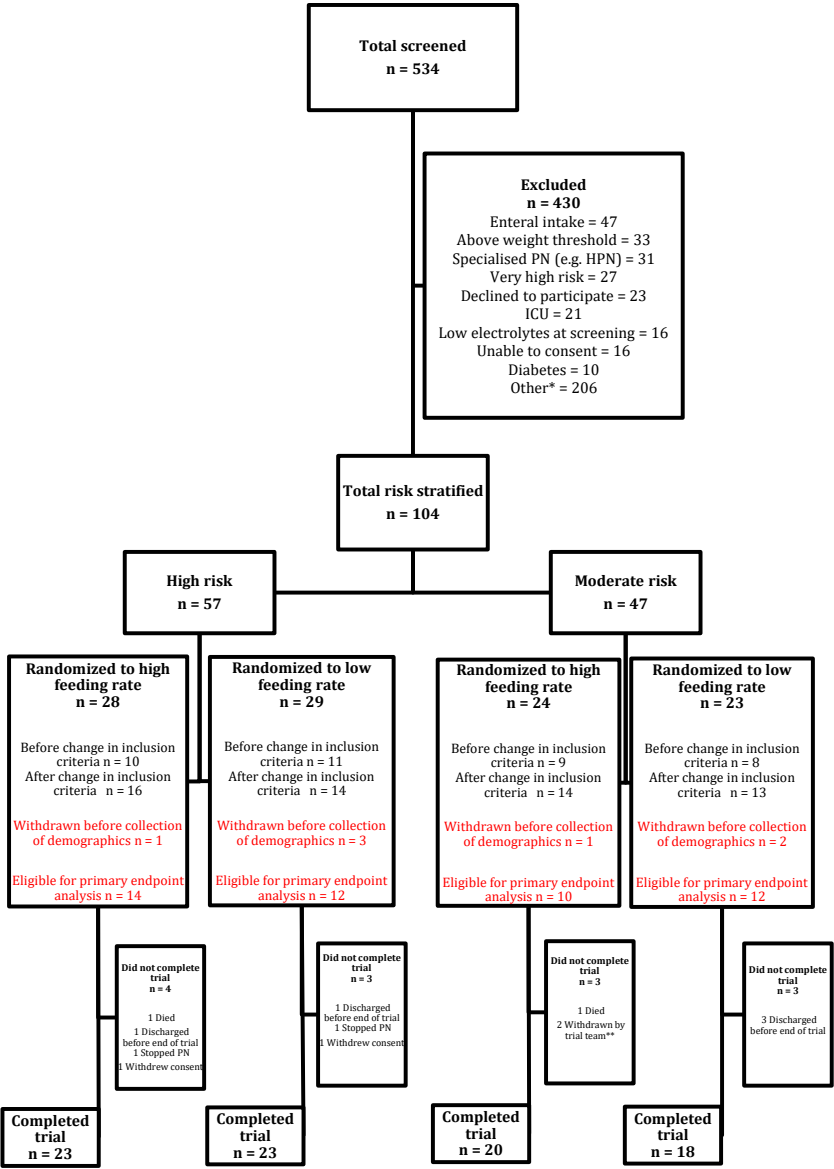
618 |

619 |

Commented [TA1]: It is not possible to Track Changes direct to the flowchart so they are listed here:

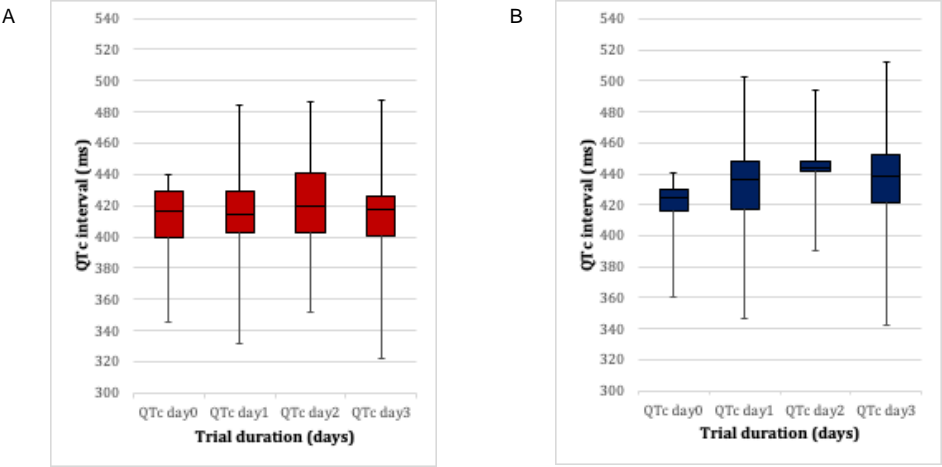
1) Box wording changed to 'Total risk stratified'

2) Addition of numbers eligible for primary endpoint analysis in each of the four randomisation boxes



621
622
623

624 **Figure 2**
625 **Change in QTc intervals over the first three days of feeding.** (A) Data for all patients (n=53)
626 with data at day 0 and then at least one further datapoint. (B) Data for patients (n=15) with pro-
627 longed QTc on days 1, 2, or 3. Data is presented as box and whisker plots demonstrating median,
628 interquartile range, and maximum/minimum values.



633 **Table 1**

634 NICE criteria to assess risk of refeeding syndrome in malnourished patients¹²

Moderate Risk	High Risk
One of: -BMI<18.5kg/m ² -Recent unintentional weight loss >10% -Little/no food intake >5 days	One of: - BMI<16kg/m ² - Recent unintentional weight loss >15% - Little/no food intake >10 days - Levels of K, Mg or PO ₄ low prior to feeding
	Two of: - BMI<18.5kg/m ² - Recent unintentional weight loss >10% - Little/no food intake >5 days - History of alcohol abuse or drugs including insulin, chemotherapy, antacids, or diuretics

635

636

637

638 **Table 2**

639 **Participant characteristics at baseline by rate of feeding.** Data are presented as n(%), mean (\pm
640 standard deviation), or median (with interquartile range) where appropriate. Numbers in square
641 brackets represent missing values. *Type 1 – self-limiting intestinal failure lasting less than 28
642 days, Type 2 – 28 days to 6 months, Type 3 - permanent intestinal failure³³. BMI = Body Mass In-
643 dex; IF = Intestinal Failure; PN = Parenteral Nutrition; MUST = Malnutrition Universal Screening
644 Tool; NICE = National Institute for Health and Care Excellence.

Characteristic	All patients n = 97	Rate = Low n = 47	Rate = High n = 50
Sex:			
- Female	40 (42%)	15 (38%)	25 (51%)
- Male	56 (58%)	32 (62%)	24 (49%)
	[1]		[1]
Age (yrs)	70 (57 – 77)	66 (58 – 75)	72 (54 – 78)
Usual weight (kg)	76.5 (66.0 – 85.2)	80.5 (65.8 – 86.0)	73.0 (67.7 – 84.7)
	[5]	[2]	[3]
Baseline weight (kg)	73.0 (60.5 – 80.4)	74.8 (60.6 – 82.0)	70.2 (60.9 – 77.9)
Weight loss (%)	6 (0 – 11)	6 (0 – 10)	5 (0 – 11)
	[5]	[2]	[3]
Usual BMI	25.9 (23.1 – 29.0)	26.1 (22.0 – 29.8)	25.9 (23.9 – 27.9)
	[5]	[2]	[3]
Baseline BMI	24.4 (22.0 – 27.3)	24.4 (22.0 – 27.6)	24.3 (21.6 – 26.4)
NICE risk category:			
- High	53 (55%)	26 (55%)	27 (54%)

- Moderate	44 (45%)	21 (45%)	23 (46%)
Type of IF*:			
- Type 1	86 (95%)	43 (98%)	43 (91%)
- Type 2	0 (0%)	0 (0%)	0 (0%)
- Type 3	5 (5%)	1 (2%)	4 (9%)
	[6]	[3]	[3]
Duration of PN (days)	7 (6 – 12)	7 (6 – 10)	8 (5 – 14)
	[6]	[3]	[3]
Length of stay (days)	27 (17 – 42)	30 (20 – 47)	26 (17 – 39)
	[5]	[3]	[2]
Days without nutrition before PN started	7 (5 – 10)	6 (5 – 9)	8 (6 – 11)
MUST category			
- Low	14 (15%)	6 (13%)	8 (17%)
- Medium	5 (5%)	4 (9%)	1 (2%)
- High	74 (80%)	36 (78%)	38 (81%)
	[4]	[1]	[3]
Diabetes mellitus	3 (3%)	2 (4%)	1 (2%)
	[2]	[1]	[1]

Table 3

Electrolyte and glucose values and insulin use at baseline by group. Data are n(%), or mean ± standard deviation. Numbers in square brackets represent missing values. Glucose values are capillary blood glucose measurements over the first 3 days of feeding.

Variable	All patients n = 97	Rate = Low n = 47	Rate = High n = 50
Potassium (mmol/l)	4.00 (0.50) [1]	3.97 (0.46)	4.03 (0.54) [1]
Magnesium (mmol/l)	0.84 (0.17) [1]	0.85 (0.18)	0.83 (0.16) [1]
Phosphate (mmol/l)	1.07 (0.30) [1]	1.04 (0.22)	1.10 (0.36) [1]
Glucose minimum (mmol/l)	5.8 (1.9) [17]	5.4 (1.4) [7]	6.2 (2.3) [10]
Glucose maximum (mmol/l)	7.5 (2.4) [22]	6.8 (2.1) [9]	8.2 (2.5) [13]
Insulin use:			
- Yes	3 (3%)	2 (4%)	1 (2%)
- No	92 (97%) [2]	44 (96%) [1]	48 (98%) [1]

653 **Table 4**

654 **Number of patients in each group meeting the primary outcome measure.** *Numbers shown do not include those with outcome at day 0. LLN =
655 lower limit of normal; K = potassium; Mg = magnesium; PO₄ = phosphate

656

	All patients*	Rate = Low	Rate = High	P-value
	n = 48	n = 24	n = 24	
Refeeding Syndrome/Feeding-induced hyperglycaemia				
(K/Mg/PO ₄ < LLN <u>or</u> glucose > 11 mmol/l requiring insulin)	22 (46%)	11 (46%)	11 (46%)	p>0.99

657

658

659 **Table 5**

660 **Number of patients in each group meeting the secondary outcome measures.** K = potassium; Mg = magnesium; PO₄ = phosphate

661

	All patients	Rate = Low	Rate = High	P-value
	n = 94	n = 46	n = 48	
Significant change in K/Mg/PO ₄	12	4	8	0.36
	All patients	Rate = Low	Rate = High	P-value
	n = 89	n = 43	n = 46	
Glucose > 11 mmol/l requiring insulin	4	2	2	>0.99

662

663 **Table 6**
664 **Occurrence of infections in the first 7 days of feeding by risk category and rate of feeding**

	Number of patients with infections	Number of infections
High rate/Moderate risk (n=23)	6	7
High rate/High risk (n=27)	4	4
Low rate/Moderate risk (n=21)	4	5
Low rate/High risk (n=26)	4	6

665
666

667 **Table 7**

668 **Descriptions of individual infections in the first 7 days of feeding.**

	Day	Suspected or confirmed?	Positive cultures?	Probable site
High rate/Moderate risk	1	Suspected	No	Urine
	2	Suspected	No	Line
	7	Suspected	No	Abdomen
	5	Confirmed	Yes	Line
	5	Confirmed	Yes	Chest
	5	Suspected	No	Line
	2	Suspected	No	Unknown
High rate/High risk	1	Confirmed	Yes	Urine
	5	Suspected	No	Line
	3	Suspected	No	Wound
	2	Confirmed	No	Wound
Low rate/Moderate risk	3	Confirmed	Yes	Urine
	5	Confirmed	Yes	Line
	2	Confirmed	Yes	Urine
	7	Confirmed	Yes	Line
	4	Suspected	Unknown	Line

Low rate/High risk	7	Confirmed	Yes	Line
	2	Confirmed	Yes	Wound
	6	Confirmed	Yes	Wound
	7	Confirmed	Yes	Urine
	3	Suspected	No	Abdomen
	5	Confirmed	Yes	Line

669

670

671

672 **Supplementary Methods**

673

674 Composition of trial PN

675 Both the higher and lower level feeds contained equal electrolyte, trace element and micronutrient
676 concentrations. In accordance with NICE guidelines, and in line with usual clinical care, all high risk
677 patients were given intravenous thiamine prior to initiation of feeding in the form of one pair of
678 Pabrinex[®] vials administered via peripheral or central catheter over 30 minutes. Thereafter, Pabrinex[®]
679 was given twice daily for a maximum of 6 doses. Moderate risk patients were not given thiamine in
680 line with guidelines at the time.

681

682 The specific composition of the trial PN was as follows:

	Low rate	High rate
Volume (mL)	2600	2600
Nitrogen (g)	7	14
Lipid (kcal)	500	1000
Glucose (kcal)	550	1100
Total kcal	1225	2450
Sodium (mmol)	80	80
Potassium (mmol)	80	80
Magnesium (mmol)	8	8
Calcium (mmol)	8	8
Phosphate (mmol)	17.5	17.5
Zinc (µmol)	200	200
Selenium (µmol)	0.8	0.8
Cernevit [™] (vials)	2	2

683

684 To meet the protocol-defined feeding levels, patients were administered 32 mL/kg per 24 hour period
685 irrespective of the regimen they were randomised to. The volume of PN administered was capped at
686 a maximum of 2548 mL per 24 hour period (equating to a maximum of 1200 kcal or 2400 kcal for
687 the low rate and high rate respectively).

688

689 Clinical Oedema Score

690 A score and stepwise reduction in calculation of body weight was required to prevent overfeeding in
691 oedematous patients which might have biased the trial results.

Oedema Score	Clinical extent of oedema	Reduction in body weight (%)
1	No oedema	0
2	Detectable	4
3	Significant but localised	7
4	Up to knee +/- arm	10
5	Up to trunk or thighs	15

692