PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Occurrence of refeeding syndrome in adults commenced on artificial nutrition support: prospective cohort study.
AUTHORS	Rio, Alan; Whelan, Kevin; Goff, Louise; Reidlinger, Dianne; Smeeton, Nigel

VERSION 1 - REVIEW

REVIEWER	Dr Stephen Taylor Research Dietitian Frenchay Hospital UK Competing interests: None
REVIEW RETURNED	05-Oct-2012

THE STUDY	My attached file details some areas where the authors need to clarify/link their description to the parameters they are describing. This happens several times and loses the meaning. It's easy to solve and would greatly improve clarity for the reader.
RESULTS & CONCLUSIONS	Interpretation: I queried 'causality' in my attached file. Authors need to check whether they mean and can prove this. Discussed: See comment in box above re. clarity.
GENERAL COMMENTS	

Page	Line	Comment
4	33	Overall the test is clearer with the exception of the Abstract: Results and several other places where there is no link between what you are describing and the parameter. Eg. shorten/clarify/link using: Poor nutritional intake for more than 10 days, weight loss >15% prior to recruitment and a low serum magnesium level at baseline **predicted refeeding syndrome with a** sensitivity of 66.7%; s**pecificity was >80% apart from weight loss of >15% which was 59.1%**. **Refeeding syndrome was only independently predicted by** low baseline serum magnesium (p=0.021). There were no deaths attributable to the refeeding syndrome but (5.3% 13/243) participants died during the feeding period and (28% 68/243) died during the hospital admission.
4	33	Insert: these...risk factors [ie. Presumably the ones

			you mentioned].
		56	What does “The risk factors for predicting the syndrome were weak and may inadvertently have contributed to malnutrition.” mean? Do you only mean starvation contributes to malnut? Obvious. Also low Mg? Or are you referring to permissive underfeeding contributing to malnut.
	5	9	Not 'earliest', say 'early'. Josephus described refeeding syndrome in AD70, though in less detail !!
	6	44/9	“:” not “;” before a list.
	7	4	Ref 9 is BMR equations. “Energy requirements were predicted from disease-specific stress factors based on the Schofield BMR equation.” You'd be better referencing PENG since they encompass both SF+BMR, though of course they are in error because the original SFs mostly came from Harris-Benedict BMR; there's not much you can do about the latter having used that approach.
	7	16	Clarify: “Severe shifts in serum electrolytes triggered an automatic electronic **response** on each participant’s blood results.” You mean **warning/caution**?
	7	56	Calculated, how?
	8	45	Delete: “Potassium was the most frequently supplemented electrolyte followed by magnesium.” The next sentence says this + more but re-order it.
	9	2	Based on your criteria? Say so.
	9	16	**Independently** predicted
	9	40	“50mmol IV phosphate” would be a better description. There are other 'polyfusors'.
	10	7	“50mmol IV phosphate” would be a better description. There are other 'polyfusors'.

10	42	Shorten: The three facet criteria provided unequivocal confirmation of the major clinical characteristics in those participants who developed the essential features of the syndrome. Occurrence of refeeding syndrome in participants with risk factors was 2% and was not associated with mortality. The three major facets of the diagnostic criteria; To: Refeeding sydrome was diagnosed from three unequivocal clinical criteria:
11	27	“but substantially different energy intakes which exceeded guideline recommendations” do you mean recommendations to keep nutritional input low? Because if you are saying these patients had intakes higher than refeeding recommendations, this might be taken as the cause of RFS.
12	44	revealed **that**
12	49	You need to re-phrase. “This supports our interpretation that 'risk factors' are weak predictors of RFS.”
13	9	**may have been** causal. Would **glucose** infusion be better.
13	58	Is 'causal' proven/ conjecture?
16		Limit decimal places to 0 (kcal) or 1 (other).
18		Limit decimal places to 0 (kcal)
19	14-18	Missing “/”kcal etc.

Page	Line	Comment
3		Capital letter after colon.
3		Key messages: Bullet point.
4	31	Replace 'authenticated' with 'diagnosed'.
4	36	• 'risk factors'? Readers won't know what these are at this point, tell them.
4	42	I'd rather try: Mortality was not attributed to refeeding syndrome either during feeding (5.3%, 13/243) or hospital admission (28.0%, 68/243).
		Overall: Needs to be more emphasis that refeeding could not be accurately predicted, occurred in spite of hypocaloric feeding and treatable and that this evidence questions the merit of current guidelines that advise slow introduction of feeding and therby increase risk of malnutrition.
5	7	• Instead of: refeeding orally, enterally or parenterally..... • try: oral, enteral or parenteral refeeding.
6	13	• 'Systematic literature review': Do you give details?
6	53	• How were energy prescriptions calculated, eg. BMR + stress factors and their reference.
7	42	• 'nutritionist' or really a dietitian; many of the former are not adequately qualified.
7	49	• 'positive refeeding syndrome' Readers would find 'refeeding syndrome risk' clearer.

	8	16	• After “)” insert “,”
	8	31	• participants
	8	38	of participants
	8	40	Q: Is there a reason for such high mortality on wards relative to HDU/ICU areas where you would expected it to be higher.
	8	58	• Try instead: Only low baseline magnesium significantly (p = 0.021) predicted refeeding syndrome; other independent variables were not significantly associated. • [NB. There's a srong move away from terming associations significant vs ns. Rather clinical importance, 95%CI are being used.
	9	18	• Just to be clear, were these single IV and oral doses: state. • State Pabrinex 1+2 as it comes in two separate parts.
	9	24	• Infused over how long? Unless it's a different polyfusor, our provides 50mmol per 500mL.
	12	11	• 'IV dextrose...' This sentence isn't clear. Are you say IV glucose may help precipitate PO4 levels <0.7mM and has been associated with resp failure when PO4 levels fell to between 0.2-0.36mM? • Please clarify.
	12	33	• 100mmol/L, oral/enteral phosphate sandoz is 16mmol/tablet.
			•
			•
			•
			•
	18	6 to 15	• Bullet point to make each point stand out separately.
			•

REVIEWER	Prof. Michael Hiesmayr Div. CTV Anesthesia and Intensive Care Medical University Vienna Austria no conflict of interest
REVIEW RETURNED	22-Oct-2012

THE STUDY	This is the second version of the manuscript that allows a much better assessment. The suggested shortening of the reporting in the first review has not been accepted but still appears to be advantageous. Two main issues need to be addressed: 1. What effect has the exclusion of approximately 50 % of the eligible? (see details below) This could be a source of selection bias with underreporting of outcome. 2. The measurement of criteria 2 & 3 (peripheral edema/heart failure and disturbed organ function) is not clear. This potential measurement bias could explain the low proportion of refeeding syndrome found. ad 1: It is still unclear whether all patients referred for artificial nutrition during a given period have included. The sentence "Researchers were alerted of potential new participants....." needs critical review against the services work reports since 484 eligible patients over a 3 year period despite including intermediate care and ICU. A small ICU (8 beds) admits about 300-500 patients per year and at least half need artificial nutrition. 50% have been excluded for reasons that could be related to refeeding syndrome. 22 died within 24 hours, many cases could be reffeeding syndromes since the most severe forms occur very early. 86 did not consent (if those were the more severe ill or unable to communicate already within 48 hours of commencement of artificial nutrition could also be a sign of nutrition related complications. Furthermore only patients with a risk profile (n=133) were analysed for the amount of nutrition subgroup analysis. the reason is unclear. ad. 2 3 criteria were used for the diagnosis of refeeding syndrome. One is lab values and two are clinical. Were the clinical signs based on direct observation or chart review? I'm concerned about the possibility that organ failure leading to death because 13 died during nutrition and an other 55 thereafter. It would be helpful to display a timeline with the frequency of clinical direct observations. The abstract background should state in line 4 ....response to nutrition ..... to be compatible with line 49 where hypocaloric should skipped. I do not know why the authors state "nutrition and hydration" . Refeeding syndrome related to hydration without energy is clearly not refeeding syndrome but "rehydration syndrome". For the subgroup analysis it would be intersting to check for those that received low and high amounts of electrolytes in addition to energy. I think it is not appropriate to report sensitivities if only 3 cases are identified. The STROBE statement is now complete but the sources of bias are still not properly addressed.
RESULTS & CONCLUSIONS	The results may answer the research question if problems of selection and measurement bias can be clarified.

	Presentation of data: Table 1: no CI if median is used IQR is sufficient and appropriate. Table 2: Were all denominators for measurements 243? I doubt since some may have died or therapy stopped. please the n for measurements. Table 3: Inappropriate for 3 cases. What does the CI mean ? It is clearly not the CI of the Sens or Spec. e.g. BMI < 16 CI 22.95-24.4 Table 4: indicate what group 1 and group 2 is e.g. caloric intake <> 800 at begin of nutrition. Table 5: omit no additional information again to many statistics. Table 6: Did the patients receive Electrolytes yes or no, phosphate yes or no. Further details in the text: page 4 line 7 it is not "prerequisite" but "risk factor" page 4 line 16 usually "missing electrolytes" also. use "enteral and parenteral feeding" AND NOT "enteral and parenteral tube feeding" because there is no parenteral tube. page 6 line 31 : Does this mean that the first electrolytes could have been measured after 72 hours of feeding? page 10 line 13: do not use any commercial names "pabrinex" that may be unknown to reader outside UK. page 12 line 18-27: should be understood to mean glucose without electrolytes. Authors state elsewhere that starvation should be prevented. this is contradictory.
REPORTING & ETHICS	Possible source of bias (selection, measurement) are not addressed completely.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1.Dr Stephen Taylor

1. My attached file details some areas where the authors need to clarify/link their description to the parameters they are describing. This happens several times and loses the meaning. It's easy to solve and would greatly improve clarity for the reader.

Interpretation: I queried 'causality' in my attached file. Authors need to check whether they mean and can prove this.

Reviewer 1. Dr Stephen Taylor.

P4, L33 Overall the test is clearer with the exception of the Abstract: Results and several other places where there is no link between what you are describing and the parameter. Eg. shorten/clarify/link using: Poor nutritional intake for more than 10 days, weight loss >15% prior to recruitment and a low serum magnesium level at baseline predicted refeeding syndrome with a sensitivity of 66.7%:

specificity was >80% apart from weight loss of >15% which was 59.1%. Refeeding syndrome was only independently predicted by low baseline serum magnesium (p=0.021). There were no deaths attributable to the refeeding syndrome but (5.3% 13/243) participants died during the feeding period and (28% 68/243) died during the hospital admission.

Response. This has been changed to.

133 participants had one or more of the following risk factors: BMI < 16 - 18.5 $\underline{\geq}$ (kg/m^2), unintentional weight loss >15% in the preceding three – six months, very little or no nutritional intake >10 days, history of alcohol or drug abuse and low baseline levels of serum potassium, phosphate or magnesium prior to recruitment. Poor nutritional intake for more than 10 days, weight loss >15% prior to recruitment and low serum magnesium level at baseline predicted the refeeding syndrome with a sensitivity of 66.7%: specificity was >80% apart from weight loss of >15% which was 59.1%. Baseline low serum magnesium was an independent predictor of the refeeding syndrome (p=0.021). Three participants (2% 3/243) developed severe electrolyte shifts, acute circulatory fluid overload and disturbance to organ function following artificial nutrition support and were diagnosed with refeeding syndrome. There were no deaths attributable to the refeeding syndrome but (5.3% 13/243) participants died during the feeding period and (28% 68/243) died during the hospital admission. Death of these participants was due to cerebrovascular accident, traumatic injury, respiratory failure or terminal end of life conditions.

P 4, L33

Insert: these...risk factors [ie. Presumably the ones you mentioned].

Response. This has been changed to

133 participants had one or more of the following risk factors: BMI < 16 - 18.5 $\underline{\geq}$ (kg/m^2), unintentional weight loss >15% in the preceding three – six months, very little or no nutritional intake >10 days, history of alcohol or drug abuse and low baseline levels of serum potassium, phosphate or magnesium prior to recruitment.

P4, L56

What does “The risk factors for predicting the syndrome were weak and may inadvertently have contributed to malnutrition.” mean? Do you only mean starvation contributes to malnut? Obvious. Also low Mg? Or are you referring to permissive underfeeding contributing to malnut.

Response. This has been changed to.

Predictors for refeeding syndrome were starvation and baseline low serum magnesium concentration. Intravenous carbohydrate infusion prior to artificial nutrition support may have precipitated the onset of the syndrome.

P5, L 9

Not 'earliest', say 'early'. Josephus described refeeding syndrome in AD70, though in less detail !!

Response. This has been changed to

A key risk factor for the syndrome is starvation with early published reports being prisoners of

war.[2]

P6, L44/9

":" not ":" before a list.

Response. This has been changed to

Exclusion criteria were:

P7, L4.

Ref 9 is BMR equations. "Energy requirements were predicted from disease-specific stress factors based on the Schofield BMR equation." You'd be better referencing PENG since they encompass both SF+BMR, though of course they are in error because the original SFs mostly came from Harris-Benedict BMR: there's not much you can do about the latter having used that approach.

Response. This has been changed to

Energy prescriptions for each participant were estimated by the dietetic speciality who used basal metabolic rate and stress related factors.[9] (the reference has been changed).

P7, L16.

Clarify: "Severe shifts in serum electrolytes triggered an automatic electronic response on each participant's blood results." You mean warning/caution?

Response. This has been changed to

The primary outcome of interest in this study was the occurrence of refeeding syndrome. The secondary outcome was analysis of the risk factor at predicting refeeding syndrome. The tertiary outcome measure was mortality due to refeeding syndrome and all cause mortality.

Data Collection

Baseline serum electrolyte concentrations were recorded within 24 hours of study enrolment then every third day for a maximum of 15 days during the period of artificial nutrition support. Serum electrolytes were not recorded when artificial nutrition support was stopped. Serum electrolyte concentrations were obtained from the hospital electronic in-patient system (iSoft, v1.0 Oxon, England).

P7, L56

Calculated, how?

Response. This has been changed.

To determine which participants had poor nutritional intake prior to artificial nutrition support, dietary caloric intake was calculated by a research assistant. Each participant was asked to recall their dietary food and fluid intake in the 10 days preceding recruitment into the study. Food portion sizes were estimated from a reference guide[10] and total daily energy intake was calculated using a nutritional analysis software package (Compeat, Oxon, England)[11]

P8, L45

Delete: “Potassium was the most frequently supplemented electrolyte followed by magnesium.” The next sentence says this + more but re-order it.

Response. This has been changed to

A total of 2765 serum electrolyte results were recorded, 1014 for potassium, 1006 for phosphate and 745 for magnesium. The total number of participants who received electrolyte supplementation were potassium 71, magnesium 52 and phosphate 49.

P9, L2

Based on your criteria? Say so.

Response. This has been changed to.

Using the criteria in Box 2 the research team confirmed the diagnosis of refeeding syndrome in three participants, asymptomatic electrolyte depletion in two participants and the remaining 238 participants did not develop symptoms.

P9, L16

Independently predicted

Response. This has been changed to.

Low baseline serum magnesium (p=0.021) independently predicted refeeding syndrome: other independent variables were not significantly associated.

P9, L40

40 “50mmol IV phosphate” would be a better description. There are other 'polyfusors'

Response. This has been changed to

Day three serum phosphate was recorded at 0.33 mol/L and 50 mmol/L intravenous phosphate in 500ml was infused over 12 hours

P10, L 7

“50mmol IV phosphate” would be a better description. There are other 'polyfusors'.

Response. This has been changed to

Intravenous phosphate replacement was commenced with 50 mmol/L phosphate in 500ml.

P10, L42.

Shorten: The three facet criteria provided unequivocal confirmation of the major clinical characteristics in those participants who developed the essential features of the syndrome. Occurrence of refeeding syndrome in participants with risk factors was 2% and was not associated with mortality. The three major facets of the diagnostic criteria:

To: Refeeding syndrome was diagnosed from three unequivocal clinical criteria:

Response. This has been changed to

This study applied a three facet diagnostic criteria to confirm the occurrence of refeeding syndrome in adults commenced on artificial nutrition support. This unequivocal clinical diagnostic criteria comprised: defined severe serum electrolyte concentration, acute circulatory fluid overload and organ dysfunction. These symptoms occurred within 72 hours of hypocaloric artificial nutrition support in three participants identified at risk.

P11, L27

"but substantially different energy intakes which exceeded guideline recommendations" do you mean recommendations to keep nutritional input low? Because if you are saying these patients had intakes higher than refeeding recommendations, this might be taken as the cause of RFS.

Response. This has been changed to.

However, the subgroup analysis revealed that one group received more energy sooner and for longer but did not develop symptoms. Applying the diagnostic criteria in Box 2 revealed the risk factors[3] for predicting refeeding syndrome were weak.

P12, L 44.

revealed **that**

Response. This has been changed to.

However, the subgroup analysis revealed that one group received more energy sooner and for longer but did not develop symptoms.

P12, L49

You need to re-phrase. "This supports our interpretation that 'risk factors' are weak predictors of RFS."

Response. This has been changed to.

Applying the diagnostic criteria in Box 2 revealed the risk factors[3] for predicting refeeding syndrome were weak.

P13, L 9.

may have been causal. Would glucose infusion be better.

Response. This has been changed to.

Infusion of intravenous glucose potentially suppressed gluconeogenesis which caused a switch to glycolysis in these three participants. This switch caused insulin to be released causing rapid cellular uptake of serum phosphate, potassium and magnesium electrolytes. We propose that the initial infusion of glucose in the three starved participants potentially triggered the metabolic sequence that resulted in the development of the syndrome.

P13, L58

Is 'causal' proven/ conjecture?

Response. This has been changed to.

However, intravenous glucose infusion prior to artificial nutrition support may have triggered the onset of the refeeding syndrome.
P16 Limit decimal places to 0 (kcal) or 1 (other). **P18** Limit decimal places to 0 (kcal)
Response. These changes have been made
P19, L14-18 Missing "/"kcal etc.
Responce. These changes have been made.

Reviewer 2. Prof. Michael Hiesmayr

Comment
What effect has the exclusion of approximately 50 % of the eligible? (see details below) This could be a source of selection bias with underreporting of outcome.
Response. This has been changed to. The results have a limited external validity due to the inherent bias of the narrow selection criteria. This selection bias effect and exclusion of participants who were able

to take oral nutritional intake may explain the low occurrence of refeeding syndrome recorded in the study population. A large number of potentially eligible participants could not be recruited due to difficulty obtaining consent. A further reduction in potential participants was death within 24 hours of commencing artificial nutrition support. The cause of death in these participants was due to their underlying medical condition of cerebrovascular accident, traumatic injury, respiratory failure due to degenerative neurological disease, organ failure or end of life causes.

The measurement of criteria 2 & 3 (peripheral edema/heart failure and disturbed organ function) is not clear. This potential measurement bias could explain the low proportion of refeeding syndrome found.

Response. This has been changed and is now included in the methods section.

Each participant's medical team diagnosed refeeding syndrome using serum electrolyte shifts and observed clinical complications of acute circulatory fluid overload and organ dysfunction. The medical teams documented this information in the participant's medical record as daily clinical observations and treatment. The research team used the participant's medical record to confirm that symptoms occurred from the onset of artificial nutrition support recording observations daily and serum electrolyte concentrations every third day from baseline.

It is still unclear whether all patients referred for artificial nutrition during a given period have included. The sentence "Researchers were alerted of potential new participants....." needs critical review against the services work reports since 484 eligible patients over a 3 year period despite including intermediate care and ICU. A small ICU (8 beds) admits about 300-500 patients per year and at least half need artificial nutrition.50% have been excluded for reasons that could be related to refeeding syndrome. 22 died within 24 hours, many cases could be reffeeding syndromes since the most severe forms occur very early. 86 did not consent (if those were the more severe ill or unable to communicate already within 48 hours of commencement of artificial nutrition could also be a sign of nutrition related complications.

Response. This has been changed to.

Participants commenced on enteral or parenteral artificial nutrition support were eligible to be recruited if they met the inclusion criteria. The inclusion criteria was: adults >18 years of age commenced on artificial nutrition support for the first time during that hospital admission. Exclusion criteria were: previous artificial nutrition support during the hospital admission, artificial nutrition support commenced at the previous institution, participants <18 years of age or failure to obtain consent/assent due to serious illness or lack of next of kin.

Furthermore only patients with a risk profile (n=133) were analyzed for the amount of nutrition subgroup analysis. the reason is unclear.

Response. This has been changed to.

A subgroup analysis of the 133 participants with risk factors for refeeding syndrome was performed to provide data on the secondary outcome measure of the study. This subgroup analysis stratified these 133 participants according to their baseline energy intake as: Group 1 <800 kcal day versus Group 2 >800 kcal day, Flow chart 1. This stratification of baseline energy intake allowed hypocaloric versus normal caloric intake

to be analysed.

3 criteria were used for the diagnosis of refeeding syndrome. One is lab values and two are clinical. Were the clinical signs based on direct observation or chart review? I'm concerned about the possibility that organ failure leading to death because 13 died during nutrition and an other 55 thereafter.

Response. This has been changed to.

The medical teams documented this information in the participant's medical record as daily clinical observations and treatment.

A further change to clarify this is

Since death occurred within 24 hours of starting artificial nutrition support we cannot exclude complications of refeeding syndrome as a contributing factor.

It would be helpful to display a timeline with the frequency of clinical direct observations.

Response. This has been changed to.

We have included information on the frequency of clinical observations and electrolyte recording of both the medical teams and the research team as follows.

The medical teams documented this information in the participant's medical record as daily clinical observations and treatment. The research team used the participant's medical record to confirm that symptoms occurred from the onset of artificial nutrition support recording observations daily and serum electrolyte concentrations every third day from baseline.

The abstract background should state in line 4 ....response to nutrition ..... to be compatible with line 49 where hypocaloric should skipped.

I do not know why the authors state "nutrition and hydration" . Refeeding syndrome related to hydration without energy is clearly not refeeding syndrome but "rehydration syndrome".

Response. The abstract background has been rewritten as.

Refeeding syndrome is a potentially life threatening condition characterised by severe intracellular electrolyte shifts, acute circulatory fluid overload and organ failure. The initial symptoms are non specific but early clinical features are severely low serum electrolyte concentrations of potassium, phosphate or magnesium. Risk factors for the syndrome include starvation, chronic alcoholism, anorexia nervosa and surgical interventions that require lengthy periods of fasting. The causes of the refeeding syndrome are excess or unbalanced enteral, parenteral or oral nutritional intake. Prevention of the syndrome includes identification of individuals at risk, controlled hypocaloric nutritional intake and supplementary electrolyte replacement.

Also Artificial nutrition and hydration **has been changed to** artificial nutrition support throughout the manuscript.
For the subgroup analysis it would be interesting to check for those that received low and high amounts of electrolytes in addition to energy.
Response. This has been addressed. The authors have added Table 5. Total number of participants who received electrolyte supplementation for the two risk groups.
I think it is not appropriate to report sensitivities if only 3 cases are identified.
Response. This has been changed. The Sensitivities table has been removed although we include the data values in the results section.
The STROBE statement is now complete but the sources of bias are still not properly addressed.
Response. This has been changed. The STROBE document section on Bias has been rewritten.
The results may answer the research question if problems of selection and measurement bias can be clarified.
Response. This has been changed. Selection and measurement bias have been addressed and are highlighted in bold within the manuscript.
Table 1: no CI if median is used IQR is sufficient and appropriate.
Response. This has been changed. Median and IQR values have been added.
Table 2: Were all denominators for measurements 243? I doubt since some may have died or therapy stopped.
Response. This has been changed. The authors have clarified the totals for the denominator in the methods section. The n values of total number of electrolyte values recorded has been added to Table 2.
Table 3: Inappropriate for 3 cases. What does the CI mean ? It is clearly not the CI of the Sens or Spec. e.g. BMI < 16 CI 22.95-24.4
Response. This has been changed. Table 3 has been removed.
Table 4: indicate what group 1 and group 2 is e.g. caloric intake <> 800 at begin of

nutrition.
Response. This has been changed. The heading now include Group 1 is < 800kcal/day and Group 2 is >800kcal/day
Table 5: omit no additional information again to many statistics.
Response. This has been changed. Table 5 has been removed.
Table 6: Did the patients receive Electrolytes yes or no, phosphate yes or no.
Response. This has been changed. Electrolyte replacement of participants x,y and z is now included in the table.
page 4 line 7 it is not "prerequisite" but "risk factor"
Response. This has been changed. A key risk factor for the syndrome is starvation with early published reports being prisoners of war.[2]
page 4 line 16 usually "missing electrolytes" also.
Response. This has been changed. The modern definition of refeeding syndrome is life threatening severely low serum electrolytes concentrations, fluid and electrolyte imbalance and disturbance of organ function resulting from over rapid or unbalanced nutrition support.[3]
use "enteral and parenteral feeding" AND NOT "enteral and parenteral tube feeding" because there is no parenteral tube.
Response. This has been changed. The term enteral or parenteral tube feeding has been replaced with Either artificial nutrition support or enteral or parenteral feeding.
page 6 line 31 : Does this mean that the first electrolytes could have been measured after 72 hours of feeding?
Response. This has been changed. Baseline serum electrolyte concentrations were recorded within 24 hours of study enrolment then every third day for a maximum of 15 days during the period of artificial nutrition support.
page 10 line 13: do not use any commercial names "pabrinex" that may be unknown to reader outside UK.
Response. This has been changed. Pabrinex has been replaced with, **intravenous dose of a standard vitamin B and C**

formulation.
page 12 line 18-27: should be understood to mean glucose without electrolytes. Authors state elsewhere that starvation should be prevented. this is contradictory.
Response. This has been changed. The impact of intravenous glucose infusion, without adequate and repeated electrolyte replacement in the three diagnosed participants, cannot be under estimated. The results of the present study indicate that glucose infusion should be avoided in starved individuals who require fluid and nutritional treatment. The finding that intravenous glucose infusion in starved individuals may initiate the refeeding syndrome requires further research.
Possible source of bias (selection, measurement) are not addressed completely.
Response. This has been changed. The paragraph discussing Bias in the manuscript and the section in the STROBE document have been rewritten and incorporate many of the reviewer's comments and suggestions.

VERSION 2 – REVIEW

REVIEWER	Stephen J. Taylor Research Dietitian Frenchay Hospital Bristol. BS16 1LE. UK.
REVIEW RETURNED	04-Dec-2012

GENERAL COMMENTS	Tiny correction: Phosphate content of polyfusor is 50mmol per 500mL not per L.