PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A protein-enriched, milk-based supplement to counteract sarcopenia in acutely ill geriatric patients offered resistance exercise training during and after hospitalization: study protocol for a randomized, double-blind, multicenter trial
AUTHORS	Gade, Josephine; Beck, AM; Bitz, Christian; Christensen, Britt; Klausen, Tobias; Vinther, Anders; Astrup, Arne

VERSION 1 – REVIEW

REVIEWER	Vincenzo Malafarina Department of Nutrition, Food Science and Physiology, School of Pharmacy and Nutrition, University of Navarra, Pamplona, Spain
REVIEW RETURNED	28-Aug-2017

GENERAL COMMENTS	Dear Editor Thanks to give me the possibility to review this paper. The aim of this study is to demostrate an improve in 30-second chair-stand test (30-s CST). I think that the paper need some corrections, and I hope that the authors can modify the protocol to improve the impact of results. Comments: 1. Title is different from the primary outcome. In the title the authors talk about sarcopenia but primary outcome is improves 30-s CST. Furthermore, the protocol available in Clinical Trials shows that BIA will be performed on a sub-population of 30 subjects. So, how do the authors think of doing the sarcopenia diagnosis? 2. Abstract. I believe that the authors should better specify the characteristics of nutritional intervention: dose, type of preparation. I also believe that the training program should be better specified: days a week, exercises. 3. Introduction a. Very long. Lower it by 30-40%. b. Line 72. I think that the age is not the cause of bed rest. As a clinician I think that the problema is that when a patient is admitted to a hospital, he or she think the he or she need to stay in the bed to improve his or her health status. It is a big mistake. Please, reformulte the sentence. 4. Methods a. The authors says that they will include 165 patients. In the protocol in Clinicaltrial define sample size as 120. Which is the correct value?

	b. Page 7 line 146. The authors says that the intervention group will get a total of 27.5 g extra protein. But few lines before, (line 140 of the same page) you can read that there are 10g of protein per 100 ml, and patients recibe 250 ml per day. Probably I wrong, but the total ammount is of 25 g. c. Line 155. Patients can take nutritional supplementation. This aspect should be taken into account at the time of calculating the sample size. d. Page 10, line 220. For the same reason stated in the previous point, hospitalization in a rehabilitation unit is an important factor of confusion. This should be taken into account at the time of calculating the sample size. e. Primary endpoint. The authors comment that the primary goal is the 30th CST. What is the goal really? What should be the improvement to be considered positive? Are there normal values for this test? f. Line 255 and later. Patients who are unable to get up alone should be excluded, or anyway, these patients should form a subpopulation. It is possible that among patients who can not get up without using their arms there are people who can not get up from the chair before the hospitalization (patient with stabilized discapacity). It is impossible to expect improvement in these patients. g. Secondary endpoint, line 261. You talk about BIA. But in the protocol available in Clinical Trials, you affirm that only in a subpopulation of 30 patients you assess BIA. Can you clarify, please? h. In general for secondary endpoint, please, define better the objective. For example you talk about BIA. Which is the endpoint, an increase of LBM? If yes, which is the limit that you utilize to define the improve? The same for the followings secondary endpoint (hand grip, gait speed, and others). i. Line 313. For sarcopenia I think that there is a problem. The prevalence of sarcopenia in the community older adults is about 20-30%. I think that at baseline moment you will find patients with sarcopenia and patients without, and probably the evolution of these two types of patients will be different. Have you considered the possibility of correcting randomization for sarcopenia? j. Statistics. Power calcilation. In the studies to be used to calculate the sample size, significant improvements are observed both in the intervention group and in the control group. The authors to whom you refer did not get significant differences between the two groups. Considering the type of intervention of your study (protein supplementation), I believe that you should make BIA on all patients and consider increasing of fat free mass as main objetive. Considering the limitation of BIA I think you should recalculate the sample size and if possible increase the number of subjects included.

REVIEWER	Michael Corcoran Merrimack College USA
REVIEW RETURNED	15-Sep-2017

GENERAL COMMENTS	It would be helpful if the authors further clarify the novelty of this study. There have been quite a few studies on resistance training / protein supplementation for older adults recovering from events requiring hospitalization. Confirm if the novelty lies mainly in the setting (conducting the study in a hospital setting rather than upon discharge), the degree of potential impairment of these patients/participants, or some other aspect not mentioned here. Few details are provided on protein quality. What kind of protein will be used? Whey protein concentrate, whey protein isolate? What is the essential amino acid content of this supplement (particularly Leucine)? Under Study Population, line 126, I would include health deterioration. This is a common reason for both withdrawal and a lack of a response from an RT program (with or without protein supplementation). This should be controlled for as much as possible. The authors mention that nutritional risk will be assessed at baseline. Will this be assessed at any other time point? Previous research with similar populations has shown a measurable deterioration in nutritional status over a span of 6-months that may have influenced the responsiveness to RT (despite protein supplementation). Line 143: Minor correction – January 2018 (not January 2017). Line 146: Clarify why this amount of protein was chosen. Some evidence suggests a positive response from 35-40 grams of whey immediately following an RT program. This is not critical, but when striving for a maximal anabolic effect, the extra 10-15 grams may be worth considering. A nitrogen balance assessment may be worth considering – if feasible. Lines 348-349: Will there be certain mandated days for diet assessment inclusion? (I.e. of the four days, must include one weekend day?) Additionally, assessing resting metabolic rate may help somewhat with identifying under-reporting. Lines 356-357: Briefly explain the interpretation of the activity level scale. (1 presume least active, 5 most, etc..) Similarly, a brief explanation of how nutrition risk screening (NRS2002) will be performed and interpreted (rather than just cite Kondrup J et al's paper) would be helpful. Will physical activity level after discharge be controlled for? With this population, there is a near certainty of the presence of numerous and severe co-morbidities. Lines 461 – the authors acknowledge a weakness in the lack of supervision of RT following discharge. I have concerns over safety. There should be some acknowledgement of supervision by a care-provider or guardian as the participant is performing an RT routine at home given their current state of health. Along these lines, will physician and guardian consent be required of all participants? I am also inclined to wonder if a licensed medical nutrition therapist should be consulted / involved throughout this study (if one is not affiliated with it yet).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
1. Title is different from the primary outcome. In the title the authors talk about sarcopenia but primary outcome is improves 30-s CST. Furthermore, the protocol available in Clinical Trials shows that BIA will be performed on a sub-population of 30 subjects. So, how do the authors think of doing the sarcopenia diagnosis?

Response: We acknowledge that we do not mention the primary endpoint (30-s CST/lower extremity strength) in our title, but as sarcopenia is defined as the loss of muscle mass and strength, which are both measured in this study, we find it appropriate to use the word 'sarcopenia' in the title.

The BIA-measurements are performed on all participants at all assessments (explained at page 13). The diagnosis of sarcopenia at baseline is determined based on the EWGSOP-definition (along with measures of 4-m gait speed and hand grip strength) – this has been clarified and added to page 16 line 374-377 (Sarcopenia is assessed according to the definition proposed by the European Working Group on Sarcopenia in Older People (EWGSOP). This is based on the assessments of LBM (measured by BIA), muscle strength (measured HGS), and physical performance (measured by 4-m gait speed)).
A sub-study, separate from this study, is validating the BIA against DXA scanning in 30 subjects.

2. Abstract. I believe that the authors should better specify the characteristics of nutritional intervention: dose, type of preparation. I also believe that the training program should be better specified: days a week, exercises.

Response: Corrections trying to better specify the intervention have been made as detailed as possible, within the allowed word count accepted in the abstract. To allow for this extra explanation, the abstract has been shortened elsewhere (page 2).

3. Introduction
a. Very long. Lower it by 30-40%.

Response: The introduction has been shortened from 867 to 426 words (page 4-5).

b. Line 72. I think that the age is not the cause of bed rest. As a clinician I think that the problema is that when a patient is admitted to a hospital, he or she think the he or she need to stay in the bed to improve his or her health status. It is a big mistake. Please, reformulte the sentence.

Response: We agree with you. The sentence has been reformulated. The point we want to make clear in the introduction is that bed-rest accelerates the loss of LBM. The sentence now reads: (Acute illness might result in stress metabolism which further increases the loss of protein and the anabolic resistance in older adults, leading to increased loss of lean body mass (LBM) [5], and this is further accelerated by bed-rest during hospitalization.) (Page 4, line 74-76)

4. Methods
a. The authors says that they will include 165 patients. In the protocol in Clinicaltrial define sample size as 120. Which is the correct value?

Response: Thank you for pointing this out. We made an amendment to the protocol (which has been approved by the relevant ethical committee) increasing the number of participants from 120 to 165, as we saw a pattern in the first participants where the compliance was lower than anticipated. Thus 165 is the correct value. We will make sure this is corrected in clinical.trials.gov.

b. Page 7 line 146. The authors says that the intervention group will get a total of 27.5 g extra protein. But few lines before, (line 140 of the same page) you can read that there are 10 g of protein per 100 ml, and patients recibe 250 ml per day. Probably I wrong, but the total ammount is of 25 g.

Response: Thank you very much for pointing out this inconsistency! The correct amount of protein per 100 ml is 11 g – 10.5 g whey protein concentrate and 0.5 g casein – adding up to 27.5 g per daily dose of 250 ml. This has been corrected in the revised manuscript at page 7 line 155.

c. Line 155. Patients can take nutritional supplementation. This aspect should be taken into account at the time of calculating the sample size.

Response: We understand your point of view, that if some participants in the control group receive the same amount of protein supplementation as the participants in the intervention group, then extra participants should be recruited to allow us to find a significant effect. This said, the participants in the 'protein group' will be instructed to take any additional supplements on a given day only after intake of the 'study beverages' (explained in the manuscript at page 8, line 178-181) – thus even if some participants in the control group receives nutritional supplementation it is still expected that the protein group will receive more protein. Furthermore, it is expected that those who are prescribed nutritional intervention eat insufficient and thus, when considered all together, still have a rather low total protein intake. As mentioned in the manuscript under the head line 'Protein and energy intake' (page 16-17) we make dietary records (4 days during hospitalization) and 4 times 24-h recall interviews (12 weeks post discharge) during the study intervention, as we know that this can be a confounding factor. Worth mentioning is also that in the power calculation, the mean difference used in the calculation of study sample size, is from a study where all the participants are exercise training. They conclude that a change of 2-2.6 is of clinical importance/relevance, and we have chosen a mean difference of 2, resulting in a bigger sample size than if we had chosen e.g. 2.6.

d. Page 10, line 220. For the same reason stated in the previous point, hospitalization in a rehabilitation unit is an important factor of confusion. This should be taken into account at the time of calculating the sample size.

Response: As the participants are training in both the protein- and the control group, and any training performed at a rehabilitation center can replace one self-training session, it is not considered a major confounding factor. Thus, it has not been taken into account at the time of performing the sample size calculation. However, we do register 'daily activity level' for all participants, as we know this can be a confounding factor (explained at page 17, line 400-407 in the revised manuscript).

e. Primary endpoint. The authors comment that the primary goal is the 30th CST. What is the goal really? What should be the improvement to be considered positive? Are there normal values for this test?

Response: The 30-s CST is a measure of lower extremity muscle strength, which is mentioned in the manuscript (page 12, line 280). The clinical relevant difference for this test is found to be 2.0-2.6, when assessed in older populations with hip and knee osteoarthritis (Wright et al. 2011). This is of course something we will take into consideration when evaluating the results.

The clinical relevant difference is added to the revised manuscript at page 13, line 289-290 (A change of 2.0-2.6 stands is considered to be clinically relevant based on data from a population of older adults with hip and knee osteoarthritis [25].)

f. Line 255 and later. Patients who are unable to get up alone should be excluded, or anyway, these patients should form a subpopulation. It is possible that among patients who can not get up without using their arms there are people who can not get up from the chair before the hospitalization (patient with stabilized discapacity). It is impossible to expect improvement in these patients.

Response: This is a very good point. As 'ability to stand independently for at least 30 seconds' is an inclusion criteria for this study, the most weak/sick patients are excluded, and thus all participants have been able to get up from the chair independently with or without using their arms. This was also expected when designing the study, as the modified 30-s CST has been shown to be both feasible and have a high inter-rater reliability among acutely admitted old medical patients [Bodilsen et al. (2015) Feasibility and inter-raterreliability of physical performance measures in acutely admitted older medical patients. PLoS One 10:e0118248]. Furthermore, this was also in accordance with experience from our former intervention studies performed in geriatric patients [Beck A et al. (2015) Does adding a dietician to the liaison team after discharge of geriatric patients improve nutritional outcome: a randomised controlled trial Clin Rehabil 29:1117-1128; Beck et al. (2013) Follow-up home visits with registered dietitians have a positive effect on the functional and nutritional status of geriatric medical patients after discharge: a randomized controlled trial. Clin Rehabil 27:483-493].

g. Secondary endpoint, line 261. You talk about BIA. But in the protocol available in Clinical Trials, you affirm that only in a subpopulation of 30 patients you assess BIA. Can you clarify, please?

Response: The BIA-measurements are performed on all participants at all assessments, as stated in clinical.trials under 'Secondary Outcome Measures'. It is correct that a sub-study is performed on 30 participants, and this is described in clinical.trials as pasted in below.

"'Sub-study: 'Validation of a portable bio-impedance analyzer in a population of older adults ≥ 70 years for the assessment of muscle mass and changes in muscle mass over time' A sub-study will be performed to investigate if the portable InBody-230 BIA correlate with DXA at single time points in 30 hospitalized older people ≥ 70 years, and to see if it is possible to track changes in LBM during the 12-week intervention. Total LBM, total fat mass, and percent LBM will be measured and compared as well as appendicular and trunk LBM. In addition, the reliability of the portable bio-impedance analyzer will be evaluated by assessing the degree of agreement between two subsequent measurements. In continuation of recruitment to the primary study, a subset of participants (n=30) will be asked if they want to participate in this sub-study, irrespective of their allocation in the main study. The measurements are going to be performed twice, while hospitalized and 12 weeks after discharge (± 5 days).'"

h. In general for secondary endpoint, please, define better the objective. For example you talk about BIA. Which is the endpoint, an increase of LBM? If yes, which is the limit that you utilize to define the improve? The same for the followings secondary endpoint (hand grip, gait speed, and others).

Response: We have explained the objective of each end-point, in the first line of each paragraph explaining a new endpoint (page 12-16). For LBM and HGS we have tried to make it more clear/consistent.

Page 13, line 292: Total, appendicular, and trunk LBM (kg and percent) Muscle mass is assessed by Bio-impedance Analysis (BIA) using the portable InBody-230 body composition analyzer (dual frequency (20 kHz, 100 kHz), tetra polar 8-Point Tactile Electrode System (InBody, Copenhagen, Denmark))

Page 13, line 306: Hand grip strength (HGS) is a proxy measure of upper extremity strength, and is measured in kg using the second handle position with a DHD-1 Digital Hand Dynamometer (Saehan Medical, 2012, Roskilde Denmark).

We understand your comment as you would like some references to established 'clinical relevant improvements'. In general for the end points, we do not know if we should expect an improvement in the intervention group compared to the control group, or no change in the intervention group compared to deterioration in the control group, thus we like to formulate it as 'Clinical relevant difference' to emphasize, that a deterioration or lack of deterioration may also be clinical relevant. Where investigated on the relevant population (or a population somewhat relevant/comparable), a clinical relevant difference have been added to the secondary endpoints along with relevant references. It has been added for 4-m gait speed and DEMMI.

4-m gait speed, Page 14, line 324-326: (In sedentary older adults, a clinical relevant difference is found to be 0.03-0.05 m/s, while 0.08 m/s is found to be a substantial relevant difference.)

DEMMI, Page 14 line 340-341: (In older acute medical patients, the clinical relevant difference is found to be 10 points on the converted scale.)

In regard to LBM – we measure both total, appendicular and trunk LBM in kg and percent. This has been clarified by mentioning it in the first line of the paragraph, as illustrated above. We collect 'reliability data' on the Inbody-230 BIA device we are using, and these results will be used to define what we consider a 'real improvement'. This 'fact' has been added to the revised manuscript at page 13, line 303-305 (The reliability of the InBody-230 body composition analyzer will be measured and used to establish the threshold of change needed beyond measurement error.). We cannot find any references stating a clinical relevant difference for LBM in regards to older adults.

i. Line 313. For sarcopenia I think that there is a problem. The prevalence of sarcopenia in the community older adults is about 20-30%. I think that at baseline moment you will find patients with sarcopenia and patients without, and probably the evolution of these two types of patients will be different. Have you considered the possibility of correcting randomization for sarcopenia?

Response: Thank you for this good point. We agree with you, and have planned to look into this in a post hoc sub-group analysis – also with respect to the EWGSOP-proposed stages of sarcopenia. Furthermore, we have planned to investigate if those who are at nutritional risk might benefit more from the intervention. This is mentioned in the manuscript at page 18, line 440-443.

j. Statistics. Power calcilation. In the studies to be used to calculate the sample size, significant improvements are observed both in the intervention group and in the control group. The authors to whom you refer did not get significant differences between the two groups. Considering the type of intervention of your study (protein supplementation), I believe that you should make BIA on all patients and consider increasing of fat free mass as main objetive.

Considering the limitation of BIA I think you should recalculate the sample size and if possible increase the number of subjects included.

Response: As mentioned, we do measure LBM using BIA on all 165 participants, and not just 30 (this is in the sub-study). It was a very conscious choice that we have chosen 'muscle strength' measured by the 30-s CST to be the primary end point. For practical reasons, we could not measure LBM using DXA, a much more widely accepted and accurate method compared to BIA – and we do not want the validity of our primary end point to be questioned. Furthermore, muscle strength and muscle function are considered to be more clinical relevant to the older adult than muscle mass as it reflects the actual physical function of the patients. The sub-study is performed to allow us to discuss the validity of the secondary endpoint LMB measured by BIA in the main study.

Reviewer: 2

- It would be helpful if the authors further clarify the novelty of this study. There have been quite a few studies on resistance training / protein supplementation for older adults recovering from events requiring hospitalization. Confirm if the novelty lies mainly in the setting (conducting the study in a hospital setting rather than upon discharge), the degree of potential impairment of these patients/participants, or some other aspect not mentioned here.

Response: We agree with your comment and have tried to state the novelty of the study more clearly in the end of the last paragraph of the introduction (page 5, line 115-117) (The novelty of this study is two-fold. Firstly the intervention involves hospitalized older adults, and secondly the intervention continues after discharge. To the best of the authors' knowledge, previous studies were only performed in one setting.).
Most studies with prolonged protein supplementation and resistance training are conducted in healthy community-dwelling older adults, and fewer studies are conducted in frail and/or sarcopenic older adults. To the best of our knowledge it has never been investigated in hospitalized older adults. The study further stands out by being conducted both in a hospital setting and after discharge to either own home, nursing home, or rehabilitation center. As far as we know, studies comparable to ours have so far been conducted in just one setting. We expect decreased functional loss during hospitalization and faster recovery after discharge.

- Few details are provided on protein quality. What kind of protein will be used? Whey protein concentrate, whey protein isolate? What is the essential amino acid content of this supplement (particularly Leucine)?

Response: We have added further details about the quality of the intervention product (page 7, different places from line 155-164). E.g. we mention the type of protein and how much leucine it contains. Furthermore, we have added an extra supplemental material showing the amino acid profile of the product, which we refer to in the revised manuscript.

- Under Study Population, line 126, I would include health deterioration. This is a common reason for both withdrawal and a lack of a response from an RT program (with or without protein supplementation). This should be controlled for as much as possible.

Response: Point taken, however, we believe it will be hard to define 'health deterioration' in a standardized manner. Also, many of our participants have good and bad days, both while hospitalized and after discharge. Having said this, the main reason for participants dropping out of the study is because of 'bad health'. We measure (re)admission to hospital within the intervention period (and after), which might indicate if the health status of the participant changes during the study.

Furthermore, we include admission diagnosis and chronic diseases in the baseline characteristics, allowing the reader some insight into the participants' disease severity. We have added these examples to the 'baseline characteristics' (page 16, line 369-371). The sentence now reads: (Actions are taken to actively reduce or register known or possible confounders. Thus, at baseline, confounders such as admission diagnosis, chronic diseases, nutritional risk (NRS 2002) [36], sarcopenia [3,37], depression [38], and mobility [39,40] are evaluated, among other.)

- The authors mention that nutritional risk will be assessed at baseline. Will this be assessed at any other time point? Previous research with similar populations has shown a measurable deterioration in nutritional status over a span of 6-months that may have influenced the responsiveness to RT (despite protein supplementation).

Response: This is very interesting and a good point. However, we only screen for nutritional risk at baseline. The screening tool we use (NRS-2002) apply to hospital settings. Nevertheless, we do measure changes in body weight at week 12, and register food intake on an ongoing basis throughout the study intervention, which to some extend can indicate whether the participants' nutritional status deteriorate. It is definitely something we will keep in mind when we are going to look at and discuss the results.

- Line 143: Minor correction – January 2018 (not January 2017).

Response: This is actually the correct year. We knew from the beginning of the study that the manufacturer of the intervention product would add vitamin D in small amounts to the product later on in the study period. To control for this - and different vitamin D supplementation between the groups in general - we decided to give vitamin D supplementation to all of our participants, so the extra protein was still the only difference between the two groups. This is discussed at page 21, line 500-510 in the revised manuscript (pasted in below):

"The majority of older adults in Denmark take vitamin D supplements as recommended by the Danish Health Authority [21]. Studies have shown that vitamin D has an independent positive effect on muscle strength [48]. In order to investigate the effect of the protein supplementation alone, vitamin D supplements will be given to all participants with serum-vitamin D levels ≤ 100 nmol/L at inclusion, to ensure similar vitamin D intakes. Another reason for ensuring that all participants are supplemented with vitamin D is that the protein-enriched beverage approximately half-way through the intervention period will have vitamin D added to the product. However, the fortification level is quite low, adding an extra amount of only 3.5 µg vitamin D per day from the beverages, which e.g. corresponds to 13 g of salmon [49]. Also, compared to the daily vitamin D supplementation of minimum 20 µg (some older adults' takes even higher amounts, as prescribed by their doctor) it is considered insignificant."

- Line 146: Clarify why this amount of protein was chosen. Some evidence suggests a positive response from 35-40 grams of whey immediately following an RT program. This is not critical, but when striving for a maximal anabolic effect, the extra 10-15 grams may be worth considering.

Response: The following has been added to the manuscript (page 7+8, line 165-170). (This amount of protein supplementation is chosen, based on previous studies finding positive effects from similar or smaller dosages (references appear in the manuscript). Furthermore, protein supplementation is satiating, and if given in higher amounts might compromise habitual food intake to a great extend – especially among older adults with low appetite. The total dosage is divided into two servings (breakfast and next cold main meal), as research indicate that 25-30 grams of high quality protein is needed per main meal to maximally stimulate post prandial protein synthesis [8].)

The reason why we divide the total dosage up into two times per day is also because we do not want to compromise the participants' appetite too much. Furthermore, based on our earlier experience, it is not possible for many older (acutely ill) to eat/drink 35-40 grams of protein at one time.

- A nitrogen balance assessment may be worth considering – if feasible.

Response: We agree, this would have been very informative/interesting. Unfortunately we did not have the resources to measure this.

- Lines 348-349: Will there be certain mandated days for diet assessment inclusion? (I.e. of the four days, must include one weekend day?) Additionally, assessing resting metabolic rate may help somewhat with identifying under-reporting.

Response: The days with dietary recall interviews are performed at the same days where adjustment visits are made. These visits are planned in agreement with the participants (a day where they are home ect.), and also visits in the same geographical area are preferably placed on the same days. Thus, a lot of practicalities are deciding what day of the week the recall is covering. We agree that it would have been more accurate, if we had included at least one Sunday for all participants (at least one visit on a Monday). This said, luckily we can see that most of our participants are very habitual in their food intake – they eat almost the same every day. We have made this clear in the revised manuscript at page 17, line 388-390. (As the home visits will be planned in collaboration with the participants, and has to be fitted into other study tasks and visits, these practicalities decide what day of the week the recall interview is covering.).

Measuring resting metabolic rate was unfortunately not possible.

- Lines 356-357: Briefly explain the interpretation of the activity level scale. (1 presume least active, 5 most, etc..) Similarly, a brief explanation of how nutrition risk screening (NRS2002) will be performed and interpreted (rather than just cite Kondrup J et al's paper) would be helpful.

Response: The activity level scale has been explained in more detail (page 17, line 405-407) (The scale is ordinal, and activity level 1 represents the least active and level 5 the most active. It is the time used on different activities and the intensities of these (low, moderate, or high) that determine the activity level.). Furthermore, we have explained more about the nutritional risk screening procedure, and the definition of sarcopenia has also been added (page16, line 371-377) (Nutritional risk is determined based on a combination of factors: unintended weight loss within the last three months, loss of appetite within the last week, body mass index, disease severity, and age. Patients screened to be at risk are expected to benefit from nutritional intervention. Sarcopenia is assessed according to the definition proposed by the European Working Group on Sarcopenia in Older People (EWGSOP). This is based on the assessments of LBM (measured by BIA), muscle strength (measured HGS), and physical performance (measured by 4-m gait speed))

- Will physical activity level after discharge be controlled for?

Response: Yes, as good as possible, within our - and the participants' resources. This is explained at page 17, line 400-407 in the manuscript (pasted in below - the last lines has been added after receiving reviewer comments):

"Daily activity level. In a semi-structured interview the participants are asked about exercise-related activities besides the RT program. This is reported four times after discharge in study week 3, 6, 9, and 12 at home visits, or by phone if the participant' is no longer compliant in the study with regard to the intervention products and the RT.

Depending on the answers given, the participants will be divided into increasing activity levels from 1-5, after predefined criteria, inspired by Saltin & Grimby (1968) [43]. The scale is ordinal, and activity level 1 represents the least active and level 5 the most active. It is the time used on different activities and the intensities of these (low, moderate, or high) that determine the activity level."

This is not the ideal way of measuring it, but most of the participants are so weak, and have so many other things to worry about following discharge from the hospital, that asking for eg. a detailed exercise diary would have been too much for them. We did not have the resources to have them wearing an accelerometer.
With regard to statistics, we are going to take the activity level, and total energy- and protein intake into account (dependent variables) – both during and after discharge. We have added this in the section of 'statistical tests' (page 18, line 434-436) (Furthermore, endpoints will be compared adjusting for randomization bias (defined as $p < 0.05$ between groups), and confounding factors (total activity level and total protein- and energy intake).

- With this population, there is a near certainty of the presence of numerous and severe co-morbidities. Lines 461 – the authors acknowledge a weakness in the lack of supervision of RT following discharge. I have concerns over safety. There should be some acknowledgement of supervision by a care-provider or guardian as the participant is performing an RT routine at home given their current state of health.
Along these lines, will physician and guardian consent be required of all participants?

Response: Study participation requires only the participants' own consent.
During hospitalization the RT is supervised daily by a physiotherapist working on the study. It is the same three exercises that the participants continues with at home, and thus, most of them have three days or more experience with performing the exercises before coming home. Furthermore, if there are any safety/pain issues this will be discovered.
Also, as 'no stand function' is an exclusion criteria – the weakest patients admitted to the department are not included in the study. Furthermore, those of our participants that are most weak, are discharged to a 24-h rehabilitation centre, and come home when they are better.
The physiotherapists instructing and supervising the training while the participants are hospitalized also make adjustment visits every three weeks, to make sure the intensity level is suitable for the participants' abilities. Furthermore, they call the participants on a weekly basis to ask them how it goes with the RT, among other. Thus, they know the participants very well. If there are any safety issues or pain, the participants can be told to leave out a specific exercise. If we have participants whose health deteriorate again after discharge from the hospital, this often results in them not doing the RT at all for a period. Furthermore, if participants are readmitted to hospital, they always receive an adjustment visit after discharge.
So far, with more than 140 participants completing the study, we have not had any safety issues.
The following has been added as an explanation to the RT intervention (page 9, line 213-215). (Participants can be asked to leave out a specific exercise, if there are safety concerns (e.g. severe dizziness or worsening of a condition) or if they experience pain related to performance a certain exercise). And in figure 1. (page 12) the weekly phone call has been added.

- I am also inclined to wonder if a licensed medical nutrition therapist should be consulted / involved throughout this study (if one is not affiliated with it yet).

Response: The intervention is a supplement to habitual care, thus some patients are/will be referred to a dietician/medical nutrition therapist (during and/or after discharge). Any changes made to the diet due to this counseling will be 'registered/captured' as part of the dietary records during hospitalization or the dietary interviews following discharge (in regard to protein- and energy intake).

We have had some participants who due to very low appetite or uncontrolled diabetes had to stop taking the daily supplement. In these cases the medical doctors'/dieticians' advice is always followed. We have added this point to the manuscript at page 8, line 181-183. (If for some reason (e.g. uncontrolled diabetes or severe reduction of habitual food intake), the participant is advised by medical doctors'/nutritional therapists' to stop taking the supplement, this advice will always be followed.)