1 **Study protocol: Cost-effectiveness of transmural nutritional support in malnourished**
2 **elderly patients in comparison with usual care**
3

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13
14

14 **ABSTRACT**

15 *Background*

16 Malnutrition is a common consequence of disease in older patients. Both in hospital setting and in
17 community setting oral nutritional support has proven to be effective. However, cost-effectiveness
18 studies are scarce. Therefore, the aim of our study is to investigate the effectiveness and cost-
19 effectiveness of transmural nutritional support in malnourished elderly patients, starting at hospital
20 admission until three months after discharge.

21

22 *Methods*

23 This study is a randomized controlled trial. Patients are included at hospital admission and followed
24 until three months after discharge. Patients are eligible to be included when they are ≥ 60 years old
25 and malnourished according to the following objective standards: Body Mass Index (BMI in kg/m^2)
26 < 20 and/or ≥5% unintentional weight loss in the previous month and/or ≥10% unintentional weight
27 loss in the previous six months. We will compare usual nutritional care with transmural nutritional
28 support (energy and protein enriched diet, two additional servings of an oral nutritional supplement,
29 vitamin D and calcium supplementation, and consultations by a dietitian). Each study arm will
30 consist of 100 patients. The primary outcome parameters will be changes in activities of daily living
31 (determined as functional limitations and physical activity) between intervention and control group.
32 Secondary outcomes will be changes in body weight, body composition, quality of life, and muscle
33 strength. An economic evaluation from a societal perspective will be conducted alongside the
34 randomised trial to evaluate the cost-effectiveness of the intervention in comparison with usual
35 care.

36

37 *Conclusion*

38 In this randomized controlled trial we will evaluate the effect of transmural nutritional support in
39 malnourished elderly patients after hospital discharge, compared to usual care. Primary endpoints
40 of the study are changes in activities of daily living, body weight, body composition, quality of life,
41 and muscle strength. An economic evaluation will be performed to evaluate the cost-effectiveness
42 of the intervention in comparison with usual care.

43

44 *Trial registration*

45 Netherlands Trial Register (ISRCTN29617677, registered 14-Sep-2005)

46

46 **BACKGROUND**

47 The primary cause of malnutrition in developed countries is disease. Malnutrition is estimated to
48 occur in 25-61% of all elderly patients suffering from a variety of diseases[1;2]. Unintentional weight
49 loss of ≥5% in the previous month and/or unintentional weight loss of ≥10% in the previous six
50 months and/or a BMI <20 kg/m^2 are often used as parameters to identify malnutrition.
51

52 Disease related malnutrition is associated with adverse effects on clinical outcome, as has been
53 shown in a large number of studies. These adverse effects vary from impaired wound healing and
54 postoperative complications to mortality [3]. Poor nutritional status has not only been associated with
55 in-hospital adverse effects, but also with adverse effects both pre-admission and post-discharge.
56 These effects include a trend for increased need for re-hospitalization, significantly higher total
57 mortality, a higher general practitioner consultation rate, higher medication prescription rate, longer
58 rehabilitation, an increased need for nursing home admission, increased likelihood of requiring
59 home health care after discharge and early institutionalization [4;5].
60

61 So far, randomized clinical trials have shown that additional Oral Nutritional Support (ONS) can be
62 effective in malnourished elderly people, both in the clinical setting and in the community [6]. In
63 hospitalized patients ONS has been shown to reduce weight loss, to shorten hospital stay and to
64 improve functional status in malnourished hospitalized patients. In the community ONS has been
65 shown to increase activities of daily living, to reduce the number of falls and to reduce health care
66 utilization [5;7-10].
67 Furthermore, a meta-analysis, including 31 studies and almost 2500 patients, showed that protein
68 and energy supplementation led to small changes in weight and, more importantly to reduced
69 mortality (RR 0,67; CI 0,52-0,87). Also, length of hospital stay was reduced by on average 3.3 days
70 (CI -9.64-3.05) [7].
71

72 Because nowadays patients spend only a minority of time in hospital and recover at home, it is not
73 very likely that patients' nutritional status will improve during the short period of admission.
74 Therefore, the problem of disease related malnutrition is more and more becoming a post-
75 discharge problem (in this manuscript further referred to as a transmural problem).
76

77 For in-hospital patients, studies on cost-effectiveness of nutritional interventions are scarce. In a
78 retrospective cost-analysis of nine randomized controlled trials on nutritional support, the cost
79 savings aggregated between €503 and €11696 per patient in surgical, orthopedic, elderly and
80 stroke patients [6]. A recent observational cohort study showed a cost reduction in patients supplied
81 with ONS of €723 per patient [8]. In a prospective study, a reduction of length of hospital stay with
82 one day was achieved with an investment of €34 per malnourished patient [11].
83

Cost-effectiveness studies of ONS in the community are lacking and are eagerly awaited for. We do expect that a nutritional intervention in the transmural setting will be accompanied by higher health care costs than usual care, but that these higher costs are negligible compared with the cost-savings they can potentially generate.

The aim of this study is to investigate the cost-effectiveness of transmural nutritional support in malnourished elderly patients after hospital discharge as compared to usual care on changes in activities of daily living. Secondary outcomes include changes in body weight, body composition, quality of life, and muscle strength between intervention and control group.

METHODS

Design

This study is designed as a randomized controlled trial comparing transmural nutritional support with usual nutritional care. The study design is in accordance with the Declaration of Helsinki and has been approved by the Medical Ethics Committee (METC) of VU University Medical Center.

Patients are eligible for this study when they are ≥ 60 years old and malnourished according to the following objective standards: Body Mass Index (BMI in kg/m^2) < 20 and/or, ≥5% unintentional weight loss in the previous month and/or ≥10% unintentional weight loss in the previous six months. We will compare usual nutritional care with transmural nutritional support (energy and protein enriched diet, two additional servings of an oral nutritional supplement, vitamin D and calcium supplementation, and consultations by a dietitian). The primary outcome parameters will be changes in activities of daily living (functional limitations and physical activity) between the intervention and control group. Secondary outcomes will be changes in body weight, body composition, quality of life, and muscle strength. An economic evaluation from a societal perspective will be conducted alongside the randomised trial to evaluate the cost-effectiveness of the intervention versus usual care.

Feasibility of recruitment and sample size

Earlier studies [12;13;14;15;16] have shown that 30% of the elderly hospital population is malnourished at admission. For a clinically relevant difference of 20% in nutritional and functional status with a statistical significance level of 0.05 and a power of 80%, two groups of 80 patients were calculated to be sufficient.

A pilot study showed that inclusion of 140 malnourished patients per year is feasible. Taking into account an expected refusal rate of 30% at inclusion and loss to follow-up of 10% during the three months following discharge, we aim to include two groups of 100, to be reached in approximately two years.

122
123 **Randomisation**
124 A computerized random number generator will be used to assign patients either to the intervention
125 group or the control group. Patients will be randomized in blocks of ten. At the end of the baseline
126 interview and measurements, the primary investigator opens a consecutively numbered opaque
127 envelope containing the patients' group assignment. Participants, research assistant and
128 researcher are no longer blinded for the intervention from this point. Before starting the analyses
129 the researcher (FN) will be re-blinded for patients' group assignment.
130
131 **Population, inclusion and exclusion criteria**
132 All elderly patients (≥60 years of age, expected length of hospital admission >2 days) newly
133 admitted to the wards of internal medicine, traumatology and vascular surgery of the VU University
134 Medical Center will be screened at admission by a dietitian and/or research assistants of nutritional
135 status. These departments represent the (sub)specialties general internal medicine, rheumatology,
136 gastroenterology, dermatology, nephrology, orthopedics, traumatology and vascular surgery.
137 Patients will be excluded from the study when they suffer from senile dementia, can not
138 understand the Dutch language or are not able to or willing to give informed consent.
139
140 **Nutritional status**
141 Patients are be eligible for this study if they are identified malnourished according to the following
142 criteria:
143 • Body Mass Index (BMI in kg/m^2) < 20 and/or
144 • ≥5% unintentional weight loss in the previous month and/or
145 • ≥10% unintentional weight loss in the previous six months.
146 Weight (in kg to the nearest decimal) is measured (with patients wearing light indoor clothes and
147 no shoes) on a calibrated chair scale (Prior MD-1512), with an accuracy of 0.1 kilogram, at
148 admission and three months after discharge. A correction factor for clothes will be made by
149 deducting weight with 2.0 kilograms for men and 1.3 kilograms for women[17].
150 BMI is calculated as actual weight in kilograms divided by the square of height in meters.
151
152 As measurement of height is often not feasible in this ill, old and frail population, data on height will
153 be retrieved from self-reported height, with an accuracy of 1.0 centimeter. These data will be
154 validated against height derived from knee height measurements (Seca 207, in cm to the nearest
155 decimal) in approximately 800 elderly patients from the same departments at our institute.
156
157 **Intervention**
158 Control patients will receive 'usual' nutritional care, i.e. hospital intervention only on referral by the
159 treating physician and without standardized transmural nutritional support.

160 Patients assigned to the intervention group strategy will receive standardized transmural nutritional
161 support (**Table 1**) starting in hospital and to be continued until three months after discharge.
162
163 **Procedure**
164 After obtaining patients' informed consent an inventory will be made of nutritional status, nutritional
165 risk profile and possible confounders. This includes the following baseline characteristics:
166 - sociodemographic data (age, gender, education level, partner status)
167 - medical history and medical diagnosis
168 - anthropometry (weight, height, BMI, percentage involuntary weight loss)
169 - biochemical parameters (CRP, IGF-1, 25(OH)D)
170 - mental state (MMSE)[18]
171 - expected care complexity (COMPRI)[19]
172
173 Information on disease, disease severity, disease course, treatment and complications will be
174 retrieved from medical records.
175 Post-discharge practice will be followed and outcome parameters will be collected for all patients at
176 three months after discharge.
177
178 **Outcome parameters**
179 Outcome parameters will be measured after inclusion and at three months after discharge.
180 Primary outcome is change in activities of daily living, determined as functional limitations and
181 physical activities. All outcome parameters that will be measured are listed below.
182
183 *Activities of daily living*
184 Activities of daily living (ADL) will be assessed with a validated questionnaire that measures the
185 degree of difficulties patients experience with six activities: climbing stairs, walking 5 minutes
186 outdoors without resting, getting up and sitting down in a chair, dressing and undressing oneself,
187 using own or public transportation, and cutting one's own toenails[20]. Functional limitations will be
188 assessed using five difficulty categories, ranging from "No I can not' to 'Yes without difficulty'. Total
189 score will be calculated by summing the scores of all activities, ranging from 0 (does not have any
190 difficulties with the activities) to 6 (has difficulties with all activities).
191
192 *Physical performance*
193 The performance test of physical function includes time measures of walking speed, rising from a
194 chair, putting on and taking off a cardigan, and maintaining balance in a tandem stand.[21-23] To test
195 walking performance a 3 meter walking course is created by a measuring line. Patients are
196 instructed to walk to the other end of the course, to turn 180 degrees, and walk back as quickly as
197 possible. Patients are allowed to use a walking aid if necessary. To test the ability to rise from a

198 chair, patients are asked to fold their arms across their chest and to stand up and sit down five
199 times from a standard hospital chair as quickly as possible. For the cardigan test, patients are
200 asked to put on and take off a cardigan as quickly as possible. To test for balance, patients are
201 asked to stand with one foot placed behind the other in a straight line for at least 10 seconds.
202 A trained research assistant records the total time needed to complete each test.
203
204 Patients who complete the walking test, chair test and cardigan test will be assigned scores
205 between 1 and 4, corresponding to the quartiles of time needed to complete the test, with the
206 fastest time scored as 4. Those who cannot complete the test will be assigned a score of 0.
207 Accordingly the maximum score for these three tests ranges from 0-12 points, after adding up the
208 result of these tree tests.
209 The balance test will be analyzed separately, yet with the same time classification as described
210 above.
211
212 *Physical activity*
213 Physical activity will be assessed with the validated LASA Physical Activity Questionnaire
214 (LAPAQ)[24]. This face-to-face questionnaire covers the frequency and duration of walking outside,
215 cycling, gardening, sports and household activities during the previous two weeks. Walking and
216 bicycling for transportation purposes are considered as common daily activities in The
217 Netherlands, and not as sports activities. For the analyses, the total time spent on physical activity
218 of the last two weeks is used (in minutes per day).
219
220 *Quality of life*
221 Quality of Life will be measured by the SF-12 and EuroQol (EQ-5D and EQ-VAS).
222 The SF-12 contains 12 questions from the SF-36[25]. These questions concern functional status -
223 both physical and social functioning- mental health, pain, vitality and evaluation of persons' state of
224 health. With these dimensions two total scores can be calculated; one physical component score
225 and one mental component score[26].
226
227 EuroQol (EQ-5D)[27] is a standardised instrument to monitor health outcome. This instrument
228 contains five short questions on mobility, self-care, daily activities, pain/discomfort and
229 anxiety/depression with three possible response categories (no problems, moderate problems,
230 severe problems). The EQ-5D scores were used to calculate utilities using the Dutch tariff [28].
231 QALYs were calculated by multiplying the utilities with the amount of time a patient spent in a
232 particular health state. Transitions between health states were linearly interpolated.
233 Additionally we will administer the EQ VAS. The EQ-VAS, a visual analog scale, generates a self-
234 rating of health-related quality of life. The patient rates his/her health state by drawing a line from

235 the box marked "Your health state today" to the appropriate point on the EQ-VAS on a scale of 0 to
236 100.
237
238 *-Hand grip strength*
239 Hand grip strength (in kg) will be measured with a hydraulic hand dynamometer (Baseline,
240 Fabrication Enterprises Inc., Elmsford, NY, USA). Respondents are asked to perform two
241 maximum force trials with their non-dominant hand. The highest value will be used. Measured data
242 will be compared to reference values by Mathiowetz. Data will be expressed as percentage of
243 reference value[29].
244
245 *-Fall-incidents*
246 Patients will be asked to report all fall incidents weekly in a fall diary for a period of three months
247 after discharge. A fall is defined as “an unintentional change in position resulting in coming to rest
248 at a lower level or on the ground” [30].
249
250 *Bio-electrical impedance spectroscopy*
251 Bio-electrical impedance spectroscopy (BIS) will be applied to calculate (changes in) body
252 composition. Measurements will be performed at the non-dominant side of the patient, using a
253 Hydra ECF/ICF Bio Impedance Spectrum Analyzer, model 4200 (Xitron Technologies, San Diego,
254 CA, USA). Shoes, socks and jewellery will be removed and patients will be in supine position. Two
255 current electrodes (tetra-polar electrodes (3M red Dot AG/AgCl)) will be placed at the dorsal
256 surfaces of the hand and foot on the distal position of the second metacarpal and metatarsal,
257 respectively. Two detector electrodes will be placed at the posterior wrist between the styloid
258 processes of the radius and ulna and at the ankle between the tibial and fibular malleoli. With this
259 technique, two body compartments, fat mass (FM) and fat free mass (FFM), can be determined.
260 Patients with a pacemaker will be excluded from this measurement.
261
262 *Resting energy expenditure*
263 Resting energy expenditure (REE) will be calculated from measurements of oxygen consumption
264 (VO_2) and carbon dioxide production (VCO_2) by with a ventilated hood system, in supine position
265 for 30 minutes, with a metabolic monitor (Vmax Encore n29, Viasys Healthcare, Houten, The
266 Netherlands). Before each measurement, gas analyzers will be calibrated with two reference gas
267 mixtures (a. 16% O_2, 4% CO_2,, bal. N_2 and b. 26% O_2, bal. N_2. (Viasys)). Patients will be monitored
268 during the measurement to prevent movements or sleeping under the hood.
269 REE will be calculated from oxygen consumption and carbon dioxide production by using the
270 equation of Weir[31].
271
272 *Dietary intake*

273 Dietary intake will be obtained by asking in broad outlines for patients' mean daily intake of food
274 and drinks in the two weeks before admission to the hospital and at three months after discharge.
275
276 *-Biochemical parameters CRP, IGF-1, 25(OH)D*
277 Two blood samples per patient will be obtained: the first on the day after inclusion and the second
278 three months after discharge. We will measure CRP, IGF-1 and 25(OH)D in both samples. The
279 blood samples will be centrifuged and stored at -80 ℃. All blood samples will be analyzed
280 simultaneously after completing full data collection.
281 C-reactive proteïn (CRP in mg/l) is a member of the class of acute-phase reactants as its levels
282 rise dramatically during inflammation processes. Plasma concentrations of C-Reactive Protein
283 (CRP) will be measured with an automated latex-enhanced immunoturbidimetric assay on a
284 Modular P800 analyzer (Roche Diagnostics, Almere, The Netherlands).
285 Insuline-like growth factor (IGF-1 in µg/l) will be obtained to observe over or under production of
286 growth-hormone. Serum levels of IGF-1 will be measured with a Immulite 2500 analyzer (Siemens,
287 Deerfield, IL, USA)
288 Serum 25(OH)D (in nmol/l) will be obtained to observe differences in vitamin D levels after the
289 three month supplementation of vitamin D in the intervention group. This will be determined using a
290 competitive protein binding assay (Nichols Diagnostics, San Juan Capistrano, CA, USA).
291 All analyses will be performed at department of Clinical Chemistry of the VU University Medical
292 Center.
293
294 *Costs*
295 Costs will be measured from a societal perspective. Direct health care costs include the costs of
296 transmural nutritional support (nutritional supplements plus dietitian), hospitalization, additional
297 visits to other health care providers (general practitioner, medical specialist), prescription and over-
298 the-counter medication, professional home care. Direct non-health care costs of paid and unpaid
299 help and indirect cost of absenteeism of paid and unpaid work will also be included.
300 Data on the use of nutritional support will be registered by the dietician implementing the
301 transmural nutritional intervention. Data on health care utilization during hospitalization will be
302 retrieved from medical records and the hospital information system. Use of other health care
303 resources after discharge from the hospital will be collected through two identical cost diaries each
304 spanning a period of 6 weeks. Medication data will be obtained from the patients' pharmacies.
305 Health care utilization will be valued using standard costs from the Dutch guidelines for cost
306 analysis in health care research [32]. If there are no standard costs available, tariffs or prices from
307 health care providers themselves or professional organizations will be used. The costs of
308 medication will be estimated on the basis of prices charged by the Royal Dutch Society for
309 Pharmacy.
310

311 *Economic evaluation*
312 The aim of the economic evaluation will be to determine and compare the total costs for patients
313 receiving either transmural nutritional support or usual care, and to relate these costs to the effects
314 of the interventions.
315 Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in mean
316 total costs between the two interventions by the difference in mean effects between the two
317 interventions. The ICERs will be calculated for the primary clinical effect measures of the trial, i.e.
318 functional status and ADL. Cost-utility ratios will also be calculated.
319 Bootstrapping will be used for pair-wise comparison of the mean differences in total costs between
320 the intervention groups. Confidence intervals will be obtained by bias corrected and accelerated
321 (Bca) bootstrapping using 5000 replications [33]. To estimate the uncertainty surrounding the ICERs
322 bias corrected accelerated bootstrapping (5000 replications) will be used. The bootstrapped cost-
323 effect pairs will be plotted on cost-effectiveness planes and will be used to estimate cost-
324 effectiveness acceptability curves.
325
326 **Organization**
327 The primary investigator is responsible for the informed consent procedure, final patient selection,
328 measurements, analysis and reports. The primary investigator will be assisted by a research
329 assistant.
330 Data flow will be controlled by the primary investigator, using an administrative database system.
331 Data-entry and control will be conducted by a research assistant under supervision of the
332 investigator. The primary investigator is responsible for the data cleaning and analysis.
333
334 **Statistical analyses**
335 All analyses will be performed according to the intention-to-treat principle. 95% confidence
336 intervals will be calculated for the differences in percentages and means. Logistic regression will
337 be used to analyze dichotomous variables, Poisson regression for the count-variables and linear
338 regression for continuous variables. Ceiling and floor effects will be taken into account in the
339 analysis of the questionnaires.
340 In order to test the independent contribution of the intervention on the outcome variables,
341 multivariate regression analysis will be used to adjust for the possible confounders.
342
343
344 **DISCUSSION**
345 When designing the study protocol we had to make a number of considerations, which may lead to
346 the following strengths and weaknesses:
347 Firstly, we have chosen a strict definition of malnutrition, because the most malnourished group is
348 most likely to benefit from oral nutritional support. Since we have used the described cut-off points

349 for malnutrition in previous studies as well, we expect that it is feasible to include a sufficient
350 number of patients in the proposed study.
351 Secondly, we have chosen not to use strict exclusion criteria, but to include all eligible patients,
352 even though they are suffering from a variety of (chronic) diseases. Their homogeneity stems from
353 their age (>60y), degree of malnutrition (severe malnutrition) and background of disease (mainly
354 non-surgical). We have performed earlier studies with this same group of relatively unselected
355 patients with positive results of the nutritional intervention (after correcting for possible confounders
356 such as age, sex, ethnicity, care complexity, disease etc) in comparison with usual care [11;34].
357 Moreover, if the results of a broad study like this one are positive, it justifies wide implementation,
358 because the included group is representative for a mixed elderly hospital population; in contrast,
359 selection of a more specific group would make the intervention less applicable to other patients
360 groups.
361 Thirdly, for research purposes, standardized oral nutritional supplementation is chosen because
362 simply advising patients to increase their intake by eating more has not proven to be a solution that
363 can be relied on. From earlier studies [35-37], it is known that providing extra supplements does
364 increase energy intake and leads to weight gain, in contrast to dietary advice alone (without extra
365 supplements) [10].
366 Fourthly, the follow-up period of three months is chosen because this seems a reasonable
367 recovery period after discharge in this particular patient group. Also, it is known that compliance of
368 patients to take extra supplements diminishes after three months [38;39]. By making regular phone
369 calls to the patients we try to maintain compliance.
370 Fifthly, care should be taken of in-hospital contamination between treatment groups. The majority
371 of in-hospital patients will not be supplemented additional nutrition, either because they are not
372 malnourished (± 70%) or because they are randomized to the control strategy (50% of the study
373 population, 15% of the total population). Except for the primary investigator and research assistant,
374 doctors and nurses will not be aware of the reason for not-supplementing. Thus we expect to be
375 able to prevent contamination between treatment groups. In addition, hospital admission will last
376 only 10 to 15 days and post-discharge treatment will be approximately three months. We expect
377 that the post-discharge period to account for the majority of the effects. Contamination between
378 treatment groups in not likely to occur after discharge.
379 Finally, this is the first prospective, randomized controlled trial evaluating whether transmural
380 nutritional support is effective and cost-effectiveness when compared to usual care.
381
382 **CONCLUSION**
383 In this study we will evaluate in a randomized controlled trial whether transmural nutritional
384 support, compared to usual care, is effective and cost-effective, in malnourished elderly patients.
385 We will determine changes in activities of daily living, physical activity, functional limitations, body

386 weight, body composition, quality of life, and muscle strength between the intervention and control
387 group during the period between admission to hospital and three months after discharge.
388
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391 development), project number 945-06-203.
392
393 **COMPETING INTERESTS**
394 The author(s) declare that they have no competing interests.
395
396 **AUTHOR'S CONTRIBUTION**
397 FN, AT, JS, JB, and MvB provided support in the design of the study and contributed input into the
398 main ideas of this manuscript. FN drafted the manuscript and all other authors contributed to the
399 further writing of the manuscript and approved it.
400
401
402
403 **Table 1: Standardised transmural nutritional support in the intervention group**
404
405
406
407

- Energy and protein enriched diet (in-hospital period) - Two additional servings of an oral nutritional supplement, leading to an expected increase in intake of ± 600 kcal/day and 24 g protein/day per day (entire study period) - 400 IE vitamin D3 and 500 mg calcium (Calci Chew-D3, Sandoz) per day (entire study period) - Six consultations by telephone by a dietitian in order to give advice and to stimulate compliance to the proposed nutritional intake (every other week after discharge from the hospital)

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