Original Investigation; Revision

Individualized nutritional support in medical inpatients at nutritional risk: a randomized clinical trial

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Abstract

Background: Guidelines recommend use of nutritional support during hospital stays of medical patients at risk for malnutrition. However, the supporting evidence is limited, and there is growing concern about possible negative effects of nutritional therapy during acute illness on recovery and clinical outcome. Our aim was thus to test the hypothesis that protocol-guided individualized nutritional support to reach protein and energy goals reduces the risk of adverse clinical outcomes in medical inpatients at nutritional risk.

Methods: In a pragmatic, investigator-initiated, open-label, multicenter trial in eight Swiss hospitals, we randomly assigned 2088 medical inpatients at nutritional risk (Nutritional Risk Screening [NRS] score ≥3 points) to receive protocol-guided individualized nutritional support to reach protein and energy goals (intervention group) or standard hospital food (control group). The composite primary endpoint was adverse clinical outcome defined as all-cause mortality, intensive care admission, non-elective hospital readmission, major complications and decline in functional status at 30 days.

Findings: During the hospital stay, energy goals were reached in 79% and protein goals in 76% of intervention group patients. By 30 days, 232 of 1015 patients (22.9%) in the intervention group experienced an adverse clinical outcome compared to 272 of 1013 (26.9%) control group patients (adjusted odds ratio 0.79 [95%CI 0.64 to 0.97], p=0.023). In the intervention group, there were lower rates of death (73 patients [7.2%] vs. 100 patients [9.9%], adjusted odds ratio 0.65 [95%CI 0.47 to 0.91], p=0.011) and functional decline (35 patients [3.7%] vs. 55 patients [6.0%], adjusted odds ratio 0.62 [95%CI 0.40 to 0.96], p=0.034).

Interpretation: Among medical inpatients at nutritional risk, use of individualized nutritional support during the hospital stay increased daily energy and protein intakes, and improved important clinical outcomes including survival as compared to standard hospital food.

Trial registration: ClinicalTrials.gov number, NCT02517476

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Introduction

Anorexia, which is part of the acute physiologic response to acute illness, predisposes patients during a hospital stay to accumulation of serious energy and protein deficits.[1] In combination with immobilization and a pronounced inflammatory and endocrine stress response, these nutritional deficits contribute to muscle wasting and progressive deterioration of metabolic and functional status, particularly in the multimorbid medical inpatient population.[2,3] As a result, more than 30% of medical inpatients are at increased risk for malnutrition, a condition that is strongly associated with higher mortality and morbidity, functional decline, prolonged hospital stays and increased health care costs.[4-6]

Current clinical practice guidelines, including the European Society for Clinical Nutrition and Metabolism (ESPEN)[7] and the American Society for Parenteral and Enteral Nutrition (ASPEN)[8], recommend to consider initiating nutritional support during the hospital stay of medical patients identified by screening and assessment as at risk of malnutrition. However, these recommendations are largely based on physiological rationales and observational studies. Some smaller trials have found that nutritional support led to shorter hospital stays and lower mortality.[9-12] Yet, two recent meta-analyses reported no significant improvements in medical outcomes associated with nutritional interventions in medical inpatients, despite higher energy and protein intake of patients receiving nutritional support.[13,14] Additionally, nutritional support in medical inpatients with acute illnesses are currently challenged by results of several recent high quality critical care trials reporting harmful effects of full replacement feeding strategies.[1] These negative effects may be explained by suppression of autophagy with inadequate clearance of acute illness-associated cell damage.[15]

In view of the lack of high-quality data in the medical inpatient setting and possible conflicts between current recommendations for medical inpatients and critical care trials, we conducted the *Effect of early nutritional support on Frailty, Functional Outcomes and Recovery of malnourished medical inpatients Trial* (EFFORT). We tested the hypothesis that protocol-guided individualized nutritional support to reach protein and energy goals reduces the risk of adverse clinical outcomes in medical inpatients at nutritional risk.

Materials and Methods

Study design, registration and oversight

EFFORT is a pragmatic, investigator-initiated, open-label, non-blinded, non-commercial, multicenter, randomized-controlled trial, that was undertaken in eight Swiss hospitals. The rationale for the trial, design details, and eligibility features have been published previously.[16]

The ethical committee of the Northwestern part of Switzerland (EKNZ; 2014_001) approved the study protocol in January 2014 and the trial was started with a pilot in April 2014. After funding for the trial was secured and the pilot showed high feasibility regarding the nutritional intervention , the trial was registered at ClinicalTrials.gov in August 2015 (https://clinicaltrials.gov/ct2/show/NCT02517476) and patient enrollment was broadened to all participating centers. There was no change in protocol regarding outcomes and interventional procedures between the initial IRB protocol and the final trial protocol.

Sites, Patient Selection and Randomization

The eight participating sites were secondary and tertiary care hospitals in Switzerland, and included the University Clinic in Aarau, the University Hospital in Bern, the Cantonal hospitals in Lucerne, Solothurn, St. Gallen, Muensterlingen and Baselland, and the hospital Lachen. All sites routinely used a validated malnutrition screening tool based on the Nutritional Risk Screening (NRS, 2002 edition).[17,18] NRS includes assessment of the patient's nutritional status (based on weight loss, body mass index (BMI) and general condition or food intake) and disease severity (stress metabolism), and is associated with higher risk for adverse outcomes. Each part is scored from 0 to 3 points, and patients receive an extra point for age above 70 years.

We enrolled patients at nutritional risk (NRS ≥3 points) with an expected length of hospital stay >4 days if they were willing to provide informed consent within 48 hours of hospital admission. We excluded patients initially admitted to intensive care units or surgical units, unable to ingest oral nutrition, already receiving nutritional support on admission, with a terminal condition (i.e., end-of-life situation), hospitalized because of anorexia nervosa, acute pancreatitis, acute liver failure, cystic fibrosis or stem cell transplantation, after gastric bypass surgery, or with contraindications for nutritional support, and patients previously included in the trial. All patients or their authorized representatives provided written informed consent.

Patients were randomly assigned in a 1:1 ratio with variable block size, stratified according to site and the severity of malnutrition, with the use of an interactive web-response system, to receive either individualized nutritional support (intervention group) or standard hospital food (control group).

Study interventions

In the intervention group, nutritional support was initiated as soon as possible after randomization within 48 hours after admission. Patients received individualized nutritional support to reach protein and energy goals according to a previously published consensus protocol[19] in accordance with recent international guidelines.[7] **Figure 1** shows a summary of the nutritional intervention. Briefly, individualized nutritional goals – including energy and protein goals – were defined for each patient upon hospital admission by a trained registered dietician. Energy requirements were predicted using the weight-adjusted Harris-Benedict equation.[20] Daily protein intake was set at 1.2–1.5 g/kg body weight to adjust for higher protein breakdown during acute disease,[21] with lower targets for patients with acute renal failure (0.8 g per kg of body weight). To reach these goals, an individual nutritional plan was developed by a trained registered dietician for each patient. This plan was initially based on oral nutrition provided by the hospital kitchen (including food adjustment according to patient preferences, food fortification [e.g., enrichment of hospital food by adding protein powder] and providing patients with between-meal snacks) and oral nutritional supplements.[10,22] A further increase in nutritional support to enteral tube feeding or parenteral feeding was recommended if at least 75% of energy and protein targets could not be reached through oral feeding within 5 days. Nutritional intake was reassessed every 24–48 h throughout the hospital stay by a trained registered dietician based on daily food records for each patient. Upon hospital discharge, patients received dietary counseling and, if indicated, a prescription for oral nutritional supplements in the outpatient setting.

Control group patients received standard hospital food according to their ability and desire to eat, with no nutritional consultation and no recommendation for additional nutritional support.

Outcome measures

The composite primary endpoint was defined as adverse clinical outcome and included all-cause mortality, admission to the intensive care unit from the medical ward, non-elective hospital readmission after discharge, and major complications including adjudicated nosocomial infection, respiratory failure, a major cardiovascular event (i.e., stroke, intracranial bleeding, cardiac arrest, myocardial infarction) or pulmonary embolism, acute renal failure, gastro-intestinal events (including hemorrhage, intestinal perforation, acute pancreatitis) or a decline in functional status of 10% or more from admission to day 30 measured by the Barthel's index (scores range from 0 to 100, with higher scores indicating better functional status).[23] Detailed definitions for each component of the primary endpoint are summarized in the supplementary material.

The main secondary endpoints were each single component of the primary endpoint, daily protein and energy intakes based on food records for each meal, and total length of hospital stay. Additional assessment at day 30 included the European Quality of Life 5 Dimensions index (German Version, EQ-5D index values range from 0 to 1, with higher scores indicating better quality of life), including the visual-analogue scale (EQ-5D VAS) (scores range from 0 to 100, with higher scores indicating better health status). Safety endpoints included side effects from nutritional therapy, defined as gastrointestinal side effects, complications due to tube feeding or central venous catheter for parenteral nutrition, liver or gallbladder dysfunction, hyperglycemia, and refeeding syndrome.[24]

We obtained outcome data through chart review by site research staff and trained registered dieticians, and phone calls at day 30 by study nurses blinded to group assignment. Mortality of patients during follow-up was verified by family members or the patient`s family physician.

Statistical analysis

We tested the hypothesis that individualized nutritional support was superior to standard hospital food in regard to our primary composite endpoint of adverse clinical outcome. Our primary hypothesis was that early nutritional therapy would reduce adverse clinical outcome and mortality within a follow up period of 30 days after the index hospitalization. From preliminary observational data,[25] we estimate that 40% of the target patient population would reach the primary endpoint within 30 days (10% mortality, 5% ICU admission from the hospital ward, 15%

complications, 10% functional decline with 10% of patients reaching more than 1 endpoint). We hypothesize that our nutritional intervention will decrease this risk by an absolute number of 6% (relative decrease of 15%), i.e., from 40% to 34%. Based on these numbers,[25] we estimated that a sample size of 1016 per group (total number 2032) would have a power of at least 80% to find a reduction in the likelihood of the primary composite endpoint from 0.40 in the control group to 0.34 in the intervention group (absolute risk reduction of 6%).

We performed all the analyses in the intention-to-treat population, which included all patients who had undergone randomization unless they withdrew consent. For the primary outcome, we compared frequencies using a chi-square test. We also fitted a logistic regression model adjusted for main prognostic factors (Barthel's index and NRS at baseline) and study center as predefined in the study protocol. We reported adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI's). We used a similar statistical approach for secondary endpoints, with use of Student's T test and linear regression models for continuous outcomes. We also used the Kaplan–Meier method to calculate the probability of the primary outcome and all-cause mortality within 30 days of randomization.

We conducted predefined subgroup analyses by including interaction terms in the regression models to test for effect modification by important baseline factors.[16] Specifically, we tested for subgroups by patient age, gender, nutritional risk (NRS), initial BMI, admission diagnosis (i.e., infection, heart failure, acute kidney injury, gastrointestinal disease, tumor) and comorbidities (diabetes, chronic kidney disease) as defined in the protocol.

We conducted all analyses with STATA 15.1 (StataCorp. 2015. *Stata Statistical Software: Release 15*. College Station, TX, USA: StataCorp LP). There were no interim analyses planned or conducted during the trial.

Role of funders

The Swiss National Science Foundation (SNSF) (PP00P3_150531) and the Research Council of the Kantonsspital Aarau (1410.000.058 and 1410.000.044) provided funding for the trial. The funders had no role in data collection, analysis, interpretation, writing of the manuscript and the decision to submit. The members of the steering committee (Supplementary Appendix) designed the trial, collected and analyzed the data, prepared the manuscript, and decided to submit the manuscript for publication. The members of the steering committee take responsibility for the accuracy of the data set and adherence to the protocol. There was no commercial involvement in the trial.

Results

Patients

From April 2014 to February 2018 we screened 5015 patients and enrolled 2088. With 60 patients requesting withdrawal of consent and no other losses to follow-up, our final analysis cohort consisted of 2028 patients (**Figure 2**).

Baseline characteristics were similar between groups (**Table 1 and supplemental Table S1**). Patients had a mean age of 72.6 years and a mean body mass index of 24.8 kg/m^2. All patients were at nutritional risk, with 31%, 38% and 31% having 3, 4 and ≥5 points in the NRS, respectively. The most frequent admission diagnoses were infection (n=613, 30.2%), cancer (n=374, 18.4%) and cardiovascular disease (n=205, 10.1%). Patients had a high burden of comorbidities, including malignant disease (n=667, 32.9%), chronic kidney disease (n=641, 31.6%), coronary artery disease (n=566, 27.9%), diabetes (n=428, 21.1%) and congestive heart failure (n=353, 17.4%).

Protocol compliance and nutritional intake

Protocol adherence during the hospital stay was high and energy goals were reached in 79% and protein goals in 76% of intervention group patients according to the study protocol. Control group patients reached energy goals in 54% and protein goals in 55%. Compared to the control group, patients in the intervention group had significantly higher mean [SD] daily energy (1211 [±517] vs. 1501 [±596] kcal/day, difference 290 (95%CI 240 to 340) kcal/day) and protein intakes (47 [±21] vs. 57 [±23] g protein/day, difference 10 (95%CI 8 to 12) g protein/day) during the hospital stay (**Figure 3 and supplemental Figure 1**). These numbers correspond to 18.2 [±8.8] vs. 22.2 [±9.6] kcal per kg bodyweight per day, and 0.70 [±0.34] vs 0.84 [±0.35] g protein per kg bodyweight per day, respectively. In the intervention group, 91% of patients received oral nutritional supplements in combination with enriched hospital nutrition (**supplemental Table S2**). Enteral and parenteral nutrition were used in 8 and 12 patients, respectively. In the control group, 122 patients (12%) received any kind of nutritional support during the hospital stay. On hospital discharge, oral nutritional supplements were prescribed in 24.1% of patients in the intervention group compared to 2.1% of patients in the control group.

Primary endpoint

We had complete information on the primary endpoint in all patients at 30 days. An adverse clinical outcome (primary endpoint) occurred in 232 of 1015 patients (22.9%) in the intervention group and in 272 of 1013 (26.9%) in the control group (adjusted odds ratio 0.79 [95%CI 0.64 to 0.97], p=0.023) (**Table 2)**. Kaplan Meier estimates also show a significant shorter time to reach the primary endpoint in the control group (**Figure 4**).

Regarding the different components of the composite primary endpoint, patients in the intervention group had a lower risk of all-cause mortality within 30 days (73/1015 [7.2%] vs. 100/1013 [9.9%], adjusted odds ratio 0.65 [95% CI 0.47 to 0.91], p=0.011) and a lower risk of functional decline at day 30 of ≥ 10% in the Barthel index compared to control patients (35/942 [3.7%] vs. 55/913 [6.0%], adjusted odds ratio 0.62 [95% CI 0.40 to 0.96], p=0.034). There were no differences in rates of intensive care unit admission, non-elective hospital readmission or major complications between groups.

Secondary endpoints

When compared to the control group, there was a significant improvement in the activities of daily living score at 30 days in the intervention group as measured by the Barthel Index (adjusted difference 3.26 points [95% CI 0.93 to 5.6], p=0.006) and higher quality of life measured by the EQ-5D index (adjusted difference 0.13 [95% CI 0.09 to 0.17], p<0.001) and the EQ-5D VAS (adjusted difference 3.06 points [95% CI 0.53 to 5.59], p=0.018). There was no difference in length of hospital stay between intervention and control group patients (9.6 days vs. 9.5 days, adjusted difference -0.21 days [95% CI -0.76 to 0.35] p=0.46).

We found no significant differences in potential side effects from nutritional support including gastrointestinal side-effects, complications due to enteral feeding and hyperglycemia (**Table 2**).

Subgroup analysis

The effect of nutritional support on the risk for the primary endpoint was consistent across predefined subgroups based on age, gender, baseline nutritional risk stratified by NRS, initial BMI, diagnosis on hospital admission, or diabetes (p interaction for each subgroup analysis >0.05). However, we found a more pronounced beneficial effect of nutritional support compared to control group patients in the population of patients with chronic kidney disease (adjusted OR 0.61 [95% CI 0.44 to 0.86], p interaction = 0.045) (**Figure 5**). Findings regarding subgroup

analysis for the outcome 30-day mortality were similar, with a consistent effect across subgroups except for a more pronounced effect in patients with chronic kidney disease (**supplemental Figure 2**).

Discussion

In this multicenter trial, compared to a control group receiving standard hospital food, individualized nutritional support increased daily energy and protein intakes and lowered the risk of adverse clinical outcomes at 30 days (primary outcome) and all-cause mortality with improvements in functional status and quality of life without an apparent increase in adverse side effects from the intervention.

Several points of this trial are worth mentioning. First, the findings of our trial validate some previous smaller trials,[9-12] but are in contrast to findings of two meta-analyses, which both reported lack of statistically significant improvements in clinical outcomes.[13,14] Set in a real-world context and without commercial funding, our large-scale trial with high nutritional protocol adherence and systematic outcome assessment may resolve the current uncertainty about benefit of nutritional support in medical inpatients. With a number need to treat of 25 to prevent one adverse clinical outcome and 37 to prevent one death, the nutritional intervention was effective at low expenditure. The mortality benefit of nutritional support found in EFFORT was more pronounced compared to results of a pooled meta-analysis including 22 previous trials (9.8% vs. 10.3%, NNT 200),[13] but in the range of the effect reported in the recent NOURISH trial (4.8% vs 9.7%, NNT 20).[9] Second, to increase external validity, EFFORT was pragmatic and included a broad and unselected population of consecutive multimorbid medical inpatients with different acute illnesses and chronic co-morbidities. Several previous trials focused on selected patient populations.[9,13,26] The beneficial effects of nutritional support were robust and similar in subgroups according to patient age, gender, severity of nutritional risk and underlying disease. The effects were even more pronounced in patients with chronic kidney disease, a condition known to predispose patients to protein-energy wasting.[27] Third, no specific adverse side effects of the intervention were noted. This is also true for patients with pre-existing diabetes, a population that was excluded in previous trials due to concerns of hyperglycemia.[9] Currently there is debate about the benefits and optimal use of nutritional support in medical patients with acute and severe illness[28] with respect to dose and quality of proteins and total energy, route of delivery, and if or how nutritional support needs to be adjusted for specific medical conditions.[28,29] Importantly, slower recovery and more complications were reported in critical care patients receiving full-replacement feeding.[1,30] There are important differences between our study and recent critical care trials with regard to patient population, severity of disease, and nutritional intervention. Due to the milder severity of illness in our population, cells may better metabolize

and use nutrients more effectively because cells are less insulin resistant and there is lower risk for autophagy.[2,31]

Our findings should not be used to support full-replacement feeding in medical inpatients. Rather our concept of using individualized nutritional support with an aim of reaching at least 75% of nutritional goals has better clinical outcomes compared to not providing nutritional support. Patients in our trial received nutritional support according to a previously published feeding protocol with individual definition of each patient's nutritional goals and individualized nutritional support to reach those goals.[19] The nutritional protocol was based on a pathophysiological rationale and results of observational and smaller randomized trials. Unlike other trials investigating the effect of specific nutritional formulas,[9] we used a variety of nutritional support strategies with the support of trained dieticians to reach nutritional goals. Our trial does thus not provide evidence regarding single nutritional components, but rather proves that the overall strategy of providing nutritional support to reach protein and energy goals during the acute phase of illness is beneficial for patients.

EFFORT also has important ethical considerations. Despite strong associations in observational research between malnutrition and adverse clinical outcome, it remained unclear whether provision of nutritional support indeed has the potential to reduce the risks associated with malnutrition, or in contrast has deleterious effects on outcomes as demonstrated in critical care trials.[30] After discussions among national experts in the field (i.e., trial collaborators) and our ethical review board, we were of the opinion that it was ethically acceptable that patients in the control group received no additional nutritional treatment. This is also in accordance with a previous Swiss consensus ethical statement pointing out that "intake of standard food and fluids is a basic right of any patients", yet any sort of nutritional therapy must be viewed as a therapeutic measure and must therefore fulfill all criteria for such including proof of clinical effectiveness, safety and cost-effectiveness.[32] For our patient population, such proofs was still missing and was thus the main aim of this trial.

We are aware of limitations in our study. First, our trial was pragmatic, and blinding of participants and personnel was deemed to be impractical. Although the primary outcome at 30 days was objective and its assessment was blinded, some of the outcomes assessed during the hospital stay may have been vulnerable to observer bias. Second, about 20% of intervention group patients did not fully reach energy and protein goals despite use of the nutritional protocol implemented by trained dieticians. Similar to real-life experience, several patient, treatment, and hospital factors (e.g., delay or refusal to start enteral or parenteral nutrition by the patient, early

discharge of patients, diagnostic exams interfering with nutritional support) may have prevented full adherence to the protocol. Still, we expect this bias to be conservative with regards to the relevant endpoints, and protocol adherence was higher as compared to previous nutritional trials in the medical inpatient setting.[13] Third, nutrition in the control group represented the reality of standard Swiss hospital food, which may not be unconditionally generalizable to other health care systems. Forth, we did not yet investigate costs of the intervention, but we have planned to perform a cost-effectiveness analysis based on the trial data in the future. Finally, we had a delay in registration as we started the trial with a pilot to assure feasibility of the complex nutritional intervention and to secure funding for the multicenter rollout. However, there was no change in trial protocol and we thus used all included patients for the final analysis.

Understanding the optimal use of nutritional support is complex because timing, route of delivery, and the amount and type of nutrients may all affect patient outcomes. In our trial, we asked the basic question of whether nutritional support during the hospital stay improves clinical outcomes of medical patients at nutritional risk compared to standard hospital food. This trial shows that early use of individualized nutritional support to reach protein and energy goals in medical inpatients at nutritional risk is effective in increasing energy and protein intakes, and in lowering the risk of adverse outcomes and mortality within 30 days. Our findings strongly support the concept of systematically screening medical inpatients on hospital admission regarding nutritional risk, independent of medical condition, followed by a nutritional assessment and institution of individualized nutritional support in at-risk patients.

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DISCLOSURES

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AUTHOR CONTRIBUTION

Prof. Philipp Schuetz was the principal investigator of this trial and was responsible for obtaining funding, drafting the trial protocol, data analysis and interpretation, and writing of the final report.

Rebecca Fehr, Valerie Baechli, Martina Geiser, Manuela Deiss, Pascal Tribolet, Nina Braun, Sarah Schmid, Carmen Benz, Silvia Mattmann and Claudia Brand were involved in drafting the trial protocol, data collection and approved the final version of the manuscript.

Filomena Gomes, Alexander Kutz, Thomas Bregenzer, Claus Hoess, Vojtech Pavlicek, Stefan Bilz, Sarah Sigrist, Michael Brändle, Christoph Henzen, Robert Thomann, Jonas Rutishauser, Drahomir Aujesky, Nicolas Rodondi and Jacques Donzé were involved in drafting the trial protocol, supervision of study sites, drafting of the final manuscript and approved the final version of the manuscript.

Zeno Stanga and Beat Mueller were involved in obtaining funding, drafting the trial protocol, supervision of study sites, drafting of the final manuscript and approved the final version of the manuscript.

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TABLES AND FIGURE LEGENDS

Figure 1. Nutritional algorithm used during the trial according to a previous consensus conference[19]

In a first step, all medical patients entering the hospital were assessed for risk of malnutrition within 24-48 h using the Nutritional Risk screening (NRS 2002).[33] In patients with nutritional risk defined as a NRS of ≥3 points, nutritional goals were defined. These included energy and protein goals, micronutrient goals and other disease-specific targets. Energy requirements were predicted using the Harris-Benedict equation. For under- and overweight patients, the formula has to be adjusted for body weight to improve its accuracy.[20] For all patients, a protein intake of 1.2-1.5 g per kg bodyweight per day was recommended, except for patients with acute renal failure. For these patients 0.8 g protein per kg per day were recommended. Also, we recommended supplementation of all patients with multivitamin/multimineral supplements.

Once goals were set, a nutritional plan to achieve these goals was established. We recommended to first use oral nutrition including food adjustment according to patient preferences, food fortification of meals and providing patients with between-meal snacks. Also, oral nutritional supplements were recommended to meet nutritional requirements.[10,22] Enteral feeding was advised if at least 75% of energy and protein targets could be reached within 5 days of oral feeding. Intakes were reassessed every 24-48h. Enteral feeding was provided by nasogastric tube or percutaneous endoscopic gastrostomy (PEG) depending on expected time course of feeding. If the enteral route failed to achieve the goal of providing at least 75% of energy and protein targets, start of parenteral nutrition with a minimal oral or enteral feeding was recommended.

Figure 2. Flow of patients through EFFORT

Figure 3. Percentage of patients reaching energy (A) and protein (B) requirements during the first 10 days post-randomization, in both control and intervention groups

Figure 4. Kaplan–Meier estimates of the cumulative incidence of the primary endpoint (A) and all-cause mortality (B)

Panel A shows the Kaplan–Meier curves for the time to the first event of the composite primary endpoint (p log rank 0.035). Panel B shows the Kaplan–Meier curves for the time to death (p log rank 0.031).

Figure 5. Odds ratios for adverse outcome (primary outcome) in prespecified subgroups

The only significant interactions between group assignment and subgroup were for chronic kidney disease. The body-mass index is the weight in kilograms divided by the square of the height in meters. NRS denotes nutritional risk screening.

Table 1. Characteristics of the Patients at Trial Entry*

Characteristic	Control group (N=1013)	Intervention group (N=1015)
Socio-demographics		
Age – yrs – mean (SD)	72.8 (±14.1)	72.4 (±14.1)
Age group – number (%)		
< 65 years	178 (17.6%)	177 (17.4%)
65-75 years	322 (31.8%)	349 (34.4%)
75 years	513 (50.6%)	489 (48.2%)
Male sex – number (%)	539 (53.2%)	525 (51.7%)
Nutritional assessment		
*Body mass Index (BMI) – kg/m^2	24.7 (±5.3)	24.9 (±5.4)
Body weight (Kg) – mean (SD)	70.9 (±16.4)	70.9 (±16.4)
****NRS – total score** – number (%)		
3 points	314 (31.0%)	310 (30.5%)
4 points	384 (37.9%)	391 (38.5%)
5 points	261 (25.8%)	263 (25.9%)
>5 points	54 (5.3%)	51 (5.0%)
Admission diagnosis – number (%)		
Infection	315 (31.1%)	298 (29.4%)
Cancer	173 (17.1%)	201 (19.8%)
Cardiovascular disease	113 (11.2%)	92 (9.1%)
Failure to thrive	95 (9.4%)	99 (9.8%)
Lung disease	75 (7.4%)	50 (4.9%)
Gastrointestinal disease	68 (6.7%)	96 (9.5%)
Neurological disease	53 (5.2%)	42 (4.1%)
Renal disease	34 (3.4%)	34 (3.3%)
***Metabolic disease	32 (3.2%)	30 (3.0%)
Other	25 (2.5%)	30 (3.0%)
Coexisting medical condition – number (%)		
Hypertension	552 (54.5%)	557 (54.9%)
Malignant disease	329 (32.5%)	338 (33.3%)
Chronic kidney disease	318 (31.4%)	323 (31.8%)
Coronary heart disease	279 (27.5%)	287 (28.3%)
Diabetes	213 (21.0%)	215 (21.2%)
Congestive heart failure	179 (17.7%)	174 (17.1%)
COPD	156 (15.4%)	147 (14.5%)
Peripheral arterial disease	106 (10.5%)	80 (7.9%)
Cerebrovascular disease	87 (8.6%)	75 (7.4%)
Dementia	36 (3.6%)	39 (3.8%)

*There were no significant differences between the groups at baseline, except for admission diagnosis of gastrointestinal disease and lung disease, and comorbidity of peripheral arterial disease.
Percentages may not total 100 because of rounding.
*The body-mass index is the weight in kilograms divided by the square of the height in meters.
** Scores on nutritional risk screening range from 0 to 7, with a score of ≥3 identifying patients at nutritional risk and higher scores indicating higher risk.
COPD denotes chronic obstructive pulmonary disease.

*** Metabolic disease included hypoglycemia, hyperglycemia, ketoacidosis, electrolyte disturbances including hyponatremia and hypernatremia, hypokalemia and hyperkalemia among others

Table 2. Primary and Secondary Endpoints

	Control group (N=1013)	Intervention group (N=1015)	Odds ratio or Coefficient (95% CI), p value
Outcome			
Primary outcome – number (%)			
Adverse outcome within 30 days	272 (26.9%)	232 (22.9%)	0.79 (0.64 to 0.97), p=0.023
Single components of primary outcome – number (%)			
All-cause mortality	100 (9.9%)	73 (7.2%)	0.65 (0.47 to 0.91), p=0.011
Admission to the intensive care unit (ICU)	26 (2.6%)	23 (2.3%)	0.85 (0.48 to 1.51), p=0.575
Non-elective hospital readmission	91 (9.0%)	89 (8.8%)	0.99 (0.73 to 1.35), p=0.958
Major complications			
- Any major complication	76 (7.5%)	74 (7.3%)	0.95 (0.68 to 1.34), p=0.788
- Nosocomial infection	39 (3.8%)	40 (3.9%)	1.01 (0.63 to 1.59), p=0.98
- Respiratory failure	13 (1.3%)	14 (1.4%)	1.06 (0.49 to 2.28), p=0.889
- Major cardiovascular event	7 (0.7%)	8 (0.8%)	1.11 (0.40 to 3.11), p=0.841
- Acute kidney failure	31 (3.1%)	32 (3.2%)	1.01 (0.61 to 1.69), p=0.956
- Gastrointestinal events	15 (1.5%)	9 (0.9%)	0.57 (0.25 to 1.31), p=0.186
Decline in functional status of ≥10%*, no./total no. (%)	55/913 (6.0%)	35/942 (3.7%)	0.62 (0.40 to 0.96), p=0.034
Additional secondary outcomes			
Length of hospital stay			
- Length of stay – days	9.6 (±6.1)	9.5 (±7.0)	-0.21 (-0.76 to 0.35), p=0.46
Activities of daily living*			
- Barthel score – points	85 (±30)	88 (±26)	3.26 (0.93 to 5.60), p=0.006
Quality of Life**			
- EQ-5D Visual-analogue scale – points	56 (±29)	59 (±26)	0.13 (0.09 to 0.17), p<0.001
- EQ-5D index	0.73 (±0.34)	0.75 (±0.32)	3.06 (0.53 to 5.59), p=0.018
Side effects – number (%)			
Side effects from nutritional support	145 (14.3%)	162 (16.0%)	1.16 (0.90 to 1.51), p=0.258
- Gastointestinal side effects	40 (3.9%)	43 (4.2%)	1.12 (0.68 to 1.83), p=0.664
- Complications due to enteral feeding or PN	3 (0.3%)	5 (0.5%)	1.63 (0.38 to 6.95), p=0.507
- Liver or gall bladder dysfunction	7 (0.7%)	4 (0.4%)	0.54 (0.15 to 1.91), p=0.34
- Severe hyperglycemia	46 (4.5%)	48 (4.7%)	1.06 (0.69 to 1.61), p=0.801
- Refeeding syndrome	73 (7.2%)	86 (8.5%)	1.21 (0.86 to 1.70), p=0.272

All odds ratios were calculated with logistic regression for binary data and linear regression for continuous data. Models were adjusted for predefined prognostic factors (initial NRS and baseline Barthel index) and study center.
ICU denotes intensive care unit; PN denotes parenteral nutrition. CI denotes confidence interval. EQ-5D denotes European Quality of Life 5 Dimensions.
Detailed definitions of outcomes are presented in the supplementary material
*To estimate decline in functional status we used the Barthel index (scores range from 0 to 100, with higher scores indicating better functional status) and compared initial scores on admission with scores at 30 days; only survivors were included in this analysis
**To estimate quality of life we used the European Quality of Life 5 Dimensions index (values range from -0.205 to 1, with higher scores indicating better quality of life) including the visual-analogue scale (EQ-5D VAS) (scores range from 0 to 100, with higher scores indicating better health status).