# Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial

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## Summary

**Background** Guidelines recommend the use of nutritional support during hospital stays for medical patients (patients not critically ill and not undergoing surgical procedures) at risk of malnutrition. However, the supporting evidence for this recommendation is insufficient, and there is growing concern about the possible negative effects of nutritional therapy during acute illness on recovery and clinical outcomes. Our aim was thus to test the hypothesis that protocol-guided individualised nutritional support to reach protein and caloric goals reduces the risk of adverse clinical outcomes in medical inpatients at nutritional risk.

**Methods** The Effect of early nutritional support on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial (EFFORT) is a pragmatic, investigator-initiated, open-label, multicentre study. We recruited medical patients at nutritional risk (nutritional risk screening 2002 [NRS 2002] score ≥3 points) and with an expected length of hospital stay of more than 4 days from eight Swiss hospitals. These participants were randomly assigned (1:1) to receive either protocol-guided individualised nutritional support to reach protein and caloric goals (intervention group) or standard hospital food (control group). Randomisation was done with variable block sizes and stratification according to study site and severity of malnutrition using an interactive web-response system. In the intervention group, individualised nutritional support goals were defined by specialist dietitians and nutritional support was initiated no later than 48 h after admission. Patients in the control group received no dietary consultation. The composite primary endpoint was any adverse clinical outcome defined as all-cause mortality, admission to intensive care, non-elective hospital readmission, major complications, and decline in functional status at 30 days, and it was measured in all randomised patients who completed the trial. This trial is registered with ClinicalTrials.gov, number NCT02517476.

**Findings** 5015 patients were screened, and 2088 were recruited and monitored between April 1, 2014, and Feb 28, 2018. 1050 patients were assigned to the intervention group and 1038 to the control group. 60 patients withdrew consent during the course of the trial (35 in the intervention group and 25 in the control group). During the hospital stay, caloric goals were reached in 800 (79%) and protein goals in 770 (76%) of 1015 patients in the intervention group. By 30 days, 232 (23%) patients in the intervention group experienced an adverse clinical outcome, compared with 272 (27%) of 1013 patients in the control group (adjusted odds ratio [OR] 0·79 [95% CI 0·64–0·97], p=0·023). By day 30, 73 [7%] patients had died in the intervention group compared with 100 [10%] patients in the control group (adjusted OR 0·65 [0·47–0·91], p=0·011). There was no difference in the proportion of patients who experienced side-effects from nutritional support between the intervention and the control group (162 [16%] *vs* 145 [14%], adjusted OR 1·16 [0·90–1·51], p=0·26).

**Interpretation** In medical inpatients at nutritional risk, the use of individualised nutritional support during the hospital stay improved important clinical outcomes, including survival, compared with standard hospital food. These findings strongly support the concept of systematically screening medical inpatients on hospital admission regarding nutritional risk, independent of their medical condition, followed by a nutritional assessment and introduction of individualised nutritional support in patients at risk.

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## Introduction

Anorexia arises as a physiological response to acute illness and predisposes hospital inpatients to serious caloric and protein deficits.[1] In combination with immobilisation 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 medical patients with multiple morbidities.[2,3] More than 30% of medical inpatients are at increased risk of malnutrition, a condition that is strongly associated with increased mortality and morbidity, functional decline, prolonged hospital stays, and increased costs of health care.[4–6]

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## Research in context

### Evidence before this study

Current clinical practice guidelines recommend to consider initiating nutritional support during the hospital stay of medical inpatients at risk of malnutrition. However, these recommendations are largely based on physiological rationales and observational studies, rather than interventional research. A systematic review and meta-analysis published in 2016 that focused on randomised trials investigating the effects of nutritional interventions on clinical outcomes in medical inpatients, found only 22 trials with a total of 3736 participants. Trials were mostly small and heterogeneous with overall low study quality. The pooled analysis showed that nutritional interventions increased caloric and protein intake, as well as patient weight, but there was no effect on mortality, functional outcomes, or length of hospital stay. Thus, based on current clinical trials, it is still unclear whether systematic screening for malnutrition in medical patients on their admission to hospital and introduction of nutritional support in patients at risk has positive effects on clinical outcomes.

### Added value of this study

This pragmatic, large-scale, multicentre trial showed that early use of individualised nutritional support to reach protein and caloric goals in medical inpatients at nutritional risk is effective in increasing caloric and protein intakes and in lowering the risk of adverse outcomes and mortality within 30 days. Patients receiving nutritional support also had improvements in functional outcomes and quality of life. The beneficial effects of nutritional support were robust and comparable in subgroups according to patient age, sex, severity of nutritional risk, and underlying disease.

### Implications of all the available evidence

Malnutrition is a highly prevalent condition in medical inpatients that negatively impacts clinical outcomes. In conjunction with results of earlier smaller trials and observational research, findings of EFFORT strongly support the concept of systematically screening medical inpatients on their admission to hospital regarding nutritional risk, independent of medical condition, followed by a nutritional assessment and introduction of individualised nutritional support in patients at risk.

Current clinical practice guidelines, including those by the European Society for Clinical Nutrition and Metabolism[7] and the American Society for Parenteral and Enteral Nutrition,[8] recommend considering placing medical inpatients identified by screening and assessment as being at risk of malnutrition on nutritional support during their hospital stay. However, these recommendations are largely based on physiological rationales and observational studies. Some small trials have found that nutritional support reduced the length of hospital stays and decreased mortality.[9–12] Yet, two meta-analyses reported no significant improvements in clinical outcomes associated with nutritional interventions in medical inpatients receiving nutritional support, despite their increased caloric and protein intake.[13,14] Additionally, the introduction of nutritional support in medical inpatients with acute illnesses is currently challenged by results of several high-quality trials in critical care settings, which reported harmful effects of full replacement nutrition strategies.[1] These negative effects might be explained by suppression of autophagy with inadequate clearance of acute cell damage associated with illness.[15]

In view of the scarcity of high-quality data from medical inpatients and possible conflicts between current recommendations for medical inpatients and trials of critical care, we did 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 individualised nutritional support to reach protein and caloric goals reduces the risk of adverse clinical outcomes in medical inpatients at nutritional risk.

## Materials and methods

### Study design and participants

EFFORT is a pragmatic, investigator-initiated, open-label, non-blinded, non-commercial, multicentre, randomised, 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 eight participating sites were secondary and tertiary care hospitals 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 in Lachen. All sites routinely used a validated screening tool for malnutrition based on the nutritional risk screening 2002 (NRS 2002) score.[17,18] Nutritional risk screening 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 increased risk of adverse outcomes. Each risk predictor is scored from 0 to 3 points, and patients receive an extra point if they are aged over 70 years.

We enrolled patients aged at least 18 years at nutritional risk of 3 or greater expected to stay in hospital for more than 4 days if they were willing to provide informed consent within 48 h of hospital admission for any reason. Patients were enrolled between April 1, 2014, and

Feb 28, 2018. We excluded patients who were initially admitted to intensive care units or surgical units; unable to ingest oral nutrition; already receiving nutritional support on admission; with a terminal condition; admitted to hospital because of anorexia nervosa, acute pancreatitis, acute liver failure, cystic fibrosis, or stem-cell transplantation; after gastric bypass surgery; with contraindications for nutritional support; and previously included in the trial. All patients or their authorised representatives provided written informed consent.

The Ethics Committee of Northwest and Central Switzerland (EKNZ) approved the study protocol in January, 2014 (registration ID 2014_001). The trial was started with a pilot study in Kantonsspital Aarau (Aarau, Switzerland) between April 1, 2014, and Aug 15, 2015, during which time 175 participants were recruited. After funding for the trial was secured and the pilot showed high feasibility of nutritional intervention to improve patient outcomes, the trial was registered at ClinicalTrials.gov (NCT02517476), in August, 2015 and enrolment of patients was broadened to all participating centres. There was no change in protocol regarding outcomes and interventional procedures between the initial institutional review board protocol and the final trial protocol.

## Randomisation

Patients were randomly assigned (1:1) to receive either individualised nutritional support (intervention group) or standard hospital food (control group). Randomisation was done with an interactive web-response system, with variable block sizes, and patients were stratified according to site and the severity of malnutrition. All participants and investigators were aware of group assignment but outcome assessment was done by masked nurses.

## Procedures

In the intervention group, nutritional support was initiated as soon as possible after randomisation and within 48 h after hospital admission. Patients received individualised nutritional support (figure 1) to reach protein and caloric goals, according to a previously published consensus protocol[19] that follows 2018 international guidelines.[7] Briefly, individualised nutritional goals were defined for each patient on hospital admission by a trained registered dietitian. Caloric requirements were predicted using the weight-adjusted Harris-Benedict equation.[20] Daily protein intake was set at 1·2–1·5 g/kg of bodyweight to adjust for increased protein breakdown during acute disease,[21] with lower targets for patients with acute renal failure (0·8 g/kg of bodyweight). To reach these goals, an individual nutritional plan was developed by a trained registered dietitian 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 such as enrichment of hospital food by adding protein powder, and snacks between meals) and oral nutritional supplements.[10,22] A

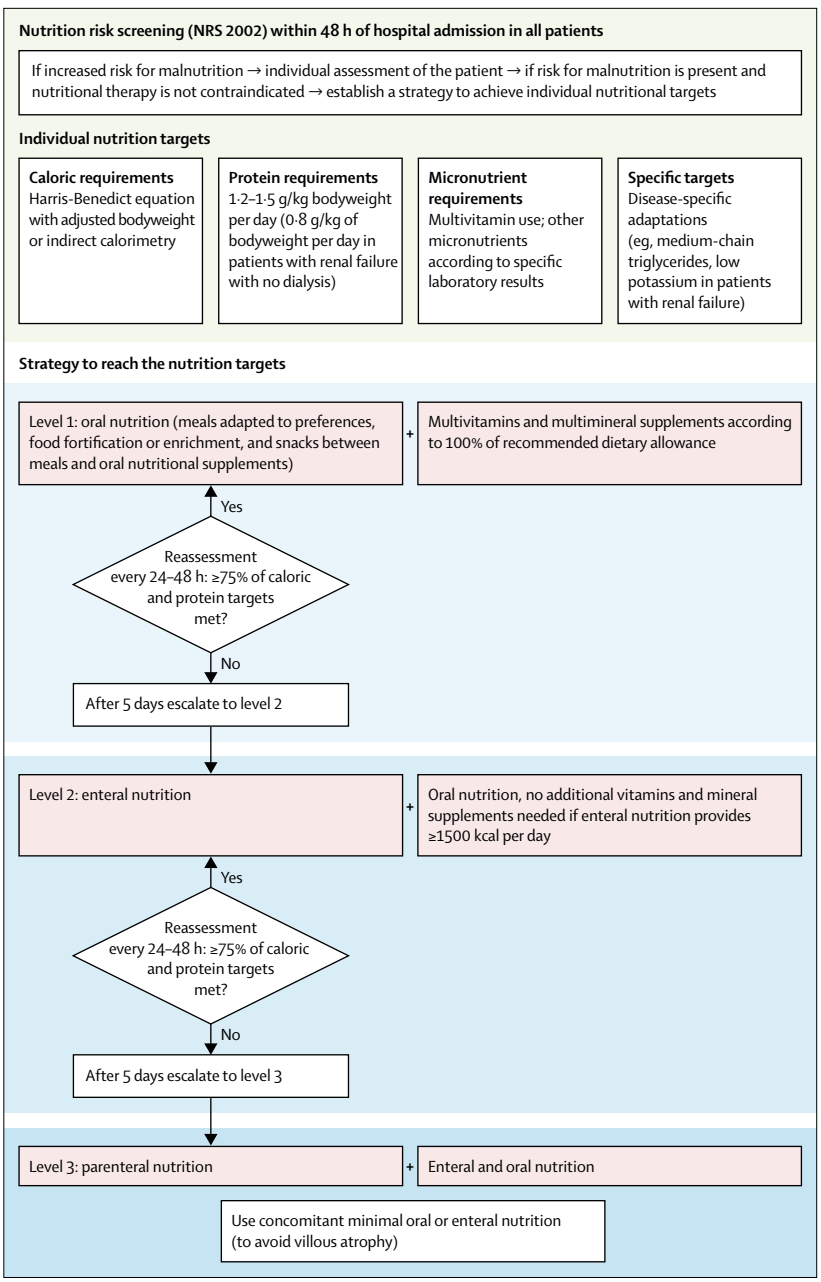


***Figure 1:*** **Nutritional algorithm used during the trial**
Reproduced from Bounoure et al,[19] by permission of Elsevier.

further increase in nutritional support to enteral tube feeding or parenteral feeding was recommended if at least 75% of the daily caloric and protein targets could not be reached through oral feeding within 5 days. Nutritional intake was re-assessed every 24–48 h throughout the hospital stay by a trained registered dietitian on the basis of daily food records for each patient. On their discharge from hospital, patients received dietary counselling and, if indicated, a prescription for oral nutritional supplements in the outpatient setting. Patients did not

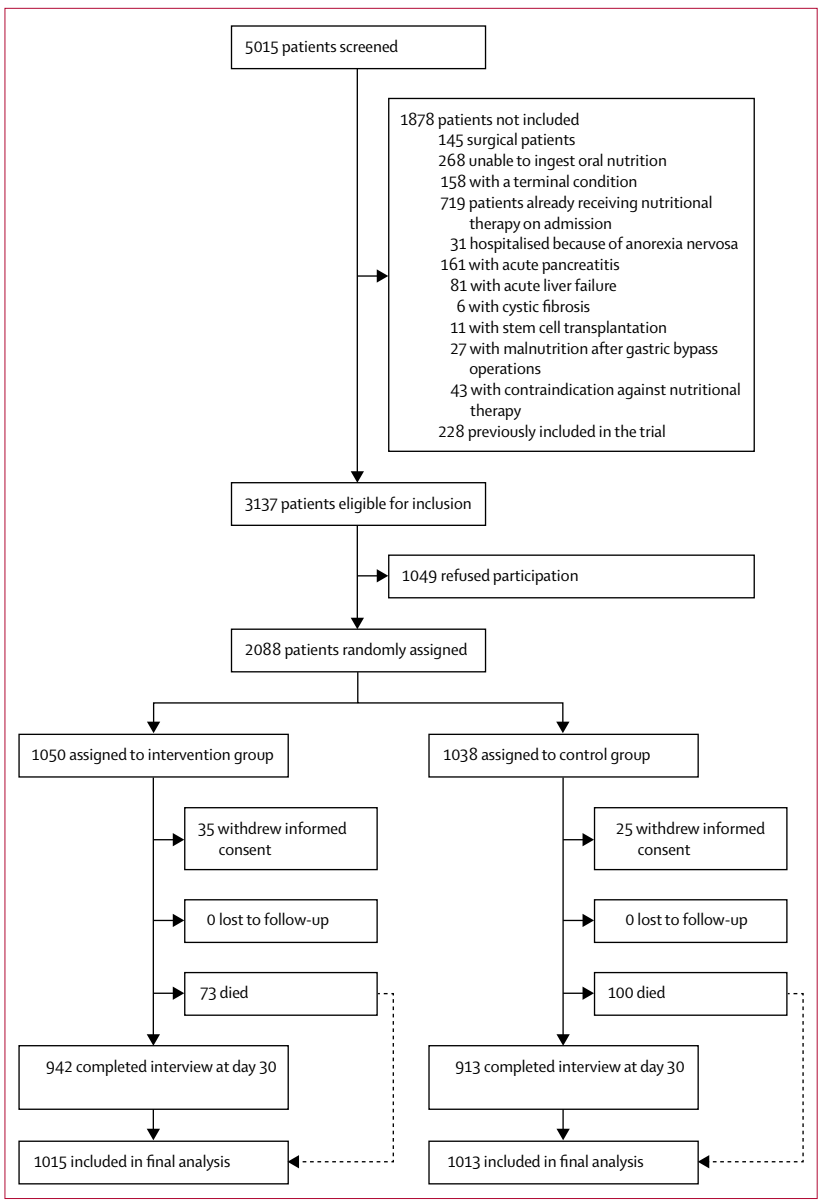


***Figure 2:*** **Trial profile**

receive dietary counselling in the outpatient setting after discharge.

Patients in the control group received standard hospital food according to their ability and desire to eat, with no nutritional consultation and no recommendation for additional nutritional support. On discharge, outcomes in these patients were followed up in the same way as patients in the intervention group but the decision to prescribe nutritional support was at the discretion of the nursing and physician team

## Outcomes

The composite primary endpoint was defined as adverse clinical outcome within 30 days, and it included: all-cause mortality; admission to the intensive care unit from the medical ward; non-elective hospital re-admission after discharge; major complications as a new occurrence including adjudicated nosocomial infection, respiratory failure, a major cardiovascular event (ie, stroke, intracranial bleeding, cardiac arrest, myocardial infarction, or pulmonary embolism), acute renal failure, gastrointestinal failure (ie, haemorrhage, intestinal perforation, acute pancreatitis); or a decline in functional status of 10% or more from admission to day 30 as 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 summarised in the appendix.

The main secondary endpoints were each individual component of the primary endpoint, daily protein and caloric intake based on food records for each meal, and total length of hospital stay, as well as short-term change in bodyweight. Our protocol paper[16] defined additional secondary outcomes, including other measurements at day 7 and after 180 days of trial inclusion; however, we did not report all because of missing (ie, outcomes at day 7) or incomplete information (long-term outcomes). Additional assessment at day 30 was done through the German version of the 5-level European Quality of Life 5 Dimensions index (EQ-5D; index values range from 0 to 1, with higher scores indicating better quality of life), including the self-assessment visual analogue scale (EQ-5D VAS; scores range from 0 to 100, with higher scores indicating better health status). We did not refer to the Functional Assessment Anorexia–Cancer Therapy questionnaire, as denoted in the EFFORT protocol,[16] because it is specifically aimed at patients with cancer and we did not investigate them separately from the overall population of medical patients in the analysis. Safety endpoints were 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, hyperglycaemia, and refeeding syndrome.[24] We obtained outcome data from charts reviewed by site research staff and trained registered dietitians, and phone calls at day 30 with study nurses masked to group assignment. Mortality during follow-up was verified by family members or the patient's family physician.

## Statistical analysis

We tested the hypothesis that individualised nutritional support was superior to standard hospital food to avoid adverse clinical outcomes, which was our primary composite endpoint. We postulated that early nutritional therapy would reduce adverse clinical outcomes and mortality within a follow-up period of 30 days after the index hospitalisation. From preliminary observational data,[25] we estimated that 40% of the target patient population would reach the primary endpoint within 30 days (10% mortality, 5% admission to an intensive care

| | Intervention group (n=1015) | Control group (n=1013) |
|---|---|---|
| **Sociodemographics** | | |
| Mean age (years) | 72·4 (14·1) | 72·8 (14·1) |
| Age group (years) | | |
| <65 | 177 (17%) | 178 (18%) |
| 65–75 | 349 (34%) | 322 (32%) |
| >75 | 489 (48%) | 513 (51%) |
| Male sex | 525 (52%) | 539 (53%) |
| **Nutritional assessment** | | |
| Mean body-mass index (kg/m²)* | 24·9 (5·4) | 24·7 (5·3) |
| Mean bodyweight (kg) | 70·9 (16·4) | 70·9 (16·4) |
| **NRS 2002 score (%)†** | | |
| 3 points | 310 (31%) | 314 (31%) |
| 4 points | 391 (39%) | 384 (38%) |
| 5 points | 263 (26%) | 261 (26%) |
| >5 points | 51 (5%) | 54 (5%) |
| **Admission diagnosis** | | |
| Infection | 298 (29%) | 315 (31%) |
| Cancer | 201 (20%) | 173 (17%) |
| Cardiovascular disease | 92 (9%) | 113 (11%) |
| Failure to thrive | 99 (10%) | 95 (9%) |
| Lung disease | 50 (5%) | 75 (7%) |
| Gastrointestinal disease | 96 (9%) | 68 (7%) |
| Neurological disease | 42 (4%) | 53 (5%) |
| Renal disease | 34 (3%) | 34 (3%) |
| Metabolic disease‡ | 30 (3%) | 32 (3%) |
| Other | 30 (3%) | 25 (2%) |
| **Comorbidity** | | |
| Hypertension | 557 (55%) | 552 (54%) |
| Malignant disease | 338 (33%) | 329 (32%) |
| Chronic kidney disease | 323 (32%) | 318 (31%) |
| Coronary heart disease | 287 (28%) | 279 (28%) |
| Diabetes | 215 (21%) | 213 (21%) |
| Congestive heart failure | 174 (17%) | 179 (18%) |
| Chronic obstructive pulmonary disease | 147 (14%) | 156 (15%) |
| Peripheral arterial disease | 80 (8%) | 106 (10%) |
| Cerebrovascular disease | 75 (7%) | 87 (9%) |
| Dementia | 39 (4%) | 36 (4%) |

Data are number of participants (%) or mean (SD). 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. *The body-mass index is the weight in kilograms divided by the square of the height in metres. †Scores on nutritional risk screening range from 0 to 7, with a score of 3 or more identifying patients at nutritional risk and higher scores indicating increased risk. ‡Metabolic disease included, but was not limited to, hypoglycaemia, hyperglycaemia, ketoacidosis, electrolyte disturbances including hyponatraemia and hypernatraemia, hypokalaemia, and hyperkalaemia. NRS 2002=nutritional risk screening 2002.

***Table 1:*** **Characteristics of the patients at trial entry**

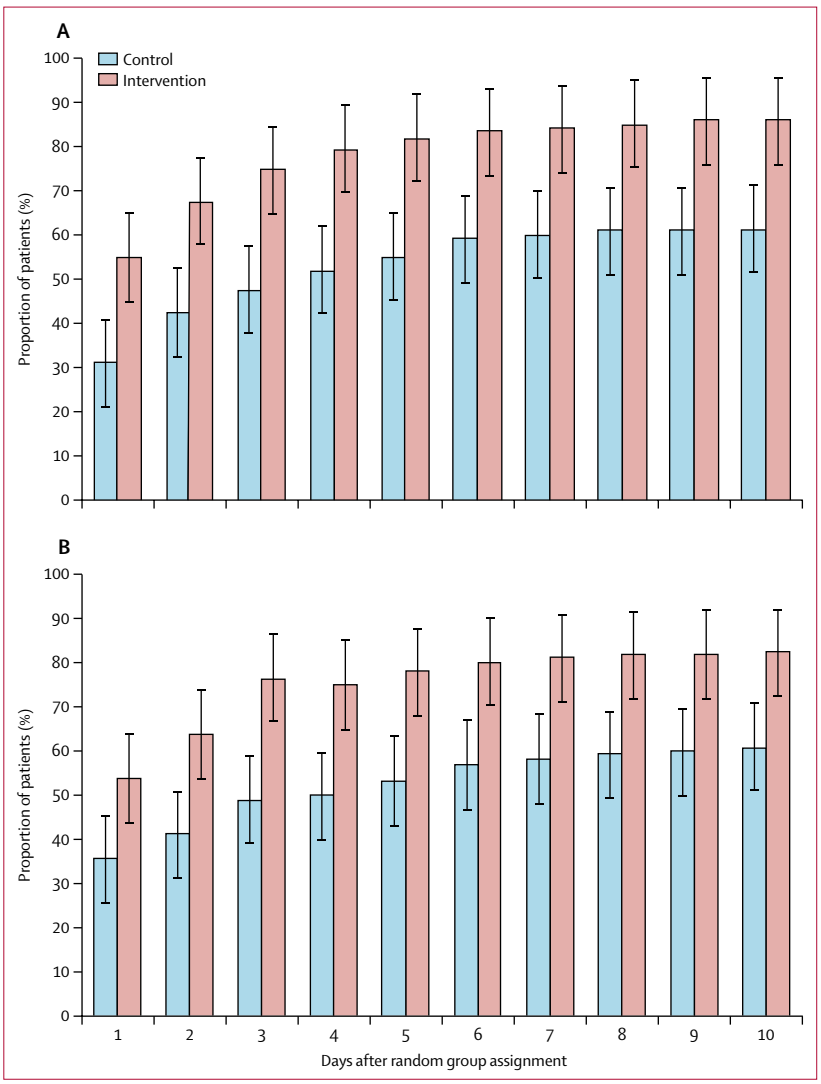


***Figure 3:*** **Proportion of patients reaching caloric (A) and protein (B) requirements during the first 10 days after random group assignment**

unit from the hospital ward, 15% complications, and 10% functional decline, with 10% of patients reaching more than one endpoint). We hypothesised that our nutritional intervention would decrease this risk by an absolute number of 6% (relative decrease of 15%), from 40% to 34%. On the basis of 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 probability of the primary composite endpoint from 0·40 in the control group to 0·34 in the intervention group, representing an absolute risk reduction of 6%.

All analyses were done in the intention-to-treat population, which included all patients who had undergone randomisation, unless they withdrew consent or were lost to follow-up. For the primary outcome, we compared frequencies of adverse events using a $\chi^2$ test. The Kaplan-Meier method was used post hoc to visualise primary outcome data over time by calculating the probability of the primary outcome and of all-cause mortality within 30 days of randomisation. We also fitted a logistic regression model predefined in the study protocol and

| | Intervention group (n=1015) | Control group (n=1013) | Odds ratio or coefficient (95% CI) | p value |
|---|---|---|---|---|
| **Outcomes** | | | | |
| Primary outcome | | | | |
| Adverse outcome within 30 days | 232 (23%) | 272 (27%) | 0·79 (0·64 to 0·97) | 0·023 |
| Single components of primary outcome | | | | |
| All-cause mortality | 73 (7%) | 100 (10%) | 0·65 (0·47 to 0·91) | 0·011 |
| Admission to the intensive care unit | 23 (2%) | 26 (3%) | 0·85 (0·48 to 1·51) | 0·58 |
| Non-elective hospital readmission | 89 (9%) | 91 (9%) | 0·99 (0·73 to 1·35) | 0·96 |
| Major complications | | | | |
| Any major complication | 74 (7%) | 76 (8%) | 0·95 (0·68 to 1·34) | 0·79 |
| Nosocomial infection | 40 (4%) | 39 (4%) | 1·01 (0·63 to 1·59) | 0·98 |
| Respiratory failure | 14 (1%) | 13 (1%) | 1·06 (0·49 to 2·28) | 0·89 |
| Major cardiovascular event | 8 (1%) | 7 (1%) | 1·11 (0·40 to 3·11) | 0·84 |
| Acute kidney failure | 32 (3%) | 31 (3%) | 1·01 (0·61 to 1·69) | 0·96 |
| Gastrointestinal events | 9 (1%) | 15 (1%) | 0·57 (0·25 to 1·31) | 0·19 |
| Decline in functional status of ≥10%* | 35 (4%) of 942 | 55 (6%) of 913 | 0·62 (0·40 to 0·96) | 0·034 |
| Additional secondary outcomes | | | | |
| Mean length of stay (days) | 9·5 (7·0) | 9·6 (6·1) | –0·21 (–0·76 to 0·35) | 0·46 |
| Mean Barthel score (points)* | 88 (26) | 85 (30) | 3·26 (0·93 to 5·60) | 0·006 |
| Mean EQ-5D VAS (points)† | 59 (26) | 56 (29) | 3·06 (0·53 to 5·59) | <0·0001 |
| Mean EQ-5D index (points) | 0·75 (0·32) | 0·73 (0·34) | 0·13 (0·09 to 0·17) | 0·018 |
| **Side-effects from nutritional support** | | | | |
| All side-effects | 162 (16%) | 145 (14%) | 1·16 (0·90 to 1·51) | 0·26 |
| Gastrointestinal side-effects | 43 (4%) | 40 (4%) | 1·12 (0·68 to 1·83) | 0·66 |
| Complications due to enteral feeding or parenteral nutrition | 5 (<1%) | 3 (<1%) | 1·63 (0·38 to 6·95) | 0·51 |
| Liver or gall bladder dysfunction | 4 (<1%) | 7 (1%) | 0·54 (0·15 to 1·91) | 0·34 |
| Severe hyperglycaemia | 48 (5%) | 46 (5%) | 1·06 (0·69 to 1·61) | 0·80 |
| Refeeding syndrome | 86 (8%) | 73 (7%) | 1·21 (0·86 to 1·70) | 0·27 |

Data are number of events (%), unless otherwise stated. All odds ratios were calculated with a logistic regression for binary data and linear regression for continuous data. Models were adjusted for predefined prognostic factors (initial nutritional risk screening score and baseline Barthel index) and study centre. *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 day 30; only surviving patients were included in this analysis. †To estimate quality of life we used the European Quality of Life 5 Dimensions index (EQ-5D; 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).

***Table 2:*** **Endpoints and adverse events**

adjusted for main prognostic factors (Barthel's index and NRS 2002 score at baseline) and study centre. Results from the regression were reported as adjusted odds ratios (OR) and corresponding 95% CIs. We used a similar statistical approach for secondary endpoints, with Student's *t* test and linear regression models for continuous outcomes.

We analysed predefined subgroups 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, sex, NRS 2002 score, initial BMI, diagnosis at admission (ie, infection, cardiovascular disease, renal failure, gastrointestinal disease, cancer), and comorbidities (diabetes, chronic kidney disease), as defined in the protocol.

Data were analysed in STATA 15.1. There were no interim analyses planned or made during the trial.

### Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, writing of the manuscript, and the decision to submit. The members of the steering committee (appendix) designed the trial, collected and analysed the data, prepared the manuscript, and decided to submit the manuscript for publication.

## Results

From April 1, 2014, to Feb 28, 2018, we screened 5015 patients and enrolled 2088. Of these, 1050 were randomly assigned to the intervention group and 1038 to the control group. With 60 patients withdrawing consent and no other participants lost to follow-up, our final evaluable cohort consisted of 2028 patients (1015 patients in the intervention group and 1013 patients in the control group; figure 2).

Baseline characteristics were similar between groups (table 1, appendix). Patients had a mean age of 72·6 years and a mean BMI of 24·8 kg/m². All patients were at nutritional risk, with 31% of patients having a score of 3, 38% a score of 4, and 31% a score of 5 points or more. The most frequent admission diagnoses were infection, cancer, and cardiovascular disease. Patients had a high burden of comorbidities, including malignant disease, chronic kidney disease, coronary artery disease, diabetes, and congestive heart failure.

Protocol adherence during the hospital stay was high and caloric goals were reached in 800 (79%) and protein goals in 770 (76%) of 1015 patients in the intervention group. 547 (54%) of 1013 patients in the control group reached their caloric goals and 557 (55%) reached their protein goals. Compared with patients in the control group, patients in the intervention group had significantly higher mean daily caloric intake (1501 kcal per day [SD 596] *vs* 1211 kcal per day [517], difference 290 kcal per day [95% CI 240–340]), and protein intake (57 g per day [23] *vs* 47 g per day [21], difference 10 g per day [8–12]) during their hospital stay (figure 3, appendix). These numbers correspond to 22·2 kcal per kg bodyweight per day (SD 9·6) versus 18·2 kcal per kg bodyweight per day (8·8) in caloric intake, and 0·84 g protein per kg bodyweight per day (0·35) versus 0·70 g protein per kg bodyweight per day (0·34) versus in protein intake. In the intervention group, 919 (91%) patients received oral nutritional supplements in combination with enriched hospital nutrition (appendix). Enteral nutrition was used in eight patients and parenteral nutrition were used in 12 in the intervention group. In the control group, 122 (12%) patients received some kind of nutritional support during their hospital stay. On hospital discharge, oral nutritional supplements were prescribed to 245 (24%) patients in the intervention group, compared with 21 (2%) patients in the control group (appendix).

We had complete information on the primary endpoint for all patients at day 30. An adverse clinical outcome (primary endpoint) occurred in 232 (23%) of 1015 patients in the intervention group and in 272 (27%) of 1013 in the control group (adjusted OR 0·79 [95% CI 0·64–0·97]; table 2). Kaplan-Meier estimates also showed a significantly 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 (table 2, appendix) and the survivors were at a lower risk of functional decline at day 30 of 10% or greater according to the Barthel index, than control patients. There were no differences in incidence of intensive care unit admission, non-elective hospital readmission, or major complications between groups.

When compared with 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 and higher quality of life measured by the EQ-5D index and the EQ-5D VAS (table 2). There was no difference in the length of hospital stay between intervention and control group patients.

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

The effect of nutritional support on the risk for the primary endpoint was consistent across predefined subgroups based on age, sex, baseline nutritional risk stratified for NRS 2002 score, initial BMI, diagnosis on hospital admission, or diabetes (p>0·05 for each subgroup analysis). However, we found a more pronounced beneficial effect of nutritional support in the population of patients with chronic kidney disease, compared with patients in the control group (adjusted OR 0·61 [95% CI 0·44–0·86], p=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 (appendix).

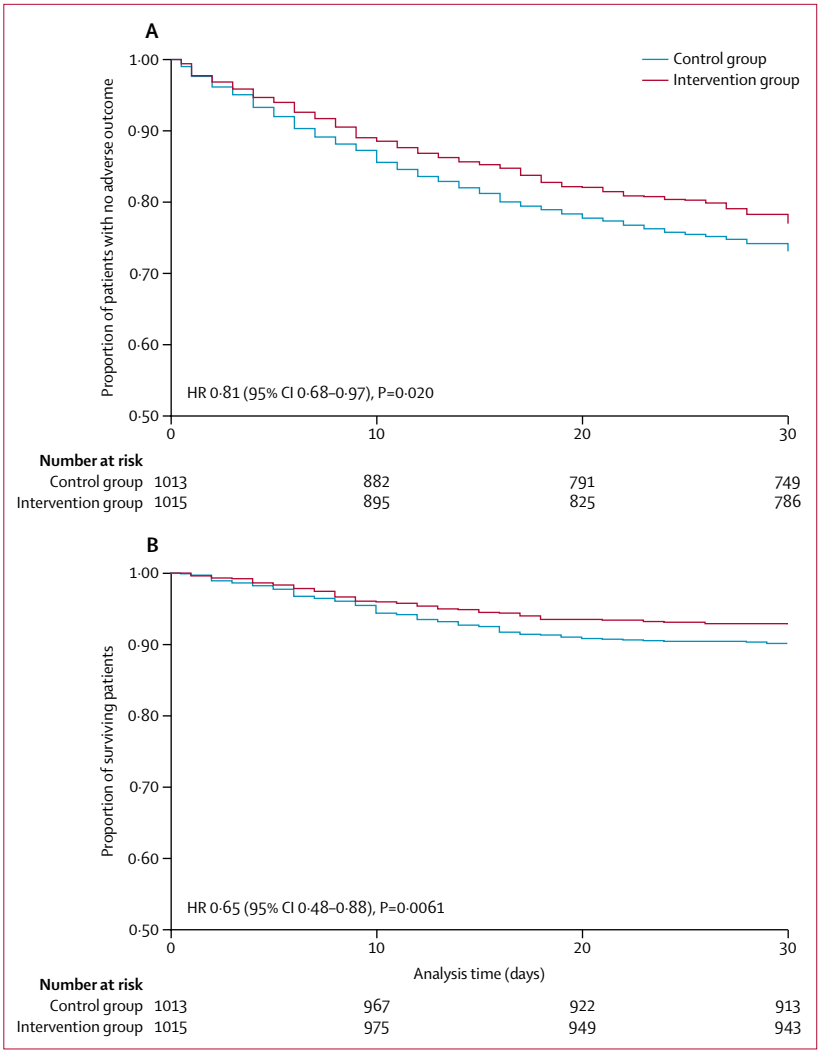


***Figure 4:*** **Kaplan-Meier estimates of the cumulative incidence of the primary endpoint and all-cause mortality**
(A) Time to the first event of the composite primary endpoint (log-rank p value=0·035). (B) Time to death (log-rank p value=0·031).

## Discussion

In this multicentre trial, compared with a control group receiving standard hospital food, individualised 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 events from the intervention.

Several points of this trial are worth mentioning. First, our findings validate some previous smaller trials[9–12] but contradict the findings of two meta-analyses, both of which reported no improvement in clinical outcomes.[13,14] Set in a real-world context and without commercial funding, our large-scale trial, which had high adherence to the nutritional protocol and systematic assessment of outcomes, might resolve the current uncertainty about the benefit of nutritional support in medical inpatients. With a number needed 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 with results of a pooled meta-analysis including 22 previous trials (9·8% *vs* 10·3% mortality, number needed to treat of 200),[13] but was in the range of the effect reported in the NOURISH trial (4·8% *vs* 9·7% mortality, number needed to treat of 20).[9] Second, to increase external validity, EFFORT was pragmatic and included a broad and heterogeneous population of medical inpatients with multiple morbidities, such as different acute illnesses

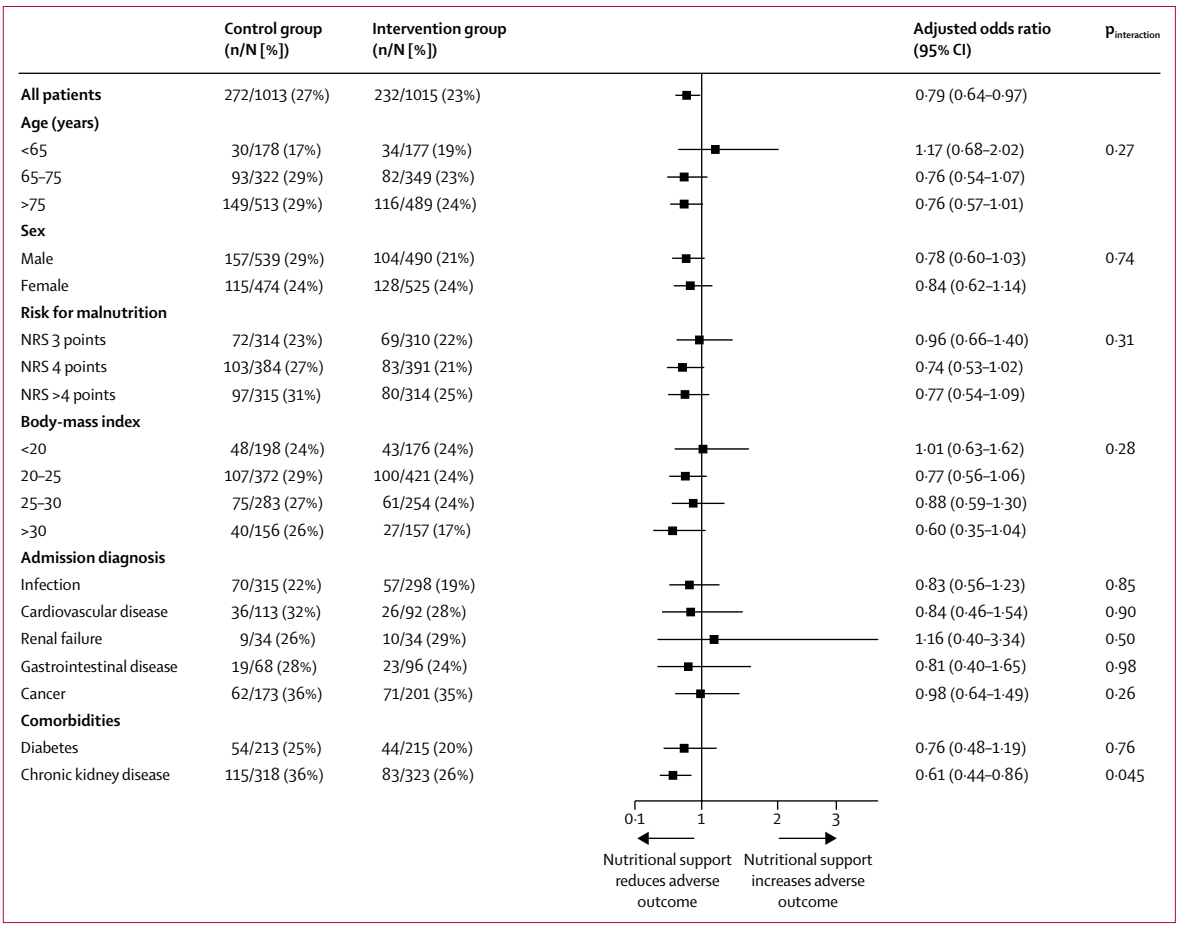


***Figure 5:*** **Odds ratios for adverse outcome in prespecified subgroups**
The only significant interactions between group assignment and subgroup were for chronic kidney disease. The body-mass index is the weight (in kg) divided by the square of the height (in m). NRS=nutritional risk screening.

and chronic comorbidities. Several previous trials focused on specific patient populations (eg, those with heart failure or cancer).[9,13,26] However, we included patients with different internal illnesses and our findings can thus be generalised to a broader patient population (ie, patients with multiple morbidities typically seen in internal medicine wards). The beneficial effects of nutritional support were robust and comparable in subgroups stratified according to patient age, sex, 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 observed in our study. This was also true for patients with diabetes, a population that was excluded in previous trials because of concerns of hyperglycaemia.[9] Currently, there is a debate about the benefits and optimal use of nutritional support in medical patients with acute and severe illness,[28] with respect to the dose and quality of protein and overall caloric intake, 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 patients in critical care receiving full replacement nutrition.[1,30] There are important differences between our study and other critical care trials with regard to patient population, severity of disease, and nutritional intervention. Because patients in our population had milder disease severities compared with patients in other trials in the critical care setting, their cells might have been better at metabolising and using nutrients because of decreased insulin resistance and decreased risk that nutrition would interfere with autophagy.[2,31]

Our findings should not be used to support full replacement nutrition in medical inpatients. Instead, our concept of using individualised nutritional support with the aim of reaching at least 75% of nutritional goals has better clinical outcomes compared with not providing nutritional support. Patients in our trial received nutritional support according to a previously published nutritional protocol with individualised definition of each patient's nutritional goals and the required nutritional support.[19] The nutritional protocol was based

on a pathophysiological rationale and results of observational and smaller randomised 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 dietitians to reach nutritional goals. Our trial does thus not provide evidence on individual nutritional components but supplies evidence that the overall strategy of providing nutritional support to reach protein and caloric 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 outcomes, it has been unclear whether the provision of nutritional support has the potential to reduce the risks associated with malnutrition, or whether it has deleterious effects on outcomes as demonstrated in critical care trials.[30] After discussions with national experts in the field (ie, 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 ethics statement[32] that pointed 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 fulfil all criteria for this, including proof of clinical effectiveness, safety, and cost-effectiveness.[32] For our population of patients, such proof 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 masking of participants and personnel was deemed to be impractical. Although the primary outcome at 30 days was objective and its assessment was masked, some of the outcomes assessed during the hospital stay might have been vulnerable to observer bias. Second, 215 (21%) of patients in the intervention group did not fully reach their caloric goals and 243 (24%) their protein goals, despite implementation of the nutritional protocol by trained dietitians. Similar to real-life experience, several patient, treatment, and hospital factors (eg, delay or refusal to start enteral or parenteral nutrition by the patient, early discharge of patients, diagnostic exams interfering with nutritional support) might have prevented full adherence to the protocol. Still, we expect this bias to be conservative with regard to the relevant endpoints, and protocol adherence was higher than in previous nutritional trials in medical inpatients.[13] Third, nutrition in the control group represented the reality of standard Swiss hospital food, which might not be unconditionally generalisable to other health-care systems. Fourth, we did not yet investigate the costs of the intervention but we have planned to do a future cost-effectiveness analysis on the basis of the trial data. Finally, the registration of the trial was delayed, as we started with a pilot study to ensure feasibility of the complex nutritional intervention and to secure funding for the multicentre rollout. However, there was no change in trial protocol and we thus included all patients in the final analysis.

Understanding the optimal use of nutritional support is complex because timing, route of delivery, and the amount and type of nutrients might all affect clinical outcomes. In our trial, we asked the basic question of whether nutritional support during the hospital stay improves outcomes in medical patients at nutritional risk, compared with standard hospital food. This trial showed that early use of individualised nutritional support to reach protein and caloric 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 admission to hospital for nutritional risk, irrespective of any underlying conditions, followed by a nutritional assessment and introduction of individualised nutritional support in at-risk patients.

#### Contributors

PS was the principal investigator of this trial and was responsible for obtaining funding, drafting the trial protocol, analysing and interpreting the data, and writing the final report. RF, VB, MG, MD, PT, NB, SSc, CBe, SM, and CBr were involved in drafting the trial protocol, data collection, and approval of the final version of the manuscript. FG, AK, TB, CH, VP, SB, SSi, MB, CH, RT, JR, DA, NR, and JD were involved in drafting the trial protocol, supervising the study sites, drafting the final manuscript, and approval of the final version of the manuscript. ZS and BM were involved in obtaining funding, drafting the trial protocol, supervising study sites, drafting the final manuscript, and approving the final version of the manuscript.

#### Declaration of interests

The study was initiated by the investigator and supported by grants from the Swiss National Science Foundation to PS and the Research Council of Kantonsspital Aarau, Switzerland. The Institution of PS has previously received unrestricted grant money unrelated to this project from Nesté Health Science and Abbott Nutrition. The institution of ZS received speaking honorariums and research support from Nesté Health Science, Abbott Nutrition, and Fresenius Kabi. All other authors report no conflicts of interest.

#### Data sharing

We intend to make data collected for the study, including anonymised individual participant data and a data dictionary defining each field in the set, available to others. Related documents will be available, including the trial protocol and the statistical analysis plan. These data will be available with the publication of our main manuscript and all secondary projects as outlined in our trial protocol on receipt of a letter of intention detailing the study hypothesis and statistical analysis plan. The steering committee of this trial will discuss all requests and decide on the basis of the scientific rigor of the proposal whether data sharing is appropriate. All applicants are asked to sign a data access agreement. Please send any request to the principal investigator of this trial.

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