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## Original article

## Economic evaluation of individualized nutritional support in medical inpatients: Secondary analysis of the EFFORT trial

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## SUMMARY

**Background & aims:** Existing guidelines support the importance of nutritional interventions for medical inpatients at malnutrition risk to alleviate the impact of malnutrition on outcomes. While recent studies have reported positive effects of nutritional support on health outcomes, limited evidence exists on whether in-hospital nutritional support also results in economic advantages. We report the results of the economic evaluation of EFFORT—a pragmatic, investigator-initiated, open-label, multicenter trial.

**Methods:** A total of 2028 medical inpatients at nutritional risk were randomly assigned to receive individualized nutritional support to reach protein and energy goals (intervention group; n = 1015) or standard hospital food (control group; n = 1013). To calculate the economic impact of nutritional support, a Markov model was developed with relevant health states. Costs were estimated for days in normal hospital ward and in the Intensive Care Unit (ICU), hospital-acquired complications, and nutritional support. We used a Euro conversion rate of 0.93216 Euro for 1 Swiss Franc (CHF).

**Results:** The estimated per-patient cost was CHF90 (83.78 €) for the in-hospital nutritional support and CHF283.85 (264.23 €) when also considering dietician consultation time. Overall costs of care within 30 days of admission averaged CHF29,263 (27,240 €) per-patient in the intervention group versus CHF29,477 (27,439 €) in the control group resulting in per-patient cost savings of CHF214 (199 €). Per-patient cost savings was CHF19.56 (18.21 €) when also accounting for dietician costs (full cost analysis). These cost savings were mainly due to reduced ICU length of stay and fewer complications. We also calculated costs to prevent adverse outcomes, which were CHF276 (256 €) for one severe complication, CHF2,675 (2490 €) for one day in ICU, and CHF7,975 (7423 €) for one death. For the full cost analysis, these numbers were CHF872 (811 €), CHF8,459 (7874 €) and CHF25,219 (23,475 €). Sensitivity analyses confirmed the original findings.

**Conclusions:** Our evaluation demonstrates that in-hospital nutritional support for medical inpatients is a highly cost-effective intervention to reduce risks for ICU admissions and hospital-associated complications, while improving patient survival. The positive clinical and economic benefits of nutritional support in at-risk medical inpatients calls for comprehensive nutrition programs, including malnutrition screening, consultation, and nutritional support.

**Trial registration:** ClinicalTrials.gov number, NCT02517476.

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## 1. Introduction

Current guidelines set forth by the European Society for Clinical Nutrition and Metabolism (ESPEN) [1] and the American Society for Parenteral and Enteral Nutrition (ASPEN) [2] recommend initiation of nutritional support for medical patients confirmed to be at-risk or malnourished during their hospital stay. Although only a limited number of studies have provided support for these recommendations [1,2], the recent publications of the EFFORT (*Effect of early nutritional support on Frailty, Functional Outcomes and Recovery of Malnourished Medical Inpatients Trial*) [3] and the NOURISH (*Nutrition Effect On Unplanned Readmissions and Survival in Hospitalized Patients*) trial [4] have added to the evidence demonstrating a significant impact of nutritional support for reducing the types of adverse clinical outcomes generally associated with malnutrition while improving overall survival.

An economic evaluation of the NOURISH trial showed that in addition to extending the lives of older malnourished hospitalized patients by 0.71 years, the use of a specialized oral nutritional supplement regimen was shown to be cost-effective [5]. The authors reported an incremental cost-effectiveness ratio (ICER) over the 90-day follow-up period of US\$33,818 per quality-adjusted life year (QALY) and a lifetime ICER of US\$524/LY. This study included malnourished medical inpatients with congestive heart failure, acute myocardial infarction, pneumonia, or chronic obstructive pulmonary disease.

For our economic evaluation, we performed a pre-planned analysis of nutritional support in medical inpatients with a large variety of diagnoses using clinical data generated from the EFFORT trial, a pragmatic, open-label, multicenter study [6]. The study, which included the largest number of medical inpatients at nutritional risk to date, showed that the use of individualized nutritional support during the hospital stay improved important clinical outcomes, including survival, compared with standard hospital food [3].

## 2. Materials and methods

### 2.1. Study design

EFFORT was a pragmatic, investigator-initiated, open-label, non-blinded, non-commercial, multicenter, randomized-controlled trial that was undertaken at eight Swiss hospitals. This is a pre-planned secondary economic analysis of the EFFORT trial. The rationale for the trial, design details, and eligibility features have been published previously [6]. The trial was registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/NCT02517476) (<https://clinicaltrials.gov/ct2/show/NCT02517476>), and primary results were recently published [3].

### 2.2. Study population

Eligible patients included patients at nutritional risk (Nutritional Risk Screening [NRS], 2002 edition  $\geq 3$  points) [6–8] with an expected length of hospital stay  $>4$  days and willing to provide informed consent within 48 h of hospital admission. Patients who were initially admitted to intensive care units (ICU) or surgical units, unable to ingest oral nutrition, already receiving nutritional support on admission, with a terminal condition, or with contraindications for nutritional support were excluded. Participants were randomly assigned in a 1:1 ratio to receive either individualized nutritional support (intervention group) or standard hospital food (control group). All patients or their authorized representatives provided written informed consent.

### 2.3. Study interventions

In the intervention group, nutritional support was initiated as soon as possible after randomization within 48 h after admission. Patients received individualized nutritional support to reach protein and energy goals according to a previously published consensus protocol [9,10] in accordance with recent international guidelines [1]. A summary of the nutritional intervention is provided in the initial report and the protocol [3,6]. Briefly, individualized nutritional goals – including energy and protein goals – were defined for each patient upon hospital admission by a trained registered dietitian. This plan was initially based on oral nutrition provided by the hospital kitchen (including food adjustment according to patient preferences, food fortification [eg, enrichment of hospital food by adding protein powder] and providing patients with between-meal snacks) and oral nutritional supplements [11,12]. A further increase in nutritional support (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 dietitian 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.

### 2.4. Outcome measures

The composite primary endpoint was defined as any adverse clinical outcome, including all-cause mortality, admission to the ICU from the medical ward, non-elective hospital readmission after discharge, and major complications. The group of major complications included adjudicated nosocomial infection, respiratory failure, a major cardiovascular event (ie, stroke, intracranial bleeding, cardiac arrest, myocardial infarction) or pulmonary embolism, acute renal failure, gastrointestinal events (including hemorrhage, intestinal perforation, acute pancreatitis), or a decline in functional status of 10% or more from admission to day 30 as measured by Barthel Index (scores range from 0 to 100, with higher scores indicating better functional status) [13]. Detailed definitions for each component of the primary composite endpoint are summarized in the original publication [3].

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 assessments at day 30 included the European Quality of Life 5 Dimensions index (EQ-5D, German Version). The EQ-5D index values range from 0 to 1, with higher scores indicating better quality of life, and the visual-analogue scale (EQ-5D VAS) scores range from 0 to 100, with higher scores indicating better health status [14].

Outcome data were obtained via chart review by site research staff and trained registered dietitians. Day 30 phone calls were completed by study nurses who were blinded to group assignment. Mortality during the follow-up period was verified by family members or the patient's family physician.

### 2.5. Economic analysis

In order to calculate the economic impact of the nutrition support from a Swiss payer's perspective, a Markov cohort model with daily cycles was developed. Markov models represent stochastic or

random processes that evolve over time and are particularly suited to modelling chronic disease and account for both costs associated with treatment/intervention and outcomes. For more information about Markov modelling, please refer to Briggs and Sculpher [15]. The time frame for the analysis was fixed for the trial duration which was 30 days. According to the EFFORT trial, the average patient was 72.6 years old and had an NRS >3 points [3].

The Markov model was designed to include the following health states (Fig. 1): discharged patients; stable malnutrition patients hospitalized; major complication; admission to ICU; and 30-day mortality.

It is assumed that all patients included in the EFFORT trial started in the stable health state. Thereafter, patients could develop major complications. This was deemed as a separate health state, as the probability of death as well as healthcare cost and utilization were assumed to be different from patients not experiencing a major complication. Additionally, patients could be admitted to the ICU either directly from the stable health state or due to major complications. Finally, patients have different probabilities of death dependent on their health state in each cycle. Death was the absorbing health state. According to the EFFORT trial, patients could also be discharged from hospital within the 30-day period. Based on the data, such a release could only happen during the stable health state (this was also assumed within the model). Furthermore, it was assumed that these patients would not be re-hospitalized within the model timeframe.

Transition probabilities for the different health states in the model were derived from the patient-level EFFORT trial data (Table 1). The rates per study arm were calculated for each health state and then transferred into daily probabilities. Mean values and standard deviations were calculated for each health state. These were used to estimate the parameters of the beta distribution, which was the assumed distribution for the probabilistic analysis. Beta distributions are a standard distribution in health economic analysis and are defined within a range of 0–1, which fits to the probabilities for each health state [15].

As part of the EFFORT trial protocol, EQ-5D data were collected for each patient at baseline [6]. Furthermore, data for the Barthel Index score were collected at baseline and at day 30 (or at hospital release, whichever occurred first). As the EQ-5D is the standard instrument for the utility derivation in health economic evaluations

[16], the baseline value for each study arm in the EFFORT trial was taken as the baseline value in the model. The changes dependent on the health states were assumed to correspond to the proportional changes in the Barthel Index score, which was applied to the EQ5D in the model. Mean values and standard deviations were calculated for each health state. These were used in order to estimate the parameters of the beta distribution which was the assumed distribution for the probabilistic analysis. Beta distributions are a standard distribution for utilities in health economic analysis, as these are also defined within the range of 0–1 (Table 2).

The costs for the various health states were assumed as follows:

- No cost was assumed for patients released from hospital
- Given the heterogeneity of underlying diseases among the EFFORT trial patients, it was assumed that the average daily cost of a non-ICU ward stay in Switzerland was applicable. This value was published by the Federal Office of Health [17]. The standard deviation was assumed to be the lower value of the reported average daily hospital cost in a non-ICU ward.
- Major medical complications observed in the EFFORT trial were heterogenous across patients which was likely due to the heterogeneous distribution of underlying disease within the study population. For simplicity, the following cost values were chosen:
  - Likely value: Swiss Diagnosis-related Group (DRG) A94B (Complex treatment for colonization or infection with multi-resistant pathogens 7 to 13 treatment days, age >15 years, without surgery procedure, without specific diseases) per day.
  - Standard deviation: Swiss DRG (Respiratory insufficiency or pulmonary embolism, one occupancy day) per day.
- For the ICU cost, the mean DRG value per day of the following events was calculated:
  - Likely value: Swiss DRG B36B (Intensive care complex treatment >392/552 expense points with complex operating room procedure, or intensive care complex treatment >980/1104 effort points) per day.
  - Standard deviation: Swiss DRG B36C (Intensive care complex treatment >392/552 effort points).
- No cost was assumed for death.
- We used a Euro conversion rate of 0.93216 Euro for 1 Swiss Franc (CHF) for all calculations

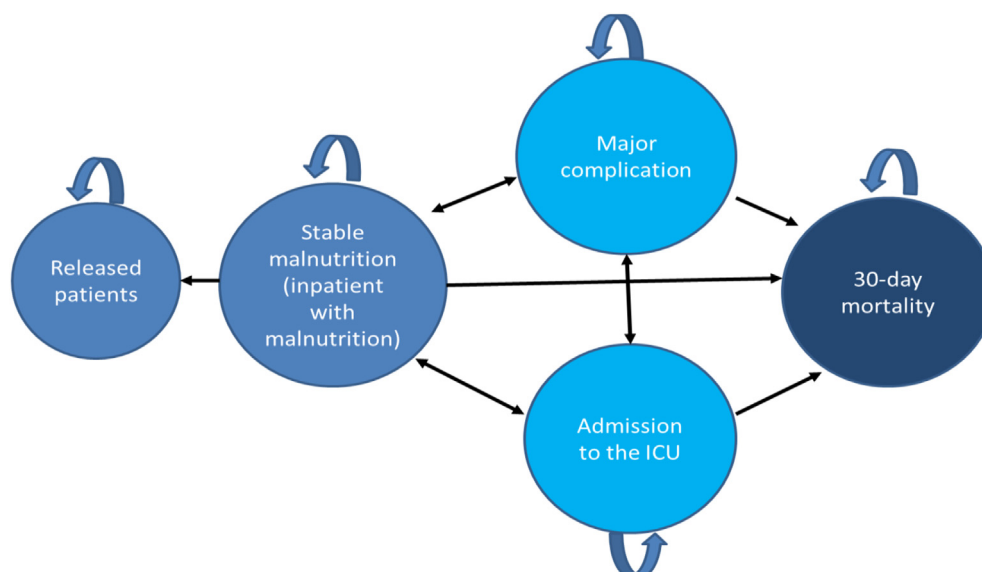


Fig. 1. Health states within the model based on the patient's pathway in the EFFORT trial. AE = adverse event; ICU = intensive care unit.

**Table 1**  
Transition probabilities in the various health states of the underlying model.

Transition probability per day <sup>a</sup>						
Transition phases	Individualized nutrition	Distribution	SD <sup>a</sup>	No nutrition support	Distribution	SD
Stable→Stable	0,048,006	Beta	0,01557	0,04288	Beta	0,01610
Stable→AE	0,007779	Beta	0,00697	0,00936	Beta	0,00813
Stable→ICU	0,000663	Beta	0,00070	0,00077	Beta	0,00080
Stable→Death	0,000000	Beta	0,00000	0,00000	Beta	0,00000
AE→Stable	0,000000	Beta	0,000000	0,00000	Beta	0,00000
AE→AE	0,036,725	Beta	0,01672	0,03094	Beta	0,01643
AE→ICU	0,000475	Beta	0,00056	0,00040	Beta	0,00048
AE→Death	0,012,356	Beta	0,01028	0,01568	Beta	0,01211
ICU→Stable	0,000000	Beta	0,00000	0,00000	Beta	0,00000
ICU→AE	0,000000	Beta	0,00000	0,00000	Beta	0,00000
ICU→ICU	0,038,877	Beta	0,01717	0,04770	Beta	0,01664
ICU→Death	0,012,024	Beta	0,01035	0,00871	Beta	0,00811
Stable→Release	0,037,760	Beta	0,01006	0,03715	Beta	0,01023

Standard deviations (SD) were calculated based on the 95% confidence interval (CI) (Clopper-Pearson CI for a binomial proportion).

AE = adverse event; ICU = intensive care unit.

<sup>a</sup> Transition probabilities were calculated from Day 30 relative risk.

**Table 2**  
Utilities per day of individual health states in the model.

Utilities per day <sup>a</sup>						
	Individualized nutrition	Distribution	SD	No nutrition support	Distribution	SD
Stable health state	0.001915068	Beta	0.00063	0.00190685	Beta	0.00120
AE health state	0.001717808	Beta	0.00065	0.00167945	Beta	0.00066
ICU health state	0.001621918	Beta	0.00059	0.00171781	Beta	0.00080

Assumption: Utility for death = 0.

EQ-5D = European Quality of Life 5 Dimensions index.

<sup>a</sup> The EQ-5D change was plotted from the changes in the Barthel Index score (no formal mapping executed).

For the cost of individualized nutrition support, the following two scenarios were applied:

- Scenario 1: Hospitals already offer nutritional support for patients (covered through the respective Swiss DRG). Hence, only the CHF5 (4.66 €) per day for the nutrition cost per patient was assumed.
- Scenario 2: Hospitals without nutrition service to date. Such hospitals would need to finance the service in the first instance before the Swiss DRG might be adjusted and therefore, a higher cost would be assumed. The assumption was as follows:
  - Nutrition cost: CHF5 (4.66 €)
  - Nutrition support: based on the assumption that a dietitian would consult the patient every second day for a maximum of 30 min (including documentation). For the model, these 30 min were calculated considering the average annual income of a dietitian in Switzerland of CHF80,600 (75,176 €) [18] and the information from the Federal office of Statistics for the working hours per year (1864 h) [17]. This resulted in a cost of CHF10.81 (10.08 €) per patient per day.

The standard deviation was used to estimate the parameters of the gamma distribution, which was the assumed distribution for cost in the probabilistic analysis. Gamma distributions are a standard distribution for cost in health economic analysis [15], as these are also defined as a positive number (means > 0) (Table 3).

Cost per health state and in total was the primary outcome of the model. The calculated days in each health state, including the utility values, were also calculated. The calculation is performed as the difference between the total costs of individualized nutrition support compared to no support. Sensitivity analyses were executed on key variables of the model:

- Probability of released patients
- Cost for complications

- Cost for ICU stay
- Cost for individualized nutrition support

Results are reported as deterministic data. A bootstrap Monte-Carlo simulation was run and forms the basis of the probabilistic results. The model was programmed in Microsoft Excel.

### 3. Results

#### 3.1. Patients

A total of 2028 patients were included in the analysis (n = 1013 in the control group and n = 1015 in the intervention group). Baseline characteristics were similar in the two groups and are reported in the original publication [3]. The mean age was 72.6 years and mean body mass index was 24.8 kg/m<sup>2</sup>. The most frequent admission diagnoses were infection, cancer and cardiovascular disease, whilst patients had a high burden of comorbid conditions.

#### 3.2. Costs associated with nutritional interventions

The cost of the in-hospital nutritional intervention alone was CHF90 (83.78 €) per patient. The total nutritional support cost including dietitian consultation time was CHF283.85 (264.23 €). In the base-case analysis, 30-day costs averaged CHF29,263 (27,240 €) per patient in the intervention group versus CHF29,477 (27,439 €) in the control group. This resulted in per-patient cost savings of CHF214 (199 €) when accounting for nutritional intervention cost only. Per-patient cost savings was CHF19.56 (18.21 €) when accounting for total nutritional support cost. The costs savings were mainly due to ICU length of stay (0.19 vs 0.23 days) and number of complications (2.11 vs 2.44). These clinical savings also translated into cost savings of CHF495 (460 €) for complications and CHF147

**Table 3**  
Cost input for the health economic model – Scenario 1.

Cost item	Cost input	For probabilistic analysis		Reference	Comment
		Distribution	SD		
Nutrition (support)- Scenario 1	CHF5 000	Gamma	CHF1.50		CHF5 for nutrition
Nutrition (support)- Scenario 2	CHF15.81	Gamma	CHF1.50		CHF5 for nutrition & Cost for dietitian (30 min every second day)
Cost per day in non-ICU ward	CHF1 604.94	Gamma	CHF1 444.44	Bundesamt für Statistik (CH; DE)– lower/upper value assumed	Cost in stable health state
Cost per day in ICU	CHF4 387.67	Gamma	CHF3 877.17	Swiss DRG: B36B, B36C	Cost in ICU
Average cost per complication (per day)	CHF1 522.02	Gamma	CHF3 718.00	Swiss DRB: A94B, E64D	Cost in AE health state

(136 €) for saved cost in ICU stays. We also calculated costs to prevent adverse outcomes, which were CHF276 (256 €) for one severe complication, CHF2,675 (2490 €) for one day in ICU, and CHF7,975 (7423 €) for one death. For the full cost analysis, these numbers were CHF872 (811 €), CHF8,459 (7874 €), and CHF25,219 (23,475 €). Detailed results of the base case analysis are presented in Table 4. Results were confirmed in probabilistic analyses and depicted in Fig. 2.

Additionally, an analysis was carried out with the assumption that a hospital would need to employ an additional registered dietitian to provide nutrition support. Therefore, the cost for the nutrition support was increased with the assumption that a dietitian would visit each patient for 30 min every two days. In Table 5 the results for this scenario are depicted confirming the base case results.

#### 4. Discussion

The implications of our economic evaluation of the largest clinical trial to date assessing the effects of nutritional support on clinical outcomes of medical inpatients at nutritional risk are twofold. First, the results suggest that the costs associated with the provision of nutritional support are insignificant compared to the overall costs of hospitalization and/or the cost of other medical treatments. Second, the results of the Markov model confirm that in-hospital nutritional support is a highly cost-effective intervention that can reduce risks for ICU admissions and hospital-associated complications while improving patient survival. These improvements lead to financial benefits for hospital systems prioritizing nutrition care for medical inpatients due to observed cost savings associated with shorter ICU length of stay and fewer complication rates.

The findings of our analysis provide additional support for the positive effect nutrition can have on the health and economic outcomes of medical inpatients at nutritional risk [19]. This is particularly important since the results from the published

literature on the effects of nutritional supplementation for medical inpatients vary considerably [20]. For example, Felder et al. recently followed a cohort of consecutive acutely ill adult medical inpatients from a Swiss tertiary care hospital for 30 days to estimate the prevalence of malnutrition and its impact on medical outcomes (N = 3186) [21]. In this observational cohort study (mean patient age of 71 years; 45% women), more than a quarter (n = 887; 28%) were at risk for malnutrition based on NRS  $\geq 3$ . In addition, the likelihood of adverse medical outcomes for the at-risk patients was substantial. Strong associations were observed for mortality (OR 7.82; 95% CI, 6.04–10.12); impaired Barthel Index (OR, 2.56; 95% CI, 2.12–3.09), time to hospital discharge (OR, 0.48; 95% CI, 0.43–0.52), hospital readmission (OR, 1.46; 95% CI, 1.08–1.97), and all five dimensions of quality of life measures. These associations remained significant even after adjusting for age, sex, comorbidities, and main medical diagnosis. In the fully adjusted model, the odds ratio for 30-day mortality for patients determined to be at nutrition risk was 4.6 (95% CI, 3.60–6.30;  $p < 0.0001$ ).

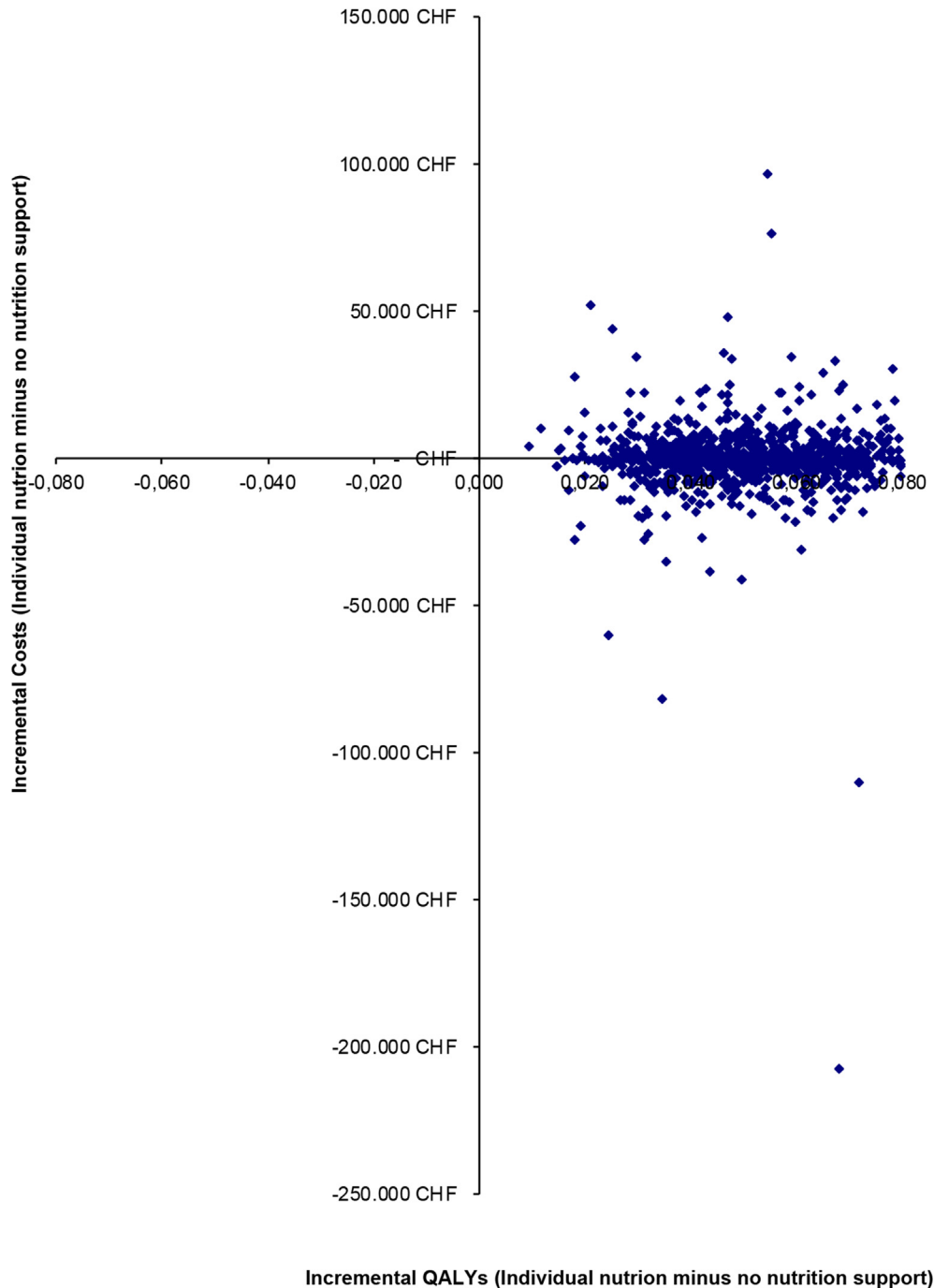
In contrast, a meta-analysis of 22 randomized clinical trials that included N = 3736 patients at risk of malnutrition found no association of nutritional support with reduced mortality, the primary endpoint [22]. In this analysis, nutritional support increased caloric and protein intake as well as body weight, but the only significant impact on clinical outcomes overall was a reduction in non-elective readmissions. Based on these results, the existing literature, and the high degree of heterogeneity among the trials analyzed, the authors recommended that well designed randomized clinical trials be conducted.

The recent NOURISH study was a step forward in this regard. NOURISH was a multicenter, randomized, placebo-controlled, double-blind, parallel-group trial hospitalized adults  $\geq 65$  years of age in the United States with moderate or suspected malnutrition [4]. Eligible patients were admitted to hospital within the past 72 h with a primary

**Table 4**  
Results of scenario 1 including only nutrition cost.

Cost item	Life days		Utilities		Cost		Incremental			
	Individualized nutrition	No nutrition support	Individualized nutrition	No nutrition support	Individualized nutrition	No nutrition support	Cost	Life days	QALYs (in terms of "life days")	ICER LD
					89.77 CHF	–				
Nutrition (support)										
Day in normal ward	15.65	15.44	0.030	0.029	25,116.59 CHF	24,777.51 CHF	339.08 CHF	0.21	0.001	1604.94 CHF
Day in ICU	0.19	0.23	0.000	0.000	841.76 CHF	988.98 CHF	–147.23 CHF	–0.03	0.000	4387.67 CHF
Complication (AE)	2.11	2.44	0.004	0.004	3215.18 CHF	3710.45 CHF	–495.26 CHF	–0.33	0.000	1522.02 CHF
Day released	11.73	11.44	0.022	0.022	– CHF	– CHF	– CHF	0.28	0.001	– CHF
Total	29.68	29.54	0.034	0.034	29263.30 CHF	29,476.94 CHF	–213.64 CHF	0.14	0.000	–1557.46 CHF





**Fig. 2.** Probabilistic analysis confirming the cost-saving potential of nutritional support based on the EFFORT trial.

diagnosis of congestive heart failure, acute myocardial infarction, pneumonia, or chronic obstructive pulmonary disease (COPD). The two study groups received either a high-protein oral nutritional supplement ( $n = 328$ ) or a placebo supplement ( $n = 324$ ), twice a day, in conjunction with standard meals. While there were no between-group differences in 90-day readmission rates, the 90-day mortality rate was significantly lower in the high-protein group—who continued to receive nutritional supplementation post-discharge—compared to the placebo group (4.8% vs 9.7%; relative risk 0.49, 95% CI, 0.27 to 0.90;  $p = 0.018$ ). The economic evaluation of the NOURISH study supported the cost-effectiveness of the specialized oral nutrition supplementation provided [5].

The aim of the current economic analysis of the EFFORT trial was to build upon the findings of previous cost-effectiveness studies such as NOURISH [6]. Our analysis was specifically designed to provide this information based on data collected in a prospective, randomized, open-label trial. The results showed that in the population studied, the provision of nutritional support during a hospital stay is a cost-effective measure to reduce the risk for complications and mortality. Our base-case cost analysis yielded a per-patient cost savings of CHF214 (199 €) when accounting for nutritional intervention cost only, and a per-patient cost savings of CHF19.56 (18.21 €) when including the total nutritional support cost. The cost savings were mainly due to a shorter ICU length of

**Table 5**  
Results of scenario 2 including nutrition support cost.

Cost item	Life days		Utilities		Cost		Incremental			ICER LD
	Individualized nutrition	No nutrition support	Individualized nutrition	No nutrition support	Individualized nutrition	No nutrition support	Cost	Life days	QALYs (in terms of "life days")	
Nutrition (support)					283.85 CHF	–				
Day in normal ward	15,65	15,44	0,030	0029	25.116,59 CHF	24.777,51 CHF	339,08 CHF	0,21	0,001	1.604,94 CHF
Day in ICU	0,19	0,23	0,000	0000	841,76 CHF	988,98 CHF	–147,23 CHF	–0,03	0,000	4.387,67 CHF
Complication (AE)	2,11	2,44	0,004	0004	3.215,18 CHF	3.710,45 CHF	–495,26 CHF	–0,33	0,000	1.522,02 CHF
Day released	11,73	11,44	0,022	0022	– CHF	– CHF	– CHF	0,28	0,001	– CHF
Total	29,68	29,54	0,034	0034	29.457,39 CHF	29.476,94 CHF	–19,56 CHF	0,14	0,000	–142,58 CHF

AE = adverse event; ICU = intensive care unit; CHF = Swiss Franc; QALY = Quality Adjusted Life Years.

stay (0.19 vs 0.23 days) and fewer complications (2.11 vs 2.44) in the intervention group vs the placebo group, respectively. Additionally, this health economic analysis is likely conservative as it did not include the remunerations provided by the Swiss DRG system for malnutrition and nutritional support which could lead into even higher cost savings.

The results of EFFORT trial are consistent with those recently reported by Hiura et al. [23] Their retrospective cohort study was designed to measure the association between severe malnutrition on hospital and ICU length of stay, and mortality among critically ill inpatients (N = 5606). Electronic medical records of patients whose admission had included an ICU stay at either of two New York City hospitals were analyzed. The 2012 diagnostic characteristics from the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition (AND/ASPEN) were used to determine levels of malnutrition. In unadjusted analyses, patients diagnosed with severe malnutrition (n = 726; 13%) had significantly longer hospital LOS (18 vs 8 days), total ICU LOS (7 vs 3 days), and in-hospital mortality (OR 2.78; 95% CI 2.33–3.31) than patients without severe malnutrition, respectively (all p-values <0.0001). The negative impact of malnutrition was further influenced by ICU location. Specifically, patients in the cardiothoracic ICU had the largest increases in hospital LOS (21.10 days; 95% CI, 18.58–23.61), ICU LOS (12.14 days; 95% CI 10.41–13.87), and in-hospital mortality (OR 8.78; 95% CI 5.11–15.07). Along with providing further evidence for the relationship between malnutrition and adverse clinical outcomes, this study raises the importance of identifying major comorbidities that may place a patient with malnutrition at greater clinical risk.

The limitations outlined in the main publication [3], are applicable to this analysis as well. Additionally, the cost data and savings reported are calculated from the perspective of a Swiss hospital; hence, this model does not take into consideration the societal perspective and the results may not be generalizable to other non-Swiss hospitals. The calculations reflect reductions in ICU length of stay and complications as measures of in-hospital nutrition support effectiveness. Other clinical outcomes not included in the analysis can influence the hospital-related costs; future research accounting for other clinical outcomes is warranted. No patient-level cost information was collected since the scope of the analysis was not to look at the direct impact of the nutrition support on episode cost data, but rather to estimate cost savings associated with a population-based in-hospital nutrition support program. Additionally, the model focused on direct costs only as the main drivers of economic decision making by Swiss hospital administrators and payers. However, indirect cost savings resulting from the decrease in healthcare resource use and possible improvement in patient and caregiver Health-Related Quality of Life (HRQoL) measures could have translated into additional economic benefits. Due to little variation observed between the study groups regarding socio-demographic and clinical characteristics in the initial trial [3], we

also did not pursue any subgroup analysis to demonstrate whether the economic benefits would vary among patients with different admission histories, severity levels or other characteristics; however, future research could further explore potential subgroup differences. Also, we did not stratify our analysis based on risk for malnutrition vs. malnutrition, because we did not collect information to make this separation in the initial trial. Although Markov models provide invaluable information about healthcare interventions such as nutrition, they have several limitations [15]. For example, they do not account for past occurrences and require that patients transitioning from one to another health state would need to spend at least one cycle within the new health state before moving into another state. Additionally, no cost per QALY or life year gained values were calculated due to shorter-term effects measured within the EFFORT trial as compared with previous nutrition studies that assessed outcomes over longer periods of time [22,24,25]. However, these studies do support the long-term cost-effectiveness of similar nutrition support programs to the ones studied in our trial. Future research in this area is needed to provide additional support for both short- and long-term effectiveness of nutrition care. However, regardless of these limitations, the design and conduct of the EFFORT trial as well as the clinical and economic results observed provide a positive benchmark for the development of high quality, randomized, controlled trials that help us understand what constitutes evidence-based and cost-effective nutritional therapy in specific populations of hospitalized patients.

In conclusion, our report confirms that in-hospital nutritional support for medical inpatients is a highly cost-effective intervention to reduce risks for ICU admissions and hospital-associated complications as well as improving patient survival. The positive clinical and economic benefits of nutritional support in at-risk medical inpatients observed in this study calls for comprehensive nutrition programs, including malnutrition screening, consultation, and continuous nutritional support [26].

## 5. Disclosures

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## Author contributions

P Schuetz: Conceptualization, Investigation, Funding acquisition, Original draft; S Sulo, J Partridge, R Rueda: Conceptualization, Writing - review & editing; S Walzer, L Vollmer: Formal analysis and Writing - review & editing; Z Stanga, F Gomez: Conceptualization, Investigation, Writing - review & editing.

## Conflict of interest

The authors declare no conflict of interest.

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## References

- [1] Gomes F, Schuetz P, Bounoure L, Austin P, Ballesteros-Pomar M, Cederholm T, et al. ESPEN guidelines on nutritional support for polymorbid internal medicine patients. *Clin Nutr* 2018;37:336–53.
- [2] Mueller C, Compher C, Ellen DM, American Society for Parenteral Nutrition Board of D. A.S.P.E.N. clinical guidelines: nutrition screening, assessment, and intervention in adults. *JPEN - J Parenter Enter Nutr* 2011;35:16–24.
- [3] Schuetz P, Fehr R, Baechli V, Geiser M, Deiss M, Gomes F, et al. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. *Lancet* 2019;393:2312–21.
- [4] Deutz NE, Matheson EM, Matarese LE, Luo M, Baggs GE, Nelson JL, et al. Readmission and mortality in malnourished, older, hospitalized adults treated with a specialized oral nutritional supplement: a randomized clinical trial. *Clin Nutr* 2016;35:18–26.
- [5] Zhong Y, Cohen JT, Goates S, Luo M, Nelson J, Neumann PJ. The cost-effectiveness of oral nutrition supplementation for malnourished older hospital patients. *Appl Health Econ Health Pol* 2017;15:75–83.
- [6] Schuetz P, Fehr R, Baechli V, Geiser M, Gomes F, Kutz A, et al. Design and rationale of the effect of early nutritional therapy on frailty, functional outcomes and recovery of malnourished medical inpatients trial (EFFORT): a pragmatic, multicenter, randomized-controlled trial. *Int J Clin Trials* 2018;5: 142–50.
- [7] Kondrup J, Allison SP, Elia M, Vellas B, Plauth M, Educational, et al. ESPEN guidelines for nutrition screening 2002. *Clin Nutr* 2003;22:415–21.
- [8] Hersberger L, Bargetzi L, Bargetzi A, Tribolet P, Fehr R, Baechli V, et al. Nutritional risk screening (NRS 2002) is a strong and modifiable predictor risk score for short-term and long-term clinical outcomes: secondary analysis of a prospective randomised trial. *Clin Nutr* 2019 [Epub ahead of print].
- [9] Bounoure L, Gomes F, Stanga Z, Keller U, Meier R, Ballmer P, et al. Detection and treatment of medical inpatients with or at-risk of malnutrition: suggested procedures based on validated guidelines. *Nutrition* 2016;32:790–8.
- [10] Bolliger R, Neeser O, Merker M, Vukajlovic T, Felder L, Fiumefreddo R, et al. Validation of a prediction rule for Legionella pneumonia in emergency department patients. *Open Forum Infect Dis* 2019;6:ofz268.
- [11] Milne AC, Potter J, Vivanti A, Avenell A. Protein and energy supplementation in elderly people at risk from malnutrition. *Cochrane Database Syst Rev* 2009: CD003288.
- [12] Potter JM, Roberts MA, McColl JH, Reilly JJ. Protein energy supplements in unwell elderly patients—a randomized controlled trial. *JPEN - J Parenter Enter Nutr* 2001;25:323–9.
- [13] Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *Md State Med J* 1965;14:61–5.
- [14] Ludwig K, Graf von der Schulenburg JM, Greiner W. German value set for the EQ-5D-5L. *Pharmacoeconomics* 2018;36:663–74.
- [15] Briggs A, Sculpher M. An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics* 1998;13:397–409.
- [16] Tolley K. What are health utilities? What is? series. UK. 2009.
- [17] Federal Office of Public Health (FOPH) Switzerland. p. Health-related statistics from the Swiss federal office of public health.
- [18] Mahlstein A, Weishaupt E. Berufsstatistik über die Ernährungsberater und Ernährungsberaterinnen in der Schweiz - resultate 2017. Berner Fachhochschule - Gesundheit. Abteilung Ernährung und Diätetik; 2018.
- [19] Gomes F, Baumgartner A, Bounoure L, Bally M, Deutz NE, Greenwald JL, et al. Association of nutritional support with clinical outcomes among medical inpatients who are malnourished or at nutritional risk: an updated systematic review and meta-analysis. *JAMA Netw Open* 2019;2:e1915138.
- [20] Schutz P, Bally M, Stanga Z, Keller U. Loss of appetite in acutely ill medical inpatients: physiological response or therapeutic target? *Swiss Med Wkly* 2014;144:w13957.
- [21] Felder S, Lechtenboehmer C, Bally M, Fehr R, Deiss M, Faessler L, et al. Association of nutritional risk and adverse medical outcomes across different medical inpatient populations. *Nutrition* 2015;31:1385–93.
- [22] Bally MR, Blaser Yildirim PZ, Bounoure L, Gloy VL, Mueller B, Briel M, et al. Nutritional support and outcomes in malnourished medical inpatients: a systematic review and meta-analysis. *JAMA Intern Med* 2016;176:43–53.
- [23] Hiura G, Leibold B, Seres DS. Malnutrition diagnosis in critically ill patients using 2012 Academy of nutrition and Dietetics/American society for parenteral and enteral nutrition standardized diagnostic characteristics is associated with longer hospital and intensive care unit length of stay and increased in-hospital mortality. *JPEN - J Parenter Enter Nutr* 2019 [Epub ahead of print].
- [24] Sanz-Paris A, Boj-Carceller D, Lardies-Sanchez B, Perez-Fernandez L, Cruz-Jentoft AJ. Health-care costs, glycemic control and nutritional status in malnourished older diabetics treated with a hypercaloric diabetes-specific enteral nutritional formula. *Nutrients* 2016;8:153.
- [25] Ballesteros-Pomar MD, Martinez Llinas D, Goates S, Sanz Barriuso R, Sanz-Paris A. Cost-effectiveness of a specialized oral nutritional supplementation for malnourished older adult patients in Spain. *Nutrients* 2018;10.
- [26] Schuetz P, Greenwald JL. Web Exclusive. *Annals for Hospitalists Inpatient Notes - Optimizing Inpatient Nutrition-Why Hospitalists Should Get Involved*. *Ann Int Med* 2020;172:HO2–3.