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Cost savings associated with nutritional support in medical inpatients: an economic model based on data from a systematic review of randomized trials

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Key Points

Question: For malnourished medical inpatients, in-hospital nutritional support has been shown to improve health outcomes. Are these health benefits associated with cost savings?

Findings: Based on findings of a systematic review (27 randomized trials), we developed an economic model for hospital costs in malnourished patients who received nutritional support. In-hospital nutritional interventions led to estimated cost savings of $1,230 USD per patient per hospital stay, largely from less resource utilization, fewer hospital-acquired infections, and lower likelihood of non-elective readmissions.

Meaning: Nutritional support for medical inpatients admitted with impaired nutritional status lowers hospital costs while improving survival and other health outcomes.

Abstract

Objectives: Nutritional support improves clinical outcomes during hospitalization as well as after discharge. Recently, a systematic review of 27 randomized controlled trials showed that nutritional support was associated with lower rates of hospital readmissions and with improved survival. In the present economic modeling study, we sought to determine whether in-hospital nutritional support would also return economic benefits.

Setting: The current economic model applied cost estimates to outcome results from our recent systematic review of hospitalized patients. **Participants:** In the underlying meta-analysis, a total of 27 trials (n = 6,803 patients) were included, of which five (n = 3,067 patients) were published between 2015 and 2019. To calculate the economic impact of nutritional support, a Markov model was developed using transitions between relevant health states. **Primary and Secondary Outcomes Measures:** Costs were estimated accounting for length of stay in normal hospital ward, hospital-acquired infections, readmissions, and nutritional support. Six-month mortality was also considered. The estimated daily per-patient cost for in-hospital nutrition was $6.23 US.

Results: Overall costs of care within the model timeframe of six months averaged $63,227 USD per-patient in the intervention group versus $66,045 USD in the control group, which corresponds to per-patient cost savings of $2,818. These cost savings were mainly due to reduced infection rate and shorter lengths of stay. We also calculated the costs to prevent a hospital-acquired infection and a non-elective readmission, i.e., $820 USD and $733 USD, respectively. The incremental cost per life-day-gained was -$1,149 USD with 2.53 additional days. The sensitivity analyses for cost per quality-adjusted life-day provided support for the original findings.

Conclusions: For medical inpatients who are malnourished or at nutritional risk, our findings showed that in-hospital nutritional support is a cost-effective way to reduce risk for readmissions, lower the frequency of hospital-associated infections, and improve survival rates.

Strengths and limitations of this study:

- Economic analysis that applied cost estimates to outcome results from a recent systematic review and meta-analysis article.
- In the underlying meta-analysis, a total of 27 trials (n = 6,803 patients) were included, of which five (n = 3,067 patients) were published between 2015 and 2019.
- Costs and cost-savings were calculated from the perspective of US hospitals, so results may not be fully generalizable to non-US hospitals where patient demographics, disease severity, and care costs may differ.
- Our modeled cost-savings calculations reflect reductions in infectious complications, hospital length of stay, and non-elective readmissions, as measures for the effectiveness of in-hospital nutritional support.

Introduction

As a significant public health issue, malnutrition has detrimental effects on the care and recovery of hospitalized patients.[1] If unrecognized or undertreated, impaired nutritional status can worsen health outcomes and escalate healthcare use and costs.[2,3] Nutritional shortfalls occur when unintended loss of weight and muscle result from collusion of various predisposing factors—older age, limited physical activity, insufficient protein and energy intake relative to needs, altered hormone function, and anorexia.[4] Studies estimate that between 30 and 50% of adult inpatients are malnourished or at nutritional risk when admitted to hospital; nutritional risk is higher in patients who are older and have underlying chronic health conditions.[5-7]

The presence of malnutrition can impair a patient's response to medical treatment and can increase susceptibility to hospital-acquired comorbidities, which include urinary tract infections, falls and fractures, acute respiratory infections, skin tears, and hospital-acquired pressure injuries.[8-10] As a result, malnutrition in a hospitalized adult can hinder the patient's recovery, prolong length of hospital stay, and increase the need for post-discharge institutional care.[8-11]

Not surprisingly, the high prevalence and adverse effects of malnutrition in hospitalized patients affect the overall cost of healthcare in the United States, as in the rest of the world. The estimated annual cost of disease-associated malnutrition in the United States is over $15.5 billion.[7] In Canada, the added cost of in-hospital care for a malnourished patient is $1,500-$2,000 per hospital stay (compared to the cost for an adequately-nourished patient); this translates to an excess $1.56-$2.1 billion per year, similar to the US when adjusted for population.[5] Studies from Latin America estimate an annual costs of $10.2 billion for management of malnourished patients in public hospitals,[12,13] and studies from Europe and Asia likewise report markedly higher costs for care of malnourished hospital patients.[14-18]

Identifying and treating malnutrition are critical to improving patient health outcomes and to reducing healthcare costs.[6] To identify and manage hospitalized patients at risk for malnutrition, nutrition-focused quality improvement programs can be used to guide nutrition screening and assessment, to intervene with nutrition care when needed, and to provide ongoing monitoring and adjustment of nutrition, as needed.[19,20] Such programs improved patient outcomes and decreased healthcare costs, as evidenced by reduced rates of hospital-acquired infections, shorter lengths of hospital stay, and lower rates of readmission.[19,21-24] A systematic review of studies using oral nutritional supplements to treat malnutrition revealed cost savings, which were attributed to fewer medical complications, shortened hospital stays, prevention of pressure ulcers, and improved quality-adjusted life years.[25] A large clinical trial on use of individualized nutrition support during hospitalization showed improved nutritional intake, functional outcome, and quality of life, along with lowered risk of adverse effects and decreased 30-day mortality.[26] Results of the follow-on economic-evaluation study demonstrated cost savings related to reduced intensive care unit (ICU) stays and fewer hospital-acquired complications.[27]

Study aim

Gomes et al recently conducted a systematic review of 27 trials of patients who were malnourished or at risk of malnutrition on admission to the hospital. Results showed that in-hospital nutritional support could significantly improve patient outcomes by increasing patients' energy and protein intake, which was associated with weight gain, lowered mortality rates, and reduced rates of non-elective hospital readmissions.[4] Based on these findings, the aim of our current analysis was to use economic modeling as a way to predict whether benefits of in-hospital nutritional support are accompanied by returns in terms of economic benefits. In modeling, we also considered other Gomes et al. endpoints that showed a clinically meaningful improvement, i.e., lowered infection rates and shorter length of stay in hospital.[4]

Methods

Patient and public involvement

No patient involved

To clarify the current economic modeling analysis, we provide definitions of health economic terms used in our report **(Table 1)**.[28]

Table 1. Definition of terms for health economic analyses

Markov model	A model used for randomly changing systems. Applied to healthcare, Markov models assume that a patient is in one of a finite number of discrete health states, e.g., inpatient with malnutrition, inpatient with infectious complication, patient discharged from hospital, or patient readmitted to hospital non-electively. In modeling, the patient transitions from one state to another, with death as an unalterable state.
Cost-effectiveness	Value for the cost. In healthcare, the goal is to maximize the benefit of a treatment for a population of patients served from a limited amount of resources.
Incremental cost-effectiveness Ratio (ICER)	Used in health economics to compare two different interventions in terms of the cost of *gained* effectiveness. ICER is computed by dividing the difference in cost of 2 interventions by the difference of their effectiveness, e.g., if treatment A costs $50 per patient and provides 2 quality-adjusted life days (QALDs), and treatment B costs $80 while providing 3 QALDS, the ICER of treatment B is $80-50/3-2 = $30. The ICER determination is also called a cost-utility analysis.
Sensitivity analysis	A "what-if" analysis. This value focuses on what happens to the dependent variable when various parameters change.

Economic modeling and analysis

For our Markov model, we assumed that all patients were in a stable health state—hospitalized and malnourished **(Figure 1)**. Thereafter, patients could develop major infections. This was modeled as a separate health state because the probability of death, as well as healthcare costs and utilization, were assumed to be higher in comparison with patients not experiencing in-hospital complications. In another state, patients could be discharged from the hospital. Following discharge, patients may require unplanned readmission to the hospital. Finally, patients have different probabilities of death in each state, depending on their health status.

Figure 1. Health states within our Markov model. Designations of health states were based on findings in the meta-analysis report by Gomes et al.[4]

We modeled the economic impact of the nutrition support from a US payer's perspective. To do so, we developed a Markov cohort model with daily cycles.[28,29] The timeframe for our model was 6 months, consistent with results reported in the meta-analysis by Gomes et al.[4] We applied utility values (cost of gained effectiveness of nutritional support) that were derived from a study by Schuetz et al, assuming that the utility value for preventing an in-hospital adverse event was a reasonable proxy for developing an infection during hospitalization.[27] Likewise, we applied a utility value from Harvey et al for preventing non-elective readmission.[30] Additionally, we assumed that the utility value for a released patient was 10% higher than for a patient in the stable health state. A more detailed description of the methods and assumptions is provided in Appendix A.2. We assumed costs for the various health states as follows: 1) no cost for patients released from hospital, 2) costs for nutritional support and re-admission were sourced from the NOURISH health economic analysis,[31] assuming standard deviation as 10% of the input value, 3) costs for a heterogeneous distribution of infections were estimated on the basis of US hospital infection costs reported,[32] 4) no cost for death, and 5) the cost of nutritional support as reported previously.[33]

The primary outcomes in our model were cost-by-health-state and total cost. We calculated days in each health state, and we calculated utility value as the difference between the total costs of individualized nutritional support compared to no support. Sensitivity analyses were executed on key variables of the model, including probability of patient release from hospital, cost for infections, cost for normal ward hospitalization, and cost for individualized nutritional support.

Results

Patient outcomes

The original systematic review included a total of 27 trials with 6,803 patients; five studies (n = 3067 patients) were published between 2015 and 2019.[4] Compared with patients in the control group, those who received nutritional support had a significantly lower mortality rate (230 of 2758 [8.3%] vs 307 of 2,787 [11.0%] with an odds ratio [OR] of 0.73 (95% CI, 0.56-0.97).

Costs and cost-benefits of nutritional intervention

A base-case analysis summarizes our cost results **(Table 2)**. Here 'Life' represents the number of patient lives in each health state. Utilities results are shown as quality-adjusted life days (QALD), which were calculated in the model. Finally, the calculated cost for each health state is shown. The per-patient cost for in-hospital nutritional support was estimated at $36.44 per patient across the patient's hospital length of stay. In terms of costs over the 6-month timeframe of the study model, hospital care averaged $63,227 per patient in the nutrition-intervention group versus $66,045 in the control group.

Table 2. Base-case results

	Life days		Utilities, QALD		Cost, $ US	
Patient state	**Nutritional support**	**No nutritional support**	**Nutritional support**	**No nutritional support**	**Nutritional support**	**No nutritional support**
Hospitalized, malnourished	11.49	12.00	0.022	0.023	63,227	66,045
Non-elective readmission	0.14	0.17	0.000	0.000	193	237
In-hospital with Infection	0.52	0.60	0.001	0.001	4,554	5,374
Discharged from hospital	162	159	0.342	0.333	37,597	36,863
Death	7.74	10.27				
Total (sum of health states above)	174.26	171.73	0.365	0.358	105,608	108,520

QALDs = quality-adjusted life days

Incremental differences in cost savings, life days, QALDs, and ICER per life days were determined (**Table 3**). When using nutritional support, the total cost savings over the 6-month modeling interval was $2,912, which was mainly driven by cost savings in the normal ward hospitalization ($2,818). Patients receiving nutritional support also had 2.5 more life days without complications during the modeled time. Finally, given the cost savings and the added life days, cost-effectiveness results show dominance for the nutritional support group.

We also calculated costs to prevent hospital-acquired infections and hospital readmission, which were $820 USD for one prevented infection and $733 for one prevented non-elective readmission. When varying the input values, the results of the sensitivity analyses provided support for the original findings.

Table 3: Results for incremental differences from base-case analysis

	Incremental changes for nutritional support vs no nutritional support			
Cost item	**Cost savings, $ US**	**Life days**	**QALDs**	**ICER LD, $ US**
Normal ward hospitalization	2,818.17	0.51*	-0.0009	-5,569.72
Readmission	43.50	-0.03	-0.0001	1,372.62
Infections	820.89	0.09*	0.0001	-8,891.82
Released	733.65	3.16	0.0081	231.92
Death		-2.53		
Total	2,912.47	2.53	0.0070	-1,149.63

QALDs = quality-adjusted life days

ICER LD = Incremental cost-effectiveness Ratio Life Days

Discussion

When hospitalized patients with malnutrition or at nutritional risk receive nutritional support, risk for hospital infections is reduced, length of stay is shortened, and the likelihood of hospital readmission is decreased. Importantly, results of our current modeling study showed that the added cost of providing nutritional support is very low, especially when considering the associated reductions in costs of hospitalization and medical treatments. Taken together, results from our present Markov health cost modeling showed that in-hospital nutritional support is a highly cost-effective intervention.

Comparison with findings in other nutrition care studies

The underlying systematic review by Gomes et al found that nutritional support led to statistically significant reductions in mortality and non-elective hospital readmissions,[4] findings that have also been reported for other hospital populations.[4,21,23,24,26,34] As well, the results of our health economic modeling analysis confirmed and extended data and messages on the ‘value of nutrition’ in care for hospitalized patients in North America,[35,36] Latin America,[13,37,38] Europe and the United Kingdom,[25,39-41] and Asia.[17,33]

Hospital nutritional care has proven particularly efficacious and cost-effective in older populations with multiple health conditions, including those living in different care settings—in the community[39,42-44] and in nursing care facilities.[42,45] Furthermore, it was recently shown that malnutrition is underdiagnosed in emergency departments, also leading to a higher burden in terms of healthcare costs.[46]

Limitations of this modeling analysis

As for all modeling analyses, our model had some limitations. Costs and cost-savings were calculated from the perspective of US hospitals, so results may not be fully generalizable to non-US hospitals where patient demographics, disease severity, and care costs may differ. As well, our modeled cost-savings calculations reflect reductions in infectious complications, hospital length of stay, and non-elective readmissions, as measures for the effectiveness of in-hospital nutritional support. Other clinical outcomes, such as non-infective complications, are not included in the evaluation but could be included in future studies on hospital-related costs. Additionally, our model used direct costs as the main drivers of economic decision-making by US hospital administrators and payers; future models could tackle savings in cost terms important to the patients, such as faster recovery with less disability and lower loss of work productivity.

The way forward

Guidelines and recommendations on the importance of nutrition care for medical nutritionally vulnerable inpatients are increasingly available in the US and elsewhere.[3,47-50] A recent European study showed that adherence to guidelines on malnutrition management in 15 hospitals was generally good, which led to improved nutritional care in hospitals.[51] Based on our modeled findings, we anticipate that increased attention to nutritional support during and after hospitalization may yield marked benefits both in terms of health outcomes and cost savings.

Conclusion

In conclusion, our modeling analysis predicted that in-hospital nutritional support for medical inpatients who are malnourished or at nutritional risk can yield significant cost-benefits along with previously reported gains in terms of health outcomes.[4] Together, these positive effects provide a compelling rationale for hospitals to follow comprehensive nutrition care pathways—including screening for malnutrition risk, assessment of causes and severity of malnutrition, and provision of nutrition-focused support during and after hospitalization.[47,48,52]

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Trial registration

Not applicable

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Author contributions

P Schuetz: study conceptualization, investigation, acquisition of funding, writing and editing manuscript; S Sulo: conceptualization, writing and editing manuscript; S Walzer, L Vollmer: analysis, writing and editing manuscript; Z Stanga, F Gomes: conceptualization, investigation, review and editing manuscript. C Brunton, N Kaegi-Braun and B Mueller provided critical feedback to the analysis and approved the final manuscript.

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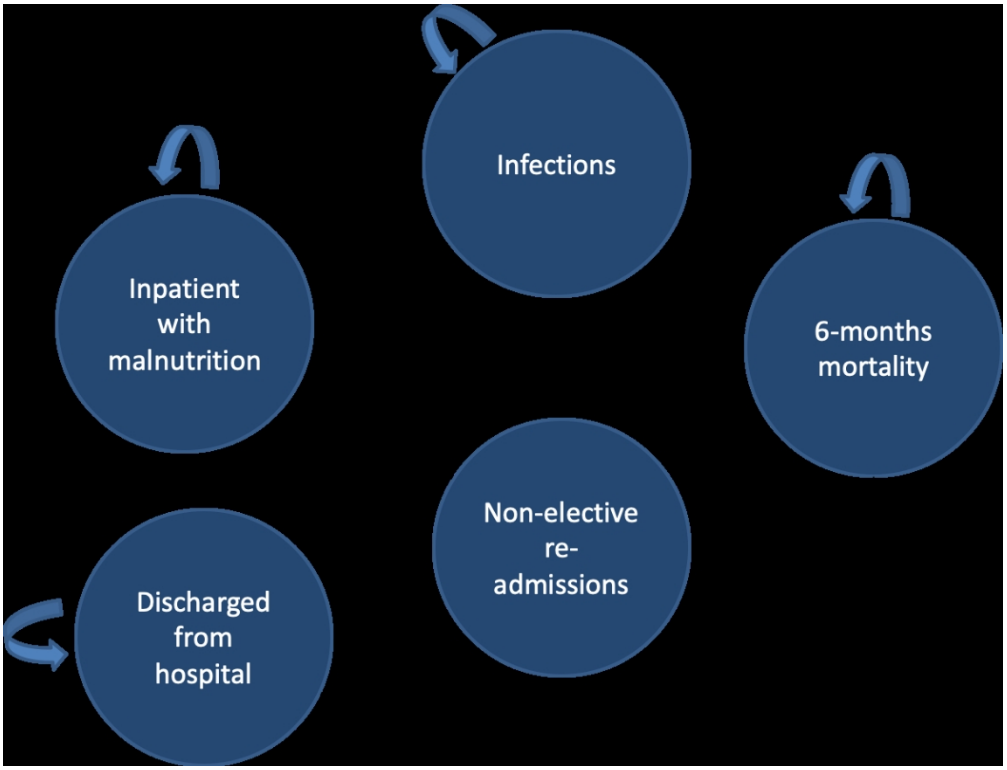

Figure 1. Health states within our Markov model. Designations of health states were based on findings in the meta-analysis report by Gomes et al

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Appendices

A. 1. Model assumptions

Transition probabilities for the different health states in the model were derived from the extracted data of the meta-analysis **(Table A.1).** The rates were calculated for each health state and then applied as daily probabilities. Mean values and standard deviations were calculated for each health state. Beta distributions are standard in health economic analysis and are defined within a range of 0 to 1 for each health state.[1] When specific values were unavailable, we assumed the following:

- Transition probability "stable -> release" was adapted from Schuetz et al,[2] adjusting that number until the published length of stay was reproducible.
- Transition probability "infection -> stable" was assumed to be the same as for "stable -> infection."
- Transition probability "Re-admission -> stable" is the complement value to the probability of "stable -> re-admission" as this "re-admission" health state is only a transition state.

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

	Transition probability per day*					
Transition phases	**Individualized nutrition**	**Distribution**	**SD**	**No nutrition support**	**Distribution**	**SD**
Stable -> Infection	0.00027273	Beta	0.00027371	0.00031596	Beta	0.00031514
Stable -> Release	0.08986880	Beta	0.02394280	0.08841700	Beta	0.02434740
Stable -> Death	0.00047833	Beta	0.00046549	0.00064104	Beta	0.00061241
Infection -> Stable	0.00027273	Beta	0.00027371	0.00031596	Beta	0.00031514
Infection -> Infection	0.00027273	Beta	0.00027371	0.00031596	Beta	0.00031514
Infection-> Death	0.00047833	Beta	0.00046549	0.00064104	Beta	0.00061241
Re-admission -> Stable	0.99952167	Beta	0.00221795	0.99935896	Beta	0.00239153
Re-admission -> Death	0.00047833	Beta	0.00046549	0.00064104	Beta	0.00061241
Release -> re-admission	0.00087410	Beta	0.00081610	0.00109193	Beta	0.00099477
Release -> death	0.00047833	Beta	0.00046549	0.00064104	Beta	0.00061241

A beta distribution was assumed for the utility values, a standard distribution for utilities in health economic analysis; these are defined within the range of 0 to 1 **(Table A.2).**

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

	Individualized nutrition	Distribution	SD	No nutrition support	Distribution	SD
Stable health state	0.001915068	Beta	0.00063	0.00190685	Beta	0,00120
Infection health state	0.001717808	Beta	0.00065	0.00167945	Beta	0,00066
Non-elective re-admission health state	0,001780822	Beta	0,00077	0,001780822	Beta	0,00077
Released health state	0.002106575	Beta	0.00069	0.00209753	Beta	0,00132
Assumption: Utility for death = 0. Utility for released patients 10% improved compared to stable health state patients.						

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,[1] as these are also defined as a positive number (means >0; **Table A.3**).

Table A.2: Cost input for the health economic model

Cost item	Cost input	For probabilistic analysis		Reference	Comment
		Distribution	SD		
Nutrition (support)	USD 3.00	Gamma	USD 0.60	Zhong 2017[3]	"intervention cost"
Cost per day in non-ICU ward	USD 5,480.74	Gamma	USD 1,370.19	Zuvekas 2017	Cost per inpatient day in state / local government hospital
Cost per re-admission	USD 1,369.62	Gamma	USD 205.44	Zuvekas 2017	Published data is per visit (fits with re-admission)
Cost per infection	USD 8,888.82	Gamma	USD 1,777.76	Schmier 2016[5]	Cost included: VAP/HAP, SSI, GI, CAUTI. Weighted infection cost based on number of cases (table I)
Average cost per released patient	USD 231.92	Gamma	USD 23.19	Zuvekas 2017	One visit to GP every second week. Published data are per visit - assumption: one visit per quarter (USD 156 / 90 days)

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CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 5-6
		Present the study question and its relevance for health policy or practice decisions.	Page 5-6
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 7-9
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 7-9
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 7-9
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 7-9
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 7-9
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	n/a

Section/item	Item No	Recommendation	Reported on page No
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 7-9
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	n/a
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Page 7-9
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Page 7-9
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	n/a
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 7-9
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 7-9
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 7-9
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 7-9
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for	Page 7-9

Section/item	Item No	Recommendation	Reported on page No
		pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 9-12
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 9-12
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	n/a
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 9-12
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Page 9-12
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 12-13
Other			

Section/item	Item No	Recommendation	Reported on page No
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 15
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 15

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Cost savings associated with nutritional support in medical inpatients: an economic model based on data from a systematic review of randomized trials

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Abstract

Background & Aims: Nutritional support improves clinical outcomes during hospitalization as well as after discharge. Recently, a systematic review of 27 randomized, controlled trials showed that nutritional support was associated with lower rates of hospital readmissions and improved survival. In the present economic modeling study, we sought to determine whether in-hospital nutritional support would also return economic benefits.

Methods: The current economic model applied cost estimates to the outcome results from our recent systematic review of hospitalized patients. In the underlying meta-analysis, a total of 27 trials (n = 6,803 patients) were included. To calculate the economic impact of nutritional support, a Markov model was developed using transitions between relevant health states. Costs were estimated accounting for length of stay in a general hospital ward, hospital-acquired infections, readmissions, and nutritional support. Six-month mortality was also considered. The estimated daily per-patient cost for in-hospital nutrition was $6.23 US.

Results: Overall costs of care within the model timeframe of six months averaged $63,227 USD per-patient in the intervention group versus $66,045 USD in the control group, which corresponds to per-patient cost savings of $2,818. These cost savings were mainly due to reduced infection rate and shorter lengths of stay. We also calculated the costs to prevent a hospital-acquired infection and a non-elective readmission, i.e., $820 USD and $733 USD, respectively. The incremental cost per life-day gained was -$1,149 USD with 2.53 additional days. The sensitivity analyses for cost per quality-adjusted life-day provided support for the original findings.

Conclusions: For medical inpatients who are malnourished or at nutritional risk, our findings showed that in-hospital nutritional support is a cost-effective way to reduce risk for readmissions, lower the frequency of hospital-associated infections, and improve survival rates.

Strength and limitations of this study

- Large data set of randomized nutritional trials based on a recent systematic search and metanalysis
- Different patient-relevant outcomes considered in the cost analyses
- Calculation of costs and cost-savings from the perspective of the 27 hospitals included in the underlying meta-analysis which limit generalizability
- Focusing on direct costs as the main drivers of economic decision, but not costs savings associated with faster recovery, less disability and lower loss of work productivity.

Introduction

As a significant public health issue, malnutrition has detrimental effects on the care and recovery of hospitalized patients [1]. If unrecognized or undertreated, impaired nutritional status can worsen health outcomes and escalate healthcare use and costs [2 3]. Nutritional shortfalls occur when unintended loss of weight and muscle result from collusion of various predisposing factors—older age, limited physical activity, insufficient protein and energy intake relative to needs, altered hormone function, and anorexia [4]. Studies estimate that between 30 and 50% of adult inpatients are malnourished or at nutritional risk when admitted to hospital; nutritional risk is higher in patients who are older and have underlying chronic health conditions [5-7].

The presence of malnutrition can impair a patient's response to medical treatment and can increase susceptibility to hospital-acquired comorbidities, which include urinary tract infections, falls and fractures, acute respiratory infections, skin tears, and hospital-acquired pressure injuries.[8-10] As a result, malnutrition in a hospitalized adult can hinder the patient's recovery, prolong length of hospital stay, and increase the need for post-discharge institutional care [8-11].

Not surprisingly, the high prevalence and adverse effects of malnutrition in hospitalized patients affect the overall cost of healthcare in the United States, as in the rest of the world. The estimated annual cost of disease-associated malnutrition in the United States is over $15.5 billion [7]. In Canada, the added cost of in-hospital care for a malnourished patient is $1,500-$2,000 per hospital stay (compared to the cost for an adequately-nourished patient); this translates to an excess $1.56-$2.1 billion per year, similar to the US when adjusted for population [5]. Studies from Latin America estimate an annual costs of $10.2 billion for management of malnourished patients in public hospitals [12 13], and studies from Europe and Asia likewise report markedly higher costs for care of malnourished hospital patients [14-18].

Identifying and treating malnutrition are critical to improving patient health outcomes and to reducing healthcare costs [6]. To identify and manage hospitalized patients at risk for malnutrition, nutrition-focused quality improvement programs can be used to guide nutrition screening and assessment, to intervene with nutrition care when needed, and to provide ongoing monitoring and adjustment of nutrition, as needed [19 20]. Such programs improved patient outcomes and decreased healthcare costs, as evidenced by reduced rates of hospital-acquired infections, shorter lengths of hospital stay, and lower rates of readmission [19 21-24]. A systematic review of studies using oral nutritional supplements to treat malnutrition revealed cost savings, which were attributed to fewer medical complications, shortened hospital stays, prevention of pressure ulcers, and improved quality-adjusted life years [25]. A large clinical trial on use of individualized nutritional support during hospitalization showed improved nutritional intake, functional outcome, and quality of life, along with lowered risk of adverse effects and decreased 30-day mortality [26]. Results of the follow-on economic-evaluation study demonstrated cost savings related to reduced intensive care unit (ICU) stays and fewer hospital-acquired complications [27].

Gomes et al recently conducted a systematic review of 27 trials of patients who were malnourished or at risk of malnutrition on admission to the hospital [4]. Results showed that in-hospital nutritional support could significantly improve patient outcomes by increasing patients' energy and protein intake, which was associated with weight gain, lowered mortality rates, and reduced rates of non-elective hospital readmissions [4]. Based on these findings, the aim of our current analysis was to use economic modeling to predict whether benefits of in-hospital nutritional support are accompanied by returns in terms of economic benefits. In modeling, we also considered other Gomes et al. endpoints that showed a clinically meaningful improvement, i.e., lowered infection rates and shorter length of stay in hospital [4].

Methods

To clarify the current economic modeling analysis, we provide definitions of health economic terms used in our report **(Table 1)** [28]. Our model examined costs and potential cost benefits of using nutritional support for hospitalized patients. Nutritional support includes (i) screening admitted patients for malnutrition or its risk, (ii) for those identified, systematic nutritional assessment by a dietitian, including recommendations for nutritional targets, (iii) development of an individualized nutritional care plan, including implementation and follow-up [26 29].

Table 1. Definition of terms for health economic analyses

Markov model	A model used for randomly changing systems. Applied to healthcare, Markov models assume that a patient is in one of a finite number of discrete health states, e.g., inpatient with malnutrition, inpatient with infectious complication, patient discharged from hospital, or patient readmitted to hospital non-electively. In modeling, the patient transitions from one state to another, with death as an unalterable state.
Cost-effectiveness	Value for the cost. In healthcare, the goal is to maximize the benefit of treatment for a patient population while using limited resources.
Incremental cost-effectiveness Ratio (ICER)	Used in health economics to compare two different interventions in terms of the cost of *gained* effectiveness. ICER is computed by dividing the difference in cost of 2 interventions by the difference of their effectiveness, e.g., if treatment A costs $50 per patient and provides 2 quality-adjusted life days (QALDs), and treatment B costs $80 while providing 3 QALDS, the ICER of treatment B is $80-50/3-2 = $30. The ICER determination is also called a cost-utility analysis.
Sensitivity analysis	A “what-if” analysis. This value focuses on what happens to the dependent variable when various parameters change.

Economic modeling and analysis

For our Markov model, we assumed that all patients were in a stable health state—hospitalized and malnourished **(Figure 1)**. Thereafter, patients could develop major infections. This was modeled as a separate health state because the probability of death, as well as healthcare costs and utilization, were assumed to be higher in comparison with patients not experiencing in-hospital complications. In another state, patients could be discharged from the hospital. Following discharge, patients may require unplanned readmission to the hospital. Finally, patients have different probabilities of death in each state, depending on their health status.

Figure 1. Health states within our Markov model. Designations of health states were based on findings in the meta-analysis report by Gomes et al [4].

We modeled the economic impact of the nutritional support from a payer's perspective. To do so, we developed a Markov cohort model with daily cycles [28 30]. The timeframe for our model was 6 months, consistent with results reported in the meta-analysis by Gomes et al [4]. We applied utility values (cost of gained effectiveness of nutritional support) that were derived from a study by Schuetz et al, assuming the utility value for preventing an in-hospital adverse event was a reasonable proxy for developing an infection during hospitalization [27]. Likewise, we applied a utility value from Harvey et al for preventing non-elective readmission [31]. Additionally, we assumed that the utility value for a released patient was 10% higher than for a patient in the stable health state. A more detailed description of the methods and assumptions is provided in Appendix A.2. We assumed costs for the various health states as follows: 1) no cost for patients released from hospital, 2) costs for nutritional support and re-admission were sourced from the NOURISH health economic analysis [32], assuming standard deviation as 10% of the input value, 3) costs for a heterogeneous distribution of infections were estimated on the basis of US hospital infection costs reported [33], 4) no cost for death, and 5) the cost of nutritional support as reported previously [34].

The primary outcomes in our model were cost-by-health-state and total cost. We calculated days in each health state, and we calculated utility value as the difference between the total costs of individualized nutritional support compared to no support. Individualized nutritional support refers to patient screening, assessment, definition of individual nutrition goals (including energy and protein, micronutrients) and a nutritional protocol to reach these goals (including oral supplements). Because we modeled real-life findings, we did not apply discount rates to any costs and outcomes.[35-37] Sensitivity analyses were executed on key variables of the model, including probability of patient release from hospital, cost for infections, cost for general ward hospitalization, and cost for individualized nutritional support. Because costs of nutritional supplements may vary in different care sites, we performed a sensitivity analysis to determine whether cost savings would be maintained when supplement costs were $3 per day (lower bound), $4 per day (medium), and $6 per day (upper bound).

To optimize our reporting of health economic evaluations, we used the CHEERS checklist[38].

Patient and Public Involvement

The data used for this study is based on a previous meta-analysis and as a result, patients were not involved in the design and conduct of the study, choice of outcome measures or recruitment to the study. However, we discussed the study concept and economic models beforehand in our multi-professional team consisting of physicians, nurses, researchers from nutritional industries and economists.

Results

Patient outcomes

The original systematic review included a total of 27 trials with 6,803 patients.[4] Compared with patients in the control group, those who received nutritional support had a significantly lower mortality rate (230 of 2758 [8.3%] vs 307 of 2,787 [11.0%] with an odds ratio [OR] of 0.73 (95% CI, 0.56-0.97).

Costs and cost-benefits of nutritional intervention

A base-case analysis summarizes our cost results **(Table 2)**. Here 'Life' represents the number of patient lives in each health state. Utilities results are shown as quality-adjusted life days (QALD), which were calculated in the model. Finally, the calculated cost for each health state is shown. The per-patient cost for in-hospital nutritional support was estimated at $36.44 per patient across the patient's hospital length of stay. In terms of costs over the 6-month timeframe of the study model, hospital care averaged $63,227 per patient in the nutrition-intervention group versus $66,045 in the control group. Sensitivity analysis within a range of $3 to $6 per day cost for the nutritional supplement did not overcome the cost-benefit for nutritional support (total cost $105,632 for $4 $105,681 for $6 in the nutritional support respectively).

Table 2. Base-case results

	Life days		Utilities, QALD		Cost, $ US	
Patient state	**Nutritional support**	**No nutritional support**	**Nutritional support**	**No nutritional support**	**Nutritional support**	**No nutritional support**
Hospitalized, malnourished	11.49	12.00	0.022	0.023	63,227	66,045
Non-elective readmission	0.14	0.17	0.000	0.000	193	237
In-hospital with Infection	0.52	0.60	0.001	0.001	4,554	5,374
Discharged from hospital	162	159	0.342	0.333	37,597	36,863
Death	7.74	10.27				
Total (sum of health states above)	174.26	171.73	0.365	0.358	105,608	108,520

QALDs = quality-adjusted life days

Incremental differences in cost savings, life days, QALDs, and ICER per life days were determined (**Table 3**). When using nutritional support, the total cost savings over the 6-month modeling interval was $2,912, which was mainly driven by cost savings in the general ward hospitalization ($2,818). Patients receiving nutritional support also had 2.5 more life days without complications during the modeled time. Finally, given the cost savings and the added life-days, cost-effectiveness results show dominance for the nutritional support group.

We also calculated costs to prevent hospital-acquired infections and hospital readmission, which were $820 USD for one prevented infection and $733 for one prevented non-elective readmission. The incremental cost per life-day gained was -$1,149 USD with 2.53 additional days. When varying the input values, the results of the sensitivity analyses provided support for the original findings.

Table 3: Results for incremental differences from base-case analysis

	Incremental changes for nutritional support vs no nutritional support			
Cost item	**Cost savings, $ US**	**Life days**	**QALDs**	**ICER LD, $ US**

General ward hospitalization	2,818.17	0.51	-0.0009	-5,569.72
Readmission	43.50	-0.03	-0.0001	1,372.62
Infections	820.89	0.09	0.0001	-8,891.82
Released	733.65	3.16	0.0081	231.92
Death		-2.53		
Total	2,912.47	2.53	0.0070	-1,149.63

QALDs = quality-adjusted life days

ICER LD = Incremental cost-effectiveness Ratio Life Days

Discussion

When hospitalized patients with malnutrition or at nutritional risk receive nutritional support, risk for hospital infections is reduced, length of stay is shortened, and the likelihood of hospital readmission is decreased. Importantly, results of our current modeling study showed that the added cost of providing nutritional support is low, especially when considering the associated reductions in costs of hospitalization and medical treatments. Taken together, results from our present Markov health cost modeling showed that in-hospital nutritional support is a highly cost-effective intervention.

Comparison with findings in other nutrition care studies

The underlying systematic review by Gomes et al found that nutritional support led to statistically significant reductions in mortality and non-elective hospital readmissions [4], findings that have also been reported for other hospital populations [4 21 23 24 26 39]. As well, the results of our health economic modeling analysis confirmed and extended data and messages on the 'value of nutrition' in care for hospitalized patients in North America [40 41], Latin America [13 42 43], Europe and the United Kingdom [25 44-46], and Asia [17 34].

Hospital nutritional care has proven particularly efficacious and cost-effective in older populations with multiple health conditions, including those living in different care settings—in the community [44 47-49] and in nursing care facilities.[47 50] Furthermore, it was recently shown that malnutrition is underdiagnosed in emergency departments, also leading to a higher burden in terms of healthcare costs [51].

Limitations of this modeling analysis

As for all modeling analyses, our model had some limitations. Costs and cost-savings were calculated from the perspective of the 27 hospitals included in the Gomes review and meta-analysis [4]; results may thus not be fully generalizable to hospitals where patient demographics, disease severity, and care costs differ markedly from those in the reviewed studies. As well, our modeled cost-savings calculations reflect reductions in infectious complications, hospital length of stay, and non-elective readmissions, as measures for the effectiveness of in-hospital nutritional support. Other clinical outcomes, such as non-infective complications, are not included in the evaluation but could be included in future studies on hospital-related costs. Additionally, our model used direct costs as the main drivers of economic decision-making by US hospital administrators and payers; future models could tackle savings in cost terms important to the patients, such as faster recovery with less disability and lower loss of work productivity.

The way forward

Guidelines and recommendations on the importance of nutrition care for medical nutritionally vulnerable inpatients are increasingly available in the US and elsewhere [3 35 52-54]. A recent European study showed that adherence to guidelines on malnutrition management in 15 hospitals was generally good, which led to improved nutritional care in hospitals [55]. Based on our modeled findings, we anticipate that increased attention to nutritional support during and after hospitalization may yield marked benefits both in terms of health outcomes and cost savings.

Conclusion

In conclusion, our modeling analysis predicted that in-hospital nutritional support for medical inpatients who are malnourished or at nutritional risk can yield significant cost-benefits along with previously reported gains in terms of health outcomes [4]. Together, these positive effects provide a compelling rationale for hospitals to follow comprehensive nutrition care pathways—including screening for malnutrition risk, assessment of causes and severity of malnutrition, and provision of nutrition-focused support during and after hospitalization [52 53 56].

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Statement of authorship

P Schuetz: study conceptualization, investigation, acquisition of funding, writing and editing manuscript; S Sulo: conceptualization, writing and editing manuscript; S Walzer, L Vollmer: analysis, writing and editing manuscript; Z Stanga, F Gomes: conceptualization, investigation, review and editing manuscript. C Brunton, N Kaegi-Braun and B Mueller provided critical feedback to the analysis and approved the final manuscript.

Conflict of interest

The Institution of P Schuetz has previously received unrestricted grant money, not related to this project, from Nestle Health Science and Abbott. The institution of Z Stanga received speaking honoraria and research support from Nestle Health Science, Abbott Nutrition and Fresenius Kabi. S. Sulo and C. Brunton are employees and stockholders of Abbott. S Walzer and L Vollmer received funding for the model development from Abbott. S Walzer has also received funding from Nestle Health Science and Fresenius Kabi for other health economic studies. All other authors report no conflicts of interest.

Funding

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Ethical Approval Statement

Not applicable

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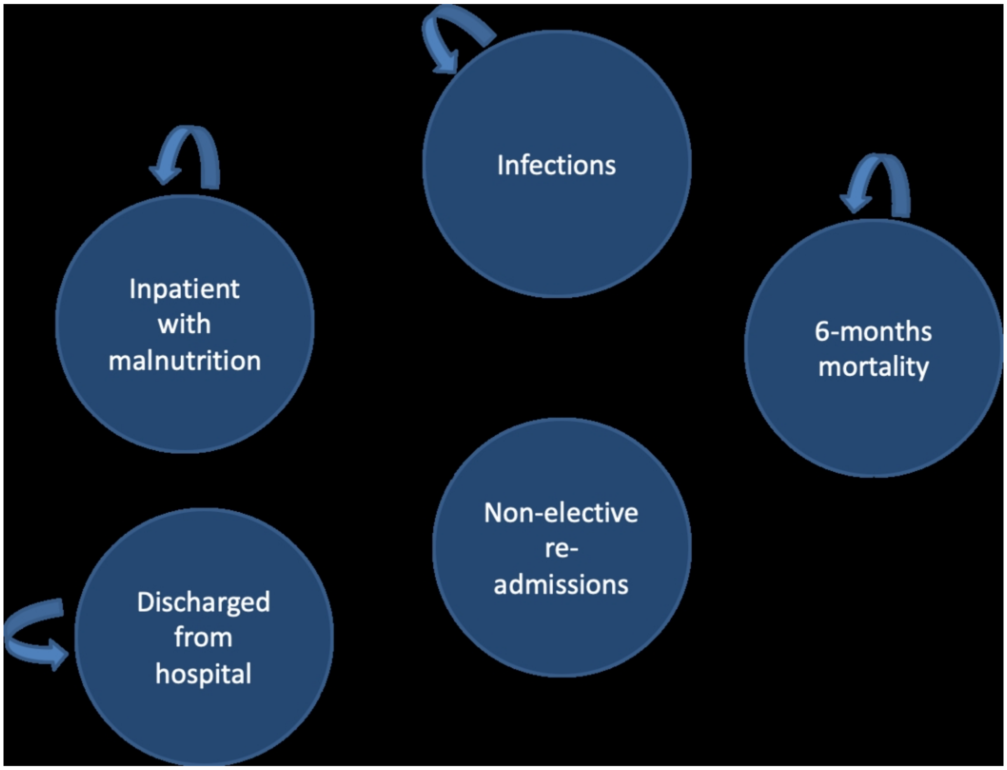

Figure 1

210x160mm (144 x 144 DPI)

Appendices

A. 1. Model assumptions

Transition probabilities for the different health states in the model were derived from the extracted data of the meta-analysis **(Table A.1).** The rates were calculated for each health state and then applied as daily probabilities. Mean values and standard deviations were calculated for each health state. Beta distributions are standard in health economic analysis and are defined within a range of 0 to 1 for each health state.[1] When specific values were unavailable, we assumed the following:

- Transition probability "stable -> release" was adapted from Schuetz et al,[2] adjusting that number until the published length of stay was reproducible.
- Transition probability "infection -> stable" was assumed to be the same as for "stable -> infection."
- Transition probability "Re-admission -> stable" is the complement value to the probability of "stable -> re-admission" as this "re-admission" health state is only a transition state.

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

	Transition probability per day*					
Transition phases	**Individualized nutrition**	**Distribution**	**SD**	**No nutrition support**	**Distribution**	**SD**
Stable -> Infection	0.00027273	Beta	0.00027371	0.00031596	Beta	0.00031514
Stable -> Release	0.08986880	Beta	0.02394280	0.08841700	Beta	0.02434740
Stable -> Death	0.00047833	Beta	0.00046549	0.00064104	Beta	0.00061241
Infection -> Stable	0.00027273	Beta	0.00027371	0.00031596	Beta	0.00031514
Infection -> Infection	0.00027273	Beta	0.00027371	0.00031596	Beta	0.00031514
Infection-> Death	0.00047833	Beta	0.00046549	0.00064104	Beta	0.00061241
Re-admission -> Stable	0.99952167	Beta	0.00221795	0.99935896	Beta	0.00239153
Re-admission -> Death	0.00047833	Beta	0.00046549	0.00064104	Beta	0.00061241
Release -> re-admission	0.00087410	Beta	0.00081610	0.00109193	Beta	0.00099477
Release -> death	0.00047833	Beta	0.00046549	0.00064104	Beta	0.00061241

A beta distribution was assumed for the utility values, a standard distribution for utilities in health economic analysis; these are defined within the range of 0 to 1 **(Table A.2).**

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

	Individualized nutrition	Distribution	SD	No nutrition support	Distribution	SD
Stable health state	0.001915068	Beta	0.00063	0.00190685	Beta	0,00120
Infection health state	0.001717808	Beta	0.00065	0.00167945	Beta	0,00066
Non-elective re-admission health state	0,001780822	Beta	0,00077	0,001780822	Beta	0,00077
Released health state	0.002106575	Beta	0.00069	0.00209753	Beta	0,00132
Assumption: Utility for death = 0. Utility for released patients 10% improved compared to stable health state patients.						

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,[1] as these are also defined as a positive number (means >0; **Table A.3**).

Table A.2: Cost input for the health economic model

Cost item	Cost input	For probabilistic analysis		Reference	Comment
		Distribution	SD		
Nutrition (support)	USD 3.00	Gamma	USD 0.60	Zhong 2017[3]	"intervention cost"
Cost per day in non-ICU ward	USD 5,480.74	Gamma	USD 1,370.19	Zuvekas 2017	Cost per inpatient day in state / local government hospital
Cost per re-admission	USD 1,369.62	Gamma	USD 205.44	Zuvekas 2017	Published data is per visit (fits with re-admission)
Cost per infection	USD 8,888.82	Gamma	USD 1,777.76	Schmier 2016[5]	Cost included: VAP/HAP, SSI, GI, CAUTI. Weighted infection cost based on number of cases (table I)
Average cost per released patient	USD 231.92	Gamma	USD 23.19	Zuvekas 2017	One visit to GP every second week. Published data are per visit - assumption: one visit per quarter (USD 156 / 90 days)

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CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 5-6
		Present the study question and its relevance for health policy or practice decisions.	Page 5-6
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 7-9
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 7-9
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 7-9
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 7-9
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 7-9
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	n/a

Section/item	Item No	Recommendation	Reported on page No
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 7-9
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	n/a
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Page 7-9
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Page 7-9
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	n/a
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 7-9
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 7-9
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 7-9
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 7-9
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for	Page 7-9

Section/item	Item No	Recommendation	Reported on page No
		pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 9-12
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 9-12
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	n/a
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 9-12
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Page 9-12
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 12-13
Other			

Section/item	Item No	Recommendation	Reported on page No
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 15
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 15

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Cost savings associated with nutritional support in medical inpatients: an economic model based on data from a systematic review of randomized trials

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Cost savings associated with nutritional support in medical inpatients: an economic model based on data from a systematic review of randomized trials

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Abstract

Background & Aims: Nutritional support improves clinical outcomes during hospitalization as well as after discharge. Recently, a systematic review of 27 randomized, controlled trials showed that nutritional support was associated with lower rates of hospital readmissions and improved survival. In the present economic modeling study, we sought to determine whether in-hospital nutritional support would also return economic benefits.

Methods: The current economic model applied cost estimates to the outcome results from our recent systematic review of hospitalized patients. In the underlying meta-analysis, a total of 27 trials (n = 6,803 patients) were included. To calculate the economic impact of nutritional support, a Markov model was developed using transitions between relevant health states. Costs were estimated accounting for length of stay in a general hospital ward, hospital-acquired infections, readmissions, and nutritional support. Six-month mortality was also considered. The estimated daily per-patient cost for in-hospital nutrition was $6.23 US.

Results: Overall costs of care within the model timeframe of six months averaged $63,227 USD per-patient in the intervention group versus $66,045 USD in the control group, which corresponds to per-patient cost savings of $2,818. These cost savings were mainly due to reduced infection rate and shorter lengths of stay. We also calculated the costs to prevent a hospital-acquired infection and a non-elective readmission, i.e., $820 USD and $733 USD, respectively. The incremental cost per life-day gained was -$1,149 USD with 2.53 additional days. The sensitivity analyses for cost per quality-adjusted life-day provided support for the original findings.

Conclusions: For medical inpatients who are malnourished or at nutritional risk, our findings showed that in-hospital nutritional support is a cost-effective way to reduce risk for readmissions, lower the frequency of hospital-associated infections, and improve survival rates.

Strength and limitations of this study

- Large data set of randomized nutritional trials based on a recent systematic search and metanalysis
- Different patient-relevant outcomes considered in the cost analyses
- Calculation of costs and cost-savings from the perspective of the 27 hospitals included in the underlying meta-analysis which limit generalizability
- Focusing on direct costs as the main drivers of economic decision, but not costs savings associated with faster recovery, less disability and lower loss of work productivity.

Introduction

As a significant public health issue, malnutrition has detrimental effects on the care and recovery of hospitalized patients [1]. If unrecognized or undertreated, impaired nutritional status can worsen health outcomes and escalate healthcare use and costs [2 3]. Nutritional shortfalls occur when unintended loss of weight and muscle result from collusion of various predisposing factors—older age, limited physical activity, insufficient protein and energy intake relative to needs, altered hormone function, and anorexia [4]. Studies estimate that between 30 and 50% of adult inpatients are malnourished or at nutritional risk when admitted to hospital; nutritional risk is higher in patients who are older and have underlying chronic health conditions [5-7].

The presence of malnutrition can impair a patient's response to medical treatment and can increase susceptibility to hospital-acquired comorbidities, which include urinary tract infections, falls and fractures, acute respiratory infections, skin tears, and hospital-acquired pressure injuries.[8-10] As a result, malnutrition in a hospitalized adult can hinder the patient's recovery, prolong length of hospital stay, and increase the need for post-discharge institutional care [8-11].

Not surprisingly, the high prevalence and adverse effects of malnutrition in hospitalized patients affect the overall cost of healthcare in the United States, as in the rest of the world. The estimated annual cost of disease-associated malnutrition in the United States is over $15.5 billion [7]. In Canada, the added cost of in-hospital care for a malnourished patient is $1,500-$2,000 per hospital stay (compared to the cost for an adequately-nourished patient); this translates to an excess $1.56-$2.1 billion per year, similar to the US when adjusted for population [5]. Studies from Latin America estimate an annual costs of $10.2 billion for management of malnourished patients in public hospitals [12 13], and studies from Europe and Asia likewise report markedly higher costs for care of malnourished hospital patients [14-18].

Identifying and treating malnutrition are critical to improving patient health outcomes and to reducing healthcare costs [6]. To identify and manage hospitalized patients at risk for malnutrition, nutrition-focused quality improvement programs can be used to guide nutrition screening and assessment, to intervene with nutrition care when needed, and to provide ongoing monitoring and adjustment of nutrition, as needed [19 20]. Such programs improved patient outcomes and decreased healthcare costs, as evidenced by reduced rates of hospital-acquired infections, shorter lengths of hospital stay, and lower rates of readmission [19 21-24]. A systematic review of studies using oral nutritional supplements to treat malnutrition revealed cost savings, which were attributed to fewer medical complications, shortened hospital stays, prevention of pressure ulcers, and improved quality-adjusted life years [25]. A large clinical trial on use of individualized nutritional support during hospitalization showed improved nutritional intake, functional outcome, and quality of life, along with lowered risk of adverse effects and decreased 30-day mortality [26]. Results of the follow-on economic-evaluation study demonstrated cost savings related to reduced intensive care unit (ICU) stays and fewer hospital-acquired complications [27].

Gomes et al recently conducted a systematic review of 27 trials of patients who were malnourished or at risk of malnutrition on admission to the hospital [4]. Results showed that in-hospital nutritional support could significantly improve patient outcomes by increasing patients' energy and protein intake, which was associated with weight gain, lowered mortality rates, and reduced rates of non-elective hospital readmissions [4]. Based on these findings, the aim of our current analysis was to use economic modeling to predict whether benefits of in-hospital nutritional support are accompanied by returns in terms of economic benefits. In modeling, we also considered other Gomes et al. endpoints that showed a clinically meaningful improvement, i.e., lowered infection rates and shorter length of stay in hospital [4].

Methods

To clarify the current economic modeling analysis, we provide definitions of health economic terms used in our report **(Table 1)** [28]. Our model examined costs and potential cost benefits of using nutritional support for hospitalized patients. Nutritional support includes (i) screening admitted patients for malnutrition or its risk, (ii) for those identified, systematic nutritional assessment by a dietitian, including recommendations for nutritional targets, (iii) development of an individualized nutritional care plan, including implementation and follow-up [26 29].

Table 1. Definition of terms for health economic analyses

Markov model	A model used for randomly changing systems. Applied to healthcare, Markov models assume that a patient is in one of a finite number of discrete health states, e.g., inpatient with malnutrition, inpatient with infectious complication, patient discharged from hospital, or patient readmitted to hospital non-electively. In modeling, the patient transitions from one state to another, with death as an unalterable state.
Cost-effectiveness	Value for the cost. In healthcare, the goal is to maximize the benefit of treatment for a patient population while using limited resources.
Incremental cost-effectiveness Ratio (ICER)	Used in health economics to compare two different interventions in terms of the cost of *gained* effectiveness. ICER is computed by dividing the difference in cost of 2 interventions by the difference of their effectiveness, e.g., if treatment A costs $50 per patient and provides 2 quality-adjusted life days (QALDs), and treatment B costs $80 while providing 3 QALDS, the ICER of treatment B is $80-50/3-2 = $30. The ICER determination is also called a cost-utility analysis.
Sensitivity analysis	A “what-if” analysis. This value focuses on what happens to the dependent variable when various parameters change.

Economic modeling and analysis

For our Markov model, we assumed that all patients were in a stable health state—hospitalized and malnourished **(Figure 1)**. Thereafter, patients could develop major infections. This was modeled as a separate health state because the probability of death, as well as healthcare costs and utilization, were assumed to be higher in comparison with patients not experiencing in-hospital complications. In another state, patients could be discharged from the hospital. Following discharge, patients may require unplanned readmission to the hospital. Finally, patients have different probabilities of death in each state, depending on their health status.

Figure 1. Health states within our Markov model. Designations of health states were based on findings in the meta-analysis report by Gomes et al [4].

We modeled the economic impact of the nutritional support from a payer's perspective. To do so, we developed a Markov cohort model with daily cycles [28 30]. The timeframe for our model was 6 months, consistent with results reported in the meta-analysis by Gomes et al [4]. We applied utility values (cost of gained effectiveness of nutritional support) that were derived from a study by Schuetz et al, assuming the utility value for preventing an in-hospital adverse event was a reasonable proxy for developing an infection during hospitalization [27]. Likewise, we applied a utility value from Harvey et al for preventing non-elective readmission [31]. Additionally, we assumed that the utility value for a released patient was 10% higher than for a patient in the stable health state. A more detailed description of the methods and assumptions is provided in Appendix A.1. We assumed costs for the various health states as follows: 1) no cost for patients released from hospital, 2) costs for nutritional support and re-admission were sourced from the NOURISH health economic analysis [32], assuming standard deviation as 10% of the input value, 3) costs for a heterogeneous distribution of infections were estimated on the basis of US hospital infection costs reported [33], 4) no cost for death, and 5) the cost of nutritional support as reported previously [34].

The primary outcomes in our model were cost-by-health-state and total cost. We calculated days in each health state, and we calculated utility value as the difference between the total costs of individualized nutritional support compared to no support. Individualized nutritional support refers to patient screening, assessment, definition of individual nutrition goals (including energy and protein, micronutrients) and a nutritional protocol to reach these goals (including oral supplements). The estimated daily per-patient cost for in-hospital nutrition was $6.23 US. Because we modeled real-life findings, we did not apply discount rates to any costs and outcomes.[35-37] Sensitivity analyses were executed on key variables of the model, including probability of patient release from hospital, cost for infections, cost for general ward hospitalization, and cost for individualized nutritional support. Because costs of nutritional supplements may vary in different care sites, we performed a sensitivity analysis to determine whether cost savings would be maintained when supplement costs were $3 per day (lower bound), $4 per day (medium), and $6 per day (upper bound).

To optimize our reporting of health economic evaluations, we used the CHEERS checklist[38].

Patient and Public Involvement

The data used for this study is based on a previous meta-analysis and as a result, patients were not involved in the design and conduct of the study, choice of outcome measures or recruitment to the study. However, we discussed the study concept and economic models beforehand in our multi-professional team consisting of physicians, nurses, researchers from nutritional industries and economists.

Results

Patient outcomes

The original systematic review included a total of 27 trials with 6,803 patients.[4] Compared with patients in the control group, those who received nutritional support had a significantly lower mortality rate (230 of 2758 [8.3%] vs 307 of 2,787 [11.0%] with an odds ratio [OR] of 0.73 (95% CI, 0.56-0.97).

Costs and cost-benefits of nutritional intervention

A base-case analysis summarizes our cost results **(Table 2)**. Here 'Life' represents the number of patient lives in each health state. Utilities results are shown as quality-adjusted life days (QALD), which were calculated in the model. Finally, the calculated cost for each health state is shown. The per-patient cost for in-hospital nutritional support was estimated at $36.44 per patient across the patient's hospital length of stay. In terms of costs over the 6-month timeframe of the study model, hospital care averaged $63,227 per patient in the nutrition-intervention group versus $66,045 in the control group. Sensitivity analysis within a range of $3 to $6 per day cost for the nutritional supplement did not overcome the cost-benefit for nutritional support (total cost $105,632 for $4 $105,681 for $6 in the nutritional support respectively).

Table 2. Base-case results

	Life days		Utilities, QALD		Cost, $ US	
Patient state	**Nutritional support**	**No nutritional support**	**Nutritional support**	**No nutritional support**	**Nutritional support**	**No nutritional support**
Hospitalized, malnourished	11.49	12.00	0.022	0.023	63,227	66,045
Non-elective readmission	0.14	0.17	0.000	0.000	193	237
In-hospital with Infection	0.52	0.60	0.001	0.001	4,554	5,374
Discharged from hospital	162	159	0.342	0.333	37,597	36,863
Death	7.74	10.27				
Total (sum of health states above)	174.26	171.73	0.365	0.358	105,608	108,520

QALDs = quality-adjusted life days

Incremental differences in cost savings, life days, QALDs, and ICER per life days were determined (**Table 3**). When using nutritional support, the total cost savings over the 6-month modeling interval was $2,912, which was mainly driven by cost savings in the general ward hospitalization ($2,818). Patients receiving nutritional support also had 2.5 more life days without complications during the modeled time. Finally, given the cost savings and the added life-days, cost-effectiveness results show dominance for the nutritional support group.

We also calculated costs to prevent hospital-acquired infections and hospital readmission, which were $820 USD for one prevented infection and $733 for one prevented non-elective readmission. The incremental cost per life-day gained was -$1,149 USD with 2.53 additional days. When varying the input values, the results of the sensitivity analyses provided support for the original findings.

Table 3: Results for incremental differences from base-case analysis

	Incremental changes for nutritional support vs no nutritional support

Cost item	Cost savings, $ US	Life days	QALDs	ICER LD, $ US
General ward hospitalization	2,818.17	0.51	-0.0009	-5,569.72
Readmission	43.50	-0.03	-0.0001	1,372.62
Infections	820.89	0.09	0.0001	-8,891.82
Released	733.65	3.16	0.0081	231.92
Death	[redacted]	-2.53	[redacted]	[redacted]
Total	2,912.47	2.53	0.0070	-1,149.63

QALDs = quality-adjusted life days

ICER LD = Incremental cost-effectiveness Ratio Life Days

Discussion

When hospitalized patients with malnutrition or at nutritional risk receive nutritional support, risk for hospital infections is reduced, length of stay is shortened, and the likelihood of hospital readmission is decreased. Importantly, results of our current modeling study showed that the added cost of providing nutritional support is low, especially when considering the associated reductions in costs of hospitalization and medical treatments. Taken together, results from our present Markov health cost modeling showed that in-hospital nutritional support is a highly cost-effective intervention.

Comparison with findings in other nutrition care studies

The underlying systematic review by Gomes et al found that nutritional support led to statistically significant reductions in mortality and non-elective hospital readmissions [4], findings that have also been reported for other hospital populations [4 21 23 24 26 39]. As well, the results of our health economic modeling analysis confirmed and extended data and messages on the 'value of nutrition' in care for hospitalized patients in North America [40 41], Latin America [13 42 43], Europe and the United Kingdom [25 44-46], and Asia [17 34].

Hospital nutritional care has proven particularly efficacious and cost-effective in older populations with multiple health conditions, including those living in different care settings—in the community [44 47-49] and in nursing care facilities.[47 50] Furthermore, it was recently shown that malnutrition is underdiagnosed in emergency departments, also leading to a higher burden in terms of healthcare costs [51].

Limitations of this modeling analysis

As for all modeling analyses, our model had some limitations. Costs and cost-savings were calculated from the perspective of the 27 hospitals included in the Gomes review and meta-analysis [4]; results may thus not be fully generalizable to hospitals where patient demographics, disease severity, and care costs differ markedly from those in the reviewed studies. As well, our modeled cost-savings calculations reflect reductions in infectious complications, hospital length of stay, and non-elective readmissions, as measures for the effectiveness of in-hospital nutritional support. Other clinical outcomes, such as non-infective complications, are not included in the evaluation but could be included in future studies on hospital-related costs. Additionally, our model used direct costs as the main drivers of economic decision-making by US hospital administrators and payers; future models could tackle savings in cost terms important to the patients, such as faster recovery with less disability and lower loss of work productivity.

The way forward

Guidelines and recommendations on the importance of nutrition care for medical nutritionally vulnerable inpatients are increasingly available in the US and elsewhere [3 35 52-54]. A recent European study showed that adherence to guidelines on malnutrition management in 15 hospitals was generally good, which led to improved nutritional care in hospitals [55]. Based on our modeled findings, we anticipate that increased attention to nutritional support during and after hospitalization may yield marked benefits both in terms of health outcomes and cost savings.

Conclusion

In conclusion, our modeling analysis predicted that in-hospital nutritional support for medical inpatients who are malnourished or at nutritional risk can yield significant cost-benefits along with previously reported gains in terms of health outcomes [4]. Together, these positive effects provide a compelling rationale for hospitals to follow comprehensive nutrition care pathways—including screening for malnutrition risk, assessment of causes and severity of malnutrition, and provision of nutrition-focused support during and after hospitalization [52 53 56].

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Statement of authorship

P Schuetz: study conceptualization, investigation, acquisition of funding, writing and editing manuscript; S Sulo: conceptualization, writing and editing manuscript; S Walzer, L Vollmer: analysis, writing and editing manuscript; Z Stanga, F Gomes: conceptualization, investigation, review and editing manuscript. C Brunton, N Kaegi-Braun and B Mueller provided critical feedback to the analysis and approved the final manuscript.

Conflict of interest

The Institution of P Schuetz has previously received unrestricted grant money, not related to this project, from Nestle Health Science and Abbott. The institution of Z Stanga received speaking honoraria and research support from Nestle Health Science, Abbott Nutrition and Fresenius Kabi. S. Sulo and C. Brunton are employees and stockholders of Abbott. S Walzer and L Vollmer received funding for the model development from Abbott. S Walzer has also received funding from Nestle Health Science and Fresenius Kabi for other health economic studies. All other authors report no conflicts of interest.

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Ethical approval statement

Not applicable

Data availability statement

Data are available in a public, open access repository

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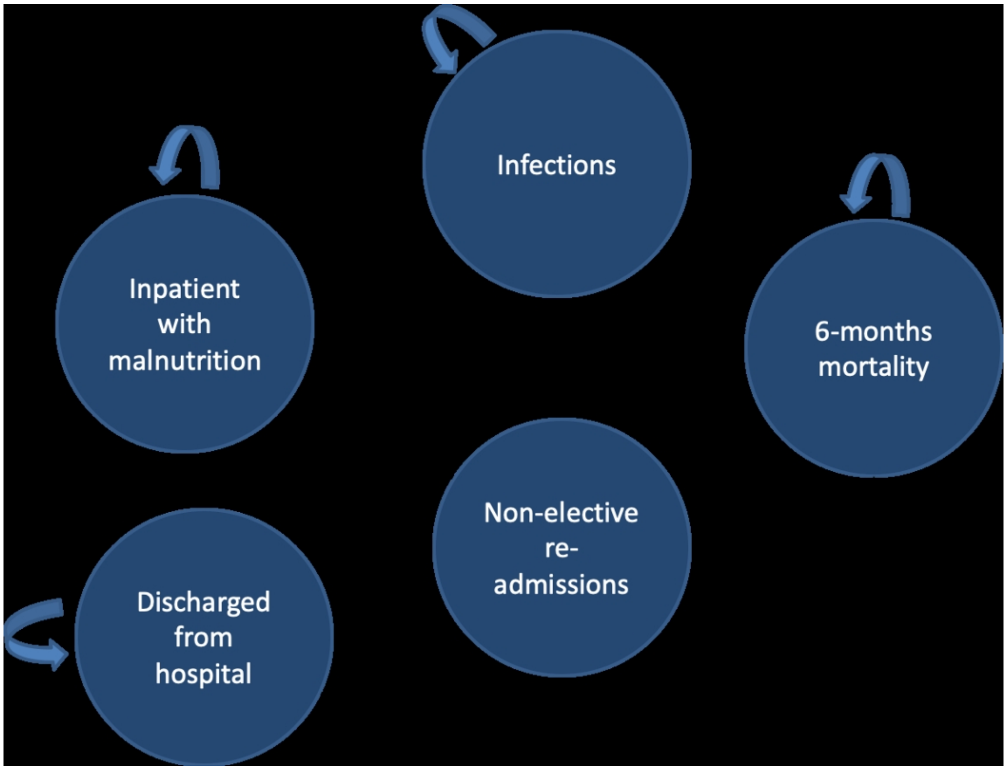

Figure 1

210x160mm (144 x 144 DPI)

Appendices

A. 1. Model assumptions

Transition probabilities for the different health states in the model were derived from the extracted data of the meta-analysis **(Table A.1).** The rates were calculated for each health state and then applied as daily probabilities. Mean values and standard deviations were calculated for each health state. Beta distributions are standard in health economic analysis and are defined within a range of 0 to 1 for each health state.[1] When specific values were unavailable, we assumed the following:

- Transition probability “stable -> release” was adapted from Schuetz et al,[2] adjusting that number until the published length of stay was reproducible.
- Transition probability “infection -> stable” was assumed to be the same as for “stable -> infection.”
- Transition probability “Re-admission -> stable” is the complement value to the probability of “stable -> re-admission” as this “re-admission” health state is only a transition state.

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

	Transition probability per day*					
Transition phases	**Individualized nutrition**	**Distribution**	**SD**	**No nutrition support**	**Distribution**	**SD**
Stable -> Infection	0.00027273	Beta	0.00027371	0.00031596	Beta	0.00031514
Stable -> Release	0.08986880	Beta	0.02394280	0.08841700	Beta	0.02434740
Stable -> Death	0.00047833	Beta	0.00046549	0.00064104	Beta	0.00061241
Infection -> Stable	0.00027273	Beta	0.00027371	0.00031596	Beta	0.00031514
Infection -> Infection	0.00027273	Beta	0.00027371	0.00031596	Beta	0.00031514
Infection-> Death	0.00047833	Beta	0.00046549	0.00064104	Beta	0.00061241
Re-admission -> Stable	0.99952167	Beta	0.00221795	0.99935896	Beta	0.00239153
Re-admission -> Death	0.00047833	Beta	0.00046549	0.00064104	Beta	0.00061241
Release -> re-admission	0.00087410	Beta	0.00081610	0.00109193	Beta	0.00099477
Release -> death	0.00047833	Beta	0.00046549	0.00064104	Beta	0.00061241

A beta distribution was assumed for the utility values, a standard distribution for utilities in health economic analysis; these are defined within the range of 0 to 1 **(Table A.2).**

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

	Individualized nutrition	Distribution	SD	No nutrition support	Distribution	SD
Stable health state	0.001915068	Beta	0.00063	0.00190685	Beta	0,00120
Infection health state	0.001717808	Beta	0.00065	0.00167945	Beta	0,00066
Non-elective re-admission health state	0,001780822	Beta	0,00077	0,001780822	Beta	0,00077
Released health state	0.002106575	Beta	0.00069	0.00209753	Beta	0,00132
Assumption: Utility for death = 0. Utility for released patients 10% improved compared to stable health state patients.						

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,[1] as these are also defined as a positive number (means >0; **Table A.3**).

Table A.2: Cost input for the health economic model

Cost item	Cost input	For probabilistic analysis		Reference	Comment
		Distribution	SD		
Nutrition (support)	USD 3.00	Gamma	USD 0.60	Zhong 2017[3]	"intervention cost"
Cost per day in non-ICU ward	USD 5,480.74	Gamma	USD 1,370.19	Zuvekas 2017	Cost per inpatient day in state / local government hospital
Cost per re-admission	USD 1,369.62	Gamma	USD 205.44	Zuvekas 2017	Published data is per visit (fits with re-admission)
Cost per infection	USD 8,888.82	Gamma	USD 1,777.76	Schmier 2016[5]	Cost included: VAP/HAP, SSI, GI, CAUTI. Weighted infection cost based on number of cases (table I)
Average cost per released patient	USD 231.92	Gamma	USD 23.19	Zuvekas 2017	One visit to GP every second week. Published data are per visit - assumption: one visit per quarter (USD 156 / 90 days)

References

1. Briggs A, Sculpher M. An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics.* 1998;13(4):397-409.
2. Schuetz P, Sulo S, Walzer S, et al. Economic evaluation of individualized nutritional support in medical inpatients: Secondary analysis of the EFFORT trial. *Clin Nutr.* 2020;[Epub ahead of print].
3. 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 Policy.* 2017;15(1):75-83.
4. Becker's Hospital Review. Average hospital expenses per inpatient day across 50 states. 2020; https://www.beckershospitalreview.com/finance/average-hospital-expenses-per-inpatient-day-across-50-states-02282020.html. Accessed Feb 28, 2020.
5. Schmier JK, Hulme-Lowe CK, Semenova S, et al. Estimated hospital costs associated with preventable health care-associated infections if health care antiseptic products were unavailable. *Clinicoecon Outcomes Res.* 2016;8:197-205.

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 5-6
		Present the study question and its relevance for health policy or practice decisions.	Page 5-6
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 7-9
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 7-9
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 7-9
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 7-9
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 7-9
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	n/a

Section/item	Item No	Recommendation	Reported on page No
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 7-9
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	n/a
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Page 7-9
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Page 7-9
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	n/a
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 7-9
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 7-9
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 7-9
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 7-9
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for	Page 7-9

Section/item	Item No	Recommendation	Reported on page No
		pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 9-12
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 9-12
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	n/a
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 9-12
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Page 9-12
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 12-13
Other			

Section/item	Item No	Recommendation	Reported on page No
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 15
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 15