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A systematic review of the cost and cost-effectiveness of standard oral nutritional supplements in the hospital setting

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SUMMARY

Background and aims: There is limited information about the economic impact of nutritional support despite its known clinical benefits. This systematic review examined the cost and cost-effectiveness of standard (non-disease specific) oral nutritional supplements (ONS) administered in the hospital setting only.

Methods: A systematic literature search of multiple databases, data synthesis and analysis were undertaken according to recommended procedures.

Results: Nine publications comprising four full text papers, two abstracts and three reports, one of which contained 11 cost analyses of controlled cohort studies, were identified. Most of these were based on retrospective analyses of randomised controlled trials designed to assess clinically relevant outcomes. The sample sizes of patients with surgical, orthopaedic and medical problems and combinations of these varied from 40 to 1.16 million. Of 14 cost analyses comparing ONS with no ONS (or routine care), 12 favoured the ONS group, and among those with quantitative data (12 studies) the mean cost-saving was 12.2 %. In a meta-analysis of five abdominal surgical studies in the UK, the mean net cost saving was £772 per patient (se £346; P `= 0.026). Cost savings were typically associated with significantly improved outcomes, demonstrated through the following meta-analyses: reduced mortality (Risk ratio 0.650, P <0.05; N = 5 studies), reduced complications (by 35% of the total; P<0.001, N = 6 studies) and reduced length of hospital stay (by 2 days, P <0.05; N = 6 surgical studies). Two studies also found ONS to be cost-effective, one by avoiding development of pressure ulcers and releasing hospital beds, and the other by gaining quality adjusted life years.

Conclusion: This review suggests that standard ONS in the hospital setting produce a cost-saving and are cost-effective. The evidence base could be further strengthened by prospective studies in which the primary outcome measures are economic.

Key words

Oral nutritional supplements; malnutrition; cost; cost-effectiveness; systematic review; hospital

1. Introduction

Although there is substantial information about the beneficial effects of nutritional support on clinical outcomes, such as mortality, development of conditions requiring hospital admissions and speed of recovery from illness[1-6], there is much less information about its economic consequences. Several systematic reviews have been undertaken[7-11] but these have often not separated the effects of different types of nutritional interventions in different settings and many analyses appear to have been missed. Furthermore, although in countries such as the UK[12] and the Republic of Ireland[13], it has been estimated that the cost of malnutrition exceeds 10% of the total public expenditure on health and social care, the extent to which nutritional interventions impact on the budget and produce cost-effective outcomes is much less clear. For example, various types of nutritional interventions, and sometimes the same types of interventions in the same setting, have been reported to produce both a net cost and net cost saving depending on the patient group and study conditions[14]. At least some of the variability between studies can be explained by the healthcare setting, the condition being treated, and the type of nutritional support, which may vary from a specialised form of nutritional support, such as enteral tube feeding and parenteral nutrition, to oral nutrition support, such as dietary advice to modify the texture or composition of the diet, food fortification and commercial oral nutritional supplements (ONS). The variability in outcomes involving ONS alone also depends on multiple factors, including the underlying disease, nutritional status and both the amount and type of ONS ingested. For example, general purpose, multi-nutrient ONS (standard ONS), designed for the management of a wide range of patients with disease related malnutrition contain a broad range of macronutrients and micronutrients in balanced proportions. These may produce different effects than

disease specific ONS for which the macro- and / or micronutrient levels have been adapted for use in specific clinical conditions.. In the hospital setting, ONS are typically used for relatively short periods of time, often in patients suffering from acute conditions (including the acute complications of elective and emergency procedures) while in the community setting, they are generally used for longer periods of time, often in patients with chronic conditions. In view of the diverse composition of ONS, the different populations for which they are prescribed, and the various clinical and economic outcomes that are influenced by care settings and transitions between care settings, this review focussed on addressing the following question: do standard ONS administered only during hospitalisation produce cost-effective outcomes and cost savings? The review also aimed to identify gaps in knowledge that need to be addressed to help guide clinical practice.

2. Methods

The systematic review was planned and conducted according to published guidelines, including those provided by the Cochrane Collaboration[15], the UK National Health Service Centre for Reviews and Dissemination[16] (CRD, Centre for Reviews and Dissemination, 2009), and the PRISMA guidelines[17]. This review on the use of ONS in hospital was part of a broader literature review that included the use of ONS in the community setting which will be reported separately[18].

2.1. Inclusion and exclusion criteria

The inclusion and exclusion criteria of the current review were defined before the literature search was undertaken. Both interventional and observational studies aiming to assess the effects of ONS interventions on economic outcomes were

eligible. Only papers or abstracts reported in English were included. Animal studies were excluded. Studies of adults and children (>1 year of age) of any nutritional status (malnourished and well nourished) treated as hospital inpatients in any country were included, but studies in pregnant and lactating women were excluded.

Studies of ONS alone or with other types of intervention, such as dietary advice (dietary counselling) or enteral tube feeding, were eligible for inclusion, but studies that included drug interventions were excluded. For the purposes of this review, only standard ONS were included which were defined as a commercially available, ready to consume, multi-nutrient (complete or incomplete), liquid or semi-solid product providing a mixture of macronutrients and micronutrients and produced by specialist medical nutrition manufacturers. Studies of disease-specific formulae adapted to the needs of specific diseases and/or digestive or metabolic disorders[19] were excluded as were immune modulating formulae. Dietary counselling was defined as dietary advice provided by a qualified healthcare worker to modify the quantity and/or proportions of food ingested. Studies of interventions with ONS, with or without other interventions, were compared with no ONS (or routine care, which may include ONS in a proportion of patients). Studies comparing ONS with another type of nutritional intervention, such as dietary advice were also eligible for inclusion. Studies that included exercise as an intervention, ONS in combination with drug therapy such as anabolic steroids, and studies of one type of ONS v. another were excluded.

The primary outcome of this review was cost or cost-effectiveness, with no restrictions on the type of effectiveness outcomes. The secondary outcome was any functional and/or clinically relevant effect pertinent to cost-effectiveness analysis.

2.3. Data extraction

The literature search was undertaken on 31 March 2014. OvidSP was used to search Embase (Embase Classic + Embase 1947 to 2014 week 13) and Medline (1946 to 2014 March week 3). On the same date, a literature search was carried out using the Health Economic Evaluation Database (HEED) and the Cochrane Library (which includes the National Health Service Economic Evaluations Database or NHS EED, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and Database of Abstracts of Reviews and Effects). Articles from all of these databases were exported into a single 'library'. The Cost Effectiveness Analysis (CEA) Registry was checked independently.

The terms shown below were used to make a broad search which included the title of publication, abstract, subject headings and any key words. They were organised into three groups: 1. economic, economics, cost, costs, finance, finances, budget, budgets, expense, expenses, price, prices, AUD, USD, EUR, GBP, dollar, dollars, euro, euros, pound and pounds 2. supplement, supplements, ONS, sip, sips, feed, feeds, nutrition and nutritional 3. utility, healthcare, resource, resources, effective, effectiveness, benefit and benefits.

The articles were exported into a database only if they included at least one search term within each of the three groups. Hand searching of the references of the retrieved final papers, and discussions with experts in the field were also carried out. Potentially eligible papers were identified by reading the titles, abstracts and key descriptor words/phrases. Full papers were obtained whenever possible according to the pre-specified inclusion criteria. The studies were initially screened by an assessor after reading the title and abstract, and if the publication was deemed to be potentially relevant, the full article was reviewed. Any uncertainty about potential relevance was

discussed with another assessor. Relevant abstracts were briefly summarised and used to search potential full papers by the same authors, but they were not subjected to detailed economic assessment as they contained insufficient information. The assessment of trial eligibility was undertaken by two independent assessors and any disagreements were resolved through discussion. Figure 1 shows the reasons for excluding certain studies. Other publications were identified from prior knowledge, contact with experts in the field and hand searching of publications on ONS. One of these publications was based on the NICE costing template[20], which was replicated by one author of the current review (ME) to examine the effect of standard ONS in hospital inpatients.

2.4. Quality assessment

The assessment of the quality of studies (risk of bias) was based on the Cochrane Handbook for Systematic Reviews of Interventions, updated in 2011[15] (controlled clinical trials), Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[21] (observational epidemiology), and Drummond et al[22] (economic studies - applied only to prospective studies with stated economic outcomes). In view of the lack of clear and unambiguous economic criteria relevant to intervention studies with ONS, a few of the items suggested by Drummond et al[22] were defined, clarified or eliminated to make them more pertinent to the current assessment (see supplementary file 1). Some publications were evaluated by more than one set of criteria.

2.5. Synthesis of data and statistical analyses

Comprehensive Meta-Analysis (version 2, Biostat Inc. New Jersey, USA) was used to undertake random effects meta-analyses using data that were extracted from

the studies included in the present review. When results were expressed in different units such as different national currencies or obtained at widely different times in different countries, the results were expressed as a proportion of the total costs or of the control group. When meta-analysis of patient level data was not possible due to lack of measures variation, the mean values from each study were analysed (study-level analysis), using simple statistical tests such as t-tests and the binomial test (for a cost outcome either favouring or not favouring the ONS group), undertaken with the Statistical Package for the Social Sciences (SPSS, version 20, Chicago USA). A P-value of <0.05 (two tailed) was considered to be significant.

3. Results

A total of 22,819 publications were retrieved from the literature search. No additional references were identified from the Cost Effectiveness Analysis Registry, but expert prior knowledge of the literature of relevant papers identified another five publications, which were not listed and/or not retrieved from the electronic databases (3 reports (not listed),[14, 20, 23], one paper[24], which was subsequently retrievable from electronic databases, and one abstract[25]). The original full text papers used by this review [24, 26-28], and previous systematic reviews[7-11] did not use or cite the 14 economic analyses from these five publications. Figure 1 shows that the vast majority of studies were eliminated either because they were duplicates or because the titles and abstracts clearly indicated they did not involve cost or a cost-effectiveness analysis using ONS in hospital. After closer scrutiny of the remaining studies, including examination of the full text for many of them, further studies were eliminated for the reasons shown in Figure 1, leaving only nine publications for analysis in this review[14, 20, 23, 24, 26-30]. Three of these publications were reports[14, 20, 23], one of which[14] included 11 economic

analyses of controlled clinical trials[26, 27, 31-39] (all of which were RCTs apart from one [27]), and another[20] representing an update of a previous report[40]. One of the excluded studies involved a multicomponent intervention in which the intake of ONS in the intervention group was less than in the control group receiving routine care[41]. Another study, with a historical control group[42] was excluded for several reasons: only a minority of patients in the control and intervention groups received ONS; the control group received more ONS than the intervention group; patients in the intervention group received different types of oral interventions (some ONS and protein enriched meals and others only protein enriched meals), with no subgroup analysis. One of the 12 hospital studies in the British Association for Parenteral and Enteral Nutrition (BAPEN) economic report[43], was also excluded because it used a 'home made' feed of unknown composition, instead of a commercial feed of known composition. A further paper from the USA[24] did not specify whether "complete nutritional supplement, oral" was restricted entirely to standard ONS, but contact with one of the authors of the paper revealed that about 80% of the ONS were standard ONS. This paper was included in the review, but interpreted with caution.

3.1. General features of studies

Supplementary file 2, Table 1 indicates the general study characteristics including the funding source of individual studies and in addition provides complementary information on the cost and cost-effectiveness studies to that provided below From 9 publications [14, 20, 23, 24, 26-30] fourteen cost-analyses based on interventions exclusively in the hospital setting were identified (including one which was part of a cost-effectiveness analysis[28], and one in which the hospital component was established from the costing template[20]). Only three cost analyses were identified from the

literature search [26-28] and only two were prospective[26, 27]. Most analyses were identified from detailed reports produced by national organisations (NICE and BAPEN). Two cost-effectiveness analyses[23, 28] used economic models that incorporated data from previous publications. Most of the controlled clinical trials used in the cost analyses included a range of clinically relevant outcomes (mortality, muscle strength and post-operative complications).) which were reviewed.

Ten cost analyses were based on data collected in the UK and another four in USA[24], Australia[28], Belgium[37] and Switzerland[35] (Supplementary File 2,Table 1). The two cost-effectiveness analyses undertaken in Australia[28] and England[23], were based on data collected in both their own countries and other countries.

Among the eleven studies comparing ONS with no ONS, one included the cost of nursing assistance to help with ingestion of ONS [28], another the labour and administrative expenses [24] and yet another the extra cost of implementing a management pathway involving screening, assessment and some enteral tube feeding[23]. Two studies compared ONS with routine care [34, 36], one of which specifically indicated that routine care included ONS (if for example it was recommended by the dietitian)[36]. The other study did not indicate this[34] although it was known that ONS was used routinely in the hospital in which the study was undertaken. Only one study compared ONS with placebo[39]. Table 1 in Supplementary File 2 summarises the comparisons. In all studies, ONS was given in addition to food. The study designs did not attempt to replace food with ONS.

Calculations of ONS costs in hospital were based on the duration and amount of the prescription, which ranged from about 5 days to 32 days and typically 300-600 kcal/day (Supplementary File 2,Table 1). In two modelling studies, the amount of

ONS used was not stated, but the prescription and administration costs were mentioned[24, 28].

Seven studies involved malnourished subjects [20, 23, 28, 34, 35, 37, 38] identified using various criteria (Supplemetary File 2,Table 1). Seven involved malnourished and non-malnourished subjects according to anthropometric criteria such as BMI[26, 31-33, 36, 39, 44], and one did not report weight or nutritional status[24].

The main outcome measure in all four modelling studies was either a cost[20, 24] or cost-effectiveness analysis[23, 28] but they relied on information obtained from previously published studies undertaken for other purposes. In two clinical studies, economic data were secondary outcome measures[26, 27]. These and other clinical studies reported a variety of outcome measures, such as weight, dietary intake, and functional and/or clinical outcome measures.

3.2. Outcomes

(a) Cost analyses: results of individual studies

Interventional studies: The two prospective controlled trials with a cost-analysis reported a net cost saving in favour of the ONS group. In the study of Smedley et al[26], which involved 89 patients undergoing abdominal surgery, the mean expenditure of the ONS group was lower than that of the control group (no ONS) by a mean of £261, with no significant differences between groups. Although the paper stated that the costing methodology would be reported in a subsequent publication, this was not identified. In the other original study which involved 181 patients undergoing orthopaedic surgery[27], the cost of the ONS group was also lower than that of the control group by a median of £130.21 per patient. The length of stay costs did not take into account the type of surgery (in contrast to the analysis of the same study in the

BAPEN report). No statistical tests of significance or measures of variation were reported, but the paper concluded that even moderate levels of untargeted nutritional support (prescription of 600 kcal/day) given post-operatively can be an effective part of routine orthopaedic care in terms of cost and reduction in post-operative complications.

Tables 1, 2 and 3 summarise the retrospectively established mean study level results from the BAPEN report, together with some additional calculated summary results. All five abdominal surgical studies meeting the inclusion criteria of this review showed a net cost saving in favour of ONS. These averaged at £873/patient according to calculations based on bed-day costs, £431/patient according to excess bed-day costs, and £216/patient based on complication costs. The combined abdominal and orthopaedic surgical studies were associated with even more favourable results (Tables 1, 2 and 3). Among the three non-surgical studies, two favoured the ONS group. When all the hospital studies in the BAPEN report were amalgamated (surgical, non-surgical and mixed surgical and non-surgical groups) the overall net cost saving favouring the ONS group was either statistically significant (calculations based on complication costs) or close to being significant (calculations based on bed-day and excess bed-day costs).

In two abstracts of economic models comparing ONS with no ONS based on previously published clinical data, the cost savings favoured the ONS group. In one of these, the cost saving was £138 per malnourished patient admitted to hospital[29], and in the other £5 - £460 per elderly patient at high risk of developing pressure ulcers[30](the range reflecting the differences in ulcer stages 1 to 4).

Observational study: The study of Philipson et al[24] involved a retrospective analysis of a hospital database of 44 million adult patients admitted to hospital over an

11 year period in the USA, from which 1.2 million were selected for the cost analysis: 0.6 million (1.6% of the total population) who received ONS and another 0.6 million who did not receive ONS but were matched for age, gender and the components of the Charlson comorbidity index (based on diagnostic groupings). The multivariate analysis, which was undertaken to control for confounding variables including hospital specific covariates such as the number of hospital beds and urban location, did not incorporate weight status or nutritional status. Instrumental variables analysis was undertaken to mitigate against potential selection bias associated with unknown variables. The reported length of hospital stay was 21.0% shorter in the ONS group (8.59 v10.88 days), which together with a consideration of other variables resulted in a net cost saving of $4734 (se $10.07) per episode in favour of the ONS group (21.6% cost saving). The authors of the paper felt that the results of instrumental variables analysis, supported by some validity tests, formed an appropriate basis to adjust for unknown confounding variables. For example they considered the possibility that ONS use (the instrument) might be related to provider 'quality' (a 'valid' instrument would be expected to show no correlation). Therefore, the authors correlated ONS use and 'hospital quality' as measured by the adoption of 11 new technologies such as cardiac catheterisation, thrombolysis and image guided surgery. They reported no significant relationships or inconsistent relationships, some of which were positively related and others negatively related. They also found that when comparing high and low ONS propensity hospitals, there were only small differences in co-morbidities, such as cardiovascular disease, although these were often significant due to large sample sizes.

Studies with interventional and observational components: The model used by Banks et al[28] predicted a total annual net cost saving of €2,869,526 (sd €2,078,715) in

Queensland, Australia, when appropriate nutritional support was used to prevent development of pressure ulcers.

The 2012 NICE costing report also concluded that there was an overall net cost saving in favour of the proposed pathway (£71,800 per 100,000 general population of England[20]). The model, which was based on an earlier one that also found a net cost saving in favour of the proposed pathway[40], was dominated by the effect of ONS in reducing length of hospital stay (the percentage reduction in costs was not reported and could not be computed from the costing template). This was more than sufficient to counteract the extra costs of screening, assessment and treatment with ONS, ultimately producing a net cost saving.

(b) Cost analyses: results of amalgamated studies

Subject level analyses (based on meta-analyses of studies comparing mean ± sd between groups): Figure 2 shows the meta-analysis of the net cost saving of five UK studies, all involving abdominal gastrointestinal surgery and all based on 2003 prices. The overall summary statistic favoured the ONS group (cost saving £772/ patient (se £346), P = 0.026; I^2 = 0%) (upper graph). The percentage cost saving (13.55% (se 6.09%), P = 0.026; I^2 = 0%) also significantly favoured the ONS group (lower graph).

Study level analysis (based only on the difference in mean values between groups): Twelve studies were found to produce a net cost saving favouring the ONS group by a mean 12.2% (sd 23.8%) (P = 0.105 using the one sample t-test for the difference between groups, and P = 0.050 using the one sample Wilcoxon signed-rank test (the results tended to be skewed; Kolgomorov Smirnov test; P = 0.135)). Out of 14 studies for which it was possible to dichotomise the results into those favouring and not favouring the ONS group, 12 favoured the ONS group (P = 0.013; the binomial test).

The results in Table 4 show the summary results of subgroup analysis according to

mean age of the study populations (<65 years v. ≥65 years), nutritional status (malnourished v. combination of malnourished and non-malnourished subjects), type of intervention (ONS v. no ONS and ONS v. routine care), and type of analysis (prospective v. retrospective; interventional v. observational). They universally favoured the ONS group, but the number of studies was small and the variation between them was large, with the result that the net cost saving was often not statistically significant. Furthermore, per cent cost-saving was not found to be significantly related to the year of publication of the study ($r = 0.298$, $P = 0.348$; $N = 12$ studies) or to the estimated average (mean or median) duration of ONS administration ($r = 0.186$, $P = 0.563$; $N = 12$ studies).

(c) *Cost-effectiveness analyses: results of individual studies*

The probabilistic cost-effectiveness model of Banks et al[28] suggested that use of nutritional support (mainly ONS; compared to no specific additional nutritional support) in elderly patients in hospitals in Queensland, Australia, avoids development of 2896 (sd 632) cases of pressure ulcers per year, whilst releasing 12396 (sd 4991) bed days, and producing savings of €2,869,526 (sd €2,078,715) per year. It was not possible to accurately assess the stage of pressure ulcers, which would have influenced the costs. This study used information from a previously published meta-analysis of 5 RCTs[45], which showed that nutritional support prevented the development of pressure ulcers (odds ratio 0.74) in a high risk group of patients. When the data was re-analysed by one of the authors of the meta-analysis who is also an author of the present review (ME), the summary result was virtually unaffected when the single tube feeding study was excluded from the meta-analysis (odds ratio 0.75) or when the single study with disease specific ONS was excluded (odds ratio 0.73).

In the report commissioned by NICE[40], the incremental cost per QALY gained was £6,608, which was considered to be cost-effective using the threshold of £20,000 per QALY gained. A large number of one-way sensitivity analyses confirmed the cost-effectiveness when the new pathway incorporating the NICE guidelines on nutritional care was compared to the current pathway of care. A possible exception concerned a scenario where the reduction in mortality attributable to ONS was small (or the relative risk high; the meta-analysis from the systematic review showed the relative risk to be 0.84 (95% CI 0.68, 1.03)) and the duration of intervention long and without increased health gains. A two-way sensitivity analysis showed that both an increase in prevalence of malnutrition and mortality amplified the cost-effectiveness. With a prevalence of malnutrition of >8% and a mortality of about 4%, which was considered to apply to the inpatient population, the incremental cost-effectiveness ratio was <£6,000 per QALY gained. Furthermore, if enteral tube feeding was excluded from the model to restrict the nutritional support to ONS, the new pathway would be expected to become more cost-effective, albeit to a small extent given that in the model, enteral tube feeding contributed little to the overall costs and apparently not at all to the additional QALYs gained. The report also indicated that the proposed pathway involving screening, using 'MUST' and use of ONS was also cost-effective compared to one involving clinical screening by nurses followed by ONS (base case analysis for incremental cost-effectiveness ratio was £4,339 per QALY gained).

Other studies without quantitative relationships between costs and effectiveness (outcome) measures have been considered in the cost-analysis section above. Reviewed studies reporting clinically relevant effectiveness measures are summarised below.

d) *Cost-effectiveness analyses: a consideration of clinically relevant outcomes from individual and amalgamated studies*

Mortality: There were no deaths in most studies involving elective surgical admissions, although in one of them there were three deaths out of a sample of 53 patients[33], and in another, two deaths before study day one, out of a sample of 100 subjects[32]. Mortality was greater among patients admitted acutely, who were also generally older[35, 36, 38]. In a study with a factorial design, no mortality statistics were reported in the subgroup analysis of ONS alone v placebo alone[39], although in the study as a whole there were 12 deaths out of 275 in the group that had ONS with or without additional vitamins and 14 deaths out of 274 in the group that received placebo with or without vitamins. In another study[37] , the two deaths in each group were reported at the end of the investigation period which included two months supplementation in the community. Further analyses were restricted to studies in which the effects of ONS administration in the hospital setting alone could be evaluated. A meta-analysis of studies reporting at least one death[32, 33, 35, 36, 38, 39] (studies with no deaths are ignored by meta-analyses of mortality), including the one in which deaths occurred before study day one[32] and two others with mortality statistics at three months[36] or six months[35] after admission, found fewer deaths in the group that received ONS in hospital (risk ratio, 0.691 (95% CI, 0.483, 089); P = 0.043; I^2 = 0%; N = 6 studies). Without the study of Vlaming et al[39], which included vitamin supplementation in some of the subjects, the summary statistics changed little (risk ratio 0.650 (95% CI, 0.432, 0.976); P = 0.038; I^2 = 0%; N = 5 studies) (Figure 3).

Complications: Out of the seven surgical studies with cost-analyses (all favouring the ONS group), six reported complication rates. Four of these [27, 31, 32, 35] found

significant differences between groups in minor or major complications or both (one of them included mortality among the complications[35]). A meta-analysis (random effects model) of complications in the ONS group (after adjustment for sample size differences between the ONS and control groups) found that the proportion of total complications was 35.3% (se 7.6%) less in the ONS than control group; $I^2 = 0\%$ (Figure 4).

Length of hospital stay: The mean length of hospital stay in all surgical studies favoured the ONS group[26, 27, 31-35] but one of the five UK studies did not report measures of variability between subjects[33]. Therefore, the meta-analysis of the five UK studies was subjected to a sensitivity analysis in which the highest and lowest standard deviations obtained from other UK studies were assigned to this study[28]. Both meta-analyses favoured the ONS group by 2.07 days (P = 0.035) and 2.25 days (P= 0.013) respectively (I^2= 0% for both meta-analyses). Among the other six hospital studies for which cost-analyses were available, four reported median length of stay. Overall, 10 out of the 12 studies had a mean or median length of stay that was shorter in the ONS group (P = 0.039, binomial test).

Other outcomes: Two studies reported fatigue scores, one in which there was no significant change in the ONS group and a significant deterioration in the no ONS group [32], and the other in which there was no significant difference between groups[26]. Among four studies that measured grip strength, one reported significantly higher strength in the ONS than the control (no ONS) group at the time of discharge[31], another a significant deterioration only in the control group at the time of discharge[32], and a further two studies no significant difference between groups during hospital stay[27, 34]. One study of elective hospital admissions measured well-being[32] and another psychological status[33], with no significant differences between groups. Of three

studies involving emergency admissions, two reported no significant differences between groups in discharge destination [36, 37] and the other did not report discharge destination (or functional outcomes)[39].

Some studies reported significantly less weight loss in the ONS than the control group[32, 34], others reported a significant weight loss in the no ONS (or routine care group) but not in the ONS group, and yet others no significant differences between groups[27, 33, 36-38]. Two studies did not report changes in weight[35, 39] and in one, the weight changes were reported only after discharge from hospital when ONS was still being used [37].

4. Assessment of risk of bias

The overall quality of the studies with respect to the combined clinical and economic outcomes, were judged to have at least a moderate risk of bias, with substantial variation between studies (for details see Supplementary file 1)

5. Discussion

This review, mainly of RCTs in which national reference costs were assigned to specific conditions and interventions, suggest that the use of ONS compared to 'no ONS' or routine care can produce significant net cost savings. Study level analyses showed a significant overall cost saving, and a series of subgroup analyses according to malnutrition, age group, type of study and study design (Table 3) universally favoured the ONS group, although only some of these cost savings were signficant., The cost savings were generally found to be associated with a range of favourable clinical outcomes, such as reduced complications (less suffering), reduced mortality

(more QALY), and reduced length of hospital stay (earlier return to the familiar home environment). These findings are consistent with other reviews on the use of ONS in clinical practice[3, 4, 6]. Economic models involving interventions with ONS e.g. that used by Banks et al [28] showing a cost-effective reduction in the risk of developing pressure ulcers (consistent with data reported previously[30]), and the NICE model showing that ONS were cost effective improvement in QALY's gained, made some assumptions (see Methods), but their conclusions were strengthened by the use of a probabilistic model[28] or a series of sensitivity analyses respectively[40].

The favourable cost and cost-effectiveness outcomes associated with the use of ONS in the hospital setting could have been predicted , partly because other studies have suggested that ONS have a range of favourable clinical effects[3, 4, 6], and partly because the cost of ONS is small compared to total hospital costs. , However, it is probably more insightful and more useful for health planning and policy making to consider these issues using a single management model that extends between settings, rather than separately within individual care setting. For example, in the NICE cost-effectiveness analysis use of ONS in hospital kept more patients alive, which required additional costs to care for their extended lifespan outside hospital.. Conversely, use of ONS in the community can reduce hospitalisation[46]. Furthermore, ONS prices can differ between care settings, which means there is a need to consider the whole health and social care economy rather than one setting is isolation.

The notable lack of primary cost-analyses in adults and the total absence of identifiable studies in children from the literature search weaken the generalizability of the findings, although one retrospective analysis based on observational data in children has been published after our literature search[47], which suggests that ONS reduces length of hospital stay by 14.8% and costs by 9.7%.

Our review included only two controlled trials that prospectively reported a cost-analysis [26, 27], and in neither of them was cost or cost-effectiveness the primary outcome variable. The only observational study reporting a retrospective cost-analysis exclusively in the hospital setting found a highly significant cost saving favouring the ONS group (21.6% or $3694 per episode)[24], but since disease-specific feeds were used in about a fifth of patients care should be exercised in attributing all the reported benefits to standard ONS. Extrapolation of the findings to the entire population of malnourished people admitted to hospital should also be made with caution since ONS were given to only 1.6% of patients admitted to hospital (the prevalence of malnutrition is expected to be more than an order of magnitude higher), whose nutritional status was not reported. This study aimed to control for both known and unknown variables from the observational data using instrumental variables analysis, but despite 'validity checks', it is not possible to definitively prove that bias due to unknown variables has been totally eliminated. Some analysts have suggested that in some circumstances misleading results may be produced by instrumental variables analysis [48-50]. There is generally less concern about this type of bias with RCTs because the randomisation aims to distribute both known and unknown variables equally between the study groups. However, whilst RCTs have greater internal validity, they have less external validity than observational studies (more representative and larger samples, e.g. 1.2 million in the study by Philipson et al)[24]. Both types of studies have merits and help to build a more complete picture.

The majority of studies compared ONS with no ONS under controlled conditions, which means that the results may not be directly extrapolated to routine practice where ONS is already given to a proportion of patients under less well controlled conditions. Nevertheless, there is a need for routine nutritional screening and

increased awareness about the importance of nutrition in clinical practice to help reduce the burden of untreated malnutrition.

It is clear from this review that much primary research needs to be undertaken to establish a more robust quantitative evidence base from studies primarily designed to examine the cost and cost-effectiveness of standard ONS in various groups of patients. This is because the quality of the reviewed studies was judged to be variable with at least a moderate overall risk of potential bias. Most of the studies were not primarily designed to assess economic outcomes, most were analysed retrospectively, and the results of the modeling studies that aimed to assess cost or cost-effectiveness as the primary outcome variable relied on data obtained by studies designed to assess non-economic outcomes. Most of the reviewed studies were funded by industry (Supplementary File 2, Table 1) raising the potential risk of publication bias, i.e. the,selective reporting of studies with favourable outcomes. However, potential publication bias also exists with government funded projects[51]. Recently a call has been made to register and publish the results of all trials, to improve on the 40-50% publication rate observed between 1999 and 2007, which applies equally to industry and government funded trials [51]. Although this review has focussed on standard ONS produced commercially, which are reimbursed to a variable extent across markets, there is also a need to review other forms of nutritional support, such as snacks, food fortification, dietary advice (for which the clinical and economic evidence base appears to be weak) and tube feeding, and to examine their relative cost and cost-effectiveness. The cost and cost-effectiveness of disease-specific ONS requires a separate review.

Given the variable nutritional status of patients included in different clinical trials and the use of different screening instruments used to identify risk of malnutrition, it

would be valuable to establish the relative benefits of the use of ONS in patients with a low body mass index, those with unintentional weight loss (which may occur in underweight as well as overweight or obese individuals), and those with major reductions in recent nutritional intake during key phases of their illness.

Despite variations in study design and quality (risk of bias), this comprehensive systematic review found that use of ONS produced a consistent cost saving and cost-effectiveness. The extent to which this can be translated into routine clinical practice depends on the degree to which a healthcare system is competent to take advantage of these findings. Such competency varies between healthcare systems, which prioritise nutritional support to a variable extent, and which operate different incentivisation schemes, including those reward high quality practice and/or penalise poor practice. Furthermore, since many of the results of this review were dominated by studies undertaken in the UK over more than two decades, some caution should be taken in extrapolating them to a wide range of other countries using different healthcare systems and national tariffs.

Finally, this work highlights two important methodological issues. First only a minority of the economic analyses were identified from by the search engines, the majority being pinpointed by specialists in clinical nutrition (see Results section) who identified relevant information in detailed reports produced by national organisations. When an evidence base is gathered by people who are familiar with systematic review methodology but not the specific topic of the review, there is a risk that important information will be missed. Second, the criteria for assessing the quality of RCTs are not necessarily the best ones for assessing economic studies and *vice versa*, which is why in this review both types of assessments were done. Furthermore, since published methods for assessing the quality of economic evaluations have not been

specifically developed for nutrition, studies the checklist by Drummond et al was carefully considered and certain items defined in order to make them more relevant and specific to nutrition studies under consideration.

6. Conclusion

This review suggests that use of standard ONS in the hospital setting generally produce cost savings and are cost-effective in patient groups with variable age, nutritional status and underlying conditions. More high quality prospective studies with adequate power to examine economic outcomes are needed to substantiate the findings of this review in countries with different healthcare economies.

Conflict of interest

ME, CN and AL have received honoraria for giving independent talks at national/international conferences supported by industry. KN has received speakers' fees, as well as financial support for research projects funded by commercial companies. None of the authors have received financial contribution for this project.

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Table 1

Net cost saving (£ per patient) due to administration of oral nutritional supplements in individual surgical, non-surgical and mixed (surgical + non-surgical) studies (based on the BAPEN report 2003 prices)[14]

	Studies	N[a]	Method of calculation[b]						
			Bed-days			Excess Bed-days	Complications		
			Average (£)	Lower Quartile (£)	Upper Quartile (£)	Average (£)	Average (£)	Lower Quartile (£)	Upper Quartile (£)
Surgical: Abdominal	Beattie et al[34] (Scotland)	101	830.6	638.5	977.7	406.7	227.0	153.3	258.7
	Keele et al[32] (England)	86	896.7	729.8	1047.2	450.2	325.6	221.5	386.5
	Rana et al[31] (England)	40	1249.4	1001.9	1478.7	612.8	596.5	387.8	752.2
	MacFie et al[33] (England)	52	1125.8	950.0	1307.6	557.6	-161.6	-111.2	-183.2
	Smedley et al[26] (England)	89	260.7	213.3	304.8	130.1	92.9	74.0	118.6
Surgical: Orthopaedic	Delmi et al[35] (Switzerland)	59	4491.2	3792.0	5280.0	2873.6	895.4	718.6	1081.5

	Studies	N[a]	Method of calculation[b]						
			Bed-days			Excess Bed-days	Complications		
			Average (£)	Lower Quartile (£)	Upper Quartile (£)	Average (£)	Average (£)	Lower Quartile (£)	Upper Quartile (£)
	Lawson et al[27] (England)	181	444.9	381.0	512.6	181.0	483.3	333.7	593.8
Non-surgical	Potter et al[36] (Scotland)	381	330.4	262.4	398.4	270.4			
	Gazzotti et al[37] (Belgium)	80	-246.4	-198.8	-294.0	-204.4			
	Gariballa et al[38] (England)	40	2090.8	1715.3	2498.6	2527.2	116.2	95.4	130.3
Mixed:	Vlaming et al[39] (England)	281	-1306.3	-1046.3	-1566.3	-942.3			

[a] N = number of subjects in intervention (ONS) and control groups

[b]Bed-day and excess bed-day costs are based on length of hospital stay. Excess bed-days are associated with prolonged length of stay (above the Healthcare Resource Group Trim point), and they are usually associated with lower costs since they mostly involve basic care and hotel costs. Complication costs are based only on the costs of complications. National reference costs (Health Related Groups or HRG provided by the Department of Health) to individual patients or

groups of patients according to the type of admission, type of treatment received and the type and number of complications. The authors of the primary studies were contacted to clarify uncertainties.

Table 2

Summary of net cost saving (£ per patient) due to administration of oral nutritional supplements in surgical, non-surgical and mixed (surgical + non-surgical) groups of studies (based on the BAPEN report 2003 prices)[14]

Studies		Method of calculation[a]						
		Bed-days			Excess bed-days	Complications		
		Average	Lower Quartile	Upper Quartile	Average	Average	Lower Quartile	Upper Quartile
Surgical: abdominal	Average	873	707	1023	431	216	145	267
	95% CI	399, 1346	317, 1097	465, 1581	199, 664	-132, 564	-83,374	-161, 694
	P value[b]	0.007	0.007	0.007	0.007	0.160	0.153	0.159
	Weighted	810.4	652.4	949.8	401.1	205.9	140.0	249.4
	average (£)	361.5, 1259.3	283.7, 1021.2	422.7, 1476.9	180.0, 622.1	-82.1, 494.0	-49.5, 329.5	-101.1, 599.9
	P value[b]	0.007	0.008	0.007	0.007	0.118	0.110	0.119
Surgical:	Average	1328.5	1100.9	1558.4	744.6	351.3	254.0	429.7
	95% CI (£)	-1.4, 2658.3	-27.5, 2229.4	-6.7, 5123.5	-139.4,	31.0, 671.6	10.1, 497.8	41.1, 818.3

Studies		Method of calculation[a]						
		Bed-days			Excess bed-days	Complications		
		Average	Lower Quartile	Upper Quartile	Average	Average	Lower Quartile	Upper Quartile
abdominal + orthopaedic					1628.5			
	P value[b]	0.050	0.054	0.051	0.085	0.036	0.044	0.035
	Weighted average (£)	1062.9 -108.9, 2234.7	880.0 -111.5, 1871.6	1244.7 -134.9, 2624.2	578.4 -196.4, 1353.2	357.9 88.3, 627.6	255.7 50.6,460.8	435.8 108.0,763.5
	P value[b]	0.064	0.065	0.065	0.094	0.029	0.033	0.028
All studies	Average	924.3	767.2	10.85.9	623.9	321.9	234.1	392.3
	95% CI (£)	-63.2, 1911.9	-58.0, 1592.4	-80.6, 2252.5	-126.3, 1374.1	45.0, 598.8	24.8, 443.5	55.2, 729.4
	P value[b]	0.064	0.065	0.065	0.094	0.029	0.033	0.028
	Weighted average (£)	332.1 -526.0, 1190.3	278.9 -430.7, 988.5	385.8 -630.0, 1401.6	194.8 -417.9, 807.5	342.8 -22.1, 707.6	245.6 -30.3, 521.6	416.6 -27.7, 861.0
	P value[b]	0.409	0.402	0.417	0.495	0.060	0.069	0.060

[a] See footnote to Table 1

[b] One sample t-test where the net cost saving is tested against a value of zero

42 **Table 3**

43 Post hoc cost analyses of hospital studies comparing ONS with no ONS or routine care[a]

Study	Country	N	Nutritional status	Age group	Type of study	Comparison	Cost saving per subject in favour of ONS group	Cost saving (% of control)
BAPEN report 2005[14]								
(i) Rana et al 1992[31]	UK	40	M + NM	<65 years	I	ONS v no ONS	£1249.4	20.71
(ii) Keele et al 1997[32]	UK	86	M + NM	<65 years	I	ONS v no ONS	£896.7	18.1
(iii) Smedley et al 2004[26b]	UK	89	M + NM	<65 years	I	ONS v no ONS	£260.7	4.93
(iv) MacFie et al 2000[33]	UK	62	M + NM	<65 years	I	ONS v no ONS	£1125.8	23.04
(v) Beattie et al 2000[34]	UK	101	M	<65 years	I	ONS v routine care	£830.6	10.59
(vi) Delmi et al 1990[35]	CH	59	M	≥65 years	I	ONS v no ONS	£4491.2	39.94
(vii) Lawson et al 2003[27b]	UK	181	M + NM	≥65 years	I	ONS v no ONS	£444.9	9.92
(viii) Potter et al 2001[36b]	UK	381	M + NM	≥65 years	I	ONS v routine care	£330.4	10.8
(ix) Gazzotti et al 2003[37]	BE	60	M	≥65 years	I	ONS v no ONS	-£246.4	-7.32
(x) Gariballa et al 1998[38]	UK	40	M	≥65 years	I	ONS v no ONS	£2090.8	42.73
(xi) Vlaming et al 2001[39]	UK	281	M	≥65 years	I	ONS v no ONS	-£1306.3	-49.29
Banks et al 2013[28]	AU	1356[c]	M[d]	≥65 years	I + O	ONS v no ONS	€143.6 (£93.25)[e]	
Philipson et al 2013[24]	US	1160088		≥65 years	O	ONS v no ONS	$4734 (£3148)[e]	21.6

NICE 2012[20]	UK	1410440[c]	M	I + O	ONS v no ONS	[g]

UK = United Kingdom; CH = Switzerland; BE = Belgium; AU = Australia; US = United States; M = malnourished; NM = non-malnourished; I = interventional study; O = observational study

[a] Calculations of costs were based on bed-day costs

[b] The data in the BAPEN report were used in preference to those reported in the original papers for consistency in calculations based on bed-day costs. In the BAPEN report the costs of specific surgical procedures were taken into account in estimating bed-day costs but the original papers the calculations did not involve the surgical procedure. For example, in the original paper by Smedley et al[26] a cost saving of £271 per patient translates to 11.91% of the cost of the no ONS group, while in the BAPEN report a cost saving of £292 per patient translates to only 4.93% of the cost of the no ONS group.

[c] These figures which are incorporated into economic models are not based on clinical studies. In the study of Banks et al[28] the number represents the point prevalence of malnourished subjects in relevant hospitals in Queensland and in NICE 2012[20] the number of relevant hospital admissions in one year. For the NICE model, see also [f].

[d] Considered to be malnourished by Banks et al, although some the patients in a meta-analysis that was used in the model were not by anthropometric criteria.

[e] Based on the average currency exchange rate for the years in which the costs were calculated by the studies. The cost per patient was calculated using data provided in the paper.

[g] Although there is clear net cost saving associated with the use of ONS, the exact amount depends on calculation procedures, which in turn depend on the proportion of patients assessed by a dietitian and the proportion given ONS by the dietitian and independently of the dietitian (calculations undertaken by one of the authors (ME) using the NICE costing template).

Table 4

Cost saving (study level analysis) in favour of the ONS group by age, nutritional status and study design[a,b]

	% cost-saving (continuous data)			Cost saving (binary	
	N studies	Mean and SD	P value[c]	N studies favouring ONS/total N	P v
< 65 years	5[e]	15.5 ± 7.5	0.010	5/5[f]	0
≥65 years	7[g]	9.8 ± 31.4	0.442	6/8[h]	0
Malnourished	64[i]	7.3 ± 37.9	0.688	5/7[j]	0.45
Malnourished + non malnourished	57[k]	14.6 ± 7.1	0.004	6/6[l]	0.03
ONS v no ONS	10[m]	12.4 ± 26.3	0.169	10/12[n]	0
ONS v routine care	2[o]	10.7 ± 0.149	0.006	2/2[p]	0
Interventional studies	11[q]	11.3 ± 24.8	0.162	9/11r	0
Observational ± interventional studies	1[s]	21.6		3/3[t]	0

[a] Based on data presented in Table 3

[b] None of the comparisons between subgroup categories was significant (Student's t-test for continuous data and Fisher's Exact test for binary (dichotomous) data)

[c] One sample t-test (against a test value of zero)

[d] Binomial test (against test proportion of 0.5 (favouring or not favouring ONS group)

[e-t] references e [26, 31-34], f [26, 31-34], g [24, 27, 35-39], h [24, 27, 28, 35-39], i [34, 35, 37, 38], j [28, 34, 35, 37, 38, 40], k [26, 27, 31-33, 36, 39, 52], l [26, 27, 31-33, 36, 39, 52] m [24, 26, 27, 31-33, 35, 37-39] n [24, 26-28, 31-33, 35, 37-40], o [34, 36], p [34, 36], q [26, 27, 31-39], r [26, 27, 31-39], s [24], t [24, 28, 40]

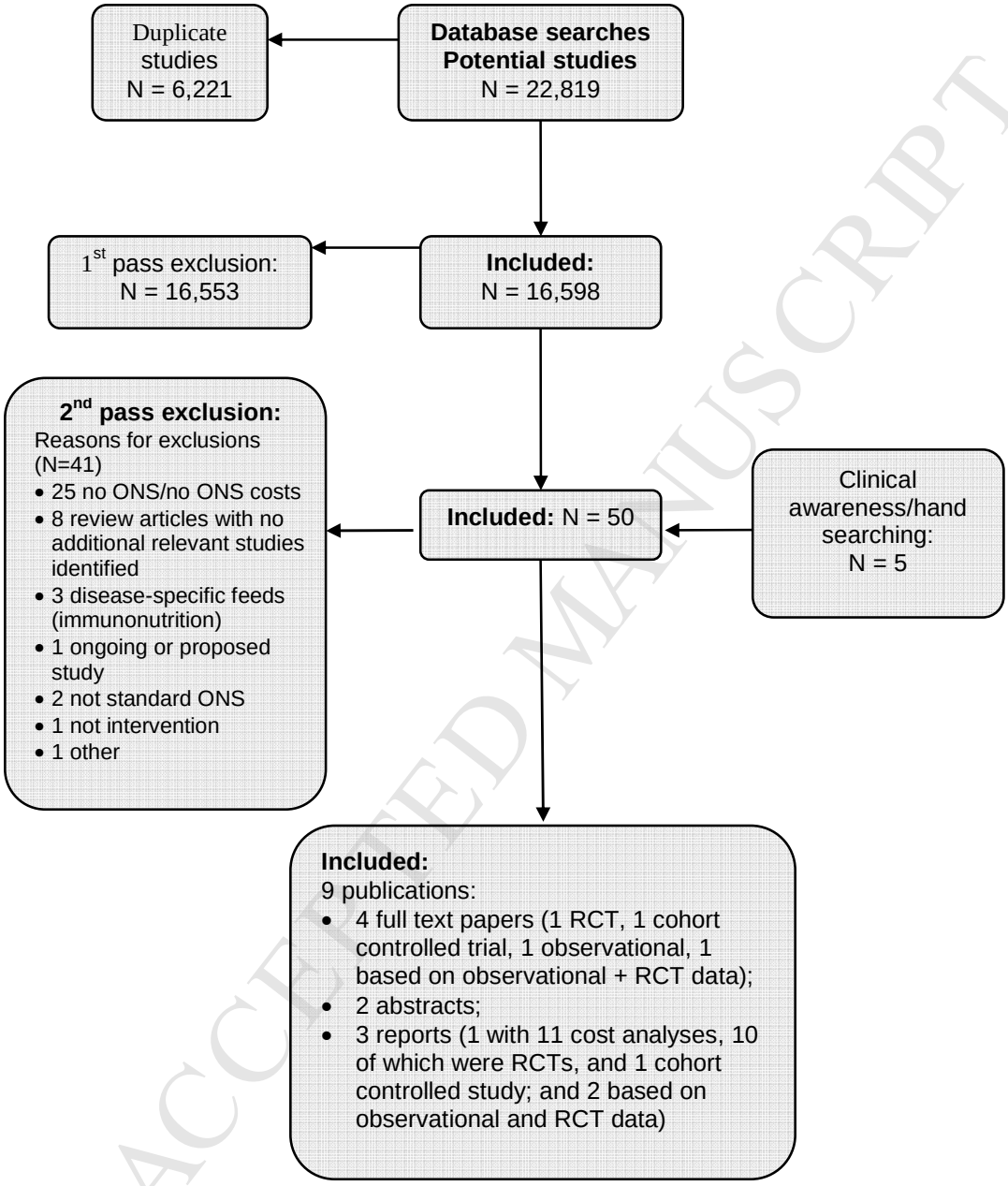


Figure 1. Flow diagram of publications included and excluded in the review

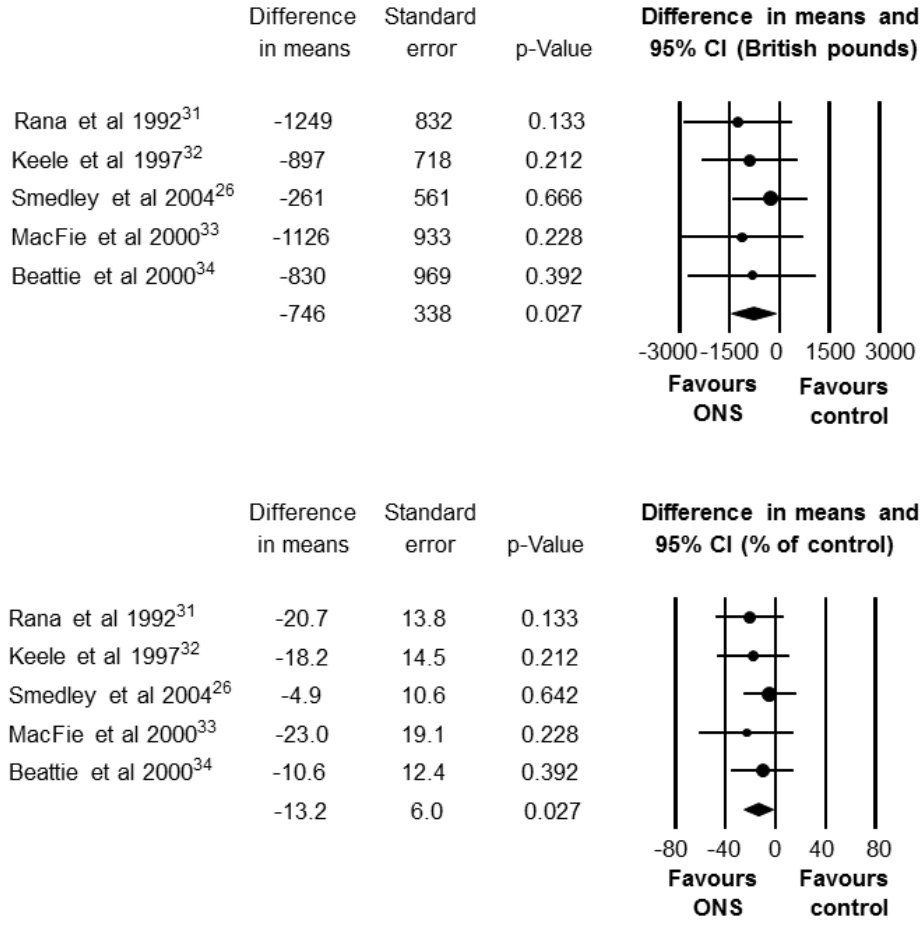
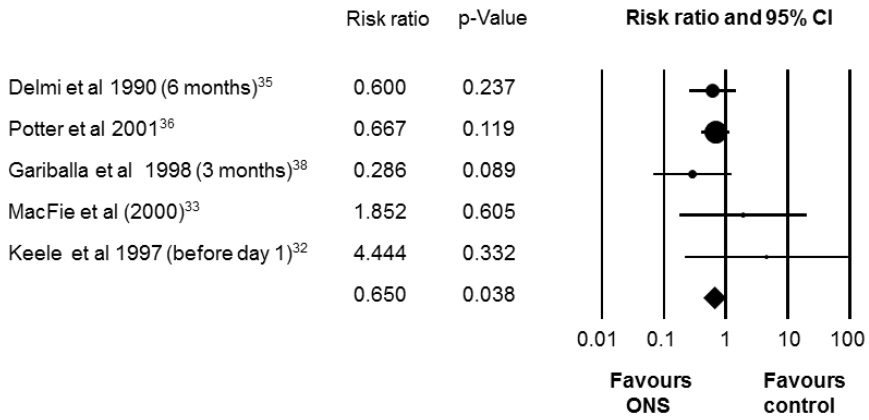


Figure 2. Meta-analysis of net cost saving of five randomised controlled trials of abdominal surgery in the UK (N=358) *Upper graph* Results are presented in GBP (£) (2003 prices) (mean cost saving £772/ patient (se £346), P = 0.026; I^2 = 0%) *Lower graph* Results presented as percent reduction of control group (mean cost saving 13.5% (se 6.1%), P = 0.026; I^2 = 0%). Negative signs indicate cost saving * based on retrospective data analysis as provided in the BAPEN report[14]



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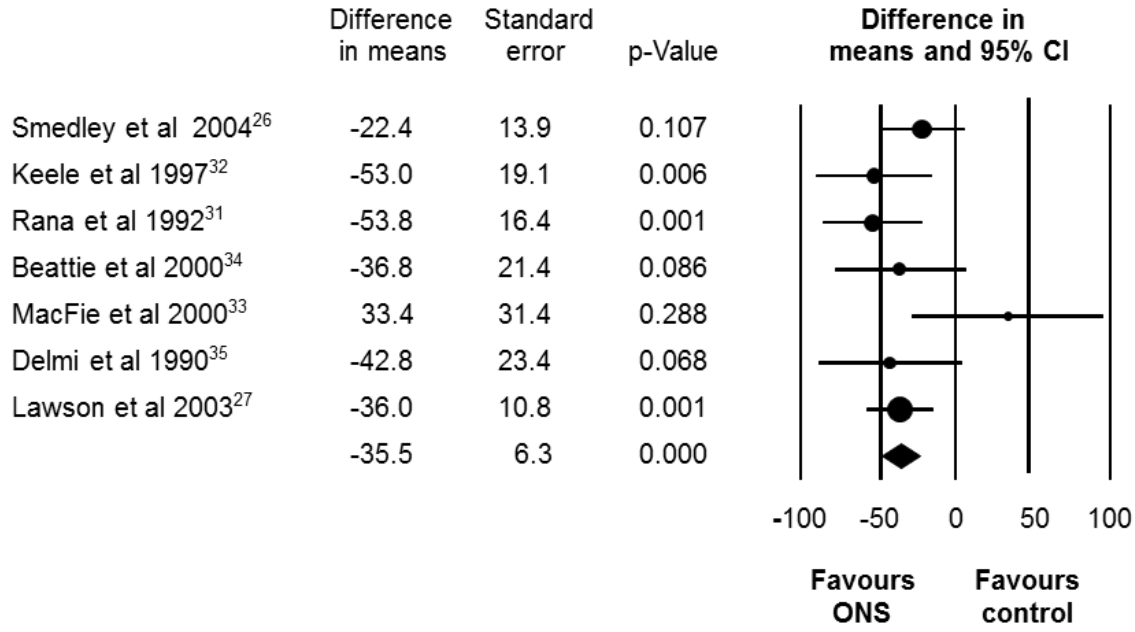
83

84 **Figure 3.** Random effects meta-analysis of mortality reported in hospital studies with
85 economic outcomes (Risk ratio 0.650 (95% CI 0.432, 0.976), P = 0.038; I^2 = 0%, P =
86 0.459). The studies that reported mortality at 3 months and 6 months are indicated.

87



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89 **Figure 4.** Random effects meta-analysis of complications in surgical patients expressed

90 as percentage of total complications. A negative sign indicates fewer complications in the

91 ONS group (difference -35.3 (se 7.6)%, P <0.001; I^2 = 23.9%, P = 0.247).

92

References

1. Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL. The biology of human starvation. University of Minnesota Press, Minneapolis, MN; 1950. p. 81-535.
2. Milne AC, Avenell A, Potter J. Meta-analysis: protein and energy supplementation in older people. *Ann Intern Med*. 2006; **144**(1): 37-48.
3. Cawood AL, Elia M, Stratton RJ. Systematic review and meta-analysis of the effects of high protein oral nutritional supplements. *Ageing Res Rev*. 2012; **11**(2): 278-96.
4. Stratton RJ, Elia M. Systematic review and meta-analysis of the effects of oral nutritional supplements on hospital admissions. *Clin Nutr (Suppl 1)*. 2011; **1**: 16-7.
5. Waitzberg DL, Saito H, Plank LD, Jamieson GG, Jagannath P, et al. Postsurgical infections are reduced with specialized nutrition support. *World J Surg*. 2006; **30**(8): 1592-604.
6. Stratton RJ, Green CJ, Elia M. Disease-related malnutrition. An evidence-based approach to treatment. Oxford: CABI Publishing (CAB International); 2003.
7. Pritchard C, Duffy S, Edington J, Pang F. Enteral nutrition and oral nutrition supplements: a review of the economics literature. *JPEN J Parenter Enteral Nutr*. 2006; **30**(1): 52-9.
8. Elia M, Bistrrian B. The Economic, Medical/Scientific and Regulatory Aspects of Clinical Nutrition Practice: What happens next? Basel: Karger; 2009.
9. Freijer K, Bours MJ, Nuijten MJ, Poley MJ, Meijers JM, et al. The economic value of enteral medical nutrition in the management of disease-related malnutrition: a systematic review. *Journal of the American Medical Directors Association*. 2014; **15**(1): 17-29.
10. Walzer S, Droeschel D, Nuijten M, Chevrou-Severac H. Health economic analyses in medical nutrition: a systematic literature review. *ClinicoEconomics and outcomes research : CEOR*. 2014; **6**: 109-24.
11. Mitchell H, Porter J. The cost-effectiveness of identifying and treating malnutrition in hospitals: a systematic review. *J Hum Nutr Diet*. 2015.
12. Elia M, Stratton RJ. Calculating the cost of disease-related malnutrition in the UK in 2007. In: Combating malnutrition: recommendations for action. A report from the Advisory Group on Malnutrition led by BAPEN ed: M Elia, C.A. Russell: BAPEN; 2009.
13. Rice N, Normand C. The cost associated with disease-related malnutrition in Ireland. *Public Health Nutr*. 2012; **15**(10): 1966-72.
14. Elia M. (chairman & editor), Stratton R, Russell C, Green C, Pang F. The cost of disease-related malnutrition in the UK and economic considerations for the use of oral nutritional supplements (ONS) in adults. A report by The Health Economic Group of The British Association for Parenteral and Enteral Nutrition (BAPEN). BAPEN; 2005. Report No.: 1 899467 01 7.
15. Higgins JPT, Green S. Cochrane Handbook for Systematic reviews of Interventions Version 5.1.0 [updated march 2011] Available from www.cochrane-handbook.org; 2011.
16. Centre for Reviews and Dissemination University of York. Systematic Reviews: CRD's Guilelines for Undertaking Reviews in Health Care; 2009.

17. Moher D, Liberati A, Tetzlaff J, Altman D, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009; **339**.
18. Elia M, Normand C, Laviano A, Norman K. A systematic review of the cost and cost-effectiveness of standard oral nutritional supplements in the community including care homes, with and without use in hospital; 2015 (submitted).
19. Lochs H, Allison SP, Meier R, Pirlich M, Kondrup J, et al. Introductory to the ESPEN Guidelines on Enteral Nutrition: Terminology, definitions and general topics. *Clin Nutr*. 2006; **25**(2): 180-6.
20. NICE. QS24 Nutrition support in adults: NICE support for commissioners and others using the quality standard on nutrition support in adults *http://publicationsniceorguk/quality-standard-for-nutrition-support-in-adults-qs24/development-sources*. 2012.
21. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007; **370**(9596): 1453-7.
22. Drummond MF, Sculpher MJ, O'Brien B, Stoddart GL. Methods for the economic evaluation of health care programmes. 3rd ed. Oxford: Oxford University press; 2005.
23. NICE. Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition. Appendix 5 cost-effectiveness analysis of malnutrition screening http://www.ncbi.nlm.nih.gov/books/NBK49257/; 2006.
24. Philipson TJ, Snider JT, Lakdawalla DN, Stryckman B, Goldman DP. Impact of oral nutritional supplementation on hospital outcomes. *The American journal of managed care*. 2013; **19**(2): 121-8.
25. Baggaley E, Whincup L, Ashman KE, Cawood AL, Davies DP, et al. Effectiveness of implementing a nurse led policy for the management of malnutrition. *Clin Nutr*. 2013; **32 (Suppl 1)**: S231
26. Smedley F, Bowling T, James M, Stokes E, Goodger C, et al. Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. *British Journal of Surgery*. 2004; **91**: 983-90.
27. Lawson RM, Doshi MK, Barton JR, Cobden I. The effect of unselected post-operative nutritional supplementation on nutritional status and clinical outcome of orthopaedic patients. *Clin Nutr*. 2003; **22**(1): 39-46.
28. Banks MD, Graves N, Bauer JD, Ash S. Cost effectiveness of nutrition support in the prevention of pressure ulcer in hospitals. *Eur J Clin Nutr*. 2013; **67**(1): 42-6.
29. Nuijten M, Freyer K. The health economic impact of oral nutritional supplements in the hospital setting in Germany. *Value in Health*. 2010; **13 (3)**: A101-A2.
30. Elia M, Stratton RJ. A cost-benefit analysis of oral nutritional supplements in preventing pressure ulcers. *Clin Nutr*. 2005; **24**: 640-1(P210).
31. Rana SK, Bray J, Menzies-Gow N, Jameson J, Payne James JJ, et al. Short term benefits of post-operative oral dietary supplements in surgical patients. *Clin Nutr*. 1992; **11**: 337-44.
32. Keele AM, Bray MJ, Emery PW, Duncan HD, Silk BDA. Two phase randomised controlled clinical trial of post-operative and dietary supplements in surgical patients. *Gut*. 1997; **40**: 393-7.

33. MacFie J, Woodcock NP, Palmer MD, Walker A, Townsend S, et al. Oral dietary supplements in pre- and post operative surgical patients: a prospective and randomized clinical trail. *Nutrition*. 2000; **16**: 723-8.
34. Beattie AH, Parch AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. *Gut*. 2000; **46**: 813-8.
35. Delmi M, Rapin C-H, Bengoa J-M, Delmas PD, Vasey H, et al. Dietary supplementation in elderly patients with fractured neck of femur. *Lancet*. 1990; **335**: 1013-6.
36. Potter JM, Roberts MA, McColl JH, Reilly JJ. Protein energy supplements in unwell elderly patients: a randomized controlled trial. *JPEN*. 2001; **25**: 323-9.
37. Gazzotti C, Arnaud-Battandier F, Parello M, Farine S, Seidel L, et al. Prevention of malnutrition in older people during and after hospitalisation: results from a randomised controlled clinical trial. *Age Ageing*. 2003; **32**: 321-5.
38. Gariballa SE, Parker SG, Taub N, Castleden CM. A randomized, controlled, a single-blind trial of nutritional supplementation after acute stroke. *JPEN*. 1998; **22**(5): 315-9.
39. Vlaming S, Biehler A, Hennessey EM, Jamieson CP, Chattophadhyay S, et al. Should the food intake of patients admitted to acute hospital services be routinely supplemented? A randomized placebo controlled trial. *Clin Nutr*. 2001; **20**: 517-26.
40. NICE. Costing report (nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition, CG32). Implementing NICE guidance in England. http://www.nice.org.uk/nicemedia/live/10978/29987/29987.pdf. 2006.
41. Rypkema G, Adang E, Dicke H, Naber T, de Swart B, et al. Cost-effectiveness of an interdisciplinary intervention in geriatric inpatients to prevent malnutrition. *Journal of Nutrition Health & Aging*. 2003; **8**: 122-7.
42. Kruizenga HM, Van Tulder MW, Seidell JC, Thijs A, Ader HJ, et al. Effectiveness and cost-effectiveness of early screening and treatment of malnourished patients. *Am J Clin Nutr*. 2005; **82**(5): 1082-9.
43. Saluja SS, Kaur N, Shrivastava K. Enteral nutrition in surgical patients. *Surgery Today*. 2002; **32**: 627-78.
44. Lawson RM, Doshi MK, Barton JR, Cobden I. The effect of unselected post-operative nutritional supplementation on nutritional status and clinical outcome of orthopaedic patients. *Clin Nutr*. 2003; **22**(1): 39-46.
45. Stratton RS, Ek A-C, Engfer M, Z. M, P. R, et al. Enteral nutrition al support in prevention and treatment of pressure ulcers: a systematic review and meta-analysis. *Aging Research Reviews*. 2005; **(in press)**.
46. Stratton RJ, Hebuterne X, Elia M. A systematic review and meta-analysis of the impact of oral nutritional supplements on hospital readmissions. *Ageing Res Rev*. 2013; **12**(4): 884-97.
47. Lakdawalla DN, Mascarenhas M, Jena AB, Vanderpuye-Orgle J, LaVallee C, et al. Impact of oral nutrition supplements on hospital outcomes in pediatric patients. *JPEN J Parenter Enteral Nutr*. 2014; **38**(2 Suppl): 42S-9S.
48. Small DS, Rosenbaum P. War and wages: the strength of instrumental variables and their sensitiviety to unobserved biases. *J Am Statist Assoc*. 2008; **103**: 924-33.

49. Swanson SA, Hernan MA. Commentary: how to report instrumental variable analyses (suggestions welcome). *Epidemiology*. 2013; **24**: 370-4.
50. Davies NM, Smith GD, Windmeijer F. Issues in the reporting and conduct of instrumental variable studies: A systematic review. *Epidemiology*. 2013; **24**: 363-9.
51. Chalmers I, Glasziou P, Godlee F. All trials must be registered and the results published. *BMJ*. 2013; **346**: f105.
52. Potter M, Schafer DF, Bohi RL. In-hospital mortality as a function of body mass index: an age dependent variable. *Journal of Gerontology*. 1988; **43**: M59-M63.

Supplementary file 1 (Assessment of risk of bias)

Table 1 shows a summary of the assessment for the risk of bias of 10 RCTs and one controlled cohort study, using criteria based on the Cochrane Handbook for Systematic Reviews of Interventions, updated in 2011[1]. The method of randomisation was not stated in four studies[2-5] and all studies apart from one[6] were not blinded. Withdrawal rates were generally small but they ranged from 0-26%. None of the studies with dropouts undertook an intention to treat analysis according to the originally designated groups. Baseline imbalances between groups were significant in some studies[5, 7, 8], of borderline significance in another study[9] and not reported in another study[6]. Statistical adjustment for the imbalances does not appear to have been carried out. Sample size calculations were not reported, even for the primary outcome variable (with the possible exception of MacFie et al[3], who undertook sample size calculations on weight change, which was one of numerous outcome variables).

A few deficiencies were identified in the economic evaluations of full text papers or reports with economic data as primary (*post hoc* analysis) or secondary outcome measurers (*a priori* analysis) using criteria adapted from Drummond et al 2005[10] (Table 2),. In addition, in studies involving economic modelling[11-14] a series of assumptions were made, including those associated with extrapolations to other populations (see Results section for a description of individual studies and the Discussion section for a consideration of the limitations). In an attempt to address specific uncertainties, NICE undertook a variety of sensitivity analyses[13, 14], Banks et al[12] used a probabilistic model and Philipson et al[11] a patient level analysis linked to regression and

instrumental variables analysis to control for confounding variables. Any disagreements between the two evaluators were eliminated by modifying or eliminating certain questions that could be interpreted in different ways. For example, the question about whether all viewpoints had been taken into account (Table 2, item 4 (ii)), was eliminated because it is possible to have a very large number of different viewpoints. The questions about establishing a summary through a systematic overview of clinical studies was only considered relevant for systematic reviews (item 3(ii)) and the discounting was considered relevant only in studies of longer than 1 year (item 7(ii)).

Using the STROBE criteria for observational investigations, the study of Philipson et al[11] was judged to be of good quality. The NICE reports on cost[14] and cost-effectiveness[13], which included observational components, were also judged to be of good quality. Like other models, the assumptions used and the extrapolations made influence the results and the quality of the conclusions. Sensitivity analyses were undertaken to examine many of the assumptions.

Since quality of the same study may be assessed very differently according to the type of criteria used (e.g. criteria for RCTs or observational studies on the one hand and criteria for economic data on the other) this systematic review attempted to summarise the risk of bias associated with specific items, both for individual and groups of studies so that an overall judgement of their quality could be made. Given the retrospective nature of most of the cost-analyses which were based on studies intended for other purposes, the overall potential risk of bias was considered to be at least moderate, especially if lack of blinding is taken into account. However, for practical reasons, it may be difficult to ensure blinding in studies of nutritional support.

Table 1

Quality assessment of controlled cohort studies involving interventions with ONS and comparability of groups at baseline[c] (based on reference[1])

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
Smedley et al 2004[8d]	Yes stratification by nutritional status	Sealed envelopes	None stated	N/A	Yes (15%)	No	Yes with the exception of BMI which was lower in the control group than the group that received ONS pre- and post-

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
							operatively
Beattie et al 2000[7]	Yes	Computer generated random numbers	None stated	N/A	Yes (8% overall; 7% after randomisation)	No	Yes, except the ONS group was younger than the control group by a mean of 8 years
Keele et al 1997[2]	Yes on admission	Not stated	None stated	N/A	Yes (14%, only 1% after	No	Yes

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
					the operation)		
MacFie et al 2000[3]	Yes double randomisation: before surgery for pre-operative ONS + diet or diet alone; and after surgery for post-	Not stated	None stated	N/A	Yes (11%, 8 were excluded due to cancellation of surgery and 4	No (but N/A if only post-op ONS is considered)	Yes

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
	operative ONS + diet or diet alone				required urgent surgery)		
Rana et al 1992[4]	Yes	Not stated	None stated	N/A	Yes (26%) according to group	No	Yes
Lawson et al 2003[15c]	No (study carried out	N/A	None stated	N/A	N/A (0%)	Yes (no withdrawals)	Yes

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
	in an intervention ward and a control ward)						
Delmi et al 1990[5]	Yes	Not stated	None stated	N/A	(0% in 1st hospital, unclear if any dropouts in 2nd hospital - not stated)	Yes if no dropouts in 2nd hospital (41% of patients went to 2nd hospital)	Yes, but vitamin D concentration on lower in the non-supplemented group

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
Gariballa et al 1998[16]	Yes	Block randomisation	Single blind study - only nurses and patients were aware of the designated groups		Yes (5%) (lost to follow up – one from each group)	No	Yes
Gazzotti et al 2003[9]	Yes	Sealed envelopes	None stated	N/A	Yes (6%)		Yes (Although

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
							not significant (p>0.05), patients in the control group appeared to be heavier (BMI 26.9±5.4 v 24.8±4.5,

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
							p=0.07) and the patients in the supplemented group were older (81.5±7.6 years v 78.8±6.1 years,

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
							p=0.09) and appeared to be slightly more malnourished (MNA score 8.31±1.6 v 8.95±1.7))
Potter et al	Yes, stratified	Sealed	Single	Yes (not	N/A (0%)	Yes (no	Yes

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
2001	according to nutritional status (BMI categories)	envelopes	blinding-anthropometry and assessment of clinical outcomes were blinded	involved in clinical care and ward visits)		withdrawals)	
Vlaming et al 2001[6]	Yes, both for the vitamin tablet and	Block randomisatio	Yes	Identical placebo	N/A (0%)	Yes (no withdrawals)	Unclear (not

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
	ONS within a factorial design	n of sequentially numbered sealed envelopes prepared by pharmacy (blocks of 100 for tablets and 10 for ONS)		and vitamin tablet, The placebo feed tasted different from the ONS			reported for those receiving ONS or placebo without tablets)

N/A = not applicable

[a] Excludes deaths except when otherwise indicated.

[b] Intention-to-treat defined according to CONSORT 2010 (A strategy for analyzing data in which all participants are included in the group to which they were assigned, whether or not they completed the intervention given to the group) [http://www.consort-statement.org/resources/glossary/e---l/intention-to-treat-analysis/ Accessed March 2014].

[c] In studies in which baseline imbalance was found, no statistical adjustments were made

[d] Cost data were established prospectively. In the other studies costs were established retrospectively on the basis of a secondary analysis of clinical data. All studies were included in the BAPEN report[17].

Table 2.

Checklist for assessing economic evaluations (adapted from Drummond et al 2005[10])

Checklist[a,b,c,d,e,f]	Philipson et al 2013[11]	Banks et al 2013[12g]	NICE 2006[13]	NICE 2012[14]	Lawson et al 2003[15]
1. Was a well-defined question posed in answerable form?	√	√	√	√	√
2.[a] Was a comprehensive description of the competing alternatives given? (that is, can you tell who did what to whom, where, and how often?)	√	√	√	√	√
3.[b] Was the effectiveness of the programmes or services established and consequences for each alternative identified?	√1/3 [b] (iii)	√[b]	√ [b]	√ [b]	√ 1/3 [b] (iii)

4.[c] Were all the important and relevant costs and consequences for each alternative identified?**	√	√	√	√	√
5. Were costs and consequences measured accurately in appropriate physical units (for example, hours of nursing time, number of physician visits, lost work-days, gained life-years)?	√	√	√	√	√ 2/3 (ii-iii)
6. Were costs and consequences valued credibly?	√	√	√		√ 2/4 (i[h];iv)
7.[d] Were costs and consequences adjusted for differential timing?	N/A	N/A	√	√	N/A
8. Was an incremental analysis of costs and	√	√	√	√	×[i]

consequences of alternatives performed?					
9.[e] Was allowance made for uncertainty in the estimates of costs and consequences?	√	√ 2/3 (i N/A)	√	√	√
10.[f] Did the presentation and discussion of study results include all issues of concern to users?	√	√	√	√	√ 2/5 (iv-v)

N/A = not applicable.

√ This character is used to indicate appropriate practice (rather than 'yes' or 'no' each of which can be the appropriate answer to specific questions). The Roman numerals indicate the question that was considered to be adequately fulfilled. What about the Arabic numbers, 1/3?

[a,b,c,d,e,f] See below under individual questions

[g] Based on information obtained from three papers

[h] Yes, but based on LOS costs of unknown origin.

[i] Based on a cost impact analysis.

1. (i) Did the study examine both costs and effects of the service(s) or programme(s)? (ii) Did the study involve a comparison of alternatives? (iii) Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?

2. (i) Were any relevant alternatives omitted? [[a]This question was omitted from the evaluation because it is almost always possible to omit a relevant alternative e.g. composition and texture of ONS] (ii) Was (should) a do-nothing alternative (be) considered?

3. (i) Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice? (ii) Were effectiveness data collected and summarised through a systematic overview of clinical studies? [[b]This question was omitted because formal systematic reviews are not generally included in primary reports of clinical studies] If so, were the search strategy and rules for inclusion or exclusion outlined? (iii) Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?

4. (i) Was the range wide enough for the research question at hand? [[c]Question (i) was evaluated but the next two were not because they were considered ambiguous or irrelevant] (ii) Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis). (iii) Were capital costs, as well as operating costs, included?

5. (i) Were the sources of resource utilisation described and justified? (ii) Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis? (iii) Were there any special circumstances (for example, joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?

6. (i) Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements.) (ii) Were market values employed for changes involving resources gained or

depleted? (iii) Where market values were absent (for example, volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values? (iv) Was the valuation of consequences appropriate for the question posed (that is, has the appropriate type or types of analysis – cost-effectiveness, cost-utility, cost-benefit – been selected)?

7. (i) Were costs and consequences that occur in the future 'discounted' to their present values? [[d]Discounting was considered necessary only for studies with a duration of longer than one year] 7(ii) Was any justification given for the discount rate used?

8. (i) Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?

9. (i) If patient-level data on costs or consequences were available, were appropriate statistical analyses performed? (ii) If a sensitivity analysis was employed, was justification provided for the ranges of distributions of values (for key study parameters), and the form of sensitivity analysis used? [[e] A comparison of results obtained with intention to treat analysis and per protocol analysis was considered to be a type of sensitivity analysis, especially when the number of subjects in the 'per protocol' or 'as completed' analysis was substantially reduced] (iii) Were the conclusions of the study sensitive to the uncertainty in the results, as quantified by the statistical and/or sensitivity analysis? [This question is not addressed by this table, but it is considered in the text]

10. (i) Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (for example, cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion? (ii) Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology? (iii) Did the study discuss the generalisation of the results to other settings and patient/client groups? [[f] Any discussion relevant to alternative care settings and/or patient/client groups was considered to satisfy this criterion]. (iv) Did the study allude to, or take account of, other important factors in the choice or decision under consideration (for example, distribution of

costs and consequences, or relevant ethical issues)? (v) Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?

References

1. Higgins JPT, Green S. Cochrane Handbook for Systematic reviews of Interventions Version 5.1.0 [updated march 2011] Available from www.cochrane-handbook.org; 2011.
2. Keele AM, Bray MJ, Emery PW, Duncan HD, Silk BDA. Two phase randomised controlled clinical trial of post-operative and dietary supplements in surgical patients. *Gut*. 1997; **40**: 393-7.
3. MacFie J, Woodcock NP, Palmer MD, Walker A, Townsend S, et al. Oral dietary supplements in pre- and post operative surgical patients: a prospective and randomized clinical trail. *Nutrition*. 2000; **16**: 723-8.
4. Rana SK, Bray J, Menzies-Gow N, Jameson J, Payne James JJ, et al. Short term benefits of post-operative oral dietary supplements in surgical patients. *Clin Nutr*. 1992; **11**: 337-44.
5. Delmi M, Rapin C-H, Bengoa J-M, Delmas PD, Vasey H, et al. Dietary supplementation in elderly patients with fractured neck of femur. *Lancet*. 1990; **335**: 1013-6.
6. Vlaming S, Biehler A, Hennessey EM, Jamieson CP, Chattophadhyay S, et al. Should the food intake of patients admitted to acute hospital services be routinely supplemented? A randomized placebo controlled trial. *Clin Nutr*. 2001; **20**: 517-26.
7. Beattie AH, Parch AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. *Gut*. 2000; **46**: 813-8.
8. Smedley F, Bowling T, James M, Stokes E, Goodger C, et al. Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. *British Journal of Surgery*. 2004; **91**: 983-90.

9. Gazzotti C, Arnaud-Battandier F, Parello M, Farine S, Seidel L, et al. Prevention of malnutrition in older people during and after hospitalisation: results from a randomised controlled clinical trial. *Age Ageing*. 2003; **32**: 321-5.
10. Drummond MF, Sculpher MJ, O'Brien B, Stoddart GL. Methods for the economic evaluation of health care programmes. 3rd ed. Oxford: Oxford University press; 2005.
11. Philipson TJ, Snider JT, Lakdawalla DN, Stryckman B, Goldman DP. Impact of oral nutritional supplementation on hospital outcomes. *The American journal of managed care*. 2013; **19**(2): 121-8.
12. Banks MD, Graves N, Bauer JD, Ash S. Cost effectiveness of nutrition support in the prevention of pressure ulcer in hospitals. *Eur J Clin Nutr*. 2013; **67**(1): 42-6.
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14. NICE. QS24 Nutrition support in adults: NICE support for commissioners and others using the quality standard on nutrition support in adults *http://publicationsniceorguk/quality-standard-for-nutrition-support-in-adults-qs24/development-sources*. 2012.
15. Lawson RM, Doshi MK, Barton JR, Cobden I. The effect of unselected post-operative nutritional supplementation on nutritional status and clinical outcome of orthopaedic patients. *Clin Nutr*. 2003; **22**(1): 39-46.
16. Gariballa SE, Parker SG, Taub N, Castleden CM. A randomized, controlled, a single-blind trial of nutritional supplementation after acute stroke. *JPEN*. 1998; **22**(5): 315-9.
17. Elia M. (chairman & editor), Stratton R, Russell C, Green C, Pang F. The cost of disease-related malnutrition in the UK and economic considerations for the use of oral nutritional supplements (ONS) in adults. A report by The Health Economic Group of The British Association for Parenteral and Enteral Nutrition (BAPEN). BAPEN; 2005. Report No.: 1 899467 01 7.

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instrumental variables analysis to control for confounding variables. Any disagreements between the two evaluators were eliminated by modifying or eliminating certain questions that could be interpreted in different ways. For example, the question about whether all viewpoints had been taken into account (Table 2, item 4 (ii)), was eliminated because it is possible to have a very large number of different viewpoints. The questions about establishing a summary through a systematic overview of clinical studies was only considered relevant for systematic reviews (item 3(ii)) and the discounting was considered relevant only in studies of longer than 1 year (item 7(ii)).

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Since quality of the same study may be assessed very differently according to the type of criteria used (e.g. criteria for RCTs or observational studies on the one hand and criteria for economic data on the other) this systematic review attempted to summarise the risk of bias associated with specific items, both for individual and groups of studies so that an overall judgement of their quality could be made. Given the retrospective nature of most of the cost-analyses which were based on studies intended for other purposes, the overall potential risk of bias was considered to be at least moderate, especially if lack of blinding is taken into account. However, for practical reasons, it may be difficult to ensure blinding in studies of nutritional support.

Table 1

Quality assessment of controlled cohort studies involving interventions with ONS and comparability of groups at baseline[c] (based on reference[1])

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
Smedley et al 2004[8d]	Yes stratification by nutritional status	Sealed envelopes	None stated	N/A	Yes (15%)	No	Yes with the exception of BMI which was lower in the control group than the group that received ONS pre- and post-

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
							operatively
Beattie et al 2000[7]	Yes	Computer generated random numbers	None stated	N/A	Yes (8% overall; 7% after randomisation)	No	Yes, except the ONS group was younger than the control group by a mean of 8 years
Keele et al 1997[2]	Yes on admission	Not stated	None stated	N/A	Yes (14%, only 1% after	No	Yes

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
					the operation)		
MacFie et al 2000[3]	Yes double randomisation: before surgery for pre-operative ONS + diet or diet alone; and after surgery for post-	Not stated	None stated	N/A	Yes (11%, 8 were excluded due to cancellation of surgery and 4	No (but N/A if only post-op ONS is considered)	Yes

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
	operative ONS + diet or diet alone				required urgent surgery)		
Rana et al 1992[4]	Yes	Not stated	None stated	N/A	Yes (26%) according to group	No	Yes
Lawson et al 2003[15c]	No (study carried out	N/A	None stated	N/A	N/A (0%)	Yes (no withdrawals)	Yes

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
	in an intervention ward and a control ward)						
Delmi et al 1990[5]	Yes	Not stated	None stated	N/A	(0% in 1st hospital, unclear if any dropouts in 2nd hospital - not stated)	Yes if no dropouts in 2nd hospital (41% of patients went to 2nd hospital)	Yes, but vitamin D concentration on lower in the non-supplemented group

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
Gariballa et al 1998[16]	Yes	Block randomisation	Single blind study - only nurses and patients were aware of the designated groups		Yes (5%) (lost to follow up – one from each group)	No	Yes
Gazzotti et al 2003[9]	Yes	Sealed envelopes	None stated	N/A	Yes (6%)		Yes (Although

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
							not significant (p>0.05), patients in the control group appeared to be heavier (BMI 26.9±5.4 v 24.8±4.5,

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
							p=0.07) and the patients in the supplemented group were older (81.5±7.6 years v 78.8±6.1 years,

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
							p=0.09) and appeared to be slightly more malnourished (MNA score 8.31±1.6 v 8.95±1.7))
Potter et al	Yes, stratified	Sealed	Single	Yes (not	N/A (0%)	Yes (no	Yes

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
2001	according to nutritional status (BMI categories)	envelopes	blinding-anthropometry and assessment of clinical outcomes were blinded	involved in clinical care and ward visits)		withdrawals)	
Vlaming et al 2001[6]	Yes, both for the vitamin tablet and	Block randomisatio	Yes	Identical placebo	N/A (0%)	Yes (no withdrawals)	Unclear (not

	Randomisation stated to have occurred	Method of randomisation	Blinding	Method of blinding	Reasons for withdrawals Reported[a] (% withdrawn)	Intention to treat analysis[b]	Study groups comparable at baseline[c]
	ONS within a factorial design	n of sequentially numbered sealed envelopes prepared by pharmacy (blocks of 100 for tablets and 10 for ONS)		and vitamin tablet, The placebo feed tasted different from the ONS			reported for those receiving ONS or placebo without tablets)

N/A = not applicable

[a] Excludes deaths except when otherwise indicated.

[b] Intention-to-treat defined according to CONSORT 2010 (A strategy for analyzing data in which all participants are included in the group to which they were assigned, whether or not they completed the intervention given to the group) [http://www.consort-statement.org/resources/glossary/e---l/intention-to-treat-analysis/ Accessed March 2014].

[c] In studies in which baseline imbalance was found, no statistical adjustments were made

[d] Cost data were established prospectively. In the other studies costs were established retrospectively on the basis of a secondary analysis of clinical data. All studies were included in the BAPEN report[17].

Table 2.

Checklist for assessing economic evaluations (adapted from Drummond et al 2005[10])

Checklist[a,b,c,d,e,f]	Philipson et al 2013[11]	Banks et al 2013[12g]	NICE 2006[13]	NICE 2012[14]	Lawson et al 2003[15]
1. Was a well-defined question posed in answerable form?	√	√	√	√	√
2.[a] Was a comprehensive description of the competing alternatives given? (that is, can you tell who did what to whom, where, and how often?)	√	√	√	√	√
3.[b] Was the effectiveness of the programmes or services established and consequences for each alternative identified?	√1/3 [b] (iii)	√[b]	√ [b]	√ [b]	√ 1/3 [b] (iii)
4.[c] Were all the important and relevant costs and consequences for each	√	√	√	√	√

alternative identified?**					
5. Were costs and consequences measured accurately in appropriate physical units (for example, hours of nursing time, number of physician visits, lost work-days, gained life-years)?	√	√	√	√	√ 2/3 (ii-iii)
6. Were costs and consequences valued credibly?	√	√	√		√ 2/4 (i[h];iv)
7.[d] Were costs and consequences adjusted for differential timing?	N/A	N/A	√	√	N/A
8. Was an incremental analysis of costs and consequences of alternatives performed?	√	√	√	√	×[i]
9.[e] Was allowance made for uncertainty in the estimates of	√	√ 2/3 (i N/A)	√	√	√

costs and consequences?					
10.[f] Did the presentation and discussion of study results include all issues of concern to users?	√	√	√	√	√ 2/5 (iv-v)

N/A = not applicable.

√ This character is used to indicate appropriate practice (rather than 'yes' or 'no' each of which can be the appropriate answer to specific questions). The Roman numerals indicate the question that was considered to be adequately fulfilled. What about the Arabic numbers, 1/3?

[a,b,c,d,e,f] See below under individual questions

[g] Based on information obtained from three papers

[h] Yes, but based on LOS costs of unknown origin.

[i] Based on a cost impact analysis.

1. (i) Did the study examine both costs and effects of the service(s) or programme(s)? (ii) Did the study involve a comparison of alternatives? (iii) Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?

2. (i) Were any relevant alternatives omitted? [[a]This question was omitted from the evaluation because it is almost always possible to omit a relevant alternative e.g. composition and texture of ONS] (ii) Was (should) a do-nothing alternative (be) considered?

3. (i) Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice? (ii) Were effectiveness data collected and summarised through a systematic overview of clinical studies? [[b]This question was omitted because formal systematic reviews are not generally included in primary reports of clinical

studies] If so, were the search strategy and rules for inclusion or exclusion outlined? (iii) Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?

4. (i) Was the range wide enough for the research question at hand? [[c]Question (i) was evaluated but the next two were not because they were considered ambiguous or irrelevant] (ii) Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis). (iii) Were capital costs, as well as operating costs, included?

5. (i) Were the sources of resource utilisation described and justified? (ii) Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis? (iii) Were there any special circumstances (for example, joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?

6. (i) Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements.) (ii) Were market values employed for changes involving resources gained or depleted? (iii) Where market values were absent (for example, volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values? (iv) Was the valuation of consequences appropriate for the question posed (that is, has the appropriate type or types of analysis – cost-effectiveness, cost-utility, cost-benefit – been selected)?

7. (i) Were costs and consequences that occur in the future 'discounted' to their present values? [[d]Discounting was considered necessary only for studies with a duration of longer than one year] 7(ii) Was any justification given for the discount rate used?

8. (i) Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?

9. (i) If patient-level data on costs or consequences were available, were appropriate statistical analyses performed? (ii) If a sensitivity analysis was employed, was justification provided for the ranges of distributions of values (for key study parameters), and the form of sensitivity analysis used? [[e] A comparison of results obtained with intention to treat analysis and per protocol analysis was considered to be a type of sensitivity analysis, especially when the number of subjects in the 'per protocol' or 'as completed' analysis was substantially reduced] (iii) Were the conclusions of the study sensitive to the uncertainty in the results, as quantified by the statistical and/or sensitivity analysis? [This question is not addressed by this table, but it is considered in the text]

10. (i) Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (for example, cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion? (ii) Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology? (iii) Did the study discuss the generalisation of the results to other settings and patient/client groups? [[f] Any discussion relevant to alternative care settings and/or patient/client groups was considered to satisfy this criterion]. (iv) Did the study allude to, or take account of, other important factors in the choice or decision under consideration (for example, distribution of costs and consequences, or relevant ethical issues)? (v) Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?

References

1. Higgins JPT, Green S. Cochrane Handbook for Systematic reviews of Interventions Version 5.1.0 [updated march 2011] Available from www.cochrane-handbook.org; 2011.
2. Keele AM, Bray MJ, Emery PW, Duncan HD, Silk BDA. Two phase randomised controlled clinical trial of post-operative and dietary supplements in surgical patients. *Gut*. 1997; **40**: 393-7.
3. MacFie J, Woodcock NP, Palmer MD, Walker A, Townsend S, et al. Oral dietary supplements in pre- and post operative surgical patients: a prospective and randomized clinical trail. *Nutrition*. 2000; **16**: 723-8.
4. Rana SK, Bray J, Menzies-Gow N, Jameson J, Payne James JJ, et al. Short term benefits of post-operative oral dietary supplements in surgical patients. *Clin Nutr*. 1992; **11**: 337-44.
5. Delmi M, Rapin C-H, Bengoa J-M, Delmas PD, Vasey H, et al. Dietary supplementation in elderly patients with fractured neck of femur. *Lancet*. 1990; **335**: 1013-6.
6. Vlaming S, Biehler A, Hennessey EM, Jamieson CP, Chattophadhyay S, et al. Should the food intake of patients admitted to acute hospital services be routinely supplemented? A randomized placebo controlled trial. *Clin Nutr*. 2001; **20**: 517-26.
7. Beattie AH, Parch AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. *Gut*. 2000; **46**: 813-8.
8. Smedley F, Bowling T, James M, Stokes E, Goodger C, et al. Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. *British Journal of Surgery*. 2004; **91**: 983-90.
9. Gazzotti C, Arnaud-Battandier F, Parello M, Farine S, Seidel L, et al. Prevention of malnutrition in older people during and after hospitalisation: results from a randomised controlled clinical trial. *Age Ageing*. 2003; **32**: 321-5.
10. Drummond MF, Sculpher MJ, O'Brien B, Stoddart GL. Methods for the economic evaluation of health care programmes. 3rd ed. Oxford: Oxford University press; 2005.
11. Philipson TJ, Snider JT, Lakdawalla DN, Stryckman B, Goldman DP. Impact of oral nutritional supplementation on hospital outcomes. *The American journal of managed care*. 2013; **19**(2): 121-8.
12. Banks MD, Graves N, Bauer JD, Ash S. Cost effectiveness of nutrition support in the prevention of pressure ulcer in hospitals. *Eur J Clin Nutr*. 2013; **67**(1): 42-6.
13. NICE. Costing report (nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition, CG32). Implementing NICE guidance in England. http://www.nice.org.uk/nicemedia/live/10978/29987/29987.pdf. 2006.
14. NICE. QS24 Nutrition support in adults: NICE support for commissioners and others using the quality standard on nutrition support in adults *http://publicationsniceorguk/quality-standard-for-nutrition-support-in-adults-qs24/development-sources*. 2012.

15. Lawson RM, Doshi MK, Barton JR, Cobden I. The effect of unselected post-operative nutritional supplementation on nutritional status and clinical outcome of orthopaedic patients. *Clin Nutr*. 2003; **22**(1): 39-46.
16. Gariballa SE, Parker SG, Taub N, Castleden CM. A randomized, controlled, a single-blind trial of nutritional supplementation after acute stroke. *JPEN*. 1998; **22**(5): 315-9.
17. Elia M. (chairman & editor), Stratton R, Russell C, Green C, Pang F. The cost of disease-related malnutrition in the UK and economic considerations for the use of oral nutritional supplements (ONS) in adults. A report by The Health Economic Group of The British Association for Parenteral and Enteral Nutrition (BAPEN). BAPEN; 2005. Report No.: 1 899467 01 7.

Supplementary file 2 (Details of included studies and type of cost and cost-effectiveness analyses)

Table 1 summarises the details of the studies included in this review. These include the type of economic analysis the type of intervention, subject characteristics, nutritional status and the country in which the investigation was undertaken. This file also provides a more detailed breakdown of cost and cost-effectiveness analyses than that found in the main paper.

1. Cost analysis

Fourteen cost-analyses based on interventions exclusively in the hospital setting were identified (including one which was part of a cost-effectiveness analysis[1], and one in which the hospital component was established from the costing template[2]). Only two of the studies involved prospective cost-analyses[3, 4]. Of the 11 cohort controlled studies found in the BAPEN report[5], five involved abdominal surgery[4, 6-9], two orthopaedic surgery[3, 10], three non-surgical treatments[11-13] and one mixed surgical and non-surgical[14]). The studies in this review were RCTs apart from four: a prospective cohort control study[3]; an observational study examining the impact of ONS[15]; a study based on an economic model with both observational and RCT data[1]; and the NICE cost-impact report, which was based on a range of published clinical data and of expert opinion about current practice. In this last document, the cost of the current pathway of nutritional care in England was compared to that of a proposed pathway which incorporated the NICE clinical guidelines/quality standard[2]. The proposed pathway incurred extra costs, due to more screening, assessment and nutritional support, but it also produced cost savings, due to the effect of ONS in reducing healthcare utilisation. Of the three papers that were picked up from the literature search, two[3, 4] were subjected to further analysis in the BAPEN report.

2. Cost-effectiveness analysis

Two cost-effectiveness analyses were identified[1, 16], both of which involved economic models based on previously published clinical data. One of these, which was published only recently[1] and which was identified by the literature search, used a sophisticated mathematical model to examine the effect of intensive nutritional support in preventing the development of pressure ulcers in a high risk population, and to calculate the potential number of bed-days gained and the cost saving (2002/03 prices) in public hospitals in Queensland Australia. The model used information from a variety of sources, including interventional data from a meta-analysis of 5 RCTs[17] of subjects with a mean age of 80 years and over, with and without malnutrition according to anthropometric criteria. It also used observational data on the prevalence of malnutrition (32%; half of which was assumed to be untreated), and the risk of developing pressure ulcers (4.6%), which were assumed to extend length of hospital stay (4.31 days)[18] . The model also assumed that the response of the general population of malnourished subjects in Queensland reflected that suggested by the above mentioned meta-analysis of older people.

The second cost-effectiveness model developed by NICE[16] (not identified by the literature search) calculated the extra costs required to gain a quality adjusted life year (QALY) when a 'don't treat' group of hospital inpatients $\geq$ 65 years old was compared to one managed by a pathway involving screening with the 'Malnutrition Universal Screening Tool' (MUST), assessment and treatment of patients identified as being 'malnourished' with ONS and a certain amount of enteral tube feeding. The much larger extra costs needed to support patients whose life was extended through use of ONS in hospital was taken into account. The model included the following information: results of systematic reviews with meta-analyses of RCTs comparing complication rates, mortality and quality of life between groups of patients

given ONS or no ONS (i.e. given only the usual hospital diet); expert opinion about current practice and national hospital episode statistics on discharge destination (8% into publically funded institutions such as care homes); and the survival of patients with disease-related malnutrition discharged from hospital, which was assumed to be half of that of subjects from the general population according to age specific mortality statistics. A pathway involving a nurse strategy which included clinical screening and treatment was also considered.

Most studies included in this review reported clinically relevant outcomes, such as mortality, muscle strength and post-operative complications without undertaking formal cost-effectiveness analyses. One RCT comparing ONS with no ONS reported that there were no significant differences in quality of life between four study groups (some of which also received ONS outside hospital) but no cost-utility analyses were reported [4].

1 **Table 1** Details of studies included in the review

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
Smedley et al 2004[4] (UK)	Cost-analysis (prospective)	RCT (4 groups; group 3 started ONS in hospital and group 4 no ONS; groups 2 and 4 involved use of ONS before admission)	ONS v no ONS	258 kcal/day; 8.7 days	Elective moderate/ major lower GI surgery (ONS (group 3): mean 62 (22-83)y; no ONS, (group 4): 63 (25-88)y))	Well-nourished and malnourished (at risk defined by combination of BMI, history of weight loss and age; 33/34% at risk and 66/67% not at risk in each group)	89 (groups 3 and 4)	Numico (now Nutricia)
Lawson et al 2003[3] (UK)	Cost-analysis (prospective)	Case control study (ward-level)	ONS v no ONS	600kcal prescribed; 6.1 days (mean value reported from earlier paper of	Elective or emergency orthopaedic surgery (ONS: mean 71.3	Well-nourished and malnourished (proportion of patients malnourished or at	181	Not stated

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
				same study[19])	(48-88) y; control: 72.9 (37-90) y)	risk not reported)		
Philipson et al 2013[15] (US)	Cost-analysis (retrospective)	Database analysis with modelling	ONS v no ONS	≤ 8.6 days (since adjusted length of hospital stay = 8.6 days); Amount of ONS not stated but costs include those of labour and administrative expenses	Adult patients, mixed conditions (Matched ONS episodes mean 67.7 y; matched non-ONS episodes 68.3 y)	No information	580,044 matched episodes (~1.16 million admissions)	Abbott Nutrition
NICE 2006[20] (UK, but used data from	CEA (retrospective: using data from	Modelling study based on	Pathway without screening/treatm	300 kcal/day assumed (based on data from BAPEN	Wide range of clinical conditions; model	Malnourished according to 'MUST'	Most of the population admitted to	NICE

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
other countries (based on systematic reviews and meta-analyses))	previously published systematic reviews and meta-analyses)	observational and interventional data	ent (only hospital diet) v screening and treatment (mainly ONS)	report);30 days to reflect duration recorded in RCTs	for people ≥65 y		hospitals in England	
NICE 2012[2] (UK)	Cost (cost impact analysis) (retrospective model using previously published data)	Modelling study based on observational and interventional data	Current pathway of care v proposed pathway (incorporating NICE standards of care)	3 units/day (1 carton = 200 mL) (not stated if energy density was 1 or 1.5 kcal/ml);7 days	Adults ≥18 y with a wide range of conditions including surgical and medical conditions reflecting routine care	Malnourished subjects based on BMI and weight loss and no intake for >5 days (comparable to 'MUST')	35,261 malnourished subjects given ONS in the proposed pathway compared to	NICE

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
							current pathway	
BAPEN report 2005[5]								
a) Beattie et al 2000[6] (UK)	Cost-analysis (retrospective)	RCT	Routine care + ONS v routine care (nutritional management; ONS not mentioned as being excluded)	Most patients consumed 300-600 kcal/day; (post-operatively from start of oral diet for the remainder of hospital stay; (total length of stay 12 days))	Elective surgery (gastrointestinal & cardiovascular) (age 18-80 y; ONS group: 54.4 (sd 19.4) y v control 62.4 (sd 10.9) y; P <0.05)	Malnutrition defined by anthropometry or resumption of oral diet by 8th post-operative day and/or wt loss of ≥5% from admission to 8th post-operative day	109 (101 completed)	Abbott Laboratories
b) Delmi et al 1990[10]	Cost-analysis (retrospective)	RCT	ONS v no ONS	254 kcal/day; 32 days	Elderly hip fracture	Well-nourished and malnourished	59	Not stated, but ONS

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
(CH)					(ONS: mean 80.4 (61-93) y; no ONS: 82.9 (66-96) y)	(proportion of patients malnourished or at risk of malnutrition not reported)		provided by Sandoz-Wander)
c) Rana et al 1992[8] (UK)	Cost-analysis (retrospective)	RCT	ONS v no ONS	471 kcal/day; 6.8 days	Elective GI surgery (ONS: 57.8 (SEM 3.5) y; no ONS: 64.5 (se 2.4) y)	Well-nourished and malnourished (proportion of patients malnourished or at risk not reported)	54 enrolled (40 completed)	Nutricia
d) Keele et al 1997[7] (UK)	Cost-analysis (retrospective)	RCT	ONS v no ONS	334 kcal/day; 5.7 days (post-operatively from time that free	Elective moderate to severe gastro-intestinal surgery (ONS: 69 (se 2.6	Malnourished and well-malnourished (14% with severe malnutrition	100 (86 completed)	Nutricia

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
				fluids/light diet were allowed until discharge)	calculated) y; no ONS 65 (se 2.5) y)	according to the Nutrition Risk Index)		
e) MacFie et al 2000[9] (UK)	Cost-analysis (retrospective)	RCTs (4 groups; group III started ONS in hospital and group IV no ONS)	ONS (post op) v no ONS	238 kcal/day; about 8 days post-operatively	Elective major GI surgery (ONS post-op: mean 66 (23-86) y; no ONS: 64 (42-85) y)	Well-nourished and malnourished (ONS group 7% BMI <19, 7% had lost ≥ 10% of pre-recalled illness BW in 6 months. No ONS group BMI <19 0%; ≥10% weight loss: 20%)	52 (groups III and IV)	Not stated
f) Potter et al 2001[11]	Cost-analysis (retrospective)	RCT	Routine care + ONS v routine	50% took 430-540 kcal/day and 25%	Elderly emergency	Well-nourished and malnourished	381	Scottish Office. ONS

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
(UK)			care including supplements if deemed appropriate	>270 kcal/day; duration of hospital stay after randomisation (total median length of ONS group stay = 16 days)	medical admissions (overall median age 83 (61-99) y with no significant difference between ONS and control groups)	(severe malnutrition, BMI <5th centile; moderate malnutrition, BMI >5th - < 25th centile; well nourished BMI >25th - <75th centile)		provided free of charge by Fresenius UK
g) Gazzotti et al 2003[13] (BE)	Cost-analysis (retrospective)	RCT	ONS v no ONS	500kcal/day prescribed; taken after baseline tests (within 3 days of admission; total length of stay 21	Acute admissions Elderly (ONS: 81.5 (sd 7.6) y; no ONS 78.87 (sd 6.1) y)	Malnourished or at risk of malnutrition (MNA score 17.0-23.5)	80	Not stated

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
				days)				
h) Gariballa et al 1998[12] (UK)	Cost-analysis (retrospective)	RCT	ONS v no ONS	600 kcal/day prescribed; duration of hospital stay after randomisation (total median length of stay 24 days)	Acute stroke (ONS: 78 (sd 10) y; no ONS: 80 (sd 7) y)	Malnourished (TSF and MAC ≤ 1sd below the mean)	42 (length of hospital stay reported in 40)	Not stated
i) Vlaming et al 2001[14] (UK)	Cost-analysis (retrospective)	RCT (factorial design)	ONS v placebo	600 kcal/day prescribed; ≤15.8 days since length of hospital stay was 15.8 days	Acute medical, surgical and orthopaedic (ONS: median 67 (inter-quartile range,47-76) y;	'Thin' subjects defined as BMI 18-22[d] or unintentional weight loss ≥5%	281 (for the arm comparing ONS v placebo and no vitamin	North Thames Regional Health Authority NHS R&D

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
					placebo: 66 (45-75) y)		supplements)	and Abbott Laboratories
Banks et al 2013[1] (AU but used data from other countries (based on meta-analysis)	Cost-analysis and CEA (retrospective 2002-2003)	Modelling study based on observational and interventional data	ONS + additional nutrition/nursing support staffing to encourage and assist patients to consume the required nutrition v standard care (but meta-analysis on	Amount of ONS not stated; estimated to be 22 days from data provided	Patients at risk of developing pressure ulcers (model based on clinical data (RCTs with mean age >80y))	Malnourished (using SGA)	Model assumes 1356 malnourished patients (point prevalence) half of whom receive nutritional support	Royal Brisbane & Women's Hospital Research Foundation

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
			which results were based compared ONS v no ONS)					
Nuijten & Freyer 2010[21] (Abst) (DE)	Cost-analysis (retrospective)	Modelling study based on clinical trials and published literature	ONS v no ONS	Amount and duration of ONS not stated	Hospitalised patients (no other details)	Disease-related malnutrition	Model	One of the authors (KF), employee of Nutricia
Elia & Stratton 2005[22] (Abst) (various countries)	Cost-analysis (retrospective)	Modelling study based on previously published systematic	ONS v no ONS	200-400 ml/day; 1-1.5 kcal/ml; 2-26 weeks	Older hospital patients (model based on RCTs with mean age >80 y)	High risk of developing pressure ulcers ± malnutrition according to	Model	Educational grant from Numico (now Nutricia)

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
		review of interventional data				anthropometry		supported a previously published systematic review

UK = United Kingdom; US = United States; CH = Switzerland; BE = Belgium; AU = Australia; DE = Germany; RCT = randomised controlled trial; ONS = oral nutritional supplement; BMI = body mass index; NICE = National Institute for Health and Care Excellence; CEA = cost-effectiveness analysis; BAPEN= British Association for Enteral and Parenteral Nutrition; 'MUST' = 'Malnutrition Universal Screening Tool'; GI = gastrointestinal; BW = body weight; MNA = Mini Nutritional Assessment; TSF = triceps skinfold thickness; MAC = mid-arm circumference; NHS RD = National Health Service Research and Development; SGA = Subjective Global Assessment; Abst = abstract. SEM =Standard Error of the Mean; SD = Standard Deviation

[a] In cost-effectiveness studies 'cost /effectiveness measure' represents the extra cost per unit effectiveness measure gained e.g. 'cost/QALY' = extra cost per Quality Adjusted Life Year gained..

[b] Number of patients randomised to intervention and control groups.

[c] Includes the studies of Smedley et al[4] and Lawson et al[3] which are summarised above

References

1. Banks MD, Graves N, Bauer JD, Ash S. Cost effectiveness of nutrition support in the prevention of pressure ulcer in hospitals. *Eur J Clin Nutr*. 2013; **67**(1): 42-6.
2. NICE. QS24 Nutrition support in adults: NICE support for commissioners and others using the quality standard on nutrition support in adults *http://publicationsniceorguk/quality-standard-for-nutrition-support-in-adults-qs24/development-sources*. 2012.
3. Lawson RM, Doshi MK, Barton JR, Cobden I. The effect of unselected post-operative nutritional supplementation on nutritional status and clinical outcome of orthopaedic patients. *Clin Nutr*. 2003; **22**(1): 39-46.
4. Smedley F, Bowling T, James M, Stokes E, Goodger C, et al. Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. *British Journal of Surgery*. 2004; **91**: 983-90.
5. Elia M. (chairman & editor), Stratton R, Russell C, Green C, Pang F. The cost of disease-related malnutrition in the UK and economic considerations for the use of oral nutritional supplements (ONS) in adults. A report by The Health Economic Group of The British Association for Parenteral and Enteral Nutrition (BAPEN). BAPEN; 2005. Report No.: 1 899467 01 7.
6. Beattie AH, Parch AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. *Gut*. 2000; **46**: 813-8.
7. Keele AM, Bray MJ, Emery PW, Duncan HD, Silk BDA. Two phase randomised controlled clinical trial of post-operative and dietary supplements in surgical patients. *Gut*. 1997; **40**: 393-7.
8. Rana SK, Bray J, Menzies-Gow N, Jameson J, Payne James JJ, et al. Short term benefits of post-operative oral dietary supplements in surgical patients. *Clin Nutr*. 1992; **11**: 337-44.
9. MacFie J, Woodcock NP, Palmer MD, Walker A, Townsend S, et al. Oral dietary supplements in pre- and post operative surgical patients: a prospective and randomized clinical trail. *Nutrition*. 2000; **16**: 723-8.
10. Delmi M, Rapin C-H, Bengoa J-M, Delmas PD, Vasey H, et al. Dietary supplementation in elderly patients with fractured neck of femur. *Lancet*. 1990; **335**: 1013-6.
11. Potter JM, Roberts MA, McColl JH, Reilly JJ. Protein energy supplements in unwell elderly patients: a randomized controlled trial. *JPEN*. 2001; **25**: 323-9.
12. Gariballa SE, Parker SG, Taub N, Castleden CM. A randomized, controlled, a single-blind trial of nutritional supplementation after acute stroke. *JPEN*. 1998; **22**(5): 315-9.
13. Gazzotti C, Arnaud-Battandier F, Parello M, Farine S, Seidel L, et al. Prevention of malnutrition in older people during and after hospitalisation: results from a randomised controlled clinical trial. *Age Ageing*. 2003; **32**: 321-5.
14. Vlaming S, Biehler A, Hennessey EM, Jamieson CP, Chattophadhyay S, et al. Should the food intake of patients admitted to acute hospital services be routinely supplemented? A randomized placebo controlled trial. *Clin Nutr*. 2001; **20**: 517-26.
15. Philipson TJ, Snider JT, Lakdawalla DN, Stryckman B, Goldman DP. Impact of oral nutritional supplementation on hospital outcomes. *The American journal of managed care*. 2013; **19**(2): 121-8.
16. National Collaborating Centre for Acute Care (commissioned by the National Institute for Clinical Excellence). Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition. Methods, evidence and guidance. London: National Collaborating Centre for Acute Care; 2006.

17. Stratton RS, Ek A-C, Engfer M, Z. M, P. R, et al. Enteral nutrition al support in prevention and treatment of pressure ulcers: a systematic review and meta-analysis. *Aging Research Reviews*. 2005; **(in press)**.
18. Graves N, Birrell F, Whitby M. Effect of pressure ulcers on length of hospital stay. *Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America*. 2005; **26**(3): 293-7.
19. Lawson RM, Doshi MK, Ingoe LE, Colligan JM, Barton JR, et al. Compliance of orthopaedic patients with postoperative oral nutritional supplementation. *Clin Nutr*. 2000; **19**(3): 171-5.
20. NICE. Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition. Appendix 5 cost-effectiveness analysis of malnutrition screening http://www.ncbi.nlm.nih.gov/books/NBK49257/; 2006.
21. Nuijten M, Freyer K. The health economic impact of oral nutritional supplements in the hospital setting in Germany. *Value in Health*. 2010; **13 (3)**: A101-A2.
22. Elia M, Stratton RJ. A cost-benefit analysis of oral nutritional supplements in preventing pressure ulcers. *Clin Nutr*. 2005; **24**: 640-1(P210).

Supplementary file 2 (Details of included studies and type of cost and cost-effectiveness analyses)

Table 1 summarises the details of the studies included in this review. These include the type of economic analysis the type of intervention, subject characteristics, nutritional status and the country in which the investigation was undertaken. This file also provides a more detailed breakdown of cost and cost-effectiveness analyses than that found in the main paper.

1. Cost analysis

Fourteen cost-analyses based on interventions exclusively in the hospital setting were identified (including one which was part of a cost-effectiveness analysis[1], and one in which the hospital component was established from the costing template[2]). Only two of the studies involved prospective cost-analyses[3, 4]. Of the 11 cohort controlled studies found in the BAPEN report[5], five involved abdominal surgery[4, 6-9], two orthopaedic surgery[3, 10], three non-surgical treatments[11-13] and one mixed surgical and non-surgical[14]). The studies in this review were RCTs apart from four: a prospective cohort control study[3]; an observational study examining the impact of ONS[15]; a study based on an economic model with both observational and RCT data[1]; and the NICE cost-impact report, which was based on a range of published clinical data and of expert opinion about current practice. In this last document, the cost of the current pathway of nutritional care in England was compared to that of a proposed pathway which incorporated the NICE clinical guidelines/quality standard[2]. The proposed pathway incurred extra costs, due to more screening, assessment and nutritional support, but it also produced cost savings, due to the effect of ONS in reducing healthcare utilisation. Of the three papers that were picked up from the literature search, two[3, 4] were subjected to further analysis in the BAPEN report.

2. Cost-effectiveness analysis

Two cost-effectiveness analyses were identified[1, 16], both of which involved economic models based on previously published clinical data. One of these, which was published only recently[1] and which was identified by the literature search, used a sophisticated mathematical model to examine the effect of intensive nutritional support in preventing the development of pressure ulcers in a high risk population, and to calculate the potential number of bed-days gained and the cost saving (2002/03 prices) in public hospitals in Queensland Australia. The model used information from a variety of sources, including interventional data from a meta-analysis of 5 RCTs[17] of subjects with a mean age of 80 years and over, with and without malnutrition according to anthropometric criteria. It also used observational data on the prevalence of malnutrition (32%; half of which was assumed to be untreated), and the risk of developing pressure ulcers (4.6%), which were assumed to extend length of hospital stay (4.31 days)[18] . The model also assumed that the response of the general population of malnourished subjects in Queensland reflected that suggested by the above mentioned meta-analysis of older people.

The second cost-effectiveness model developed by NICE[16] (not identified by the literature search) calculated the extra costs required to gain a quality adjusted life year (QALY) when a 'don't treat' group of hospital inpatients $\geq$ 65 years old was compared to one managed by a pathway involving screening with the 'Malnutrition Universal Screening Tool' (MUST), assessment and treatment of patients identified as being 'malnourished' with ONS and a certain amount of enteral tube feeding. The much larger extra costs needed to support patients whose life was extended through use of ONS in hospital was taken into account. The model included the following information: results of systematic reviews with meta-analyses of RCTs comparing complication rates, mortality and quality of life between groups of patients

given ONS or no ONS (i.e. given only the usual hospital diet); expert opinion about current practice and national hospital episode statistics on discharge destination (8% into publically funded institutions such as care homes); and the survival of patients with disease-related malnutrition discharged from hospital, which was assumed to be half of that of subjects from the general population according to age specific mortality statistics. A pathway involving a nurse strategy which included clinical screening and treatment was also considered.

Most studies included in this review reported clinically relevant outcomes, such as mortality, muscle strength and post-operative complications without undertaking formal cost-effectiveness analyses. One RCT comparing ONS with no ONS reported that there were no significant differences in quality of life between four study groups (some of which also received ONS outside hospital) but no cost-utility analyses were reported [4].

1 **Table 1** Details of studies included in the review

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
Smedley et al 2004[4] (UK)	Cost-analysis (prospective)	RCT (4 groups; group 3 started ONS in hospital and group 4 no ONS; groups 2 and 4 involved use of ONS before admission)	ONS v no ONS	258 kcal/day; 8.7 days	Elective moderate/ major lower GI surgery (ONS (group 3): mean 62 (22-83)y; no ONS, (group 4): 63 (25-88)y))	Well-nourished and malnourished (at risk defined by combination of BMI, history of weight loss and age; 33/34% at risk and 66/67% not at risk in each group)	89 (groups 3 and 4)	Numico (now Nutricia)
Lawson et al 2003[3] (UK)	Cost-analysis (prospective)	Case control study (ward-level)	ONS v no ONS	600kcal prescribed; 6.1 days (mean value reported from earlier paper of	Elective or emergency orthopaedic surgery (ONS: mean 71.3	Well-nourished and malnourished (proportion of patients malnourished or at	181	Not stated

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
				same study[19])	(48-88) y; control: 72.9 (37-90) y)	risk not reported)		
Philipson et al 2013[15] (US)	Cost-analysis (retrospective)	Database analysis with modelling	ONS v no ONS	≤ 8.6 days (since adjusted length of hospital stay = 8.6 days); Amount of ONS not stated but costs include those of labour and administrative expenses	Adult patients, mixed conditions (Matched ONS episodes mean 67.7 y; matched non-ONS episodes 68.3 y)	No information	580,044 matched episodes (~1.16 million admissions)	Abbott Nutrition
NICE 2006[20] (UK, but used data from	CEA (retrospective: using data from	Modelling study based on	Pathway without screening/treatm	300 kcal/day assumed (based on data from BAPEN	Wide range of clinical conditions; model	Malnourished according to 'MUST'	Most of the population admitted to	NICE

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
other countries (based on systematic reviews and meta-analyses))	previously published systematic reviews and meta-analyses)	observational and interventional data	ent (only hospital diet) v screening and treatment (mainly ONS)	report);30 days to reflect duration recorded in RCTs	for people ≥65 y		hospitals in England	
NICE 2012[2] (UK)	Cost (cost impact analysis) (retrospective model using previously published data)	Modelling study based on observational and interventional data	Current pathway of care v proposed pathway (incorporating NICE standards of care)	3 units/day (1 carton = 200 mL) (not stated if energy density was 1 or 1.5 kcal/ml);7 days	Adults ≥18 y with a wide range of conditions including surgical and medical conditions reflecting routine care	Malnourished subjects based on BMI and weight loss and no intake for >5 days (comparable to 'MUST')	35,261 malnourished subjects given ONS in the proposed pathway compared to	NICE

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
							current pathway	
BAPEN report 2005[5]								
a) Beattie et al 2000[6] (UK)	Cost-analysis (retrospective)	RCT	Routine care + ONS v routine care (nutritional management; ONS not mentioned as being excluded)	Most patients consumed 300-600 kcal/day; (post-operatively from start of oral diet for the remainder of hospital stay; (total length of stay 12 days))	Elective surgery (gastrointestinal & cardiovascular) (age 18-80 y; ONS group: 54.4 (sd 19.4) y v control 62.4 (sd 10.9) y; P <0.05)	Malnutrition defined by anthropometry or resumption of oral diet by 8th post-operative day and/or wt loss of ≥5% from admission to 8th post-operative day	109 (101 completed)	Abbott Laboratories
b) Delmi et al 1990[10]	Cost-analysis (retrospective)	RCT	ONS v no ONS	254 kcal/day; 32 days	Elderly hip fracture	Well-nourished and malnourished	59	Not stated, but ONS

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
(CH)					(ONS: mean 80.4 (61-93) y; no ONS: 82.9 (66-96) y)	(proportion of patients malnourished or at risk of malnutrition not reported)		provided by Sandoz-Wander)
c) Rana et al 1992[8] (UK)	Cost-analysis (retrospective)	RCT	ONS v no ONS	471 kcal/day; 6.8 days	Elective GI surgery (ONS: 57.8 (SEM 3.5) y; no ONS: 64.5 (se 2.4) y)	Well-nourished and malnourished (proportion of patients malnourished or at risk not reported)	54 enrolled (40 completed)	Nutricia
d) Keele et al 1997[7] (UK)	Cost-analysis (retrospective)	RCT	ONS v no ONS	334 kcal/day; 5.7 days (post-operatively from time that free	Elective moderate to severe gastro-intestinal surgery (ONS: 69 (se 2.6	Malnourished and well-malnourished (14% with severe malnutrition	100 (86 completed)	Nutricia

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
				fluids/light diet were allowed until discharge)	calculated) y; no ONS 65 (se 2.5) y)	according to the Nutrition Risk Index)		
e) MacFie et al 2000[9] (UK)	Cost-analysis (retrospective)	RCTs (4 groups; group III started ONS in hospital and group IV no ONS)	ONS (post op) v no ONS	238 kcal/day; about 8 days post-operatively	Elective major GI surgery (ONS post-op: mean 66 (23-86) y; no ONS: 64 (42-85) y)	Well-nourished and malnourished (ONS group 7% BMI <19, 7% had lost ≥ 10% of pre-recalled illness BW in 6 months. No ONS group BMI <19 0%; ≥10% weight loss: 20%)	52 (groups III and IV)	Not stated
f) Potter et al 2001[11]	Cost-analysis (retrospective)	RCT	Routine care + ONS v routine	50% took 430-540 kcal/day and 25%	Elderly emergency	Well-nourished and malnourished	381	Scottish Office. ONS

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
(UK)			care including supplements if deemed appropriate	>270 kcal/day; duration of hospital stay after randomisation (total median length of ONS group stay = 16 days)	medical admissions (overall median age 83 (61-99) y with no significant difference between ONS and control groups)	(severe malnutrition, BMI <5th centile; moderate malnutrition, BMI >5th - < 25th centile; well nourished BMI >25th - <75th centile)		provided free of charge by Fresenius UK
g) Gazzotti et al 2003[13] (BE)	Cost-analysis (retrospective)	RCT	ONS v no ONS	500kcal/day prescribed; taken after baseline tests (within 3 days of admission; total length of stay 21	Acute admissions Elderly (ONS: 81.5 (sd 7.6) y; no ONS 78.87 (sd 6.1) y)	Malnourished or at risk of malnutrition (MNA score 17.0-23.5)	80	Not stated

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
				days)				
h) Gariballa et al 1998[12] (UK)	Cost-analysis (retrospective)	RCT	ONS v no ONS	600 kcal/day prescribed; duration of hospital stay after randomisation (total median length of stay 24 days)	Acute stroke (ONS: 78 (sd 10) y; no ONS: 80 (sd 7) y)	Malnourished (TSF and MAC ≤ 1sd below the mean)	42 (length of hospital stay reported in 40)	Not stated
i) Vlaming et al 2001[14] (UK)	Cost-analysis (retrospective)	RCT (factorial design)	ONS v placebo	600 kcal/day prescribed; ≤15.8 days since length of hospital stay was 15.8 days	Acute medical, surgical and orthopaedic (ONS: median 67 (inter-quartile range,47-76) y;	'Thin' subjects defined as BMI 18-22[d] or unintentional weight loss ≥5%	281 (for the arm comparing ONS v placebo and no vitamin	North Thames Regional Health Authority NHS R&D

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
					placebo: 66 (45-75) y)		supplements)	and Abbott Laboratories
Banks et al 2013[1] (AU but used data from other countries (based on meta-analysis)	Cost-analysis and CEA (retrospective 2002-2003)	Modelling study based on observational and interventional data	ONS + additional nutrition/nursing support staffing to encourage and assist patients to consume the required nutrition v standard care (but meta-analysis on	Amount of ONS not stated; estimated to be 22 days from data provided	Patients at risk of developing pressure ulcers (model based on clinical data (RCTs with mean age >80y))	Malnourished (using SGA)	Model assumes 1356 malnourished patients (point prevalence) half of whom receive nutritional support	Royal Brisbane & Women's Hospital Research Foundation

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
			which results were based compared ONS v no ONS)					
Nuijten & Freyer 2010[21] (Abst) (DE)	Cost-analysis (retrospective)	Modelling study based on clinical trials and published literature	ONS v no ONS	Amount and duration of ONS not stated	Hospitalised patients (no other details)	Disease-related malnutrition	Model	One of the authors (KF), employee of Nutricia
Elia & Stratton 2005[22] (Abst) (various countries)	Cost-analysis (retrospective)	Modelling study based on previously published systematic	ONS v no ONS	200-400 ml/day; 1-1.5 kcal/ml; 2-26 weeks	Older hospital patients (model based on RCTs with mean age >80 y)	High risk of developing pressure ulcers ± malnutrition according to	Model	Educational grant from Numico (now Nutricia)

Authors (country)	Type of economic analysis[a]	Type of study	Comparison	Amount and duration of ONS use	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding
		review of interventional data				anthropometry		supported a previously published systematic review

UK = United Kingdom; US = United States; CH = Switzerland; BE = Belgium; AU = Australia; DE = Germany; RCT = randomised controlled trial; ONS = oral nutritional supplement; BMI = body mass index; NICE = National Institute for Health and Care Excellence; CEA = cost-effectiveness analysis; BAPEN= British Association for Enteral and Parenteral Nutrition; 'MUST' = 'Malnutrition Universal Screening Tool'; GI = gastrointestinal; BW = body weight; MNA = Mini Nutritional Assessment; TSF = triceps skinfold thickness; MAC = mid-arm circumference; NHS RD = National Health Service Research and Development; SGA = Subjective Global Assessment; Abst = abstract. SEM =Standard Error of the Mean; SD = Standard Deviation

[a] In cost-effectiveness studies 'cost /effectiveness measure' represents the extra cost per unit effectiveness measure gained e.g. 'cost/QALY' = extra cost per Quality Adjusted Life Year gained..

[b] Number of patients randomised to intervention and control groups.

[c] Includes the studies of Smedley et al[4] and Lawson et al[3] which are summarised above

References

1. Banks MD, Graves N, Bauer JD, Ash S. Cost effectiveness of nutrition support in the prevention of pressure ulcer in hospitals. *Eur J Clin Nutr*. 2013; **67**(1): 42-6.
2. NICE. QS24 Nutrition support in adults: NICE support for commissioners and others using the quality standard on nutrition support in adults *http://publicationsniceorguk/quality-standard-for-nutrition-support-in-adults-qs24/development-sources*. 2012.
3. Lawson RM, Doshi MK, Barton JR, Cobden I. The effect of unselected post-operative nutritional supplementation on nutritional status and clinical outcome of orthopaedic patients. *Clin Nutr*. 2003; **22**(1): 39-46.
4. Smedley F, Bowling T, James M, Stokes E, Goodger C, et al. Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. *British Journal of Surgery*. 2004; **91**: 983-90.
5. Elia M. (chairman & editor), Stratton R, Russell C, Green C, Pang F. The cost of disease-related malnutrition in the UK and economic considerations for the use of oral nutritional supplements (ONS) in adults. A report by The Health Economic Group of The British Association for Parenteral and Enteral Nutrition (BAPEN). BAPEN; 2005. Report No.: 1 899467 01 7.
6. Beattie AH, Parch AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. *Gut*. 2000; **46**: 813-8.
7. Keele AM, Bray MJ, Emery PW, Duncan HD, Silk BDA. Two phase randomised controlled clinical trial of post-operative and dietary supplements in surgical patients. *Gut*. 1997; **40**: 393-7.
8. Rana SK, Bray J, Menzies-Gow N, Jameson J, Payne James JJ, et al. Short term benefits of post-operative oral dietary supplements in surgical patients. *Clin Nutr*. 1992; **11**: 337-44.
9. MacFie J, Woodcock NP, Palmer MD, Walker A, Townsend S, et al. Oral dietary supplements in pre- and post operative surgical patients: a prospective and randomized clinical trail. *Nutrition*. 2000; **16**: 723-8.
10. Delmi M, Rapin C-H, Bengoa J-M, Delmas PD, Vasey H, et al. Dietary supplementation in elderly patients with fractured neck of femur. *Lancet*. 1990; **335**: 1013-6.
11. Potter JM, Roberts MA, McColl JH, Reilly JJ. Protein energy supplements in unwell elderly patients: a randomized controlled trial. *JPEN*. 2001; **25**: 323-9.
12. Gariballa SE, Parker SG, Taub N, Castleden CM. A randomized, controlled, a single-blind trial of nutritional supplementation after acute stroke. *JPEN*. 1998; **22**(5): 315-9.
13. Gazzotti C, Arnaud-Battandier F, Parello M, Farine S, Seidel L, et al. Prevention of malnutrition in older people during and after hospitalisation: results from a randomised controlled clinical trial. *Age Ageing*. 2003; **32**: 321-5.
14. Vlaming S, Biehler A, Hennessey EM, Jamieson CP, Chattophadhyay S, et al. Should the food intake of patients admitted to acute hospital services be routinely supplemented? A randomized placebo controlled trial. *Clin Nutr*. 2001; **20**: 517-26.
15. Philipson TJ, Snider JT, Lakdawalla DN, Stryckman B, Goldman DP. Impact of oral nutritional supplementation on hospital outcomes. *The American journal of managed care*. 2013; **19**(2): 121-8.
16. National Collaborating Centre for Acute Care (commissioned by the National Institute for Clinical Excellence). Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition. Methods, evidence and guidance. London: National Collaborating Centre for Acute Care; 2006.

17. Stratton RS, Ek A-C, Engfer M, Z. M, P. R, et al. Enteral nutrition al support in prevention and treatment of pressure ulcers: a systematic review and meta-analysis. *Aging Research Reviews*. 2005; **(in press)**.
18. Graves N, Birrell F, Whitby M. Effect of pressure ulcers on length of hospital stay. *Infection control and hospital epidemiology : the official journal of the Society of Hospital Epidemiologists of America*. 2005; **26**(3): 293-7.
19. Lawson RM, Doshi MK, Ingoe LE, Colligan JM, Barton JR, et al. Compliance of orthopaedic patients with postoperative oral nutritional supplementation. *Clin Nutr*. 2000; **19**(3): 171-5.
20. NICE. Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition. Appendix 5 cost-effectiveness analysis of malnutrition screening http://www.ncbi.nlm.nih.gov/books/NBK49257/; 2006.
21. Nuijten M, Freyer K. The health economic impact of oral nutritional supplements in the hospital setting in Germany. *Value in Health*. 2010; **13 (3)**: A101-A2.
22. Elia M, Stratton RJ. A cost-benefit analysis of oral nutritional supplements in preventing pressure ulcers. *Clin Nutr*. 2005; **24**: 640-1(P210).