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A systematic review of the cost and cost effectiveness of using standard oral nutritional supplements in community and care home settings

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SUMMARY

Background and aims: Despite the clinical benefits of using standard (non-disease specific) oral nutritional supplements (ONS) in the community and care homes, there is uncertainty about their economic consequences.

Methods: A systematic review was undertaken according to recommended procedures to assess whether ONS can produce cost savings and cost-effective outcomes.

Results: 19 publications with and without a hospital component were identified: 9 full text papers, 9 abstracts, and 1 report with retrospective analyses of 6 randomised controlled trials. From these publications a total of 31 cost and 4 cost-effectiveness analyses were identified. Most were retrospective analyses based on clinical data from randomised controlled trials (RCTs). In 9 studies/economic models involving ONS use for <3 months, there were consistent cost savings compared to the control group (median cost saving 9.2%; P <0.01). When used for ≥3 months, the median cost saving was 5% (P>0.05; 5 studies). In RCTs, ONS accounted for less than 5% of the total costs and the investment in the community produced a cost saving in hospital. Meta-analysis indicated that ONS reduced hospitalisation significantly (16.5%; P <0.001; 9 comparisons) and mortality non-significantly (Relative risk 0.86 (95% CI, 0.61, 1.22); 8 comparisons). Many clinically relevant outcomes favouring ONS were reported: improved quality of life, reduced infections, reduced minor post-operative complications, reduced falls, and functional limitations. Of the cost-effectiveness analyses involving quality adjusted life years or functional limitations, most favoured the ONS group. The care home studies (4 cost analyses; 2 cost-effectiveness analyses) had differing aims, designs and conclusions.

Conclusions: Overall, the reviewed studies, mostly based on retrospective cost analyses, indicate that ONS use in the community produce an overall cost advantage or near neutral balance, often in association with clinically relevant outcomes, suggesting cost effectiveness. There is a need for prospective studies designed to examine primary economic outcomes.

Key words

Oral nutritional supplements; malnutrition; cost; cost effectiveness; systematic review; community

1. Introduction

Malnutrition is a common clinical and public health problem, and at a given point in time, more than 97% of it exists outside hospital[1]. It not only produces a burden to the individuals concerned such as delayed recovery, more complications and increased dependency on others, but also to the services and the public providing health and social care support. Whilst the general benefits of treating malnutrition are well recognised[2, 3] and while the effects of specific forms of nutritional support, such as oral nutritional supplements (ONS) have been reviewed in the community[4, 5] and in care homes[6], information on the economic consequences are limited[7-11]. An accurate overview of the cost and cost effectiveness of ONS can be difficult to establish from the existing reviews[7-11] which have often reported the effects of a combination of interventions in various care settings, including tube feeding, parenteral nutrition, disease and non-disease specific ONS, and others in which snacks rather than ONS have dominated. Furthermore, most of the economic analyses involving standard ONS in hospital and community settings appear to have been missed, while most of the reviewed studies have been largely based on disease-specific ONS (those specifically modified for particular patient groups), rather than the standard ONS, which are used in the majority of patients. There are also apparent contradictions in the cost[12] and cost effectiveness [13-15] of ONS, which may be due to differences in methodology[16], and type of ONS used.

For patients moving from one care setting to another, the situation can become complicated because the cost of management in one setting may be offset by a larger cost saving in another setting. Furthermore, regulatory agencies have identified the need to clinically justify and monitor the effects of ONS, so that nutritional support is

started only when it is appropriate to do so, according to existing evidence or guidelines, and continued for no longer than is necessary[17]. To address these issues there is a need to review the effects of ONS, which may depend on age, disease, nutritional status and whether or not ONS are given alone or in combination with other interventions, such as dietary counselling. They may also depend on whether the investigations are randomised controlled trials (RCTs)[14, 18] or observational[19] studies carried out prospectively or retrospectively, and whether ONS are administered exclusively in the community and care homes, or additionally in other care settings. The purpose of this systematic review was to critically examine the cost (or cost saving) and cost effectiveness of standard ONS in the community and care home settings in the light of the above factors. In particular, it aimed to distinguish between studies undertaken exclusively outside hospital (e.g. community and care homes), and those that are started outside hospital and continued in the hospital setting and vice versa. The review also aimed to identify gaps in the current literature, so that they can be addressed by future research.

2. Methods

2.1. Inclusion and exclusion criteria

The pre-specified inclusion and exclusion criteria are summarised in Table 1. Standard ONS was defined as a commercially available, ready to consume, multi-nutrient (complete or incomplete), liquid or semi-solid product providing a mix of macronutrients and micronutrients produced by specialist medical nutrition manufacturers. Disease-specific ONS were excluded.

2.2. Outcomes

The primary outcome measure of this review was a cost- and/or a cost-effectiveness analysis, irrespective of the type of effectiveness outcomes used (e.g. Quality Adjusted Life Year (QALY), energy intake or physical activity). The secondary outcome measures were functional and clinically relevant outcomes.

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). The Health Economic Evaluation Database (HEED) and the Cochrane library (which includes the National Health Service Economic Evaluations Database NHS EED), Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and Database of Abstracts of Reviews and Effects were searched on the same date. Articles from all of these databases were exported into a single 'library'. The Cost-Effectiveness Analysis (CEA) Registry was cross checked independently. The search was undertaken as part of a larger systematic review that included use of ONS exclusively in the hospital setting[20] .

Three sets of terms were used to search various parts of publications including the title, abstract, subject heading and any key words. These were: 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. Only articles that included at least one search term within each of the three groups were exported into a common library. Potentially eligible papers were identified by

reading the titles, abstracts and key descriptor words/phrases. They were initially screened by reading the title and abstract, and if deemed to be potentially relevant the full article was reviewed. Other publications were identified from prior knowledge, discussions with experts in the field and hand searching of retrieved full text ONS papers. The assessment of trial eligibility was undertaken by two independent assessors and any disagreements were resolved through discussion. The reasons for exclusion are shown in Figure 1. Authors of several publications[15, 21-24] were contacted to clarify specific issues.

2.4. Quality assessment

The procedure for assessing the quality of controlled trials (assessment of risk of bias) was based on the Cochrane Handbook for Systematic Reviews of Interventions, updated in 2011[25]. The quality of the economic studies was assessed using the checklist provided by Drummond et al[16], which was adapted for nutritional studies on the basis that some items were ambiguous or not relevant to the types of studies being assessed. Abstracts (see below) were not evaluated for quality because the brief information provided was considered to be inadequate for the detailed economic evaluation demanded by the assessment procedure. One full text paper[18], which provided a brief summary of the economic data, indicated that further data would be forthcoming, but since no such information was identified the study was only evaluated for the quality of the RCT. Evaluations based on economic criteria were only undertaken for studies reporting economic outcomes in the original paper and not those subsequently subjected to secondary analyses to establish economic outcomes.

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. When costs were expressed in different national currency units, such as British pounds and Euros (the value of which can vary considerably between different European Union countries), two procedures were undertaken: a forest plot was presented along with the statistics for each study, but without a summary statistic for the combination of studies; and a meta-analysis in which the results were expressed as a proportion of the standard deviation or as a proportion of the control group. When meta-analysis was not possible due to lack of measures of variation, the mean values from each study were analysed using standard statistical tests, such as one sample t-tests for the difference between intervention and control groups and the binomial test; SPSS (version 21, Chicago, USA). Some results were reported narratively. A P-value of <0.05 (two tailed) was considered to be significant. Synthesis of data for statistical analyses, including meta-analyses, did not include abstracts which have obvious limitations.

3. Results

A total of 22,819 potentially relevant publications were identified by the electronic literature search and another seven by hand searching and expert prior knowledge of the literature. Figure 1 shows the steps that led to the final 19 publications included in the review[12-14, 18, 19, 21-24, 26-35]. Two abstracts of the same study, each with some complementary information, were considered to represent a single publication[23]. Of the 19 publications, nine were full text papers[13, 14, 18, 19, 26-29, 35], nine were abstracts[21-24, 30-34], and one was a report[12]. Nine publications reported the results of primary studies with prospective cost analyses[14, 18, 19, 21-23, 26, 29, 34] and the remainder

retrospective (post hoc) cost analyses. The British Association for Parenteral and Enteral Nutrition (BAPEN) report[12], which included 10 retrospective cost analyses from six full text papers of RCTs[18, 36-40], was largely based on a published systematic review of ONS[3]. Economic data from individual studies in the BAPEN report were extracted, amalgamated with other data and used to undertake new meta-analyses (the BAPEN report included no meta-analyses of community studies). The original papers were also systematically examined for clinically relevant outcome measures (which were also not reported in the BAPEN report) so that further meta-analyses relevant to cost effectiveness could be undertaken.

Overall there were 31 cost analyses (including four analyses in the BAPEN report based on data from Smedley et al[18]) and cost-effectiveness analyses (which also included cost analyses). The number of analyses exceeded the number of publications for three reasons: some RCTs included more than two arms (e.g. references[18, 36] analysed by BAPEN); some results were analysed prospectively by the authors and retrospectively using different methods by other groups[12, 18]; and some cost-effectiveness studies also provided data on overall costs[14, 23]. Of the 31 cost analyses, only 17 were identified by the electronic literature search. The remaining 14 were based on prior knowledge of two full text papers[19, 26] (subsequently retrieved using different search terms), three abstracts[21, 22, 24] and the BAPEN report[12] with its 10 cost analyses (not listed). Most of these were not included in previous reviews[7-10].

3.1 General features of the studies

Supplementary file 1 summarises key features of individual studies. Both single and multi-centre studies were undertaken in various European countries and the USA. The studies included either malnourished or a combination of malnourished and non-

malnourished subjects. Most comparisons involved ONS v. no ONS (papers[13, 18, 27, 28, 35] ; abstracts[30-32]) but a variety of other comparisons were made including: ONS plus dietary advice plus calcium/vitamin D v. routine care[14]; ONS plus dietary advice v. routine care[26]; ONS v. snacks[29]; and expenditure in general practices with a history of high v. low rates of ONS prescriptions[19]. Additional comparisons were reported in some abstracts e.g. ONS v. dietary advice[23], or the 'Malnutrition Universal Screening Tool' ('MUST') framework of nutritional care which includes ONS v. routine care[21, 22]. Some studies began administering ONS in hospital and continued into the community, others started in the community and continued in hospital, and yet others were carried out in the community following admission to hospital. Only one clinical study recruited directly from the community[19].

The cost of screening and assessment, needed to identify subjects for ONS prescription and monitoring, appear to have been included in only two abstracts[22, 24] (and personal communication from A Cawood). Economic models examining the impact of ONS in specific countries typically used national tariffs operating in the countries and clinical data obtained from various countries with different healthcare systems (papers[27, 28, 35]) or from unspecified countries (abstracts[24, 30-33]).

Cost was the primary outcome in one prospectively undertaken clinical study[19] and the secondary outcome in three clinical studies [18, 26, 34], two of which had a hospital component[18, 34]. Cost-effectiveness analysis was probably the secondary outcome in a community study[14] (see Supplementary file 1) with some uncertainty as to whether it was a primary or secondary outcome measure in a care home study[29]. Other clinical studies were designed with non-economic outcomes in mind (Supplementary file 1).

In studies involving both short-term (<3 months, and as little as 15 days) and long-term administration of ONS in the community (≥3 months, and up to 8 months in

some patient groups) the reported ONS intake ranged from 259 to 720 kcal/day. Lack of information prevented calculation of compliance from both papers/reports[14, 18, 19, 29, 38-40], and abstracts[23, 34], but it was possible to estimate that ONS intake accounted for 50-100% of the target intake in one study (variable intake reported)[37] ,34-57% in another (variable target intake reported)[26], and about 80%[13] in a third study. Adherence to oral nutritional support was reported to be 80% in a further study [14]. Methodological details for assessing intake were usually not provided, but some studies relied on diaries[36] or records kept by patients[13]. Daily intake was assessed to the nearest half carton in one study[18]. Attempts were made to improve compliance in some studies (e.g.[14, 29, 37]) but it is unclear if this represented routine practice. In one study research staff and not regular staff encouraged better compliance[29].

3.2. Outcomes: community (ONS use in community ± hospital)

The results of cost and cost-effectiveness analyses are reported separately below in sections that consider individual studies first and amalgamated studies next. Care homes studies are reported in section 3.3.

3.2.1. Cost analysis

(a)Individual studies

Short-term, pre-and /or post-operative supplementation studies (<3 months supplementation): The results of the short-term (<3 months) retrospective analyses of surgical studies undertaken by the BAPEN group are shown in Table 2. The analyses uniformly favoured the ONS group when the calculations were based on bed-day costs or excess bed-day costs (costs of unusually long stays that typically include basic care and hotel costs but exclude the costs of surgical procedures); and in four out of the five analyses when the calculations were based on complication costs. One

of the original papers briefly reported that in comparison with the control group (no ONS) there was a net cost saving favouring the group given ONS pre-operatively in the community (£332/patient) as well as in the group given ONS before, during and after hospitalisation (£329/patient)[18]. These were within the values established by the BAPEN group using different methodologies based on bed-day and excess bed-day costs. There was also a cost saving favouring a third group given ONS post-operatively both in hospital and after discharge from hospital , which was more favourable (£292/patient) than those calculated by the BAPEN group using bed-day (£260.7/patient) and excess bed-day costs (£130.1/patient). Another primary study crudely estimated the cost saving associated with a reduction in length of hospital stay ($2,298/patient)[38]. Finally, an abstract of a RCT in which ONS appears to have been administered before, during and after hospitalisation reported a significant cost saving in favour of the ONS (10% cost saving 6 months after surgery which included the cost of hospitalisation[34]).

Long-term, community studies (≥3 months supplementation): Two prospective economic studies involving use of ONS for ≥3 months were identified. In the multi-centre prospective open label control trial of Edington et al[26] there was no significant difference between the ONS and control group in health and social care costs, or in the costs of prescriptions, General Practitioner (GP) consultations, outpatient appointments and hospital inpatient admissions. In the other RCT, beginning in the hospital setting and continuing in the community, there was also no significant difference in costs between the ONS and the control group (€23,353 ±16,124 v. €22,896±16,834; direct costs, which accounted for ca. 95% of total costs)[14].

The observational study of Arnaud-Battandier et al[19] reported an overall cost saving in general practices with high ONS prescription rates compared to those with

low prescription rates, but the difference was not significant (€195; 90% CI -€478, €929 per patient per year). The extra costs of the ONS (€528 per patient per year) were offset by greater cost savings (€723 per patient per year), predominantly due to reduced hospital admissions (€551 per patient per year).

In one of the retrospective analyses undertaken by the BAPEN group, the cost of ONS given to mildly malnourished and hypoalbuminaemic patients who had been on dialysis for at least 3 months[40], was estimated to outweigh the cost saving from reduced hospitalisation. In contrast, another analysis involving 51 patients with decompensated alcoholic liver disease[39], the cost of the ONS was considered to be more than offset by reduced number of days spent in hospital (71, ONS group v. 107 days, control group).

Economic modelling studies: All publications of economic modelling of ONS administration used information from previously published clinical studies, and all favoured the ONS group. The three full text papers are described first[27, 28, 35].

A model for assessing the cost impact of ONS in the Netherlands[35], which included some observational data from the BAPEN economic report[12], calculated a net cost saving of €252 per malnourished patient undergoing abdominal surgical procedures (2004 prices inflated to 2008 prices) in favour of the ONS group. The cost of the supplement, which was assumed to have been taken both in the community pre-operatively and in hospital post-operatively for a total of 17 days, was more than counterbalanced by the assumed reduction in length of hospital stay. The cost saving per patient was extrapolated to an annual cost saving in the whole of the Netherlands.

The second full text paper, which assumed that ONS was administered for 3 months in patients with benign gastrointestinal disease following discharge from hospital[27], concluded that there was an overall net cost saving in the ONS group

compared to the control group receiving no ONS (€768 based on calculations using Diagnosis Related Groups (DRG); €791 based on calculations using bed-day costs, even after taking into account the extra cost of the ONS (€534) (net cost saving, €234 per patient based on DRG and €257 based on LOS costs (2007 prices)). When extrapolated to the whole of Germany, the overall annual savings were €604 million, using DRG costs, and €681 million, using bed-day costs. The calculations were dominated by hospital readmission rates over a 6 month period, which were taken to be significantly lower in the ONS group (26.3% v. 47.6%). The clinical data were largely based on a German study[41] but a UK study was also used in sensitivity analyses, which consistently favoured the ONS group.

The third full text paper[28], using a similar type of model as the previous one[27], assumed that ONS (600 kcal/day) were administered for 3 months to malnourished community dwelling subjects ≥65 years, considered to represent 20% of the home care population in the Netherlands. The model further assumed that the intervention would reduce hospitalisation by 25% on the basis of three RCTs. Two of these recruited patients recently discharged from hospital[41, 42], one involving patients with a mean age <65 years[41], and the other[42] a mixture of malnourished and non-malnourished older subjects, who started taking ONS in hospital and then continued them in the community. The third study used ONS in the community for 12 months[43], or four times longer than the model specification. The base case analysis favoured the ONS group (€90.15 per malnourished patient (calculated using the data provided)). Sensitivity analyses almost always favoured the ONS group.

All four abstracts[24, 30-32] of economic modelling involving ONS administration in the community also favoured the ONS group. One of these[24] based on clinical data from 19 community-based RCTs, predicted that a two month course of ONS in older

(≥65 years) community dwelling patients at risk of malnutrition in England would produce a net annual cost saving of £16 million favouring the ONS group. The three other abstracts comparing the effects of ONS (taken over an unstated period) v. no ONS in community dwelling older people (>65 years) reported the following net cost savings in favour of the ONS group: 18.9% or €13.3 million in the Netherlands[31]; 12.8% or €173 per patient in the Netherlands[30]; and 13.0% or €179 per patient or a total of €344 million in Germany[32].

(b) Amalgamated studies

Subject level analyses (based on meta-analysis of studies comparing mean ± sd between groups): Figure 2 shows two forest plots of subject level analyses based on prospective cost analyses of supplementation studies in the community (± in hospital). The upper forest plot shows the absolute difference in costs, expressed in national currency units, between ONS and no ONS (or routine care), while the lower forest plot shows the results expressed as standardised differences with no significant differences between groups (see Supplementary file 1 for further meta-analyses)..

Study level analysis (based only on the difference in mean values between groups): The amalgamated study results were based only on full text papers and those presented in the BAPEN report, which were based on retrospective cost analyses of full text papers[12]. In an attempt to provide an overview of the average results of 14 cost analyses based on studies undertaken in different countries at different times using various currencies, the results were expressed as percentage cost savings. Since the distribution of these cost savings was highly skewed the results were analysed non-parametrically. Overall, there was a significant cost saving (median 8.1% (inter-quartile range 9.3; P = 0.022; N = 14 analyses)) in favour of the ONS group. When examined using the binomial test, which allowed the inclusion of an additional two

studies, 13 out of 16 cost analyses favoured the ONS group (P = 0.021). There was no significant relationship between cost saving on the one hand and year of publication of study or the duration or estimated duration of supplementation on the other. The results of individual studies (Table 3) were used to undertake subgroup analyses according to patient characteristics (age category and nutritional status) and study design (type of intervention, care setting), which are presented in Table 4. Overall, the cost saving favoured the ONS group which was significant for the following subgroups: short-term studies (often with a hospital component); those involving younger groups of patients; those retrospectively analysed; and those comparing ONS with no ONS. Several subgroup analyses were not significant, especially when one particular study with a large financial loss[26] was included in the subgroup analysis.

Although abstracts of community studies were not included in the above analyses, they all favoured the ONS group[24, 30-32, 34].

(c) Distribution of costs

In the RCTs that pre-planned to undertake a cost analysis, ONS administration for 0.5-3.1 months, contributed to only 1% - 11% of the total cost (mean <5%), while hospitalisation contributed to 69% - >90% of the costs (Table 5). In the only observational study in which ONS was estimated to have been administered for longer than 3 months, and perhaps ≥6 months (see footnote to Table 5), ONS contributed to 23% of the costs, and hospitalisation to 63% of the costs. All six cost analyses summarised in Table 5 involved administration of ONS either exclusively or predominantly in the community. One cost analysis[14], in which ONS was started in hospital and continued ONS for a much longer period, in the community, reported only the post discharge costs.

3.2.2. Cost-effectiveness analysis

In an attempt to relate the cost outcomes reported above to effectiveness measures, a variety of clinically relevant outcomes from the same studies are summarised below. The more formal cost-effectiveness (cost-utility) analyses, typically with cost effectiveness acceptability curves, [13, 14] are presented subsequently.

(a) Clinically relevant benefits

Anthropometry: Individual studies involving use of ONS in the community (with or without additional use in hospital), reported significantly greater improvements in anthropometry in the ONS than control group: weight [18]; weight, skinfold thickness and mid arm muscle circumference[37]; and nutritional status assessed by MNA[19]. Edington et al[26] reported significant improvements in weight, skinfold thickness, and mid-arm circumference in the ONS group but not in the control group, and Neelemaat et al[14] reported a tendency for greater weight gain in the ONS group, which was significant only for the highest weight subgroup[44].

Hospitalisation: Two studies reported significant reduction in the number of hospital admissions[13, 39]. Other studies reported hospitalisation in different ways e.g. number of days in hospital including ICU[14]; total number of days in hospital during the observational period from which the proportion (and standard deviation of this proportion) of the time spent in hospital during the study period could be calculated[40]. A series of meta-analyses involving 10 datasets from eight publications[13, 14, 18, 19, 26, 39, 40, 45] found reduced hospitalisation in favour of the ONS group. For the nine datasets from full text papers only it was reduced by 16.5% ((se 4.0), P = 0.001; N = 1051 subjects; I^2 = 16%, P = 0.307) (Figure 3). Further meta-analyses, including those involving only long-term studies, only short-term studies and only RCTs also favoured the ONS group (see Supplementary file 1)..

Mortality: Mortality was reported in seven studies[13, 14, 18, 26, 36, 37, 39] (53 deaths in ONS group and 59 in the comparison group; no deaths in two other studies[18, 37], but a meta-analysis showed no significant differences between them (Relative risk 0.859 (95% CI, 0.606, 1.217), P = 0.393; I^2 = 0%, P = 0.825; 7 datasets, N= 943). The results remained non-significant when the only observational study was excluded (Relative risk 0.924 (95% CI, 0.556, 1.534), P = 0.706; I^2 =0%, P = 0.743) or when the only pre-operative supplementation study (ONS given in the community) was excluded (Relative risk 0.853 (95% CI, 0.598, 1.216), P = 0.380; I^2 = 0%, P = 0.587).

Quality of life: The study of Beattie et al[37] which started ONS in hospital (used for <12 days) and continued for 51 days in the community, reported significant improvements in physical and mental health, assessed using the quality of life questionnaire SF-36 (36-item Medical Outcomes Study Short Form Survey), favouring the ONS group (P<0.001). In the community study of Norman et al[13] there was a significant gain in QALYs favouring the ONS group, but since there was only one death out of 60 in the intervention group and three deaths out of 54 in the control group, almost all the variability in QALYs was due to quality of life. The main analysis undertaken by Neelemaat et al[14] appears to have excluded patients who died, implying that QALYs gained were based entirely on quality of life. From the statistics provided it would appear that there was a strong tendency for the changes to favour the ONS group (by 0.02 (95% CI, 0.00, 0.04) QALYs). A peri-operative study[18] and a community study in elderly subjects[26] reported no significant differences in quality of life between groups.

Other Outcomes: Of the eight RCTs reporting functional or clinical outcomes, all found at least one outcome significantly favouring the ONS group and none significantly favouring the control group. For example, Neelemaat et al[14] reported that

in comparison with the control group, the ONS group significantly improved in functional limitations by 0.72 units on a scale of 0 to 6, and a related paper of the same study reported significant reductions in the number of falls[46] (0.21 v. 0.55/patient; P <0.01). Edington et al[26] reported a greater proportion of patients with no mobility problems at 6 months (32.4 v. 7.7%; P = 0.022) and Hirsch et al[39] a significant reduction in number of infections, although not in the total number of complications. Grip strength improved in favour of the ONS group, at least at some point during the course of certain investigations[13, 26] but not others[14, 39] (in one of them[14] this was reported in an earlier publication of the same RCT[44]). In one of the studies[13] the increase in grip strength was accompanied by an improvement in peak expiratory flow[13] (also reported in an earlier publication of the same RCT[41]). In surgical studies[18, 34, 36, 37] in which ONS was administered pre- and/or post-operatively in the community, and in some cases during elective hospital admissions, significant benefits were frequently reported. Smedley et al[18] found a significant reduction in minor complications (but not major complications) in the absence of significant differences in quality of life and fatigue scores between the groups studied. Manasek et al [34] also reported in abstract form clinical benefits favouring the ONS group (× 2.9 reduction in wound dehiscence, ×2.9 in anastomotic dehiscence, ×1.8 wound infection, and ×1.8 re-hospitalisation) without p-values).

(b) Cost-utility analysis

Cost-effectiveness analyses involving QALYs were reported in only two community studies, which recruited patients from hospital and evaluated the costs only after discharge from hospital. Further details are shown in Table 6. In one of the studies[13], the mean 'cost/QALY' (extra cost per QALY gained) was sufficiently low (€12,099 (high price ONS) or €9,497 (low price ONS)) and the shape of the cost-

effectiveness acceptability curve (CEAC) was such that the authors concluded that the intervention was cost effective (with an assumed threshold value of €50,000 there was about 90% probability that the intervention was cost effective, and with a threshold value of €20,000, the CEAC showed there was about 80% probability).The analysis of this economic 'pilot study' considered only the costs of the ONS. The much larger cost savings, due to the significantly reduced re-hospitalisation rates favoured the ONS group[27], were not included in the calculations.

In the other study involving older patients[44] the mean 'cost/QALY' in the main analysis, which involved multiple imputation for missing data, was €26,962, and for 'cost/unit' improvement in functional limitation was €618. On the assumption that in the Netherlands an investment of less than €20,000 is cost effective, the authors concluded that the intervention was cost effective in improving functional limitations but not in QALYs or physical activity.

Two other studies[18, 26] measured costs and quality of life but no cost-utility analyses were presented.

3.3. Outcomes: care homes

Five publications with economic results relevant to ONS administration in care homes[21-23, 29, 33] were identified, only one of which was a full text paper[29]. Since they differed widely in their designs and methodology, no attempt was made to produce summary statistics from meta-analyses of other types of analyses.

(a) Cost analysis

Of the four prospective care home cost-analyses reported in abstracts, two were based on RCTs [23, 29] and the other two on studies with a 'before and after' design[21, 22]. Those with 'before and after' designs involved 3 months of routine care followed by 3

months of intervention with ONS in care homes in England, the intervention being implementation of the 'MUST' framework, which included screening and use of ONS in those participants identified as malnourished. One of these studies[21] reported a significant reduction in the cost of hospitalisation in favour of the intervention (£599 over 3 months) but the calculations did not include the cost of ONS. The other study with a 'before and after design'[22] also included the cost of screening, management and monitoring of residents, reported a net cost saving of £187.91/resident over 3 months (£751.64 annually). Like the above studies, a cost saving in favour of the ONS group was also reported in the only retrospective cost analysis of care home residents using an economic model[32]. In comparison with no ONS, use of ONS for an unspecified period of time reduced total costs from €16,617 to €15,453 /resident (€1,164 /resident (7.0%)), but no details of the clinical studies underpinning the model or its assumptions were provided in the abstract. In contrast, a prospective cost analysis involving a RCT of care home residents identified as being malnourished using 'MUST'[23], reported that the overall costs including those of hospitalisation was greater in the ONS group than the dietary advice group (£376±214 v. £174±240 /patient over the 3 month period using an intention to treat analysis involving multiple imputation). The cost-effectiveness analysis of this study is reported below.

(b) Cost effectiveness analysis

Two cost-effectiveness analyses in care homes were identified, one from the USA[29] and the other in the UK[23], both of which were based on RCTs. The UK study (a cost-utility study), which established QALYs from a combination of mortality and quality of life using EQ-5D (EuroQol five dimension scale), found that ONS was cost effective compared to dietary advice. The incremental cost effectiveness ratio ('extra cost/QALY gained') was found to be £10,698 which was well below the reference

threshold of ~£25,000. In the USA study[29], in which 54% of care home residents had dementia, the incremental (above baseline measurements) between meal costs (extra costs for fluid, food and labour) were $0.03/patient/day for the control group receiving routine care, $2.10/patient/day for the ONS group, and $2.06/patient/day for the 'snack' group. The effectiveness outcome measure was total calories gained, which was reported to be greater in the snack group (paradoxically with the smallest weight gain; 0.04 kg) than the ONS group (with the largest weight gain; 2.04 kg). Given the willingness to pay is $0.04 for each extra kcal gained, the probability of 'benefit' (compared to the control group) was 80% for the snack group and 65% for the ONS group. Therefore, both forms of nutritional support had a 'beneficial' effect. The authors concluded that snacks may be more cost-effective at increasing energy intake than ONS, but they acknowledged that the sample size of their 'pilot study' was small. The composition of the between meal snacks was not reported, so cost effectiveness associated with the intake of other nutrients could not be assessed.

3.4. Assessment of risk of bias

The overall risk of bias of the included controlled trials and observational studies was judged to be at least moderate. The supplementary file 2 provides an assessment of individual studies based on economic criteria as well as criteria for randomised controlled trials and observational studies.

4. Discussion

This review of studies, mainly of randomised controlled clinical trials, suggests that the use of standard ONS in the community, with or without additional use in hospital, produces an overall net cost saving favouring the ONS group, or a near

neutral balance. These cost outcomes were associated with clinically relevant benefits such as improved quality of life, reduced infections, reduced minor post-operative complications, reduced falls, and functional limitations Indeed, most cost analyses based on full text papers (and all abstracts) favoured the ONS group even when considered in subgroups according to nutritional status and age, study design, duration of intervention and setting. This comprehensive review also emphasises the importance of involving specialists in the field, who identified many analyses from detailed national reports and other papers that were not retrieved from the electronic literature searches.

4.1. Community studies

The direct contribution of ONS to total expenditure in the community studies was found to be small, but their potential beneficial impact on the budget was large. For example, hospitalisation, which dominated the expenditure (Table 5), was significantly reduced by ONS (meta-analysis; Figure 3). Practical difficulties in prescription and reimbursement may arise if there are separate funding streams, so that the community absorbs the prescription costs while hospitals profit from a reduced workload resulting from fewer complications or fewer re-admissions. Furthermore, since various reimbursement schemes exist within and between care settings in different countries, which may affect access to ONS, a single budget that follows the patient may help overcome such problems[47].

Although this review is primarily concerned with ONS, the interventions sometimes included other components, such as dietary advice, additional vitamin D and calcium supplementation. This means that it is not always possible to ascribe all the benefits to ONS. Furthermore, it can be difficult to separate the contribution of

ONS provided in the community from that provided to the same patients in another setting e.g. started in the community pre-operatively and continued in hospital post-operatively or vice versa. A further point is the comparison of ONS v. no ONS which featured in most clinical studies (papers[13, 18, 27, 28, 35] ; abstracts[30-32]), and all but one of the economic modelling studies (abstract[24]). This may not represent the situation in real practice because ONS may already be given to some vulnerable and malnourished patients, although the extent varies by region, country, speciality and time. Furthermore, the costs associated with screening and assessment to identify the study population appear to have been largely ignored, despite their clinical and economic importance[48]. More sophisticated models could address the concerns of regulatory agencies and advisory bodies about possible inappropriate ONS prescriptions, and also the need to regularly monitor patients so that ONS are not administered for longer than is required[17]. Such bodies also recommend taking measures to ensure that malnourished subjects do not go unrecognised and untreated.

4.2 Care homes

It is difficult to evaluate the cost effectiveness of ONS at improving energy intake, from the only full text paper (a pilot study) examining the effects of between meal interventions[29]. This is partly because of potential methodological problems, including small sample sizes. Furthermore, the intake of a range of nutrients that were not evaluated, may be just as important clinically as energy intake. Four abstracts suggested favourable effects of ONS on costs and one on cost-effectiveness compared to simple dietary advice and QALYs gained as the effectiveness outcome measure. Until the full reports of these studies become available and the literature expanded with additional studies, it is difficult to come to robust conclusions.

4.3 General issues concerning community and care home studies

All the economic models based on retrospective cost analysis of a range of clinical data reported favourable cost outcomes in both community and care home settings, and several of these have been extrapolated to establish national cost savings, for example in models of people receiving standard ONS in the community[28] or community and hospital [35] in the Netherlands. Whilst such models can serve a very useful purpose, they also have limitations. None of the reviewed modelling studies appear to have established templates based on systematic reviews of clinical studies, raising the possibility of selection bias i.e. use of specific clinical studies with favourable outcomes. Among the other limitations were extrapolations from certain study populations to others (e.g. from one age group to another, from a population of malnourished and non-malnourished subjects to malnourished subjects alone) and for periods of ONS use that fell well outside the range specified in the models. In addition, the models used the national tariffs of the country they aimed to target, but often obtained the clinical data from other countries with different healthcare systems.

The limited data on actual and target ONS intake prevented a detailed assessment of compliance (estimated to be 34-100% in 3 studies). A separate systematic review[49] reported 37-100% ONS compliance (mean of 81% for community studies) but the extent to which this reflects study conditions rather than those operating in routine clinical care is uncertain. The same applies to the present systematic review.

A substantial part of the evidence base was established using only simple economic calculations or theoretical models lacking the robustness of prospective full economic analyses that incorporate costs of screening plus assessment and monitoring. Indeed, most results were established from a secondary analysis of papers

that were primarily undertaken to address non-economic issues. Among the reviewed clinical studies only one observational study was clearly identified in which the primary outcome was economic[19], and only a few [18, 26, 34] (probably including Neelemaat et al[14]) in which it was a secondary outcome. The potential overall risk of bias was judged to be at least moderate. The extent to which potential bias (including publication bias) of industry and non-industry funded projects may differ is difficult to assess without further information.

4.4. Future research

The reviewed studies, mainly based on retrospective analyses, generally suggest that economic and clinical effects favour the ONS group, but the economic evidence base in the community and care home settings needs strengthening through prospective studies with primary economic outcome measures and expansion of the range of population groups studied. The shortage of economic studies in care homes and the lack of studies in children need to be addressed. In addition, economic models need to be extended to take into account the benefits that may occur when ONS are compared to routine practice rather than no ONS, and also the extent to which they depend on the method of recruitment. For example, all three RCTs with prospective cost or cost-effectiveness analyses in the community (excluding surgical studies in which the study design was based on hospital admissions) involved recruitment from the hospital setting[13, 14, 26], generally after an acute illness or an acute stress. In one of these[14], ONS administration began in hospital[44], raising the possibility of a carry-over effect into the community. Although recruitment from hospital may be convenient, it does not represent the general population of malnourished subjects in the community, who account for the vast majority of malnourished individuals in society. The only

reviewed paper with a prospective cost-analysis with direct recruitment from the community was an observational study[19] which reported a non-significant cost advantage (€195/patient/year) in malnourished subjects registered with practices with high rather than low ONS prescriptions rates. In the meantime there is a clinical need to reduce the extent to which malnutrition goes undetected and untreated. The extent to which this can be achieved cost effectively by education and training, inspection and regulation, and incentivisation (e.g. by providing a bonus for high quality care and penalising inadequate care), requires investigations in the light of the type of healthcare system operating in different countries.

5. Conclusion

This systematic review with meta-analysis suggests that use of standard ONS in the community, with and without additional use in hospital, can produce favourable financial outcomes and can be cost effective. There is a need to embed appropriate nutritional support with ONS into routine clinical practice, and to undertake more high quality studies to further define the patient groups likely to benefit from appropriate amount and duration of ONS administration in different care settings.

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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 by commercial companies.

Table 1

Summary of inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	- Any setting in the community e.g. care home, free-living individuals, sheltered accommodation - Aged ≥ 1 year of age - Any nutritional status (well-nourished, malnourished or at risk of malnutrition)	- Animal studies - Pregnancy and lactation
Intervention	- Oral nutritional supplements (ONS) alone or with other oral nutrition interventions such as: - Dietary counselling (dietary advice) - Provision of special menus and/or snacks (e.g. energy/protein enriched) - Supplements containing vitamins and/or minerals only (single or multi-nutrient) - ONS in combination with enteral tube feeding	- Non-commercially available or home-prepared ONS - Studies including exercise as an intervention and sports studies - Disease-specific ONS[a] including "immunonutrition" [b] - ONS in combination with drug therapy such as anabolic hormones - Parenteral nutrition - Enteral tube feeding alone - Supplementation with vitamins and/or minerals only (single or multi-nutrient) used without ONS

	Inclusion criteria	Exclusion criteria
Comparison	- ONS v. no ONS - ONS + other nutrition intervention(s) v. other nutrition intervention(s) alone - ONS v. routine care (which may include some ONS) - ONS v. other nutrition intervention e.g. dietary advice	- ONS v another ONS
Publications	- Full text paper, abstracts and reports in the English Language	- Language other than English

[a] Disease-specific ONS include those with macro- and micronutrient compositions adapted to the needs of a specific disease and/or digestive or metabolic disorder (can be either nutritionally complete or incomplete).

[b] Immune modulating formulae contain substrates to modulate (enhance or attenuate) immune functions (also known as immunonutrition, immune-enhancing diets or pharmaconutrition, and typically include nutrients such as arginine, glutamine, omega-3 fatty acids and nucleotides)[50]

Table 2

Summary of net cost saving due to perioperative ONS administration in the community (± hospital) (data from BAPEN report[12])

Studies	N[a]	Method of calculation[b]						
		Bed-days			Excess bed-days	Complications		
		Average (£/patient)	Lower Quartile (£/patient)	Upper Quartile (£/patient)	Average (£/patient)	Average (£/patient)	Lower Quartile (£/patient)	Upper Quartile (£/patient)
Pre-operative (community)								
Smedley et al 2004[18]	85	440.6	350.8	521.2	190.9	13.3	1.3	25.2
MacFie et al 2000[36]	49	330.1	273.4	391.7	140.4			
Flynn et al 1987[38]	40	1113.1	583.7	1401.5	745.8			
Pre-operative (community) + post operative (hospital)								
Smedley et al 2004[18]	76	853.2	687.6	1002.0	392.2	113.4	81.5	145.3
MacFie et al 2000[36]	49	704.8	591.3	827.9	325.4			
Pre-operative (community) + post-operative (hospital & community)								

Studies	N[a]	Method of calculation[b]						
		Bed-days			Excess bed-days	Complications		
		Average (£/patient)	Lower Quartile (£/patient)	Upper Quartile (£/patient)	Average (£/patient)	Average (£/patient)	Lower Quartile (£/patient)	Upper Quartile (£/patient)
Smedley et al 2004[18]	76	899.2	733.6	1048.1	327.6	-79.5	-85.7	-73.3
Post-operative (hospital & community)								
Beattie et al 2000[37]	101	668.2	476.3	815.5	244.5	64.82	-8.9	96.5
Smedley et al 2004[18]	76	260.7	213.3	304.8	130.1	157.6	125.7	189.5

[a] N refers to the total number of subjects in the control and intervention groups.

[b] Both bed-day and excess bed-day costs are based on length of hospital stay. Excess bed-days relate to admissions with prolonged length of stay (above the Healthcare Resource Group trim point) and they are usually associated with lower costs than bed-day costs, as they generally involve basic care and hotel costs. Complication costs are calculated on the basis of the costs of complications only.

Table 3

Retrospective cost-analyses of community studies comparing ONS with control group[a]

Study[b]	N	Setting	Cost saving per subject in favour of ONS group[c]	Cost saving (% of control)[c]	Nutritional status	Age group	Type of study	Single- or multi-centre	Comparison	ONS use (months)
Smedley et al 2004[18]	85	C(pre-op)	£440.6 [b]	9.2	M + NM	<65 y	I	Multi	ONS v no ONS	<3 mo
MacFie et al 2000[36]	49	C(pre-op)	£330.1 [b]	7.3	M + NM	≥65 y[d]	I	Single	ONS v no ONS	<3 mo
Flynn et al 1987[38]	36	C(pre-op)	£1113.1 [b]	13.7	M	<65 y	I	Single	ONS v no ONS	<3 mo
Smedley et al 2004[18]	76	C(pre-op)H	£853.2 [b]	16.2	M + NM	<65 y	I	Multi	ONS v no ONS	<3 mo
MacFie et al 2000[36]	49	C(pre-op)H	£704.8 [b]	14.4	M + NM	<65 y[d]	I	Single	ONS v no ONS	<3 mo
Freijer & Nuijten 2010[35]	Model	C(pre-op)H	€252.0 [b]	7.6	M		I O	Multi	ONS v no ONS	<3 mo
Smedley et al 2004[18]	76	C(pre-op)HC (post-op)	£788.5 [b]	14.9	M + NM	<65 y	I	Multi	ONS v no ONS	<3 mo
Beattie et al 2000[37]	101	HC(post-op)	£668.2 [b]	8.5	M	<65 y	I	Single	Other[f]	<3 mo
Smedley et al 2000[18]	79	HC(post-op)	£260.7 [b]	4.9	M + NM	<65 y	I	Multi	ONS v no ONS	<3 mo
Neelemaat et al 2012[14]	184	HC(post-discharge)	- €403.0	-4.9	M	≥65 y	I	Single	Other	≥3 mo
Edington et al 2004[26]	100	C	-£1159.34 [b]	-54.0	M	≥65 y	I	Multi	Other	≥3 mo
Arnaud-Battandier et al 1999[19]	378	C	€195.0	7.2	M	≥65 y	O	Multi	Other	≥3 mo
Nuijten & Mittendorf 2012[27]	Model	C	€245.5	14.1	M	<65 y[e]	I	Multi	ONS v no ONS	≥3 mo

Study[b]	N	Setting	Cost saving per subject in favour of ONS group[c]	Cost saving (% of control)[c]	Nutritional status	Age group	Type of study	Single- or multi-centre	Comparison	ONS use (months)
Freijer et al 2012[28]	Model	C	€90.1	4.7	M	≥65 y	I	Multi	ONS v no ONS	≥3 mo
Hirsch et al 1993[39]	51	C	- (loss) [b]	loss	M + NM	<65 y	I	Single	ONS v no ONS	≥3 mo
Wilson et al 2001[40]	32	C	+ (saving) [b]	saving	M	<65 y	I	Multi	Other	≥3 mo

[a] Only full text papers and analyses of full text papers in reports are included.

[b] Details of the retrospective economic analyses can be found in the BAPEN report[12]

[c] Positive values indicate that the net balance favours the ONS group (lower cost in the ONS group than the comparison group) and the negative sign, the comparison group (higher cost in the ONS group than the comparison group)

[d] Based on average of the mean age of the groups involved

[e] largely based on study[41] in which the mean age was <65 years

H = Hospital; C = Community; pre-op = pre-operative; post-op = post-operative. The sequence indicates the order in which ONS was administered (e.g. HC = hospital first and then community); M = malnourished; NM = non-malnourished; I = interventional; O = observational

[f] ONS v routine care (which may include use of some ONS)

Table 4

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

	% cost-saving (continuous data)			Cost saving (binary data)	
	N analyses	Median (inter-quartile range)	P value[b]	N analyses favouring ONS/total N	P value[c]
< 65 years	8	13.9 (11.2)[d]	0.012	9/10	0.021
≥65 years	5	4.7 (36.7)	0.893	3/5	1.000
Malnourished	8	7.4 (14.1)	0.893	8/9	0. 039
Malnourished + non malnourished	6	8.9 (11.2)	0.263	6/7	0.125
ONS v no ONS	10	11.5 (7.8)	0.006	10/11	0.012
Other comparisons[d]	4	11.2 (49.9)	1.000	3/5	1.000
Interventional studies	12	8.9 (9.6)	0.050	11/14	0.057
Observational ± interventional	2	7.4 (0.4)	0.180	2/2	0.500
Single centre studies	5	8.5 (12.9)	0.080	4/6	0.688
Multi-centre studies	9	7.6 (9.7)	0.110	9/10	0.021
ONS use <3 months	9	9.2 (7.1)[d]	0.008[d]	9/9	0.004
ONS use ≥3 months	5	4.7 (40.1)	0.893	4/7	1.000
ONS community	7	7.3 (9.0)	0.237	7/9	0.180
ONS community + hospital	7	8.5 (10.0)	0.028	6/7	0.125

	% cost-saving (continuous data)			Cost saving (binary data)	
	N analyses	Median (inter-quartile range)	P value[b]	N analyses favouring ONS/total N	P value[c]
Modelling studies	3	7.59	0.109	3/3	0.250
Other studies	11	8.52 (9.5)	0.062	10/13	0.092

[a] Based on data presented in Table 3

[b] One sample Wilcoxon signed rank test of the difference between groups (against a test value of 0). All median values are positive indicating a cost saving in favour of the ONS group

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

[d] P <0.05 for < 65 years v >65 years and short-term v long-term (Mann Whitney U test)

Table 5

Contribution of ONS and the overall intervention to healthcare costs according to prospectively undertaken studies which included cost as an outcome variable

	Setting of ONS administration	Comparison	Duration of intervention (months)	Period of cost assessment (months)	Details of costs	% costs due to		% costs hospital	
						ONS	Intervention[a]	ONS group	Control group
Smedley et al 2004[18]	Community (pre-op), hospital	ONS v no ONS	~0.5	~1.7	Costs include staff time, consumables, ward costs, ward-based tasks e.g. wound dressing, urinary catheterisation[a].	~1	~1	>90	>90
Smedley et al 2004[18]	Community (pre-op), hospital and	ONS v no ONS	~1.75	~1.7	As above[b]	<5	<5	>85	>90

	Setting of ONS administration	Comparison	Duration of intervention (months)	Period of cost assessment (months)	Details of costs	% costs due to		% costs hospital	
						ONS	Intervention[a]	ONS group	Control group
	community (post-op)								
Smedley et al 2004[18]	Hospital, Community (post-op)	ONS v no ONS	~1.25	~1.7	As above[b]	<3	<3	>90	>90
Neelemaat et al 2012[14]	Hospital, Community	ONS + dietary advice + Ca/Vitamin D v routine care	Hospital stay + 3 months following discharge	3[c]	Direct healthcare costs (hospital admission, specialist visits), non-direct healthcare costs (complementary medicine, informal care) and indirect costs (absenteeism	≤6	6	69	73

	Setting of ONS administration	Comparison	Duration of intervention (months)	Period of cost assessment (months)	Details of costs	% costs due to		% costs hospital	
						ONS	Intervention[a]	ONS group	Control group
					paid and unpaid labour)				
Edington et al 2004[26]	Community	ONS v no ONS	3.1	6	Cost of GP consultations, district nurse visits, hospital admissions, outpatient appointment and costs of other social services	7-11[d] (<10)	7-11[c] (<10)	87	80
Arnaud-Battandier et al 2004[19]	Community	High ONS v low ONS prescribing GP practices	>3[e]	12	Hospital admissions, visits by GP, physiotherapist, and other specialists,	23	23	63	79

	Setting of ONS administration	Comparison	Duration of intervention (months)	Period of cost assessment (months)	Details of costs	% costs due to		% costs hospital	
						ONS	Intervention[a]	ONS group	Control group
					examinations and other costs.				

[a] In the case of Neelemaat et al 2012 the intervention included more than ONS (see column 3)

[b]The calculations of hospital cost were based on bed-day costs which included the cost of surgery (the original paper by Smedley et al[18] excluded the cost of surgery). The non-hospital costs were based on Smedley et al[18].

[c]Assessed during the 3 months after discharge from hospital

[d]Based on costs of supplements (£308.14) estimated from the BAPEN report [12]). The range allows for ±15% uncertainty for the cost of the supplements (in reality a mixture of supplements) as well as an apparent discrepancy between two sets of calculated total costs reported in the original paper.

[e]Since the cost for ONS was €565 per patient, an estimated duration of 3 months of ONS administration is likely to be a conservative estimate (€565 could have purchased a standard ONS (200mL(300 kcal/day) per day) for ≥6 months at the time of the study)

Table 6

Cost-effectiveness analyses in the community setting with quality adjusted life year (QALY) as the effectiveness measure

	Norman et al 2011[13]	Neelemaat et al 2012[14]
Country	Germany	Netherlands
Conditions (age of patients)	Benign gastrointestinal conditions (mean age 51 years)	Wide range of medical and surgical conditions (≥ 60 years; mean age 74.5 years)
Intervention	ONS + dietary counselling v dietary counselling	ONS, dietary counselling and vit D + calcium v routine care
Costs	Direct healthcare costs of supplement only	Direct healthcare costs + direct non-healthcare costs + indirect healthcare costs[a]
Quality of life tool	SF-36	EQ-5D
Average incremental cost effectiveness ratio:		
'Cost/QALY'[b]	€12,099 (high price ONS) €9,497 (low price ONS)	€26,962[c]
'Cost/unit' improvement in functional limitation (scale 0-6)		€618
'Cost/unit' improvement in physical activity (scale 0-6)		€4,470

[a] Direct healthcare costs accounted for 94.4% of the total costs in the intervention group and 94.6% in the control group.

[b] cost/QALY' = extra cost per QALY gained (Incremental cost effectiveness ratio). A negative sign indicates that there is an overall cost saving.

[c] The result shown is the main analysis involving intention to treat analysis for patients who did not die. Results were also calculated using complete case analysis (€13,581) and per protocol analysis (€314,808).

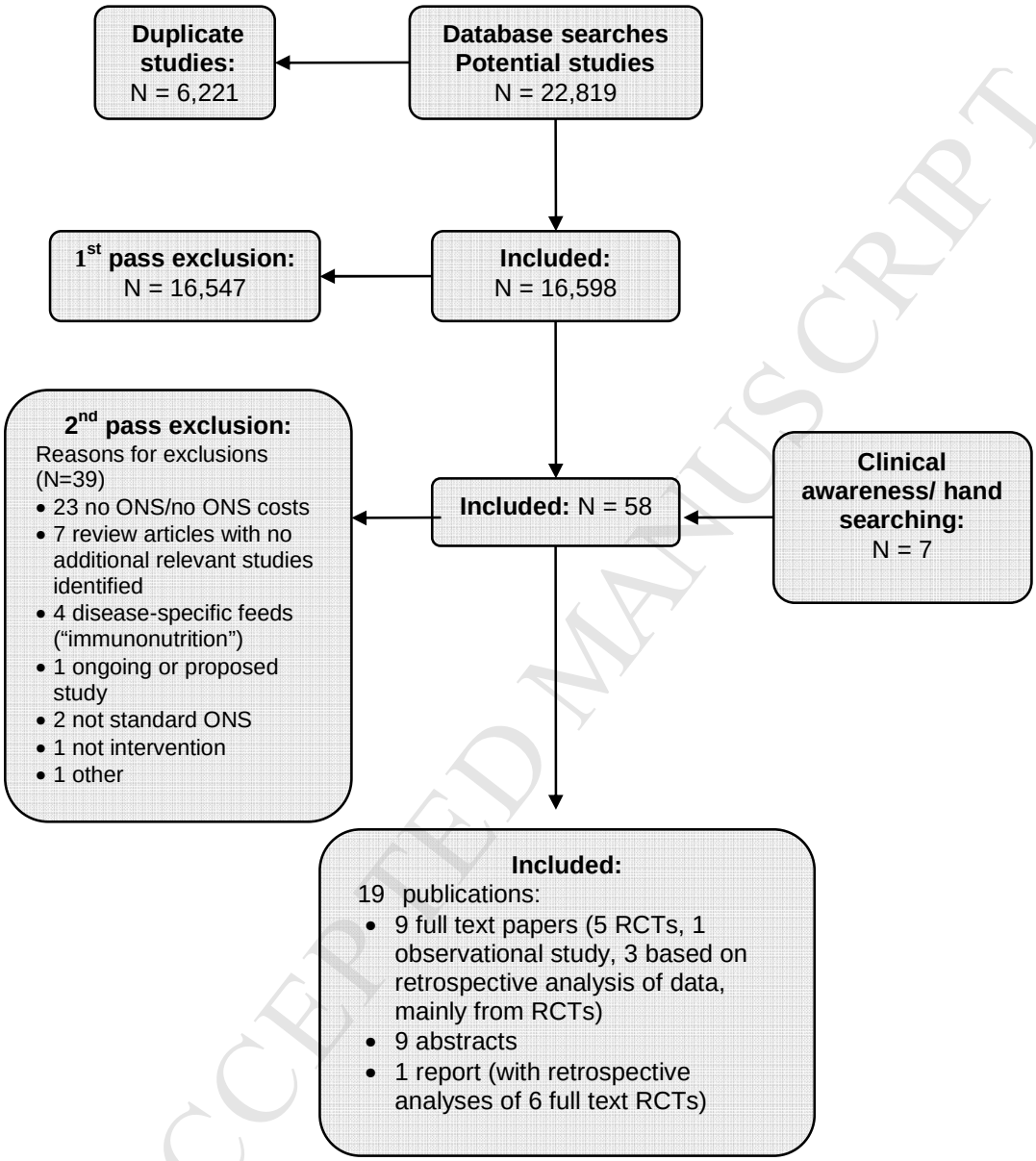

Figure 1. Flow diagram of publication included and excluded in the review (RCTs = randomised controlled trials)

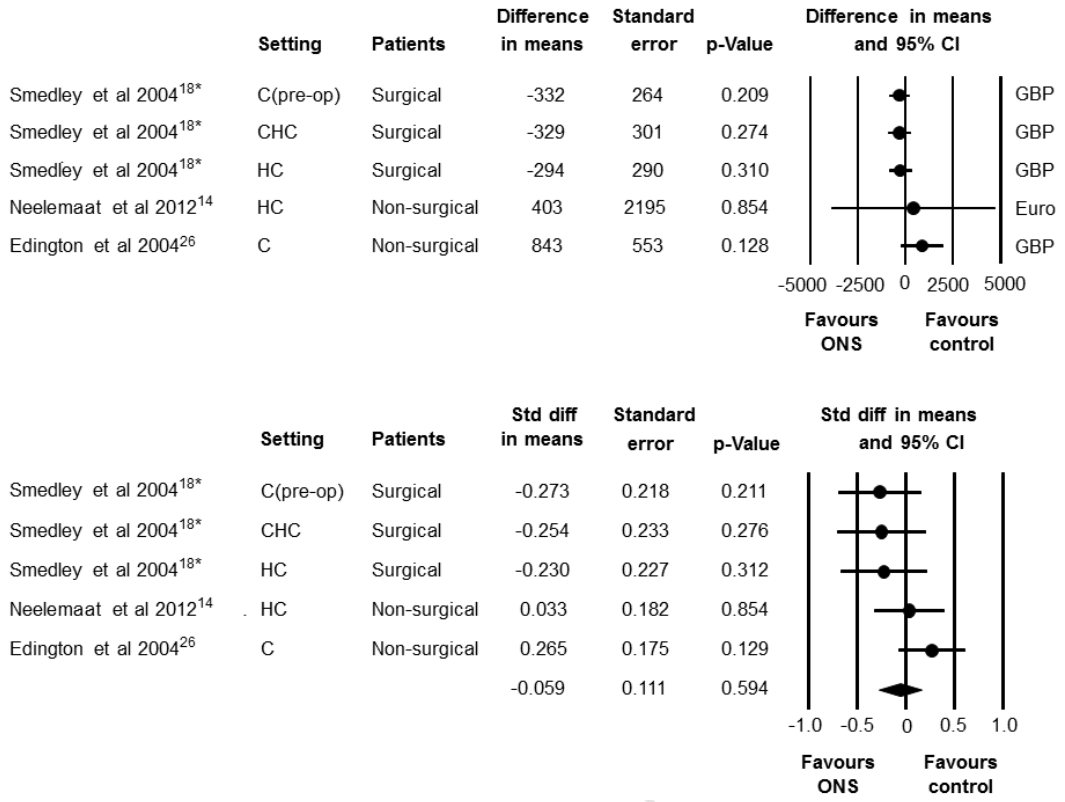

Figure 2. *Upper* Forest plot of absolute cost savings expressed in national currency units (GBP = British pound; Euro = European currency unit) *Lower* Standardised meta-analysis of costs in the ONS and comparison (control) groups based on RCTs. A negative value indicates a cost saving in favour of the ONS group. The setting of ONS administration is indicated (C = community; CHC = community followed by hospital and in the community again after discharge from hospital; HC = hospital followed by the community; C(pre-op) = preoperatively although it may have been continued for a short period in hospital before surgery). * Calculated using data presented in the BAPEN report[12].

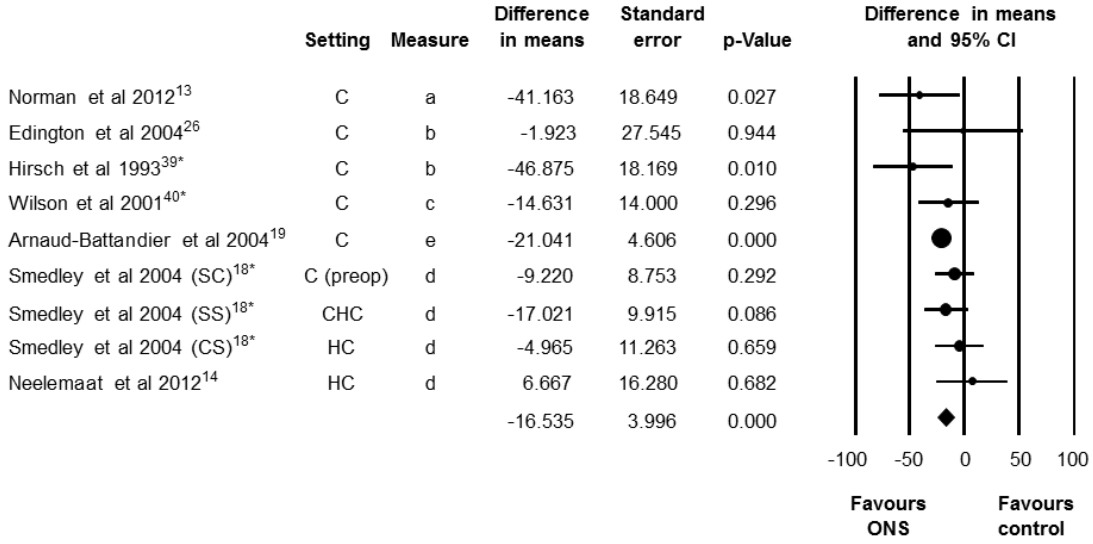

Figure 3. Meta-analysis of hospitalization in the ONS and comparison (control) groups based on RCTs. The results expressed as a percentage of control group (negative values indicate a cost saving in favour of the ONS group; C = community; CHC = community followed by hospital and in the community again after discharge from hospital; HC = hospital followed by the community; C(pre-op) = preoperatively although it may have been continued for a short period in hospital before surgery). a=proportion of patients admitted; b = N admission/patient; c = proportion of study period spent in hospital; d= bed-days/patient. * Calculated using data presented in the BAPEN report[12].

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Supplementary file 1 (Details of included studies and further meta-analyses)

A systematic review of the cost and cost effectiveness of using standard oral nutritional supplements in community and care home settings

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This supplementary file contains additional information on the included studies and on meta-analyses.

1 Details of included studies

1. 1 General features of included studies

Table 1 indicates the general study characteristics [1-23] (including abstracts[8, 15-18, 20-23], which are identified below) and the funding source..These studies were either single centre or multi-centre studies involving either malnourished (e.g. [3-5, 7, 9, 10, 12-14]) or a combination of malnourished and non-malnourished subjects (e.g. [1, 14, 19-22]). The BAPEN report included both single-[3, 4, 6] and multi-centre studies[1, 7] in which ONS is given in the community setting (± hospital). The intervention was generally targeted at specific patients, who were typically randomised to receive ONS or no ONS (patient level intervention), but in two care home studies (both reported as abstracts), it was targeted at the institution which were studied before and after implementation of policies that applied to all residents with a wide range of clinical conditions (institution level intervention) [20, 21].

1.1.1 Cost analysis

Nine publications involved administration of ONS in the community only (papers[10-14]; abstracts[15-18]), three in hospital and the community (papers,[5, 9] and abstract[8]) and one a combination of the above (a component in the community alone and other components in community and hospital)[1] (additional data in the BAPEN report from personal communication with the authors[24]). In those involving ONS, administration in both hospital

and community settings, the sequence of ONS administration varied (Table 1): in the community followed by hospital (surgical studies)[1, 2, 5]; in hospital and post discharge from hospital[1, 2, 9]; and before (community), during (hospital) and after (community) admission to hospital[1, 8]. Of the nine primary studies with prospective cost analyses (papers[1, 9, 11, 14, 19], abstracts[8, 20-22]) one was an observational study with a parallel design[14] and eight were interventional studies (six of which were RCTs (papers[1, 9, 11, 19]; abstracts[8, 22]) and two others with 'before and after' designs (abstracts[20, 21]). Most publications (papers[5, 10, 12, 13], abstracts[16-18, 20, 23]) reported retrospectively analysed data, including the BAPEN report [24], which undertook 10 cost analyses using data from six published papers of RCTs[1-4, 6, 7].

Only four studies with cost analyses involved care homes: an RCT[22], two studies with a before-and-after design (abstracts[20, 21]) and another based on modelling (abstract)[23].

Only two studies, reported as abstracts, appear to have considered the cost of both screening and assessment. One of these was a prospective care home study[21] and the other of a modelling study in the community[15](personal communication, A Cawood).

1.1.2 Cost-effectiveness analysis

Of the four prospective RCTs with cost-effectiveness analyses (papers [9, 10, 19], abstract[22]) one started with ONS in hospital and continued in the community[(12)], another in the community after recruitment from hospital[10], and the other two in care homes [19, 22]. Publications[5, 12, 13] in which the costs were not quantitatively related to specific effectiveness outcome measures were included in the 'cost-analysis' category.

1.2. Country

1.2.1. Cost analysis

Prospective cost analyses were undertaken in the UK (papers[1, 11] abstracts [21, 22]), the Netherlands[9], France[14], and the Czech Republic (abstract[8]). The BAPEN report[24] included retrospectively analysed studies from the UK, USA and Chile. The remaining publications

reported retrospective analyses based on costs and tariffs from specific countries (Netherlands (papers [5, 12],abstracts[16, 17]), Germany (papers[10, 12] abstracts[18, 23]), UK (abstract[15])), but modelling studies typically used clinical information gathered in other countries (full text papers[5, 12, 13]) or unspecified countries (all abstracts[15-18, 23]). Of 31 cost analyses, 16 were based on clinical data from the UK.

1.2.2 Cost-effectiveness analysis

The four cost-effectiveness analyses were based on studies undertaken in the Netherlands[9], Germany[25], USA (care home study[19]), and the UK (care home study reported only as an abstract[22]).

1. 3. Intervention v. alternative group

The following comparisons were made in community studies (± hospital): ONS v. no ONS (papers[1, 5, 10, 12, 13] and abstracts[16-18]); ONS plus dietary advice plus calcium/vitamin D v. routine care[9]; ONS plus dietary advice v. routine care[11]; and the cost of treating malnourished patients in high v. low ONS prescribing general practices[14]. Modelling studies depended on a range of previously published clinical data in which the comparison was ONS v. no ONS, with the exception of one which compared the group taking ONS with a range of alternative groups (standard care, placebo, dietary advice and/or normal diet; abstract[15]), to reflect the designs of clinical trials that underpinned the model. The BAPEN report included studies that made various types of comparisons: ONS v. no ONS[1]; ONS v. routine care [4]; ONS v. placebo capsules[6]; and ONS plus dietary advice v. routine care (dietary advice when needed)[7].

In the care home studies, the comparisons were as follows: ONS v. snacks taken between meals (plus a control group for further comparisons)[19];'Malnutrition Universal Screening Tool' ('MUST') framework of nutritional care which includes ONS v. routine care (abstracts[20, 21]); ONS v. dietary advice (abstract[22]); and ONS v. no ONS (abstract[23]).

1.4. The duration and amount of ONS prescribed

Cost analyses were based on short-term administration of ONS in the community (<3 months, and as short as 15 days) as well as long-term administration (≥3 months, and up to 8 months in some patient groups). The amount of ONS ingested ranged from 259-720 kcal/day depending on the study and setting. Some studies reported only the amount of ONS prescribed and several abstracts did not report either the amount or duration of prescription. Details are shown in Table1.

1.5. Primary and secondary outcomes

The only clinical study in the community, in which the primary outcome measure was a cost analysis, was a long-term observational study comparing the cost of treating malnourished patients at general practices with a history of high v. low rates of ONS prescriptions[14]. Another report suggested that the primary aim was a cost-effectiveness analysis[9], but this appears to be contradicted in other publications of the same RCT [9, 26, 27], including a thesis describing the overall design of the RCT which indicated that the primary outcome was a change in activities of daily living (also stated in one of the publications that reported sample size calculations based on functional status[26]). Another paper, which stated that it aimed to assess the cost-effectiveness analysis of ONS, was based on clinical data of a previously published clinical trial, which primarily aimed to investigate the effect of ONS on functional status and body composition[25]. In three community studies (papers [1, 11], abstract[8]) two of which had a hospital component[1, 8], a secondary outcome measure was a cost analysis.

Within the care home setting, one study did not make it clear if the cost-effectiveness analysis was the primary or secondary outcome measure[19]. It stated that it aimed to address three outcomes (total caloric intake, staff time required to implement the interventions, and cost effectiveness) without specifying the primary outcome measure and without undertaking sample size calculations on any of these outcomes. In another study, the secondary outcome

was a cost-effectiveness analysis (abstract[22]). Two other prospectively undertaken care home studies, reported only in abstract form, also provided some economic data[20, 21].

In abstracts of economic models in the community and care home settings, the primary outcome was a cost analysis established using national tariffs for specific countries and clinical data from various countries (papers[5, 12, 13]) or an unspecified source of clinical data (abstracts[15-18, 23]).

1.6. Sample size calculations

None of the publications included sample size calculations for costs or cost effectiveness.

2. Meta-analyses

Two sets of additional meta-analyses are presented below, one involving costs and the other hospitalisation.

2,1. Costs

In the main paper Figure 2 shows two forest plots of prospective cost analyses based on randomised controlled trials undertaken in the community (± in hospital). The upper forest plot was not linked to a meta-analysis because the costs from these studies, which were undertaken in different countries at different times, are reported in various national currency units. The lower forest plot shows the results expressed as standardised differences, which were amalgamated using a random effects meta-analysis to produce summary statistics (-0.059 (se 0.111); P = 0.594). A series of subgroup meta-analyses were also undertaken. The first of these, which involved three datasets from only one study[1] involving patients undergoing abdominal surgery who were given ONS in the community (± subsequently in hospital). The meta-analysis showed a net cost saving of borderline significance in favour of the ONS group, irrespective of whether the results were expressed in British pounds (£318.92 (se £163.69, P = 0.051 (3 datasets); I^2 = 0%, P = 0.995) or as standardised differences (-

0.253 (se 0.130), P = 0.053); I^2 = 0%, P = 0.003). The second of the meta-analyses involved the addition of another study in which ONS was given in both hospital and community (standardised difference, -0.127 (se 0.098), P = 0.193 (4 datasets); I^2 = 0%, P = 0.546). The third meta-analysis involved the addition of yet another study in which ONS was given to patients recently discharged from hospital[11] and resulted in the standardised difference becoming even smaller (-0.067 (se 0.096), P = 0.491 (5 datasets); I^2 = 14%, P = 0.322). Although all meta- analyses favoured the ONS group, none was significant.

2.2. Hospitalisation

The main paper reported that a series of meta-analysis involving 10 datasets from eight publications[1, 6, 7, 9-11, 14, 28] had been undertaken. The surgical study of Smedley et al[1] provided three datasets that compared a control group receiving no ONS with three groups receiving ONS in the community (± hospital); the first receiving ONS pre-operatively only; the second before, during and after hospitalisation; and the third during and after discharge from hospital.

When only the longer term studies of three or more months of ONS supplementation[6, 7, 9-11, 14] were included in the meta-analysis, hospitalisation was reduced as much as 20% in favour of the ONS group (point estimate 20.3% (se 6.4%), P=0.001; 6 datasets, N = 747 subjects; I^2 =26%, P = 0.239). When only the short-term (<3 months of ONS supplementation) surgical studies were included in the meta-analysis[1, 8] hospitalisation was also reduced in favour of the ONS group (12.9%, (se 4.9%), P = 0.008; 4 datasets, N = 383); I^2 = 0%, P = 0.716). And when only the surgical studies involving pre-operative ONS administration in community component are considered there was little change in the result (14.9%, (se 5.4%), P = 0.007; 5 datasets, N = 304); I^2 = 0%, P = 0.694).

A meta-analysis involving both long-term and short-term studies showed an overall reduction in hospitalization in favour of the ONS group by 17.3% (se 3.6%; P < 0.001; 10 datasets, N = 1140); I^2 = 3%, P =0.386), which changed little when the study of Arnaud-

Battandier et al[14], the only one that was not a RCT, was excluded (14.9%, (se 4.4%), P = 0.001; 9 datasets, N = 819 subjects); I^2 =7%, P = 0.380). And finally when only the full text papers are considered in the meta-analysis (this involved removing the study of Manasek et al[8], the only study reported in abstract form) the reduction in hospitalisation again favoured the ONS group (16.5%, (se 4.0), P = 0.001; 9 datasets, N = 1051 subjects); I^2 =16%, P = 0.307.

1 **Table 1**

2 Details of studies included in the review

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
Smedley et al 2004[1] (UK)	Cost analysis: prospective (not reported)	RCT	Gp l: Community (pre-op + Hospital + Community post-op) Gp 2: Community (pre-op) Gp 3: Hospital	*Ad-libitum* ONS encouraged	Gp 1: Pre-op: 536 kcals/day ; Post-op: 300 kcals/day (inpatient); 340 kcals/day (outpatie	Gp1: Pre-op- 14.5days; Post-op- 7 days inpatient - 4 weeks outpatient Gp2: Pre-op-	ONS v no ONS	Elective moderate/ major lower GI surgery (Gp 1: mean 55 (range 26-81) y; Gp 2: 61(23-84) y; Gp 3: 62 (22-83) y;	Well-nourished and malnourished (at risk defined by combination of BMI, history of weight loss and age; 33% at risk and 67% not at risk in each group)	179 (4 groups; 152 completed)	Numico (now Nutricia)

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
			(post-op + Community post-op)		nt) Gp 2: Pre-op: 542 kcals/day; Gp 3: Post-op: 258 kcals/day; (inpatient	15.1days Gp3: Post-op 8.7 days inpatient - 4 weeks outpatient Gp4: No ONS		Control:63 (25-88) y)			

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
					); 259 kcals/day ; (outpatient) Gp 4: No ONS						
BAPEN report[24]											
(i) MacFie et al 2000[2] (UK)	Cost analysis: retrospective (2003 prices	RCT (4 groups with pre- and post-op	Gp 1: Community (pre-op + Hospital) Gp	Minimum 500-600kcals/day, ONS intake	Gp 1: Pre-op: 484 kcals/day	Gp 1: Pre-op~15 days Post-op:	ONS v no ONS	Elective major GI surgery (Gp 1 (ONS pre- and	Well-nourished and malnourished BMI <19 kg/m^2: Gp 1: 4%; Gp 2:	73 (groups 1,2 and 4) (after 12% had	Not stated.

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
	in BAPEN report)	interventio n)	2:Commun ity (pre-op)	assessed by patient held diary.	; Post-op 268 kcals/day , (inpatient) Gp 2: Pre-op: 536 kcals/day ; Gp 3:	7-10 days (inpatient) Gp 2: Pre-op ~15 days Gp 3: ONS in hospital only Gp 4:		post-op) mean 63 (41-86) y; Gp 2 (ONS pre-op) 68 (23-84) y; Gp 4 (no ONS) 66 (23-86) y)	13%; Gp 4: 0%. ≥ 10% of recalled pre-illness BW in 6/12: Gp 1: 33%; Gp 2: 8%; Gp 4: 20%	operations cancelled or required urgent surgery)	

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
					ONS in hospital only Gp 4: No ONS	No ONS					
(ii) Flynn et al 1987[3] (US)	Cost analysis: retrospective (2003 prices in BAPEN report)	RCT	Community (pre-op)	Amount not stated but prescribed according to patient requirements;	Not stated	10-21 days	ONS + diet counselling v no ONS (diet counselling only)	Elective surgery for head and neck cancer (mean age 64 y)	Malnourished (<80% standard weight for height (insurance tables); body weight or loss 5% in 1 month	36	Not stated

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
									or 3 or more abnormal nutritionally-relevant blood tests		
(iii) Beattie et al 2000[4] (UK)	Cost analysis: retrospective (2003 prices in BAPEN report)	RCT	Hospital & Community	Encouraged to consume 600 kcals/day	Most patients consumed 300-600 kcal/day;	≤12 days and continued for 51 days after hospital discharge	ONS + routine care v (ONS not mentioned as being excluded)	Elective surgery (gastrointestinal & cardiovascular) (Age 18-80 y; ONS Gp: 54.4 (sd	Malnourished BMI <18 kg/m^2 or BMI <20 kg/m^2 and/or <15% upper arm anthropometry and/or ≥5% weight loss from	109 (101 completed)	Study funded and supported by Abbott Laboratories

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
								19.4) y v control 62.4 (sd 10.9) y; P <0.05)	admission to 8th post-op day)		
Freijer & Nuijten 2010[5] (NL)	Cost analysis: retrospective model using previously published	Modelling study based on observational and interventional data	Community & hospital	Assumed that 600kcal/day was prescribed;	Actual intake not stated (modelling study)	17 days (8.5 days before surgery and 8.5 days after surgery).	ONS v no ONS	Abdominal surgery	Malnourished Source data involved 'MUST' and other criteria	160,283 abdominal procedures per annum	Funded by the Association of Dutch Infant and Dietetic Food

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
	data) (2008 – inflated from 2004 prices)										Industries (VNFKD)
Community studies											
BAPEN report[24]											
(iv) Hirsch et al 1993[6] (CL)	Cost analysis: retrospective (2003 prices in BAPEN report)	RCT	Community	Instructed to consume 1000kcal/day.	Actual intake not stated	3.2-8 months	ONS v no ONS (placebo capsule)	Decompensated alcoholic liver disease (ONS 49.9 (sd 8.7) y, control 46.0 (sd 8.0) y)	No restrictions according to protein energy-energy status	51	Not stated

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
(iv) Wilson et al 2001[7] (US)	Cost analysis: retrospective (2003 prices in BAPEN report)	RCT	Community	250-500 kcal prescribed;	Actual intake not stated	Up to 6 months but not for those who became replete at 2 months (28%)	ONS + dietary advice v routine care (dietary advice when needed)	Chronic kidney disease (haemodialysis) (ONS 64 (sd 8.6) y, Comparison 68 (sd 10.5) y)	'Malnourished' (hypoalbuminaemia 25-34 g/L)	32	Assistance and support from Nestlé Clinical Nutrition
Manasek et al 2013[8] (Abst)	Cost analysis: prospective (not	RCT	Community (pre-op), Hospital and	600 kcal/day prescribed	Actual intake not stated	10 days pre-op and 2 weeks	ONS v conventional care	Abdominal surgery (colorectal cancer) (18-	Malnourished and non-malnourished	143 (37 ONS, 106 control)	One of the authors, employee of Nutricia

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
(CR)	reported)		Community (post-op)			post-op (length of hospital stay 9.6 days)		80 y; mean 64 y)			
Neelemat et al 2012[9] (NL)	Cost analysis and CEA (ICER: 'cost/ QALY', 'cost/unit functional disability'	RCT	Hospital and Community	Expected to increase intake by 600 kcal/day	80% adherence to oral nutritional support	3 months after hospital discharge (but started on admission to	ONS, dietary counselling , vitamin D + calcium v routine care	Elderly patients, mixed conditions (Gp with ONS, 74.6 (sd 9.7) y;	Malnourished (BMI<20 and or >5% unintentional weight loss in last month or >10% in last 6 months)	210	The Netherlands Organisation for Health Research and

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
	and 'cost/unit physical activity'): prospective (2008)					hospital)		control, 74.4 (sd 9.3)y)			Development
Norman et al 2011[10] (DE)	CEA (ICER: 'Cost/QALY'): retrospective (2008)	RCT	Community (post discharge from hospital)	900 kcal/day	~720 kcal/day intake	3months	ONS + dietary counselling v dietary counselling	Benign GI conditions (ONS, 50.6 (sd15.3) y; control, 50.9 (sd 15.9) y)	Malnourished (SGA grade B or C)	114	Financially supported by Fresenius Kabi

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
Edington et al 2004[11] (UK)	Cost analysis: prospective (2000)	RCT	Community (post discharge from Hospital)	600-1000 kcal/day)	342 kcal/day;	99 days	ONS + dietary advice v control (standard care, no ONS)	Elderly patients, mixed conditions (ONS 76.8 (sd 5.3) y; control 79.3 (sd 8.0) y)	Malnourished BMI <20, or 20 to<25 kg/m^2, with weight loss ≥10% in last 6 months or ≥5% in last 3 months	100	Study funded by Abbott Nutrition. Some of the authors, employees of Abbott Laboratories
Nuijten & Mittendo	Cost analysis: retrospectiv	RCT (Norman et al 2008)	Community	Cost based on 600 kcal/day;	Actual amount not stated	3 months (with sensitivity	ONS v no ONS	Clinical data largely based on data	Malnourished or at risk of malnutrition	RCT (80 analysed) extrapolat	Supported by unrestricte

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
rf 2012[12] (DE)	e (2007 prices for ONS)				(modelling study)	analysis performed on range of 2 and 4 months)		obtained from patients with benign GI disease/acute illness (Norman et al 2008)[25]	(SGA in RCT by Norman et al 2008)[25]	ed to national populations	d grant from Nutricia GmbH, Germany
Friejer, Nuijten & Schols 2012[13] (NL)	Cost analysis: retrospective model using	Modelling study based on observational and	Community	600 kcal/day prescribed	Actual amount not stated (modelling study)	3 months	ONS v no ONS	Elderly >65 years		720,223	Not stated (one author (KF) employee of

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
	previously published data (2009)	interventional data)									Nutricia)
Arnaud-Battandier et al 2004[14] (FR)	Cost analysis: prospective (2000)	Observational study (of high and low prescribing general practices)	Community (patients in own homes and care homes)	Amount not stated	Actual amount not stated	costs of €565/patient suggests >3 months)	High frequency of ONS prescription v low frequency of ONS prescription	Elderly (infrequent ONS, mean 85.2 y; frequent ONS 85.0 y)	Malnourished (MNA <17 57%) and at risk of malnutrition (MNA <23.5 43%)	378	Nestlé Clinical Nutrition (part funding)
Cawood, Green &	Cost analysis:	Modelling study	Community	2 units/day (600	Actual amount	2 months	ONS v combination	Multiple conditions	Treatment of malnutrition	Model	All authors employees

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
Stratton 2010[15] (Abst) Model for UK (clinical data established in several countries)	retrospective model using previously published data (2009/10)	based on interventional data		kcal/day);	not stated (modelling study)		of alternative groups (no ONS, standard care, placebo, dietary advice, and/or normal diet)		according to 'MUST'		of Nutricia
Freyer &	Cost	Modelling	Communit	Amount	Actual	Duration	ONS v no	Not stated	Malnutrition	Model	One of the

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
Nuijten 2010[16] (Abst) (Model for the NL)	analysis: retrospective model using previously published data (2009)	study based on clinical trials and published literature	y	not reported	mount not stated (modelling study)	not reported	ONS		(criteria not specified)		authors (KF), employee of Nutricia
Nuijten & Freijer 2010[17] (Abst) (Model for the	Cost analysis: retrospective model using previously	Modelling study based on clinical trials and published	Community	Amount not reported	Actual amount not stated (modelling study)	Duration not reported	ONS v no ONS	Not stated	Malnutrition (criteria not specified)	Model	One of the authors (KF), employee of Nutricia

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
NL)	published data (2009)	literature									
Nuijten & Freijer 2010[18] (Abst) (Model for DE)	Cost-analysis: retrospective model using previously published data (2009)	Modelling study based on clinical trials and published literature	Community (ambulatory setting)	Amount not reported	Actual amount not stated (modelling study)	Duration not reported	ONS v no ONS	Not stated	Malnutrition (criteria not specified)	Model	One of the authors (KF), employee of Nutricia
Care home studies											

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
Simmons et al 2010[19] (US)	CEA (ICER: 'Cost/kcal gained'): prospective (2006)	RCT	Long-term care facilities (2 nursing homes and 1 Veteran Affairs facility)	Amount not stated	324 kcal/day (weekly mean) or 391 kcal/day (post intervention mean)	5 days per week for 6 weeks	ONS v snacks v control (usual care)	Elderly, 54% with dementia; (mean MMSE 14.12 (sd 8.88)) (86.86 (sd 11.26) y)	Malnourished (24% BMI <20kg/m^2) and well nourished	63	National Alzheimer's Association and National Institute of Aging
Cawood et al 2009 [20] (Abst)	Cost analysis: prospective (not	Interventional study (care home level) with	Care home	Amount not reported	Amount not stated	3 months	Before v after implementation of	Elderly (median 86 (37-105)y)	Treatment of malnutrition according to 'MUST'	208	Some authors, employees of Nutricia

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
(UK)	reported)	a before and after design					'MUST' Framework (including use of ONS for high risk patients)				
Baggaley et al 2013[21] (Abst) (UK)	Cost analysis: prospective (2011)	Interventional study (care home level) with a before and after design	Care home	Amount not reported	Amount not stated	3 months	Before v after implement-ation of 'MUST' Framework (including	Multiple conditions in care homes (83 (sd 9) y)	Treatment of malnutrition according to 'MUST'	132	Some authors, employees of Nutricia

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
							use of ONS for high risk patients)				
Parsons et al 2012[22] (Abst) (UK)	CEA (ICER: 'Cost/QALY'): prospective (2006/09)	RCT	Care home	Amount not stated	333 kcal/day intake	3 months	ONS v dietary advice	Elderly (88 (sd 8) y)	Malnourished ('MUST' medium + high risk)	104	Nutricia (unrestricted educational grant)
Nuijten & Freyer 2010[23] (Abst) (Model	Cost analysis: retrospective - model using	Modelling study based on clinical trials and	Care home	Amount not stated	Actual amount not stated (modelling study)	Duration not reported	ONS v no ONS	Not stated	Malnutrition (criteria not specified)	Model	One of the authors (KF), employee of Nutricia

Authors (Country)	Type of economic analysis[a] (year of prices)	Type of study	Setting	Target amount of ONS	Actual amount of ONS used	Duration of ONS use	Comparison	General subject characteristics (age in years (y))	Nutritional status (method)	Sample size[b]	Funding / support
for DE)	previously published data (2009)	published literature									

UK = United Kingdom; US = United States; NL = Netherlands; CL = Chile; CR = Czech Republic; DE = Germany; FR = France; RCT = randomised controlled trial; Gp = group; ONS = oral nutritional supplement; BMI = body mass index; BAPEN= British Association for Enteral and Parenteral Nutrition; BW = body weight; 'MUST' = 'Malnutrition Universal Screening Tool'; CEA = cost-effectiveness analysis; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; GI = gastrointestinal; SGA = Subjective Global Assessment; MNA = Mini Nutritional Assessment; MMSE = Mini Mental State Examination; Abst = abstract

[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.

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Supplementary file 2 (Assessment of the risk of bias)

A systematic review of the cost and cost effectiveness of using standard oral nutritional supplements in community and care home settings

M. Elia, C. Normand, K Norman, A Laviano

This supplementary file contains additional information on the risk of bias associated with the papers included in the review.

Table 1 shows a summary of the assessment of the quality of RCTs (based on Cochrane Handbook for Systematic reviews of Interventions[1]) and Table 2 the quality of studies with economic data (based on the criteria provided by Drummond et al[2]). Since the RCT and economic criteria differ and since the same study may score very differently depending on the type of criteria used, specific economic and non-economic criteria were applied to individual as well as groups of studies to enable an overall judgement on the risk of bias to be made. A narrative discussion of the potential risk of bias is provided in the text below as well as in the main paper including the limitations of assumptions used in modelling studies, which may be based on a combination of economic outcomes and clinical outcomes derived from both RCTs and observational studies).

Overall, the potential risk of bias among most reviewed studies was considered to be medium. The method of randomisation was not stated in several studies, and blinding not stated to have been undertaken, although in one study the investigators were blinded to certain aspects of the trial[3]. There were two RCTs with no dropouts, another with 2% dropouts, and the remaining 10 RCTs with 6-42% dropouts. One study indicated that it used intention to treat analysis using unstated methodology[4] and another using multiple imputation[3], although the calculations did not include those who died, despite the influence of death on cost-effectiveness (cost-utility) analyses involving QALYs. In a few RCTs there were significant baseline imbalances in subject

characteristics[5-7] that were not adjusted for using statistical analyses. The single observational study[8] (not included in Table 8 of RCTs) was considered potentially to be subject to at least moderate or high risk of bias, according to the STROBE criteria[9]. The reasons for dropouts/excluded subjects were not reported. A follow up rate of 74% of patients was reported in three districts and only 41% from another district (n= 59 patients), the latter being excluded from the analysis because the investigators felt that the data were of poor quality. The study also excluded outliers with unusually high costs, and also costs associated with medical care utilisation were not considered to be directly related to malnutrition (including falls), in an attempt to reduce variability. The two groups in this study also differed significantly in certain baseline characteristics, such as housing status, nutritional status, nutrition-related morbidities and prescription of drugs affecting gastrointestinal function, but attempts were made to adjust for baseline differences in the regression analysis using the propensity score method.

The only full text paper of a pilot study involving care home residents[10] was also considered to be at potentially substantial risk of bias. In the presence of a 27% dropout rate, and a highly significant baseline imbalance between the control group and the two intervention groups in the between meal costs, an intention to treat analysis with statistical adjustments was not undertaken. The dietary intake methodology, the main outcome measure, may also be potentially at risk of some bias, since 56% of residents had a measured intake that was below their estimated resting energy needs (implying that the mean reported energy intake would fall well below their estimated total energy needs) but their weight tended to increase rather than decrease.

The studies reporting economic outcomes in the primary papers generally met most of the criteria listed in Table 2 (see footnotes for adaptations), although some deficiencies were identified.

Table 1

Quality assessment of randomised controlled trials 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[6]	Yes Stratification by nutritional status	Sealed envelopes	None stated	N/A	Yes (15%)	No	Yes with the exception of BMI which was lower in control group than the group that received ONS pre- and post-operatively
Neelemaat et al 2012[3]	Yes	Computer random number generation and	Primary investigator of the analyses was	Unclear	Limited (17% excluding deaths)	No (not according to originally designated group; multiple	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]
		use of opaque envelopes	not aware of patient group allocation			imputation used only for those who survived)	
Norman et al 2011[11]	Yes	Computer generated randomisation kept by co-worker not involved in the study	None stated	N/A	Yes (25%)	No (not according to originally designated group)	Yes
Edington et al 2004[4]	Yes	Envelopes prepared by statistician	No (Open label trial)	N/A	Yes (42%) but not for separate groups	Yes	Yes
BAPEN report[12d]							

	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]
a) Hirsch et al 1993[7]	Yes	Not stated	None stated	N/A	Yes (22%)	No	Yes, including liver function, but renal function was significantly worse in the control group
b) Wilson et al 2001[13]	Yes	Not stated	None stated	N/A	(0%)	N/A	Yes (experimental v control group)
c) MacFie et al 2000[14]	Yes, with double randomisation, one before surgery for pre-operative ONS + diet or diet alone, and the other after surgery for post-operative ONS + diet or	Not stated	None stated	N/A	Yes (7%, all before surgery)	No (but N/A if only post-operative 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]
	diet alone.						
d) Beattie et al 2000[5]	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
e) Flynn et al 1987[15]	Yes	Random assignment carried out by a dietitian independent of medical evaluation	None stated	N/A	(0%)	N/A	No baseline information on randomised groups

	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]
Simmons et al 2010[10]	Yes	Not stated	None stated	N/A	No (27%; but unclear if this includes deaths)	No	Yes

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 those studies in which baseline imbalance was found, no statistical adjustments were made

[d]The BAPEN report includes Smedley et al[6], which is listed above

Table 2

Check-list for assessing economic evaluations (adapted from Drummond et al 2005)[2]

Checklist[a,b,c,d,e,f]	Cost-effectiveness analysis			Cost analysis			
	Neelemaat et al 2012[3]	Norman et al 2011[11]	Simmons et al 2010[10]	Edington et al 2004[4]	Nuijten & Mittendorf 2012[16]	Freijer et al 2012[17]	Arnaud-Battandier et al 2004[8]
1 Was a well-defined question posed in answerable form?	√	√	√ 2/3 (i,ii)	√	√	√	√
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?)	√	x	√	√	√	√	√
3.[b] Was the effectiveness of the programmes or services established and consequences for each alternative identified?	√[g]	√2/3[g] (i;iii)	√ 2/3[g] (i,iii)	√	√ 1/3[g] (iii)	√ 1/3 (iii)	√ 1/3[g] (iii)

Checklist[a,b,c,d,e,f]	Cost-effectiveness analysis			Cost analysis			
	Neelemaat et al 2012[3]	Norman et al 2011[11]	Simmons et al 2010[10]	Edington et al 2004[4]	Nuijten & Mittendorf 2012[16]	Freijer et al 2012[17]	Arnaud-Battandier et al 2004[8]
4.[c] Were all the important and relevant costs and consequences for each alternative identified?[h]	√	x[i]	√	√	√	√	√
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)?	√	√	√	√	√	√	√
6. Were costs and consequences valued credibly?	√	√ 3/4(i,ii,iv[j] ; iii N/A)	√2/4 (i,iv)	√	√	√3/4 (i,ii,iii; iv N/A)	√ 2/4 (i,ii; iii N/A)

Checklist[a,b,c,d,e,f]	Cost-effectiveness analysis			Cost analysis			
	Neelemaat et al 2012[3]	Norman et al 2011[11]	Simmons et al 2010[10]	Edington et al 2004[4]	Nuijten & Mittendorf 2012[16]	Freijer et al 2012[17]	Arnaud-Battandier et al 2004[8]
7. Were costs and consequences adjusted for differential timing?	N/A	N/A	N/A	N/A	N/A	N/A	N/A
8. Was an incremental analysis of costs and consequences of alternatives performed?	√	√	√	N/A	√	√	√
9.[e] Was allowance made for uncertainty in the estimates of costs and consequences?	√	√	√ 2/3 (i;iii)	√ 1/3(i; ii N/A)	√ 2/3 (i N/A)	√ 2/3 (ii,iii;i N/A)	√ 1/3 (iii)
10.[f] Did the presentation and discussion of study results include all issues of concern to users?	√	√ (i[i])	√ 4/5 (i,ii,iv,v)	√ 3/5 (ii-iv;i N/A)	√ 1/5 (i)	√ 3/5 (i,ii,iv)	√ 2/5 (ii,v)

1 N/A = not applicable.

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

[g] Search strategy for systematic review considered not relevant

[h] Q4 (iii) capital costs considered not relevant

[i] Only cost considered was that of the ONS (authors state this was because the study was a pilot study).

√ 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 and the Arabic numbers refer to the proportion of questions that were adequately fulfilled on that topic (e.g. 1/3 (iii) indicates that only one (item iii) out of three questions was adequately fulfilled).

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] (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?

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