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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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SUMMARY

Background & 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.

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 from illness, more complications and increased dependency on others, but also to the services and the public providing health and social care support. Whilst the

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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 is 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 1947–2014 week 13) and Medline (1946–2014 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 Fig. 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 over time and between different European Union countries), two procedures were undertaken: a forest plot was presented along with the statistics for each study, but without a

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
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) [20].

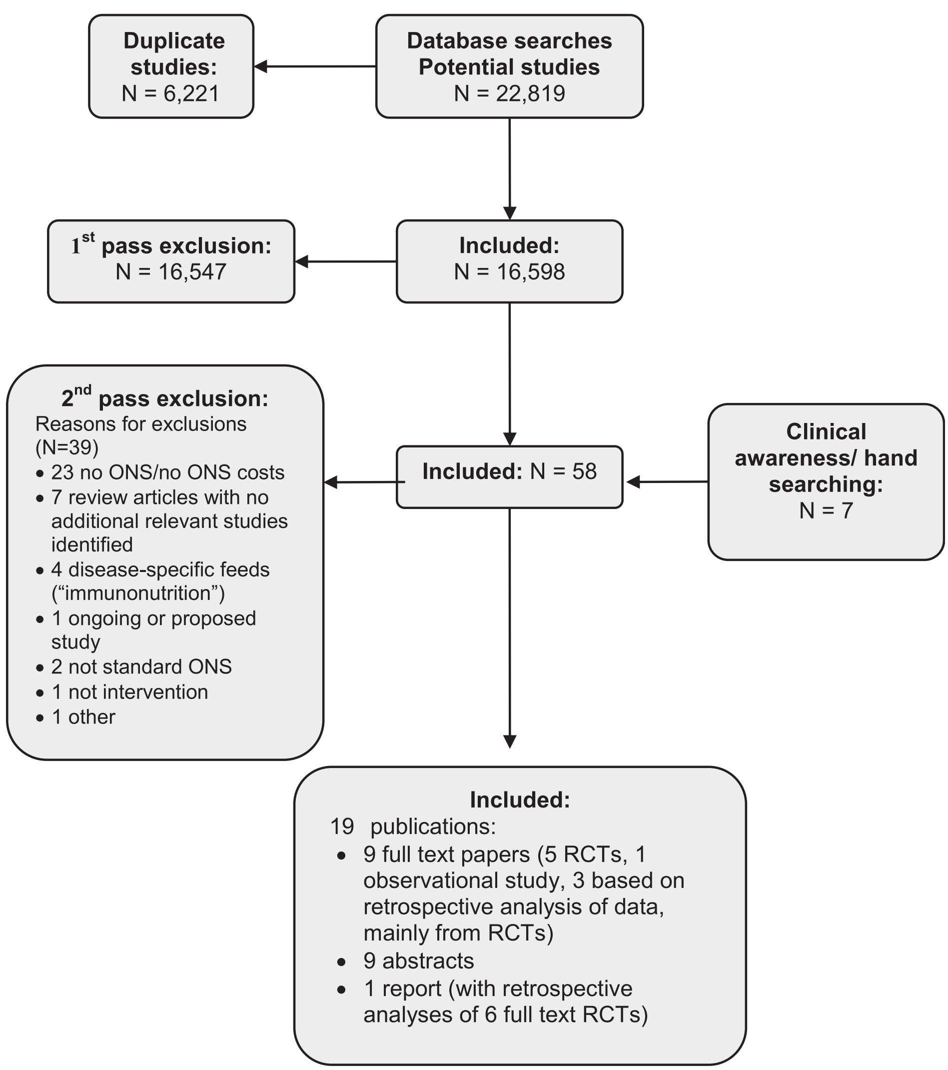

Fig. 1. Flow diagram of publications included and excluded in the review (RCTs = randomised controlled trials).

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. Fig. 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 discharge from 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 individual countries, and clinical data from various countries (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), and unclear 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 ($\geq$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

3.2.1.1. 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 savings are consistent with those established by the BAPEN group using different

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)								
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.

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 ($2298/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 length of stay (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].

3.2.1.2. Amalgamated studies. Subject level analyses (based on meta-analysis of studies comparing mean ± sd between groups): Fig. 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.

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

3.2.1.3. 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

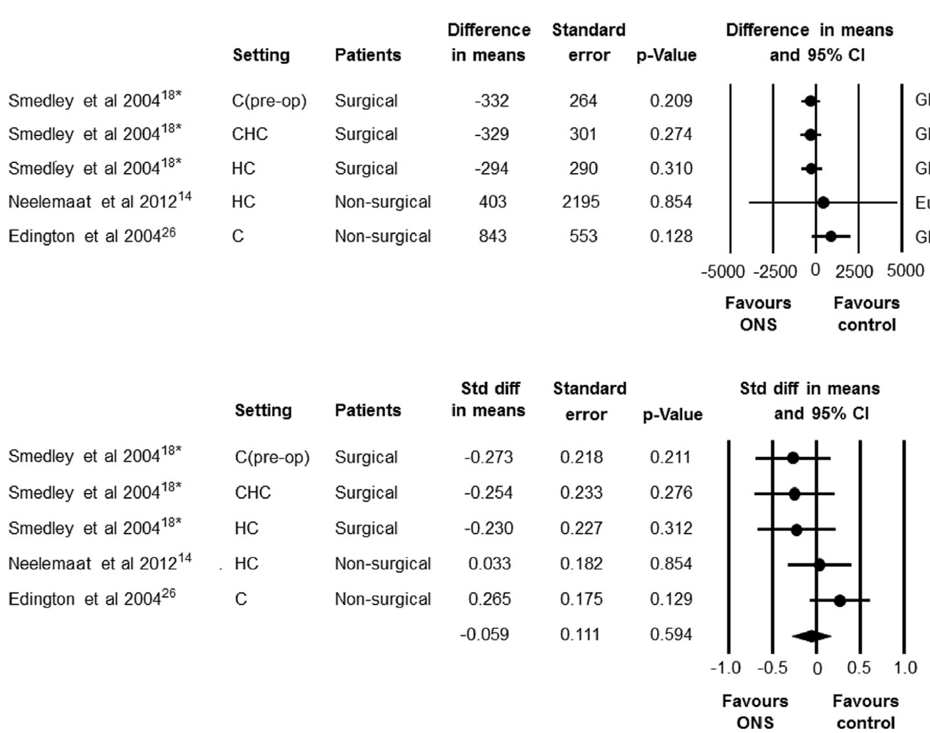

Fig. 2. *Upper* Forest plot of absolute cost savings expressed in national currency units (GBP = British pound; Euro = European currency unit) *Lower* Standardised meta-analysis of costs in the ONS and comparison (control) groups based on RCTs. A negative value indicates a cost saving in favour of the 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].

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
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

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

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.

3.2.2.1. 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:

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
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 community (post-op)	ONS v no ONS	~1.75	~1.7	As above[b]	<5	<5	>85	>90
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 paid and unpaid labour)	≤6	6	69	73
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[d](<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, examinations and other costs.	23	23	63	79

[a] In the case of Neelemaat et al., 2012 the intervention included more than ONS (see column 3).
[b] The calculations of hospital costs 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 (200 ml (300 kcal/day) per day) for ≥6 months at the time of the study).

	Setting	Measure	Difference in means	Standard error	p-Value
Norman et al 2012[13]	C	a	-41.163	18.649	0.027
Edington et al 2004[26]	C	b	-1.923	27.545	0.944
Hirsch et al 1993[39*]	C	b	-46.875	18.169	0.010
Wilson et al 2001[40*]	C	c	-14.631	14.000	0.296
Arnaud-Battandier et al 2004[19]	C	e	-21.041	4.606	0.000
Smedley et al 2004 (SC)[18*]	C (preop)	d	-9.220	8.753	0.292
Smedley et al 2004 (SS)[18*]	CHC	d	-17.021	9.915	0.086
Smedley et al 2004 (CS)[18*]	HC	d	-4.965	11.263	0.659
Neelemaat et al 2012[14]	HC	d	6.667	16.280	0.682
			-16.535	3.996	0.000

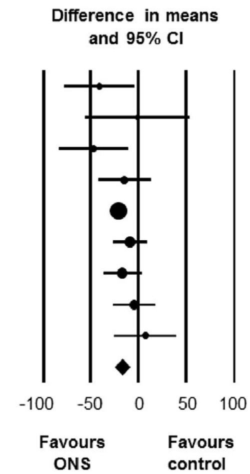

Fig. 3. Meta-analysis of hospitalisation in the ONS and comparison (control) groups based on RCTs. The results expressed as a percentage of control group (negative values indicate a cost saving in favour of the ONS group; C = community; CHC = community followed by hospital and in the community again 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].

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) (Fig. 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 with no deaths in two 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 0–6, 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 (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 post operative 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.

3.2.2.2. 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

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) €9497 (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)		€4470

[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).
[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).

gained) was sufficiently low (€12,099 (high price ONS) or €9497 (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 in the ONS group, 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 these differed widely in their designs and methodology, no attempt was made to produce summary statistics from meta-analyses of other types of analyses.

3.3.1. 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, and it 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 [33]. In comparison with no ONS, use of ONS for an unspecified period of time reduced total costs from €16,617 to €15,453/resident (€1164/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, were 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.

3.3.2. 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; Fig. 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 remain 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 a penalty for 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.

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.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2015.07.012.

References

[1] Elia M, Russell CA. Combating malnutrition: recommendations for action. A report from the advisory group on malnutrition, led by BAPEN. 2009. London. Report No.: 978 1 899467 36 5, http://www.bapen.org.uk/professionals/publications-and-resources/bapen-reports/combating-malnutrition-recommendations-for-action.
[2] Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL. The biology of human starvation. Minneapolis, MN: University of Minnesota Press; 1950. p. 81–535.
[3] Stratton RJ, Green CJ, Elia M. Disease-related malnutrition. An evidence-based approach to treatment. Oxford: CABI Publishing (CAB International); 2003.
[4] Stratton RJ, Elia M. A review of reviews: a new look at the evidence for oral nutritional supplements in clinical practice. Clin Nutr Suppl 2007;2:5–23.
[5] Cawood AL, Elia M, Stratton RJ. Systematic review and meta-analysis of the effects of high protein oral nutritional supplements. Ageing Res Rev 2012;11(2):278–96.
[6] Parsons EL, Stratton RJ, Elia M. Systematic review of the effects of oral nutritional supplements in care homes. Proc Nutr Soc 2010;69. OCE& E57.
[7] Pritchard C, Duffy S, Edington J, Pang F. Enteral nutrition and oral nutrition supplements: a review of the economics literature. J Parenter Enteral Nutr 2006;30(1):52–9.
[8] Elia M, Bistrian B. The economic, medical/scientific and regulatory aspects of clinical nutrition practice: what happens next?. Basel: Karger; 2009.
[9] Freijer K, Bours MJ, Nuijten MJ, Poley MJ, Meijers JM, Halfens RJ, et al. The economic value of enteral medical nutrition in the management of disease-related malnutrition: a systematic review. J Am Med Dir Assoc 2014;15(1):17–29.
[10] Walzer S, Droeschel D, Nuijten M, Chevrou-Severac H. Health economic analyses in medical nutrition: a systematic literature review. Clin Outcomes Res CEOR 2014;6:109–24.
[11] Mitchell H, Porter J. The cost-effectiveness of identifying and treating malnutrition in hospitals: a systematic review. J Hum Nutr Diet 2015 [epub ahead of print].
[12] Elia M, Stratton R, Russell C, Green C, Pang F. The cost of disease-related malnutrition in the UK and economic considerations for the use of oral nutritional supplements (ONS) in adults. A report by The Health Economic Group of The British Association for Parenteral and Enteral Nutrition (BAPEN). BAPEN; 2005. Report No.: 1 899467 01 7.
[13] Norman K, Pirlich M, Smoliner C, Kilbert A, Schulzke JD, Ockenga J, et al. Cost-effectiveness of a 3-month intervention with oral nutritional supplements in disease-related malnutrition: a randomised controlled pilot study. Eur J Clin Nutr 2011;65(6):735–42.
[14] Neelemaat F, Bosmans JE, Thijs A, Seidell JC, van Bokhorst-de van der Schueren MA. Oral nutritional support in malnourished elderly decreases functional limitations with no extra costs. Clin Nutr 2012;31(2):183–90.
[15] Wyers CE, Reijven PL, Evers SM, Willems PC, Heyligers IC, Verburg AD, et al. Cost-effectiveness of nutritional intervention in elderly subjects after hip fracture. A randomized controlled trial. Osteoporos Int J Establ Result Coop Between Eur Found Osteoporos Natl Osteoporos Found U. S. A 2013;24(1):151–62.
[16] Drummond MF, Sculpher MJ, O'Brien B, Stoddart GL. Methods for the economic evaluation of health care programmes. 3rd ed. Oxford: Oxford University Press; 2005.
[17] National Prescribing Centre (provided by NICE). Prescribing of adult oral nutritional supplements: guiding principles for improving the systems and processes for ONS use. 2012. http://www.webarchive.org.uk/wayback/archive/20140627111700/http://www.npc.nhs.uk/quality/ONS/resources/borderline_substances_final.pdf.
[18] Smedley F, Bowling T, James M, Stokes E, Goodger C, O'Connor O, et al. Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. Br J Surg 2004;91:983–90.
[19] Arnaud-Battandier F, Malvy D, Jeandel C, Schmitt C, Aussage P, Beaufrere B, et al. Use of oral supplements in malnourished elderly patients living in the community: a pharmaco-economic study. Clin Nutr 2004;23:1096–103.
[20] Elia M, Normand C, Norman K, Laviano A. A systematic review of the cost and cost-effectiveness of standard oral nutritional supplements in the hospital setting. Clin Nutr 2015. in press.
[21] Cawood AL, Smith A, Pickles S, Church S, Dalrymple-Smith J, Elia M, et al. Effectiveness of implementing 'MUST' into care homes within Peterborough primary care trust. Engl Clin Nutr 2009;4(Suppl. 2). 81 (P133).
[22] Baggaley E, Whincup L, Ashman KE, Cawood AL, Davies DP, Burns E, et al. Effectiveness of implementing a nurse led policy for the management of malnutrition. Clin Nutr 2013;32(Suppl. 1):S231.
[23] Parsons EL, Stratton RJ, Cawood AL, Jackson JM, Elia M. Oral nutritional supplements are more cost effective in improving quality adjusted life years (QALYs) in malnourished care home residents. Clin Nutr 2012;7(1):PP047. Parsons EL, Stratton RJ, Jackson EM, Elia M. Oral nutritional supplements are cost effective in improving quality adjusted life years in malnourished care home residents. Gut 2012;91(Suppl 2):A17.
[24] Cawood AL, Green C, Stratton RJ. The budget impact of using oral nutritional supplements in older community patients at risk of malnutrition in England. Proc Nut Soc 2010;69(OEE7):E544.

[25] Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0. 2011 [updated march 2011] Available from: www.cochrane-handbook.org.
[26] Edington J, Barnes R, Bryan F, Dupree E, Frost G, Hickson M, et al. A prospective randomised controlled trial of nutritional supplementation in malnourished elderly in the community: clinical and health economic outcomes. Clin Nutr 2004;23:195–204.
[27] Nuijten M, Mittendorf T. The health economic impact of oral nutritional supplements (ONS) in Germany. Aktuelle Ernahrungsmedizin 2012;37:126–33.
[28] Freijer K, Nuijten MJ, Schols JM. The budget impact of oral nutritional supplements for disease related malnutrition in elderly in the community setting. Front Pharmacol 2012;3:1–8 (article 78).
[29] Simmons SF, Zhuo X, Keeler E. Cost-effectiveness of nutrition interventions in nursing home residents: a pilot intervention. J Nutr Health Aging 2010;14(5):367–72.
[30] Freyer K, Nuijten M. The health economic impact of oral nutritional supplements in the community setting in the Netherlands. Value Health 2010;13(3):A101.
[31] Nuijten M, Freyer K. The budget impact of oral nutritional supplements in the community setting in the Netherlands. Value Health 2010;13(3):A101.
[32] Nuijten M, Freyer K. The economic impact of oral nutritional supplements in ambulatory setting in Germany. Value Health 2010;13(3):A102.
[33] Nuijten M, Freyer K. The health economic impact of oral nutritional supplements in residential care in Germany. Value Health 2010;13(3):A102.
[34] Manasek V, Bezdek K, Foltys A, Klos K, Smitka J, Nmehlik D. Effect of perioperative high protein nutritional support on post-operative complications and costs of treatment in patients with colorectal cancer. Eur J Cancer 2013;49:S519.
[35] Freijer K, Nuijten MJ. Analysis of the health economic impact of medical nutrition in the Netherlands. Eur J Clin Nutr 2010;64(10):1229–34.
[36] MacFie J, Woodcock NP, Palmer MD, Walker A, Townsend S, Mitchell CJ. Oral dietary supplements in pre- and post operative surgical patients: a prospective and randomized clinical trail. Nutrition 2000;16:723–8.
[37] Beattie AH, Parch AT, Baxter JP, Pennington CR. A randomised controlled trial evaluating the use of enteral nutritional supplements postoperatively in malnourished surgical patients. Gut 2000;46:813–8.
[38] Flynn MB, Leightty FF. Preoperative outpatient nutritional support of patients with squamous cancer of the upper aerodigestive tract. Am J Surg 1987;154:359–62.
[39] Hirsch S, Bunout D, Maza PDL, Iturriaga H, Petermann M, Icazar G, et al. Controlled trial on nutritional supplementation in outpatients with symptomatic alcoholic cirrhosis. J Parenter Enteral Nutr 1993;17:119–24.
[40] Wilson B, Fernandez-Madrid A, Hayes A, Hermann K, Smith J, Wassell A. Comparison of the effects of two early intervention strategies on the health outcomes of malnourished hemodialysis patients. J Ren Nutr 2001;11:166–71.
[41] Norman K, Kirchner H, Freudenreich M, Ockenga J, Lochs H, Pirlich M. Three month intervention with protein and energy rich supplements improve muscle function and quality of life in malnourished patients with non-neoplastic gastrointestinal disease–a randomized controlled trial. Clin Nutr 2008;27(1):48–56.
[42] Gariballa S, Forster S, Walters S, Powers H. A randomized, double-blind, placebo-controlled trial of nutritional supplementation during acute illness. Am J Med 2006;119(8):693–9.
[43] Chapman IM, Visvanathan R, Hammond AJ, Morley JE, Field JB, Tai K, et al. Effect of testosterone and a nutritional supplement, alone and in combination, on hospital admissions in undernourished older men and women. Am J Clin Nutr 2009;89(3):880–9.
[44] Neelemaat F, Bosmans JE, Thijs A, Seidell JC, van Bokhorst-de van der Schueren MA. Post-discharge nutritional support in malnourished elderly individuals improves functional limitations. J Am Med Dir Assoc 2011;12(4):295–301.
[45] Wilson A, Evans S, Frost G. A comparison of the amount of food served and consumed according to meal service system. J Hum Nutr Diet 2000;13:271–5.
[46] Neelemaat F, Lips P, Bosmans JE, Thijs A, Seidell JC, van Bokhorst-de van der Schueren MA. Short-term oral nutritional intervention with protein and vitamin D decreases falls in malnourished older adults. J Am Geriatrics Soc 2012;60(4):691–9.
[47] Royal College of Physicians, Royal College of General Practitioners, Royal College of Paediatrics and Child Health. Teams without walls: publication unit of Royal College of Physicians & the Lavenham group Ltd. Suffolk 2008. pp13.
[48] NICE. QS24 Nutrition support in adults: NICE support for commissioners and others using the quality standard on nutrition support in adults. 2012. http://publicationsniceorguk/quality-standard-for-nutrition-support-in-adults-qs24/development-sources.
[49] Hubbard GP, Elia M, Holdoway A, Stratton RJ. A systematic review of compliance to oral nutritional supplements. Clin Nutr 2012;31(3):293–312.