Economic impact of feeding a phenylalanine-restricted diet to adults with previously untreated phenylketonuria

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The health intervention examined in the study was a restricted dietary treatment aimed at reducing the intake of phenylalanine (PHE) in patients with previously untreated phenylketonuria (PKU).

Type of intervention
Feeding treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with previously untreated PKU.

Setting
The setting was hospital. The economic study was carried out in UK.

Dates to which data relate
The dates during which effectiveness evidence and data concerning use of resources were gathered were not reported, but 1996/1997 prices were used.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was conducted retrospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
No power calculations were carried out and the method of sample selection was not clearly reported. No evidence, in terms of baseline characteristics, was provided that the initial study sample was appropriate for the clinical study question other than that a sample of 8 hospital-based patients (age range: 30-50 years) was examined. A sub-group analysis was also conducted on the basis of the average number of nursing hours needed; low-users being defined as those patients requiring less than 2,000 hours of nursing time annually and high-users as those requiring more than 7,000 hours.
Study design
This was a retrospective study, based on a cohort of patients selected from several hospitals in the UK. The number of centres was not reported. Patients' charts were reviewed for one year before, and one year after, the introduction of the restricted feeding programme.

Analysis of effectiveness
The primary health outcomes assessed were average serum PHE levels, number of negative behaviours (such as screaming and shouting, aggression towards others, self-injury, stealing food from other peoples' plate, and stubbornness), time in hospital for asthma and respiratory tract infections, number of outpatient clinic visits to dermatologists and chest physicians, nursing time to care for hospitalised patients, length of long-term hospital stay, time on medication for antibiotics, antiepileptics, antihistamines, anxiolytics, inhaled anti-inflammatories, neuroleptics, and topical anti-inflammatories. The comparability of the study groups was not relevant as the same cohort of patients was used in the effectiveness analysis.

Effectiveness results
The effectiveness results were as follow:

Average serum PHE levels (available only for 4 patients) fell from 1,614 +/- 355 micromol L^-1 to 617 +/- 139 micromol L^-1.

The number of negative behaviours was between 20 and 74 weekly episodes over 6-9 weeks before the introduction of a PHE-restricted diet and decreased to between 3 and 19 episodes over first 12-24 weeks on a restricted diet (the reduction was 59 +/- 23% and the difference was statistically significant, (p<0.03)).

After the introduction of the restricted diet, patients experienced a reduction in the incidence of concurrent illnesses with no further details being given.

Time in hospital for asthma and respiratory tract infections was 2.6 +/- 5.1 days with the unrestricted diet and 0.3 +/- 0.6 days with the restricted diet.

The number of outpatient clinic visits to dermatologists and chest physicians was 1.8 +/- 2.4 with the unrestricted diet and 0.2 +/- 0.3 with the restricted diet.

Nursing time to care for hospitalised patients amounted to 6,354 +/- 3,249.2 with the unrestricted diet and to 3,714.8 +/- 1,934.8 with the restricted diet and the difference was statistically significant, (p<0.05).

Length of long-term hospital stay was 365 +/- 0 with the unrestricted diet and 365 +/- 0 with the restricted diet.

Times on medication with the unrestricted and the restricted diet were 2.6 +/- 10.3 days and 0.3 +/- 0.6 days for antibiotics, 91.3 +/- 146.0 days and 91.3 +/- 111.5 days for antiepileptics, 91.3 +/- 146.0 days and 10.5 +/- 12.9 days for antihistamines, 45.6 +/- 178.8 days and 5.3 +/- 9.7 days for anxiolytics, 45.6 +/- 178.8 days and 45.6 +/- 84.3 days for inhaled anti-inflammatories, 182.5 +/- 113.1 days and 142.1 +/- 124.4 days for neuroleptics, and 136.9 +/- 126.5 days and 15.8 +/- 14.6 days for topical anti-inflammatories.

Clinical conclusions
The PHE-restricted diet was highly effective in improving patients' conditions in terms of the various outcomes. The incidence of concurrent illnesses (reflected by resources used) was also reduced after one year of restricted feeding programme.

Measure of benefits used in the economic analysis
No summary benefit measure was used; therefore a cost-consequences analysis was conducted.
Direct costs
Discounting was not relevant due to the short time horizon of the analysis. Quantities of resources used were reported, but unit costs were not. The cost/resource boundary adopted was that of the NHS. The health service costs included in the costing analysis were hospitalisation for asthma and respiratory tract infections, outpatient clinic visits to dermatologists and chest physicians, nursing time, long-term hospital stay, drugs, and PHE-restricted diet. The estimation of costs was based on actual costs derived from published sources. Quantities of resources were stated to have been estimated through experts’ opinions and medical records. The period of collection of resources was not stated, but 1996/1997 prices were used.

The opinions of several health care professionals (6 dietitians, 11 nursing managers, 1 pharmacist, 6 psychiatrists, and 4 psychologists) were used to assess health resources and client management. The experts were identified from a long-stay hospital in UK with some experience with feeding a PHE-restricted diet to adults with previously untreated PKU. In addition, the authors made some assumptions.

To minimise any placebo effect, the authors assumed that patients did not experience improvements affecting resource use before six months of PHE-restricted diet. The experts’ opinions were used to support the collection of data from hospital records.

Statistical analysis of costs
No statistical analyses of costs were conducted, although costs were given as means.

Indirect Costs
Indirect costs were not included.

Currency
UK pounds sterling (£).

Sensitivity analysis
Sensitivity analyses were conducted to assess the robustness of the estimated costs to variations in nursing time, response rate (in the base analysis, all patients responded to the therapy), and heterogeneity of patients in terms of whether high or low users. The type of analysis was not reported, but it appears that one-way sensitivity analyses were conducted.

Estimated benefits used in the economic analysis
See effectiveness results above.

Cost results
Costs in the unrestricted diet group and in the PHE-restricted diet group were 364.9 +/- 715.5 and 42.1 +/- 82.5 for hospitalisation for asthma and respiratory tract infections, 70.6 +/- 112.4 and 8.1 +/- 13.0 for outpatient clinic visits to dermatologists and chest physicians, 60.509 +/- 30,942.7 and 35,376.2 +/- 18,424.9 for nursing time, 206.7 +/- 219.7 and 78.2 +/- 105.1 for drugs, and 0 and 5,000 for PHE-restricted diet.

Costs of long-term hospital stay amounted to 22,843.7 in both groups.

Total annual costs were 83,995.6 +/- 31,046.6 in the unrestricted diet group and 63,348.4 +/- 18,385 in the PHE-restricted diet group. As a result, the PHE-restricted diet led to an average cost-saving of 20,647, despite the additional cost of 5,000 for the specific diet regimen.

The mean annual cost for a high-user patient was 114,362 with unrestricted diet and 78,407 with the PHE-restricted
The mean annual cost for a low-user patient was 33,384 with unrestricted diet and 38,251 with the PHE-restricted diet, with an additional cost of 4,866. Sensitivity analysis showed that there would be a reduction in cost as long as mean nursing times were reduced by at least 8%. In addition, cost-savings could be realised if the response rate were greater than 5%, which is far below the observed rate.

Finally, the PHE-restricted diet programme reduces annual costs when the percentage of high-users is at least 12% (break-even point).

**Synthesis of costs and benefits**
Not relevant.

**Authors’ conclusions**
The PHE-restricted diet programme was effective in improving the challenging behaviour of patients with PKU. The reduction in costs was even more substantial, especially for patients requiring a high use of nursing time, which was the main cost-driver.

**CRD COMMENTARY - Selection of comparators**
The rationale for the selection of the comparator was clear. The restricted feeding programme was compared with a no-restriction programme, since this was the previous practice. You, as a user of this database, should assess whether it represents a widely used intervention in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence was derived from a sample of hospitalised patients. However, the sample size was quite small and no power calculations were performed, whilst the subgroup analysis was conducted on a still smaller sample. No evidence was provided that the initial study sample was appropriate for the clinical study question as detailed demographics and clinical characteristics of the patients included in the study were not reported. As a result, it was not clear whether the patient population in the study was representative of the general population suffering from PKU. Due to the retrospective nature of the study design it was not possible to take into account potential bias or confounding factors. The period of collection of the effectiveness evidence was not reported. These issues could limit the internal validity of the study. However, it has to be noted that, due to the very low incidence of PKU in UK, it would appear to be somewhat difficult to collect data for a large prospective study.

**Validity of estimate of measure of benefit**
No summary benefit measure was used in the economic analysis and, hence, a cost-consequences analysis was conducted. It would have been interesting to have used a benefit measure reflecting preferences of patients (or caregivers) for the interventions, since the adoption of a restricted feeding programme appears to affect the quality of life of both patients and caregivers.

**Validity of estimate of costs**
It appears that all the categories of costs relevant to the perspective adopted in the study were included in the analysis. Unfortunately, the estimation of quantities was mainly based on experts’ opinions with little information on the method being provided. No statistical analyses of costs were conducted, and unit costs were not reported. As the authors noted, it would have been interesting to have taken into account direct costs borne by patients' families as well as indirect costs.

**Other issues**
The issue of the generalisability of the study results to other settings was not explicitly addressed and sensitivity
analyses were conducted for only a few variables. Only limited comparisons of the study findings with those from other studies were made. These issues could have reduced the external validity of the analysis. The authors pointed out some limitations of the analysis, already reported in the previous fields.

**Implications of the study**
The study showed improvements in terms of reduced costs and fewer negative behaviours due to the implementation of a PHE-restricted diet. The authors highlighted that these benefits could be even more substantial over several years than in the first year after the introduction of the programme. Further prospective studies are required to better explore the cost-effectiveness of the PHE-restricted diet programme.

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