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 study examined the effectiveness of augmentation therapy (Aug) with pooled human plasma alpha-one proteinase for the treatment of severe alpha-one antitrypsin (AAT) deficiency. The study compared three strategies. These were Aug for life, Aug until the forced expiratory volume in 1 second (FEV1) was below 35% predicted, and no Aug. Aug was provided in 1-hour infusions of 60 mg/kg.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The hypothetical study population comprised a hypothetical cohort of 30,000 patients aged 46 years old with an FEV1 of 49% predicted (50% were male).

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data related to 1998. The resource use data were from 1995 to 2001. The price year was 2001.

Source of effectiveness data
The effectiveness data were derived from a patient registry, supplemented with modelling assumptions. The utility estimates were derived from a prospective study.

Link between effectiveness and cost data
The cost data were not derived from the patient registry used to provide the effectiveness data.

Modelling
A Markov model was used to estimate the lifetime costs and health outcomes associated with each of the treatment strategies examined. The Markov model consisted of five health states:

FEV1 49 to 80% predicted;
FEV1 35 to 49% predicted;
FEV1 less than 35% predicted;
lung transplantation; and
death.

The cycle length was one year. Patients could progress through the model in only one direction, from higher FEV1 to lower FEV1 predicted. Progression to lung transplantation was from FEV1 less than 35% predicted. Patients could die from any state in the model.

Outcomes assessed in the review
The outcomes assessed included:

the probability of FEV1 decline depending on Aug status (receiving versus not receiving),
the mortality rates,
the probability of lung transplantation, and
the costs of managing patients with AAT deficiency.

The authors did not state that a systematic review of the literature was undertaken.

Study designs and other criteria for inclusion in the review
The authors did not specify any inclusion or exclusion criteria for the review. The majority of the effectiveness data were derived from the NHLBI Registry for Individuals with Severe Deficiency of AAT.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
The review included four primary studies.

Methods of combining primary studies
Data from the primary studies were not combined.

Investigation of differences between primary studies
Not reported.
Results of the review

The annual FEV1 decline for patients receiving Aug was 73.7 (standard deviation, SD=56.9) for patients with FEV1 50 to 79% predicted, 66.4 (SD=59.4) for patients with FEV1 35 to 49% predicted, and 43.9 (SD=63.5) for patients with FEV1 less than 35% predicted.

The annual FEV1 decline for patients not receiving Aug was 81.2 (SD=56.3) for patients with FEV1 50 to 79% predicted, 93.2 (SD=56.6) for patients with FEV1 35 to 49% predicted, and 46.5 (SD=61.7) for patients with FEV1 less than 35% predicted.

The annual probability of death was 0.006 for patients with FEV1 greater than 50% predicted.

The annual probability of AAT deficiency-related death was 0.02905 for patients with FEV1 less than 50% predicted who received Aug, compared with 0.07405 for patients with FEV1 less than 50% predicted who did not receive Aug.

Methods used to derive estimates of effectiveness

The authors made modelling assumptions.

Estimates of effectiveness and key assumptions

The authors assumed that 19% of patients with FEV1 less than 15% predicted would receive lung transplantation. They also assumed that Aug would only affect the probability of death in patients with FEV1 less than 50% predicted.

Measure of benefits used in the economic analysis

The measure of health benefits used was the quality-adjusted life-years (QALYs). The utility weights for each health state were obtained from pulmonologists using a generic valuation matrix, the Health Utilities Index (Mark III). Discounting was performed at a rate of 3%.

Direct costs

The authors provide some disaggregated cost data. The study included the direct costs to the health service. These were for the costs of Aug and other medications used to treat AAT deficiency, oxygen therapy, laboratory and diagnostic tests, outpatient clinic and emergency department visits, hospitalisations and lung transplantation, and the cost of post-transplantation care. The unit costs were derived from pricing lists, Medicare reimbursement rates and published retrospective studies. A model was used to estimate the lifetime costs associated with the treatment of AAT deficiency. Discounting was relevant, given the lifetime horizon, and a rate of 3% per annum was applied. The study reported average and incremental costs. The price data referred to 2001, and were adjusted for inflation using the medical care component of the Consumer Price Index.

Statistical analysis of costs

Sampled data were not available for statistical analysis.

Indirect Costs

The indirect costs were not included in the analysis, which was appropriate given the study perspective.

Currency

US dollars ($).

Sensitivity analysis

The authors conducted a one-way sensitivity analysis on every variable in the model in order to explore uncertainty in
the parameter estimates and sensitivity to modelling assumptions. The authors reported the ranges tested in the sensitivity analyses, but the justification for these ranges was not clear in all cases.

**Estimated benefits used in the economic analysis**

No treatment was estimated to result in an average of 4.62 QALYs over a lifetime horizon, using a discount rate of 3% per annum.

The incremental gain in QALYs with the strategy of providing Aug until FEV1 was less than 35% predicted was 2.02.

The incremental gain in QALYs by extending Aug therapy to lifetime was 0.55.

**Cost results**

The average lifetime cost of a patient with AAT deficiency who received no treatment was $92,091, using a discount rate of 3% per annum.

The incremental increase in cost with the strategy of providing Aug until FEV1 was less than 35% predicted was $419,839.

The incremental increase in cost by extending Aug therapy to lifetime was $383,313.

The authors made no mention of adverse events from Aug.

**Synthesis of costs and benefits**

The costs and benefits were combined to calculate the cost per QALY gained.

Providing Aug until FEV1 was less than 35% predicted was estimated to cost $207,841 per QALY gained in comparison with no treatment.

Providing lifetime Aug was estimated to cost $696,933 per QALY gained in comparison with providing Aug until FEV1 was less than 35% predicted.

These estimates were calculated for a lifetime horizon, applying a discount rate of 3% per annum to both the costs and outcomes. The incremental cost-effectiveness ratios were reported to exceed $100,000 per QALY in all of the sensitivity analyses.

**Authors' conclusions**

Unfavourable cost-effectiveness estimates must be considered alongside the fact that augmentation therapy (Aug) is the only approved therapy for severe alpha-1 antitrypsin (AAT) deficiency.

**CRD COMMENTARY - Selection of comparators**

The choice of the comparators was explicitly justified with reference to the fact that Aug is the only approved therapy for severe AAT deficiency in the study setting. You must decide whether this is a widely used therapy and whether there are any alternatives in your own setting.

**Validity of estimate of measure of effectiveness**

The estimate of effectiveness was based on data from a patient registry. This is not an appropriate source of data for effectiveness estimates, as patients in the registry will have been selected to receive or not to receive Aug. Although the patients are likely to have been representative of the study population, the benefits of Aug may have been overestimated. The authors did not discuss whether patients receiving Aug were comparable with those not receiving Aug, but it is unlikely that they were well matched given that they were not randomised to treatment.
Validity of estimate of measure of benefit
The QALYs were estimated from a Markov model, using utility estimates derived from pulmonologists. The model used was appropriate. The use of experts to provide utility values may have been justified given the lack of patient-derived utility values.

Validity of estimate of costs
All the categories of costs relevant to the perspective adopted were included in the analysis. The authors acknowledged that they did not consider the indirect costs. The costs were reported separately from the quantities, which will improve the generalisability of the study results. The resource use estimates were based on authors’ assumptions and published retrospective analyses. The authors conducted extensive one-way sensitivity analyses around the cost data, stating that they used wide ranges in order to reflect the uncertainty. The authors made appropriate use of discounting and reported the price year and the method used to adjust prices for inflation.

Other issues
The authors compared their findings with those from two prior analyses that had reported lower incremental cost-effectiveness ratios for Aug. The authors explored the differences between the studies that were responsible for the different results. The issue of generalisability to other settings was not addressed. The authors do not appear to have presented their results selectively. No further limitations of the study were reported.

Implications of the study
The future development of alternative treatments that are more clinically and cost-effective should be encouraged.

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None stated.

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