Technology assessment of the Dutch lung transplantation program

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 intervention health technology considered in the study was a lung transplantation programme for patients with irreversible, progressively disabling end-stage pulmonary or cardiopulmonary disease. The following phases were distinguished in the transplantation programme: application, outpatient screening, inpatient screening, waiting list, transplantation (perioperative and intensive care), inpatient follow-up, and outpatient follow-up. In the application phase, potential candidates were identified on the basis of written information of the referring physician. In the outpatient screening phase, patients visited the outpatient clinic for an initial screening. Once beyond this initial screening, the acceptable candidates were invited for an inpatient screening. After formal inpatient screening, a decision was made about the placement of the patient on the waiting list. Patients were dropped from the programme when they were rejected for transplantation, when they died, when they withdrew from the programme, or when they did not contact the lung transplant team for more than 12 months.

Type of intervention
Treatment and secondary prevention.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population consisted of patients with irreversible, progressively disabling end-stage pulmonary or cardiopulmonary disease with a predicted life expectancy of less than 12 to 18 months. The indications and contraindications were reported elsewhere.

Setting
The study setting was a hospital. The economic study was carried out in The Netherlands.

Dates to which data relate
Effectiveness and resource use data corresponded to patients treated between November 1990 and April 1995. The price year was 1992.

Source of effectiveness data
Survival figures and health-related quality of life were derived from a single study.

Link between effectiveness and cost data
Costing was undertaken on the same patient sample as that used in the effectiveness study and appears to have been conducted both prospectively (resource use data in the study institution) and retrospectively (outside the study institution, gathered by questionnaires).
Study sample
Power calculations were not used to determine the sample size. The study sample was made up of 425 patients, with a mean age of 43 years, who were referred for transplantation. Of these patients 303 were accepted for outpatient screening and 179 for inpatient screening. After complete screening, 120 patients were put on the waiting list. At data closure, 57 patients had received a transplantation. Twenty patients were included in the longitudinal analysis of quality of life.

Study design
The study design appears to have been a before-and-after study (the effects both with and without the programme were based on data from a single group of patients; pretransplant evidence was adapted to provide estimates of the "without" option) or a case series. The study was carried out in a single centre. The mean period of follow-up of patients was 1.5 years (range: 0 - 5 years). The loss to follow-up appears to have been 11 patients. In view of the expected positive effects of lung transplantation, it was considered ethically unacceptable to perform a randomised clinical trial. Therefore, the patients admitted to the lung transplantation programme formed the only study group.

Analysis of effectiveness
The analysis of the clinical study was based on treatment completers only. The primary health outcomes used in the analysis were survival and quality of life. The health-related quality of life of the study patients was measured at different points of time before (every 3 months) and after transplantation (1, 4, 7, 13, and so on, months post transplantation) by means of self-assessment questionnaires.

The instruments used were:

- number of hours of work/school daily;
- the Nottingham Health Profile (NHP, part 1);
- Karnofsky Performance Index;
- the Index of Well Being;
- the Self-rating Depression scale (SDS-Zung);
- the State Trait Anxiety Inventory (STAI-DY);
- Activities of Daily Life (ADL);
- the EUROQol.

Survival figures for the study patients were based on a registration of the patients' health status during their participation in the programme. The need for lung transplantation and donor lungs was estimated by means of two methods. Firstly, extrapolation of the number of patients accepted for transplantation in the study programme during the period 1990-95. Secondly, an analysis of national age- and sex-specific mortality data for pulmonary and cardiopulmonary diseases. Current supply data were derived from the registration of the transplant coordinators of the study institution. Based on the literature, possible future developments in the supply of lung donors were identified, and the effect of these developments on the donor supply in the Netherlands was analysed.

Effectiveness results
The 1- and 2-year survival after transplantation was 86% and 75%. Up to April 1995, 11 patients died. Two patients died of primary graft failure shortly after transplantation. In the follow-up phase, chronic rejection was the primary cause of death.
Two years before the start of the screening phase, 40% of the 20 patients were able to work for more than 4 hours a day. At the start of the screening phase this percentage decreased to 10%. Seven months after transplantation, 15% of the patients were able to work for more than 4 hours a day. The results on the NHP showed that, at the beginning of the application phase, patients felt extremely restricted along the dimensions of mobility and energy, while some sleeping disorders were present. Seven months after transplantation, the scores on all six dimensions of the NHP were comparable to those of the general population. Before transplantation, the majority of the patients (70%) could dress, wash, and go up and down the stairs independently. However, these activities could be done independently only with a lot of effort. Seven months after transplantation almost all of the patients were able to perform the four activities of daily life independently and without great effort.

The annual need for lung transplantation in the Netherlands was estimated at between 50 and 75 for the next 10 years (3.3 - 5.0 per million inhabitants a year). For that period the supply of donor lungs in the Netherlands was estimated to be between 17 and 27 a year (1.1 - 1.8 per million inhabitants). As a consequence, only about one-third of future patients who will be in need of lung transplantation can be transplanted.

Clinical conclusions
The observed survival rates of the transplanted patients are in line with those published by others. In addition to survival, improvements in the quality of life of the patients receiving transplants were substantial.

Modelling
A microsimulation model was used to perform scenario analyses to assess the cost-effectiveness in the long run.

Measure of benefits used in the economic analysis
The benefit measures used in the analysis were life-years gained and quality-adjusted life-years (QALYs) gained. Survival times for the transplanted patients were based on three sources. The first three years were based on the observed survival of the study patients. Survival from the fourth year onwards was based on world-wide survival data from lung and heart transplantation patients, and survival time for the patients without a transplantation programme was based on the observed survival of the study patients after a stay of 9 months on the waiting list (defined as the "fictitious" transplantation moment) and extrapolation of those survival data using a Weibull model.

For the assessment of utilities, the quality-of-life measurements on the EuroQol questionnaire were transformed to utility scores, using the preference of the general population. For the estimation of long-term utility scores of the transplanted patients it was assumed that quality of life did not change from the third year after transplantation, with the exception of a limited period before death. Utility scores for the non-transplanted patients were based on the utility scores of the patients on the waiting list (after 9 months). The utility scores of the waiting list patients were based on the scores of the surviving patients only. The utility scores of the deceased patients averaged 0.31 in the 3-month period before death.

Direct costs
Costs were discounted, but no justification was provided for the choice of the discount rate. Quantities and costs were not reported separately. Cost items were reported separately. The costs included were direct medical costs inside and outside of the hospital (hospitalisation, outpatient visits, transplantation operation, visits to general practitioner, medication), and direct non-medical costs (travelling expenses, special food, home help). The source of resource use and cost data inside the hospital was the study hospital accounting system and the financial administration. Programme costs as well as non-programme costs were registered from the moment patients entered the programme until they left the programme or until death. Programme costs were defined as costs induced by the programme while non-programme costs were costs caused by the conventional treatment of the patients. The cost study took a societal perspective: all costs incurred by society (hospital, patients, family) were included in the analysis. The majority of the costs were based on real costs as opposed to charges.

Resource use data outside the study hospital were gathered using questionnaires. Prices of these items were obtained
from external information resources. Costs were compared from a lifetime perspective (until the patient's death). Data needed for the cost-effectiveness analyses could be based only partly on primary data. Long-term costs had to be estimated. The assessment of the incremental costs compared the costs of the situation with and without the programme. In this comparison only the costs that differed between the situations were considered. Non-programme costs in the period before transplantation were assumed to be the same for both situations. For programme costs from the fourth year onward, costs were extrapolated on the basis of the estimated survival figures and the average weekly costs at the end of the third follow-up year. Average non-programme costs after the fictitious time of transplantation were assessed per patient, based on the estimated survival figures of the non-transplanted patients and the measured non-programme costs in the period before transplantation. The price year was 1992.

**Statistical analysis of costs**

Descriptive statistics were used to provide information on the number of days that patients spent in each phase before a decision was made.

**Indirect Costs**

Costs were discounted. Quantities and costs were not reported separately. The indirect non-medical costs included the costs of production losses. Indirect costs were estimated using the friction cost method. Unit costs were not reported. 1992 price data were used.

**Currency**

Dutch Guilders (Dfl). The exchange rate was US$1 = Dfl 1.7.

**Sensitivity analysis**

To assess the cost-effectiveness in the long run, scenario analyses were performed with a microsimulation model. Alternative scenarios were performed in which, respectively, the number of screened patients and the number of available donor lungs were altered.

**Estimated benefits used in the economic analysis**

For the transplanted patients survival percentages were estimated as follows:

1 year, 85%; 5 year, 60%; 10 year, 35%; and 15 year, 10%.

Survival percentages of patients without a transplantation programme were estimated to be:

1 year, 75%; 5 year, 19%; 10 year, 3%; and 15 year, 0% after the fictitious time of transplantation.

The average number of years from the time of transplantation was 7.41 years with the transplantation procedure and 3.04 without the procedure, yielding 4.37 life-years gained with a transplant.

The average number of QALYs was 6.41 with and 1.21 without transplantation, yielding 5.20 QALYs gained with a transplant.

Benefits were discounted at 5%.

**Cost results**

Costs were discounted at 5%. The total programme cost per transplanted patient was $394,330. The total non-programme costs from the fictitious time of transplantation until death were $79,073 per patient. The incremental cost per transplanted patient was $315,257.
Synthesis of costs and benefits
The estimated benefits and costs were combined as incremental cost per life-year gained and incremental cost per QALY with and without a 5% discount rate for both effects and costs. The incremental cost-effectiveness and utility ratios were $72,000 per life-year gained and $61,000 per QALY gained. The incremental cost-effectiveness and utility ratios were $90,000 per life-year gained and $71,000 per QALY gained at a 5% discount rate for both effects and costs. In the scenario analysis, with a death rate of 66% on the waiting list, the cost-effectiveness ratio were $114,000 per life-year gained and $98,000 per QALY gained (both discounted). As shown by the baseline scenario, in the long run the cost-effectiveness ratios become even higher as a result of the great discrepancy between the need for and supply of donor lungs. Alternative scenarios showed that additional inflow restrictions and an increase in the donor supply could lower the ratios, but again the cost-effectiveness ratios remained high.

Authors’ conclusions
The results showed that lung transplantation is a very costly intervention that improves both survival and quality of life.

CRD COMMENTARY - Selection of comparators
The reason for the choice of the comparator was clear. The lung transplantation programme was compared with a ‘no transplantation programme’ situation in which patients received the conventional treatment for lung disease. You, as the database user, should consider whether this is the widely used health technology in your own setting.

Validity of estimate of measure of effectiveness
The internal validity of the programme's effectiveness may have been hampered by the lack of power analysis to determine the sample size, and the fact that the analysis of effectiveness was based on treatment completers only. It was reasoned that due to the expected positive effects of lung transplantation, it was considered ethically unacceptable to perform a randomized clinical trial. The study sample appears to have been representative of the study population.

Validity of estimate of measure of benefit
Benefit measures were derived using a combination of sources, including the single study, national statistics, published literature, and a separate study to derive utility values. The choice of the benefit measures was justified. The instruments used to derive the quality of life and utility values also appear to be justified.

Validity of estimate of costs
The validity of the cost analysis was enhanced by the fact that the total cost was disaggregated, and that the price year, exchange rate, and perspective adopted in the cost analysis were reported. Most cost data were reported to have been based on true costs rather than on charges and the cost analysis does not appear to have omitted any important cost items. The effects of indirect costs were incorporated in the cost analysis.

However, resource use data from outside the hospital were gathered using questionnaires that may expose the study to recall bias and the resource use profile was not reported separately. Statistical analysis was not performed on resource use items and cost data, and sensitivity analysis was not employed to investigate the robustness of the cost results to changes in the assumptions made in the cost calculations or changes in unit costs. These limitations may impede the generalisability of the cost results to other settings or countries.

Other issues
Given the lack of sensitivity analysis, and statistical analysis of the costs, some caution may need to be exercised in interpreting the study results. No discussion was reported around the generalisability of the study results although some comparison was made with other studies. The issue of how far the study sample was representative of the study population was not addressed in the authors’ comments.

Other issues:
The following limitations of the study were acknowledged by the authors. As no randomised control data were available, an unbiased estimate of the costs and effects in the situation without the programme was impossible. Survival and quality of life of patients on the waiting list were used to proxy survival and quality of life in the situation without a transplantation programme. Since patients on the waiting list participate in preoperative exercise programmes to increase exercise tolerance, their condition could be (temporarily) improved. Consequently, survival and quality of life in the situation without a programme could have been overestimated, which leads to an underestimation of the life-years and QALYs gained and to an overestimation of the cost-effectiveness ratio. Considering the costs, the improved condition of the patients could lead to a decrease in the non-programme costs during the waiting list period. Consequently, non-programme costs in the situation without the programme could have been underestimated, which also leads to an overestimation of the cost-effectiveness ratio. However, the authors expected this bias to be small, as the non-programme costs were quite steady during the total period before transplantation.

**Implications of the study**

Positive effects on the costs per QALY can be expected from:

- an improvement in the survival of the transplanted patients;
- a reduction in the follow-up costs;
- additional restrictions toward screening; and
- an increase in the supply of donors.

However, major changes in one of those variables or a combination of significant changes in all those variables is necessary to realise costs per QALY on a par with those of the heart and liver transplantation programmes. Unfortunately, those changes cannot be expected in the short term. To realise the desired changes in the future, additional research is necessary about the infection and rejection problems of the transplanted patients, the possibility and effect of changes in the follow-up procedures (e.g. fewer control visits or fewer diagnostic tests), the possibility of decreasing the costs of drugs (e.g. by government pricing rules), the possibility of the implementation of additional restrictions for screening, and the possibility of changing rules regarding the donor supply (e.g. legislation, donor procedures within the hospital).

It was reported that, on the basis of the results of the assessment of lung transplantation, the Minister of Health Affairs in the Netherlands decided to include lung transplantation in the Dutch benefits package, because of its proven effectiveness. However, because of the relatively unfavourable cost-effectiveness of lung transplantation, the Minister has encouraged further research on the possibility of decreasing the costs and improving cost-effectiveness.

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