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OP1. Analysis and presentation of cost data from randomised trials

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Background: When evaluating alternative therapies or policies for the treatment and management of patients, randomised controlled trials (RCTs) play an important role. Economic analyses are increasingly being proposed or required alongside trials, and a range of statistical issues specific to these evaluations arise. This research focuses on the appropriate statistical methods for comparing costs between the arms of a trial. When summarising costs the measure of interest is the total or mean cost in each group of patients. The usual approach for comparing two means would be to use a t-test, and summarise with a difference in means and a confidence interval. The distribution of cost data is however usually highly skewed with some extreme outliers. In this case the use of the t-test, which assumes normality, may be invalid. The aims of this project are, firstly to summarise the methods used and results presented in published trials, and secondly to explore the validity of these methods and alternative approaches for the analysis and presentation of cost data from RCTs.
Method: Articles published in 1995 and reporting results of RCTs including individual cost data were identified via MEDLINE. These have been reviewed and the type of summary statistics and methods used to compare costs between the randomised groups were recorded. The most often used approaches have been examined in detail for their statistical validity and interpretation. In addition further investigations have focused on the usefulness of bootstrap and permutation resampling methods for the comparison of mean costs and the calculation of confidence limits.
Results: The review has shown that there is, in general, an appreciation of the need to use means or total costs to compare groups in an RCT. Many papers did not present tests or measures of uncertainty, and in those that did there is little consensus as to the 'correct' approach. The most commonly reported tests were the non-parametric Mann-Whitney test and the two sample t-test. The Mann-Whitney test is clearly inappropriate since it does not compare the mean costs but provides a more general comparison of the distributions. The t-test however does compare means and provided that it is robust to the non normality of the data, it is a valid approach. Robustness however is highly dependent on both the skewness of the data and the study sample size. The non-parametric bootstrap and permutation resampling techniques are useful for carrying out the analyses directly and also for checking results obtained using other methods.

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OP2. Cost-effectiveness analysis of Paclitaxel and Cisplatinum versus Cyclophosphamide and Cisplatin as first-line therapy in advanced ovarian cancer - a European perspective

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Background: Ovarian cancer is the sixth most common form of cancer worldwide and has the highest mortality rate of all gynaecological cancers. The results of a randomized clinical trial (GOG111) of paclitaxel/cisplatin (PC) versus standard therapy with cyclophosphamide/cisplatin (CC) as first-line chemotherapy in patients with advanced ovarian cancer showed a significant improvement in response rate, progression-free survival and overall survival for the PC group. As the focus on cost-containment among decision makers becomes more intense, the medical benefits could easily be diminished by the fact that therapy with paclitaxel might appear to be more xpensive than other chemotherapies, therefore economic evaluations are necessary. Two previous economic analyses of PC reported 14,700 US$ per. life year saved (Canada) and 19,800 - 21,200 US$ per life year saved (USA). This study is an evaluation of the cost-effectiveness of PC in Europe.
Methods: This is a retrospective, incremental cost-effectiveness analysis based on the GOG111 trial and conducted from the national payers point of view. In a first step the cost-structures of PC and CC were determined based on structured face-to-face interviews with oncologists, literature analysis and telephone interviews with hospital administrators. The total costs were calculated for 6 cycles of chemotherapy, with taxol being given at a dose of 135mg/m² over 24 hours as in the GOG 111 trial. In a second step the incremental effectiveness ("live years saved") in the PC group was determined using a declining exponential approximation of life expectancy (DEALE approach). The analysis was done separately for 6 European countries (D, E, F, I, NL, UK). The robustness of the results was tested using a series of sensitivity analyses.
Results: The incremental costs in the PC group were approximately 11,900, 8,200, 8,700, 14,700, 10,000 and 8,100 US$ in D, E, F, I, NL and the UK, respectively. The incremental life expectancy in the PC group ranged between 1.27 and 1.30 years in all countries. The corresponding cost-effectiveness ratios were approximately 9,400, 6,400, 6,600, 11,500, 7,900 and 6,400 US$ per life year saved in D, E, F, 1, NL and the UK, respectively. A supplementary analysis showed better cost-effectiveness ratios when hospitalization costs are reduced, e.g. when paclitaxel is administered as a 3-hour infusion.
Discussion: The results compare favourably with other life-saving interventions. The findings from the GOG111 trial and this analysis suggest that healthcare decision makers should consider PC as a cost-effective therapeutic option for first-line management of advanced ovarian cancer.

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OP3. Applying time-dependent outcomes and Markov modelling to the economic evaluation of cytotoxics: A case study of Paclitaxel and Topotecan in the treatment of advanced ovarian cancer

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Background: As a case study in the approach for assessing oncological interventions, we have built a Markov process model to assess two treatments, paclitaxel and topotecan, using time-dependent outcomes that integrate both toxicity and response.
Methods: To capture the cost per Time Without Symptoms (TWS), cost per Time Without Symptoms and Toxicity (TWiST) and cost per Quality-adjusted Time Without Symptoms and Toxicity (Q-TWiST), we built a Markov process model. The Markov approach was chosen because it explicitly measures time periods relevant to the outcome and to the experiences of the patient, furthermore, it acts as a good mirror for the clinical decision-making process. Data to populate the model came from a randomised phase III clinical study on advanced epithelial ovarian cancer. This was combined with local UK treatment information and corresponding costing data derived from City hospital in Birmingham. Nine health states were developed in the model based on treatment, follow-up, palliative care and death. Cycle time was 3 weeks and patients were followed-up in the model until death or two years after treatment. As this is work in progress, only a Q-TWiST proxy has been measured, however Q-TWiST measures will be incorporated into the model in the near future.
Results: Preliminary results suggest that the cost-effectiveness of topotecan is more favourable than paclitaxel for all parameeters measured. The major toxicity for both agents was myelosuppression which was significantly greater for topotecan. The model proves to be robust in light of changes in the costs of treating adverse events, hospital costs, changes in utility scores, point of response assessment and inclusion of clinical trial protocol violators. Differences between TWS, TWiST and the Q-TWiST proxy are substantial between treatments: as would be expected, TWS outcomes are more favourable as they only capture response rates, alternatively, scores are lower for TWIST and the Q-TWiST proxy because of the added consideration of toxicity.