Step by step guide to economic evaluation in cancer trials

What is CREST?
The Centre for Health Economics Research and Evaluation (CHERE) at UTS has been contracted by Cancer Australia to establish a dedicated Cancer Research Economics Support Team (CREST) to provide high quality, expert advice and support to Multi-site Collaborative Cancer Clinical Trials Groups.

Factsheets
CREST will produce a series of factsheets as resources for cancer collaborative group researchers wishing to include economic evaluation in their clinical trials.

SUMMARY
This factsheet provides a guide to the steps in an economic evaluation in cancer trials. These include:

1. Define the alternatives to be assessed in the trial
2. Consider the perspective and timeframe. This includes the timeframes for:
   a. Trial
   b. Follow up
   c. Beyond the trial
3. Identify, measure and value the resource use associated with each alternative
4. Identify, measure and value the consequences of each alternative
5. Combine the costs and consequences to produce an Incremental Cost-Effectiveness Ratio (ICER)
6. Assess the robustness of the results through a sensitivity analysis
7. Interpret the results

An example of a cost utility analysis of radiotherapy in non-small cell lung cancer will be used to illustrate each of these steps.

For more information about CREST, or for other factsheets in this series, please see our website:

www.chere.uts.edu.au/crest
What are the steps in an economic evaluation in the context of cancer research?

Economic evaluation is “the comparative analysis of alternative courses of action in terms of both their costs and consequences” (Drummond 2005, p9). Figure 1 below shows the typical representation of an economic evaluation.

Figure 1: Economic evaluation framework

There are seven main steps which are typical to economic evaluations, including those conducted within or alongside cancer clinical trials. Each of these will be described in this factsheet.

An example from the literature has been selected to demonstrate each of these steps in practice. The reference for this paper is:


This article is available for download from the CREST website (www.chere.uts.edu.au/crest) or is freely available online.

This example article describes a ‘societal cost-utility analysis of a Dutch multicenter randomised trial... that compared the efficacy of radiotherapy schedules...in 297 patients with inoperable non-small-cell lung cancer’.

**Step 1: Define alternatives**

Economic evaluation is always concerned with comparing alternatives. It may be that one of the alternatives is a ‘do nothing’ or ‘standard practice’ arm, however the costs and outcomes of such alternatives must still be defined, measured and valued.

In defining the alternatives, you must consider what kind of economic evaluation will be most appropriate. This decision should be based on the nature of the research question, and the anticipated differences between the costs and consequences of your alternatives. The three types of economic evaluation to consider are cost effectiveness analysis, cost utility analysis and cost benefit analysis.

In a cost effectiveness analysis (CEA), the benefits of the interventions are measured in “natural” units. For example, such measures include cases detected, or life years saved. In a CEA, the research question is directed at assessing how to maximise the achievement of a particular health outcome using available health resources. Thus, the results of a CEA are reported as (for example) cost per case detected or cost per life year gained.
In a cost utility analysis (CUA), effectiveness is measured in preference based units. This means that the natural units (e.g., lives saved or life years gained) are combined with a measure of the value that individuals place on that outcome. The most common example of a preference-based measure is the Quality Adjusted Life Year (QALY). In a CUA the research question is directed at assessing how to maximise health gain from available resources. The results of a CUA are reported as cost per QALY gained.

Finally, in a cost benefit analysis (CBA), the effectiveness of an intervention is measured terms of its monetary value (i.e., in dollars). This allows the net benefit (i.e., the cost of intervention minus the value of the benefit) to be calculated. In a CBA, the research question is directed at assessing how to maximise social welfare. Whilst this has some logical appeal, the valuation of health care outcomes in dollar terms is difficult, and CBA is not often used in health research.

Example

The alternatives to be considered in the example paper are long course versus short course radiotherapy. The background section to the paper describes the differences that the authors anticipate observing between long and short course treatment in terms of survival gains (evidence was inconclusive prior to their study which found long course more effective) and costs (higher medical, patient and ongoing costs with long course treatment). The type of study selected was a cost-utility analysis, as they used QALYs as an ‘overall measure of the patients’ quantity and quality of life’, and compared this to the total costs to society.

Step 2: Define perspective, timeframe and population

The time period for an economic evaluation should be considered in the context of the costs and consequences of the interventions under investigation. A clinical trial is usually designed to follow patients up until a specific outcome of interest or endpoint has been reached. While in some cases this may be sufficient time for the relevant costs associated with the intervention and its long term outcomes to be observed, in some cases additional follow up beyond the end of the trial may be required.

An alternative to extended follow up, which can be time consuming and expensive, is the use of modelling. This approach involves the use of trial data plus additional information about the longer term effects (usually sourced from the literature) and local information about the ongoing and/or long term costs to be used to model the costs and effects beyond the study follow up period.

The perspective of a study is primarily related to the intended audience for the results. In selecting a perspective, you are in effect selecting the range of costs and consequences to be included in the economic evaluation. A societal perspective will include all costs and consequences which are borne by society related to that intervention. This is the gold standard for economic evaluations, but can be complex to implement. In Australia, the Pharmaceutical Benefits Advisory Committee
(PBAC) define a societal perspective to include a broad definition of health care resources, including those paid for by patients, governments, health insurance agencies and any other part of society are included. However indirect costs such as productivity losses for patients and carers are usually not included. While this is not a true societal perspective, it is one which is more practical than considering all potential costs. More commonly, a hospital or health service perspective is taken, as this is often the most relevant to the decision makers who will be utilising the results of the economic evaluation.

Similarly, defining a target population is also important for perspective, because factors such as age, comorbidities, risk factors, location and socioeconomics can influence both the resource use and consequences of interventions.

**Example**

The example paper followed patients for one year after randomisation. Given the relatively short survival time of patients receiving palliative care for non-small-cell lung cancer, this would appear to be an appropriate timeframe for both costs and consequences.

The perspective taken in the example paper is an example of the societal perspective as defined by PBAC, including “medical costs of radiotherapy as well as other health care costs and costs incurred by the patients during their remaining lifetime”.

**Step 3: Identify, measure and value resource use**

First, the resources required for each arm of the trial need to be identified. Things to consider include who is required to do what to patients, when each activity occurs and how often, and how these activities may be different to standard clinical practice.

The next consideration is what reliable sources of information can be accessed to measure the resource use. Options include collecting data directly from patients or providers during the trial (patient diaries for example), identifying similar work done previously which can be adapted to your study (through a literature review), or using administrative data applied to your sample (for example, local admission rates for chemotherapy).

Finally, the value of each resource used needs to be determined. In this step, dollar values are obtained for all resources. Again, some costs may be able to be collected directly during the trial (eg patient out-of-pocket costs), but it is also common to use administrative data or tariffs to determine appropriate dollar values. Examples of this include using MBS item numbers and associated values to determine the cost of diagnostic, medical or procedural costs, or the PBS to determine prescription drug costs.

**Example**

The resources identified for inclusion in the example paper were medical costs of radiotherapy, non-medical costs of radiotherapy, such as time and travel costs for
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patients, other medical costs, health related non-medical costs, and additional health costs related to longer survival.

The usage rates and values for these resources were obtained from a variety of sources including previously published information, patient questionnaires, local ‘standard pricing’ lists for medical services and pharmaceutical products, and national administrative data.

Step 4: Identify, measure and value consequences

The same process then needs to be followed to identify, measure and value the consequences of treatment. These outcomes of treatment are often related to health gains such as a reduction in mortality, reduction in morbidity or improvements in quality of life. However additional outputs may include information, convenience, reassurance, patient satisfaction or impacts on productivity.

It is increasingly common for economic evaluations to use cost utility analyses, in which both duration and quality of life are collected.

Where an economic evaluation is being conducted alongside a clinical trial, the treatment consequences are usually collected directly from patients during the trial period. Measures such as survival, time to progression or adverse events are collected through clinical assessments, while quality of life and patient preferences are captured through patient questionnaires. To calculate QALYs, ideally the quality of life instruments should include a multi-attribute utility instrument, where the scoring captures preferences for different health states. In some cases it may be necessary to supplement information collected in a trial with additional data. For example, an economic evaluation may be concerned with outcomes beyond the endpoint of the trial, and so may use the results of previous studies with longer follow up, or administrative data to extrapolate beyond the end of the trial.

Example

The example paper collected survival and quality of life as the treatment outcomes, allowing a cost utility analysis to be conducted. Survival is specified as being collected through ‘systematic assessment’. Quality of life was measured using the EQ-5D instrument, as well as a visual analogue scale. These data were collected at baseline, weekly for the first 12 weeks, and then every second week for the rest of the year.

Step 5: Combine costs and consequences

Cost effectiveness analysis is a comparison of two or more options, in terms of the costs and outcomes associated with each. The fundamental question is whether the difference in outcomes between the approaches justify the difference in costs. The tool used for the comparison is the Incremental Cost-Effectiveness Ratio (ICER). This is defined as the extra cost of the additional service, divided by the extra outcome of effectiveness. We are interested in how much we, as a society, are paying for each unit of outcome (year of life gained, adverse event avoided etc), and whether we
could gain more of these units by using our limited resources elsewhere.

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\text{ICER} = \frac{\text{Cost}_{\text{New}} - \text{Cost}_{\text{Comparator}}}{\text{Effectiveness}_{\text{New}} - \text{Effectiveness}_{\text{Comparator}}}
\]

**Example**

Overall, the example paper found long-course radiotherapy increased survival, increased costs and improved quality of life. There was a survival advantage of long course over short course radiotherapy (38.1 vs 27.4 weeks, difference 10.7 weeks, 95% CI=0.9 to 20.6 weeks, p=0.03). However, long course radiotherapy had a total societal cost of $16,490, compared to short course societal costs of $11,164. The average utility (measured using the EQ-5D) of long course was also higher (0.41) than for short course (0.37).

These results can then be combined to obtain quality adjusted life expectancy, in this case in weeks (QALWs). The long course radiotherapy resulted in 20 QALWs, compared to short-course, with 13.2 QALWs. This is a difference of 6.8 QALWs (85% CI 0.1 to 13.5 weeks, p=0.05).

The Incremental cost-utility ratio for 10x2Gy vs 2x8Gy was $40,900 per QALY gained (95%CI = $19,400-$1,100,000 per QALY gained).

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\frac{16,490-11,160}{20-13.2} - \$40,900/QALY
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**Step 6: Assess robustness**

Sensitivity analysis helps to test the robustness of the results of the economic evaluation, and thus indicates the degree of uncertainty associated with the ICER. Sensitivity analysis also provides an understanding of the key drivers of the results and ensures transparency. If the conclusions do not change significantly as a result of the sensitivity analysis then the results are said to be ‘robust’.

Good quality trial data can overcome many of the problems which sensitivity analysis attempts to address; however, one aspect of uncertainty which cannot be overcome in this way is sampling, which can be addressed with bootstrapping. For more information about the different methods of sensitivity analysis, please contact the CREST team.

**Example**

The areas of uncertainty identified in the example article were the unknown date of death, the utilities used, and the cost estimates. Changing the date of death to assume longer survival led to increased life expectancy and quality adjusted life expectancy, however costs also increased and so overall the ICER decreased ($40,800/QALY gained).

By using self-assessed health utilities rather than the values collected through the EQ-5D, the number of QALYs gained increased for both groups, and differences in terms of QALYs gained between the groups were reduced. In this case the ICER decreased to $43,300/QALY gained.
Finally, the cost estimates had a significant impact on the ICER. Excluding the survival related costs reduced the ICER to $20,900/QALY gained. Including consumption costs led to an ICER of $64,500/QALY gained, while excluding non-radiotherapy costs decreased the ICER to $12,800/QALY gained.

Step 7: Interpret results.

The ICER represents the additional amount of resources required to gain an additional unit of health outcome. However, in order to interpret this result we need to know either how much society is willing to spend to gain a unit of health outcome (i.e. to have a threshold above which an ICER is not considered cost-effective), or to be faced with a budget constraint (i.e. to have a fixed amount of money we are able to spend). If there is a non-fixed (endogenous) budget the threshold may be interpreted as the societal willingness to spend on health care. In cases where there is a fixed (exogenous) budget the threshold may be interpreted as the opportunity cost of the health intervention displaced by the expenditure on the new intervention.

Example

In Australia in the context of MSAC and PBAC decision making, the budget is not fixed. Previous research has indicated that an implicit threshold of $50,000 per QALY exists in Australia. In other words interventions are usually funded if they have an ICER that is less than $50,000 per QALY, however these committees do not have a fixed or explicit threshold. At a threshold of $50,000 per QALY the long-course radiotherapy may have an acceptable ICER and consequently may be accepted for funding. However, considerations such as the extent of uncertainty associated with the ICER, whether the increased costs can be afforded by the funding body, the radiotherapy services capacity, and the ability of these results to be generalized to other contexts would all need to be considered.

For more information

For more information on any part of this factsheet, please contact either Rosalie Viney (rosalie.viney@chere.uts.edu.au) or Alison Pearce (Alison.pearce@chere.uts.edu.au)

References
