

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.

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SUMMARY

- The aim of economic evaluation is to inform clinical and health system decision making and policy
- Every time a decision is made about a new technology or treatment, a decision is also made about resource allocation
- Economic evaluation is a formal and systematic comparison of the costs and benefits associated with two or more interventions
- Once the costs and benefits are known for each treatment group the results are expressed as an *incremental cost-effectiveness ratio*
- Randomised controlled trials are commonly used as a vehicle for economic evaluations, however not all clinical trials are suitable
- Some modification of the trial design may be required to incorporate an economic evaluation. Areas to consider include
 - population
 - comparators
 - sample size
 - endpoints
 - follow up
 - perspective and
 - data collection

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

www.chere.uts.edu.au/crest

Why would I do an economic evaluation as part of my clinical trial?

Clinical trials are designed to evaluate the safety, efficacy and/or effectiveness of one or more health care interventions or technologies. Every sort of evaluation is undertaken with the assumption that the results will assist some kind of decision – a decision about whether a new technology or intervention is safe and efficacious for introduction into clinical practice (e.g. by the TGA), a decision about whether a particular patient group will benefit from a new technology or intervention (e.g. to inform clinical decision making by individual providers), whether technology A should be recommended as best practice over technology B (e.g. to inform the development of clinical guidelines by the NHMRC), or whether technology A should be funded by the health service.

Every time such a decision is made, an *implicit* or *explicit* decision is also made that resources will be allocated in one way and not in another. If, as well as evaluating whether a treatment is effective, we also evaluate whether it represents value for money, i.e. whether it is relatively cost-effective compared with the current treatment, we are adding to the information available to decision makers at every level of the health system. Economic evaluation is an aid to, not a substitute for, decision making, and, like all evaluations, requires value judgements. The main difference is that using the results of economic evaluations makes these value

judgements more *explicit* than might otherwise be the case.

The aim of economic evaluation is to inform clinical and health system decision making and policy. This is also the aim of many trials, that is, to determine if an intervention is likely to be of value. Hence, considering the implications of any trial in terms of how clinical decisions might be affected depending on the outcomes of the trial should be an essential component of trial design, and informs whether the trial is worth doing. In considering this, it is essential to address not just the outcomes for patients, but also the implications for resource use, recognising that clinical decisions are made in the context of scarce health system resources.

What is an economic evaluation?

Economic evaluation is a formal and systematic comparison of the costs and benefits associated with two or more interventions. In essence an economic evaluation compares the additional net costs and the additional net health benefits of a new treatment compared with the existing treatment. If all the costs and outcomes are measured, an estimate of the average cost and benefit across all patients in the treatment(s) and control groups can be calculated for each group. Once the costs (impacts on resource use) and outcomes have been determined it is possible to derive the cost-effectiveness of the new treatment

relative to the alternative. This is simply the difference in costs divided by the differences in benefits. Formally this ratio is known as the incremental cost-effectiveness ratio (ICER) and can be written:

$$ICER = C_{new} - C_{comparator} / E_{new} - E_{comparator}$$

where C equals costs and E equals effect.

Using the ICER a number of cost-effectiveness options can be identified.

- *The new treatment may be more effective and less costly than the alternative.* In this case the new treatment is said to dominate the alternative and the new treatment should be adopted.
- *The new treatment may be less effective and more costly than the alternative.* In this case the new treatment is said to be dominated by the alternative and the new treatment should not be adopted.
- *The new treatment may be less effective and less costly than the alternative.* Consequently there is a trade-off between costs saved and health benefit forgone.
- *The new treatment may be more effective and more costly than the alternative.* Consequently there is a trade-off, since additional health benefits can be obtained at higher costs.

For the last two possibilities, the question is whether the trade-off in terms of health gain (or cost saving) is worth the additional cost (or health loss). In both these cases more information is required regarding the decision maker's willingness-to-pay for a health effect (i.e. a threshold). Once this is known, it is possible to determine whether the new

treatment is cost-effective, and subsequently should be adopted.

Is my trial suitable for economic evaluation?

Randomised controlled trials are commonly used as a vehicle for economic evaluations. As with all clinical trials, a clinical trial that incorporates an economic evaluation should be designed to maximise the internal and external validity, reduce bias and confounding and aim to measure the true net effect of the new treatment. The only additional aim of incorporating an economic evaluation within a trial is to determine the cost-effectiveness of the new intervention.

Not all clinical trials are suitable for the inclusion of an economic evaluation.

- If the new treatment is still in early development (i.e. Phase II). For example, the aim of the trial might be to determine the most effective dosing regimen for a new chemotherapy agent. In this case an economic evaluation may provide an inaccurate cost-effectiveness estimate because the dosing regimens used in the trial may be sub-optimal.
- If the treatment in the trial is atypical or very different to current/expected practice. The results of an economic evaluation may be meaningless to the decision maker. This is particularly important when trials are non-naturalistic. For example, if the radiotherapy treatment schedule is markedly different to what a patient would normally receive, the cost-effectiveness of the new treatment

relative to current practice will be bias and non-informative.

- If it is clear that the differences between the interventions in terms of cost is likely to be negligible, then it may not be worth doing an economic evaluation - the evaluation of the effectiveness of the alternatives may provide the most useful information. For example, if a trial was investigating different radiotherapy dosages, but the number of study visits and side-effect profiles were expected to be similar, the expected differences in terms of costs may be minimal.

In the following cases, where economic information may not alter the funding decision, an economic evaluation may not be required. However, it would be preferable to include one where possible:

- The new intervention is so effective that cost is unlikely to prevent implementation, particularly when the therapy is effective in a group of patients that are currently untreatable. For example, the new treatment may add a year of life expectancy for individuals with a type of cancer that was previously untreatable and highly fatal.
- The therapy is novel so clinicians will use it even if not cost-effective. For example a new surgical procedure may become available following improvements in surgical techniques and equipment.

In summary, if you have good reason to believe that the new treatment will be cheaper *and* equally or more effective than the alternative OR that the new treatment

will be both more expensive and more effective than the alternative, it may be worth incorporating an economic evaluation into your clinical trial. It is worth noting that even when a trial is suitable for economic evaluation, it may be necessary to undertake economic modelling beyond the time frame and outcomes of the trial to determine the overall cost-effectiveness of the intervention. Economic evaluations typically combine information from trials and from other sources to model the costs and outcomes of the intervention.

What additional information would I need to consider when incorporating an economic evaluation into my planned trial?

For some clinical trials an economic evaluation can be simply added to the existing trials design, without amendment. However for most trials, some modification of the original trial design may be required, these design issues are discussed below. Ideally an economic evaluation should be planned during early study development and a health economist should be included in the study team.

Comparator – Choosing the correct comparator is one of the most important considerations for any economic evaluation. In many clinical trials a placebo may be an appropriate comparator, however for economic evaluations the comparator should be commonly used, ideally the next best alternative available to the patient, and the treatment most likely to be displaced if the new treatment adopted. In addition, the comparator should be used in the trial as it is

intended to be used in current practice. The comparator may be best supportive care if this is the treatment usually provided. Of course it is possible for more than one comparator to be compared. Ideally, the cost-effectiveness of the comparator should be known.

Patient population – The trial population should be as similar to the intended patient population as possible. This means that the inclusion and exclusion criteria of the trial may need to be modified if an economic evaluation is included.

Sample size – The sample size of the trial is usually based on the primary clinical outcome rather than the economic endpoint. It is possible to adjust sample size calculations to reflect the economic evaluation endpoints. However, more often than not economic comparisons are underpowered. This sample size restriction means that the cost-effectiveness is usually estimated rather than analysed formally through hypothesis testing.

Endpoints – The choice of clinical endpoint for the trial may not be ideal for an economic evaluation. For example, composite endpoints are unsatisfactory since the endpoints are rarely of equal importance. Intermediate and surrogate endpoints may also be problematic, if the relationship to the final outcome of interest is uncertain. However, if intermediate outcomes are unavoidable, two approaches may be used: 1) additional evidence may be acquired that links the intermediate outcome with long term costs and outcomes, or 2) further follow-up data may be required.

For most economic evaluations, the preferred outcome measure is the quality adjusted life year (QALY). This is because the QALY incorporates morbidity and mortality into a single measure and it can be used to compare different health technologies.

Follow-up – Clinical follow-up and the follow-up period required for the economic evaluation may differ. Ideally, economic evaluations should include lifetime costs and outcomes, whereas clinical trials are usually conducted over much shorter periods. In many cases if costs and benefits accrue outside the study period the actual cost-effectiveness of the new treatment may change over time. Subsequently there is a trade-off between the follow-up period required for the trial and the desired follow-up for the economic evaluation. The stronger that relationship between the intermediate outcome and the long term disease outcome, the more a reliance on intermediate endpoints can be justified. When the relationship between intermediate and final outcome is weak the economist should request a longer follow-up period.

A solution to short follow-up periods is to conduct decision analytical models that use data from the trial and extrapolate into the future based on other clinical studies or registry data

Perspective – Consideration should be given to the study perspective, since this affects the types of resource use information collected. For example, if the study is conducted from a societal perspective, the following costs might be included: Direct medical costs, patients'

costs for transportation, time spent undergoing treatment, caregiver time, and non-medical goods and services attributable to the disease or treatment.

Data Collection – Collection and management of the economic data should be integrated with the collection of the clinical data. (i.e. there should be no distinction between the clinical and economic data elements). There should be a plan for ongoing data quality monitoring to address missing and poor quality data issues immediately. Queries should be managed on an ongoing basis rather than at the end of the trial.

For economic evaluations it is important that the results of the trial are generalisable

Most clinical trials have high internal validity, but may have low external validity. In other words the results of the trial may not be generalisable to the general population. The threats to external validity come from:

- 1) Restrictive inclusion and exclusion criteria (patient population, disease severity, co-morbidities). In other words the trial population does not reflect the actual patient population.
- 2) Protocol-driven resource use (which can bias costs in each treatment arm),
- 3) Unrepresentative recruiting centres (e.g. academic hospitals),
- 4) Inclusion of study sites from countries with varying access and availability of healthcare services, and
- 5) Artificially enhanced compliance to study medication.

In summary, economic evaluations alongside clinical trials share many design issues with traditional clinical trials. The more naturalistic the trial the more likely the data will answer the decision maker's question.

Importantly, successful economic evaluations requires planning, support and early involvement with study team

For more information

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