

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

Economic evaluations aim to assess the effectiveness of interventions in clinical practice and hence the data collected in a clinical trial setting may need to be adapted or translated. More specifically:

- Differences between the trial population and target population for the intervention may impact on the baseline risk of events and/or the efficacy of the intervention. If the baseline risk differs, the event rate from the control arm of the trial may need to be modified for use in the economic evaluation. If the efficacy differs, it may be appropriate to adjust the trial efficacy estimates or to use the results of trial subgroup analyses in the economic evaluation.
- The resource use in the clinical trial may not reflect local clinical practice. Additional local data may need to be collected for use in the economic evaluation.
- The follow-up in the clinical trial may be shorter than the timeframe for the economic evaluation. Therefore, the data may need to be extrapolated beyond the duration of the trial for use in the economic evaluation.
- The outcome measures in the clinical trial may need to be translated into final patient relevant outcomes for use in the economic evaluation. For example, tumour response or progression free survival may need to be translated into overall quality-adjusted survival.

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Translating Clinical Trial Data for use in an Economic Evaluation

Clinical trials are a key source of information for use in preparing economic evaluations. Trials provide information on the efficacy of an intervention when used in a particular way, helping to inform not only measures of effect or outcomes, but also how resources are used. However, the purpose of an economic evaluation is to provide information about the costs and effectiveness of interventions once they enter clinical practice. This means that the information collected in clinical trials may need to be adapted or translated for use in an economic evaluation. For example:

1. The trial participants may be different in important ways from the population seen in usual clinical practice;
2. The use of the intervention in the trial may differ from its use in clinical practice;
3. The period of follow-up in the trial may be shorter than the expected duration of treatment or expected duration over which health benefits or resource use accrue in usual clinical practice; or
4. The outcome measure in the trial may not be a patient-relevant final outcome that can be used to estimate a meaningful incremental cost-effectiveness ratio.

Examples 1 and 2 are referred to as applicability issues, example 3 is an extrapolation issue and example 4 is a transformation issue. Each of these translation issues is discussed in this FactSheet with examples provided.

Applicability Issues

The populations seen in usual clinical practice (and thus the population of interest for the economic evaluation) may differ from the population enrolled in the efficacy trials. For example, there may be differences in terms of their demographic factors, disease characteristics and prognostic indicators. There may also be differences in the way the intervention is used in clinical practice compared with its use in the clinical trials. For example, there may be differences in terms of the dose used, the treatment duration or the co-administered therapies.

In an economic evaluation the absolute (or incremental) treatment effect is measured. The absolute treatment effect is a function of the baseline risk of events (risk of events in the control group) and the relative treatment effect (eg. relative risk, hazard ratio).¹ Differences between the trial and target populations may affect the baseline risk, the relative treatment effect or both of these measures. There may be a number of differences between the trial and target populations. However, only those differences that substantially impact on the baseline risk of events or the relative efficacy of the intervention need to be accounted for in the economic evaluation

(<http://www.pbac.pbs.gov.au/section-c/c1-identification-issues-to-be-addressed.html>). It

is more common for the baseline risk of events to be varied than the relative efficacy of the intervention.

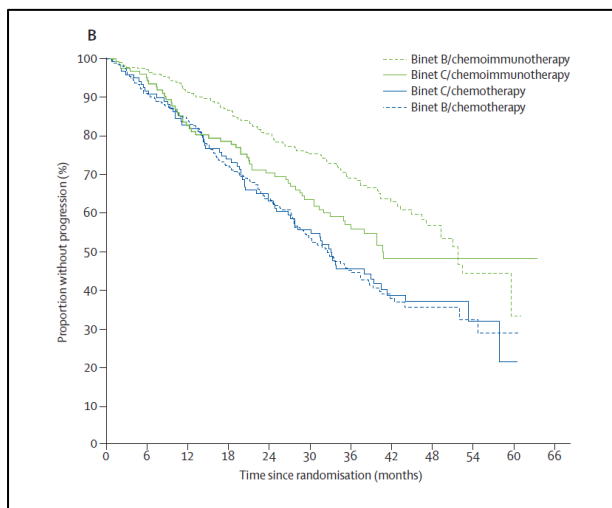
An example of the baseline risk being different for the target population compared with the trial population is where an economic evaluation is restricted to patients with more severe disease. In this situation a higher rate of events (regardless of treatment) can be

expected in the target population than was observed in the trial population. The event rate for the control arm of the economic evaluation may be sourced from a different study, or from a subgroup of the trial population. The information from the clinical trial(s) on the relative efficacy for the intent-to-treat population would then be applied to the event rate of the control arm.

Example: Impact of CLL disease characteristics on baseline risk and rituximab treatment effect.

The CLL-8 trial by Hallek et al (2010) randomised patients with chronic lymphocytic leukaemia (CLL) to treatment with fludarabine, cyclophosphamide and rituximab (chemoimmunotherapy) or fludarabine and cyclophosphamide (chemotherapy).² The results for progression free survival (PFS) by Binet disease stage are presented in Figure 1.

Figure 1: Progression-free survival in the CLL-8 trial by treatment and Binet stage



For patients treated with chemotherapy the risk of progression is the same for patients with Binet stage B and Binet stage C disease. Thus the baseline risk of events (progression) is the same regardless of Binet stage. However, the relative efficacy of chemoimmunotherapy in terms of PFS appears to be greater for patients with stage B disease compared with stage C disease (Binet stage B HR: 0.50, 95% CI: 0.39-0.65; Binet stage C HR: 0.73, 95% CI: 0.51-1.04). Thus if the economic evaluation was restricted to patients with Binet stage B disease it may be appropriate to use the efficacy estimate from the Binet stage B subgroup rather than the ITT population. Ideally, the heterogeneity of treatment effect across Binet stage should be shown to be statistically significant if the results from a subgroup are to be used in an economic evaluation.

Source: Hallek M, Fischer K, Fingerle-Rowson G et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet* (2010) 376:1164-74

In the chemotherapy group of the CLL-8 trial, the risk of progression was higher in patients with an unmutated IGHV status compared with that for patients with a mutated IGHV status (PFS at 3 years of 35% versus 55%). Thus if the economic evaluation was restricted to patients with unmutated IGHV status it may be appropriate to estimate the risk of events in the chemotherapy (control) arm from the subgroup of patients with unmutated IGHV status. The ITT efficacy estimate would then be applied to estimate the risk of events with chemoimmunotherapy.

An example of the relative efficacy of the intervention being different for the target population compared with the trial population is where an economic evaluation is restricted to patients with a specific genetic mutation in which the treatment is more effective (such as in the CLL-8 trial described above). In this situation the relative efficacy of the intervention may be sourced from a subgroup of the trial.

Another applicability issue that commonly arises is that the resource use in the clinical trial does not reflect that in clinical practice. This may be because the trial reflects resource use in overseas health care systems or the requirements of the trial protocol mean that additional resources are used, for example in testing for recurrence more frequently than would occur in usual clinical practice. Australian patterns of health care resource use can be estimated by undertaking a cross-sectional study or chart audit, or by surveying Australian experts. If possible, the results of the additional research should be compared with the resource use reported in the trial to understand whether there are any differences that might give rise to differences in the observed outcomes. For example, use of granulocyte colony stimulating factors (G-CSFs) in fewer patients or less often in usual practice compared with the trial may result in a higher incidence of neutropenia in patients receiving usual care.

Extrapolation Issues

As noted in the CREST FactSheet entitled “Step by Step Guide to Economic Evaluations in Cancer Trials”, the timeframe for the economic

evaluation should be long enough to capture all relevant costs associated with the intervention and for its long-term outcomes to be observed. In some cases this requires modelling in which the trial data are extrapolated using additional information about the longer term effects and ongoing and/or long-term costs. It is important to ensure that the costs and outcomes are modelled over the same time period; for example, if outcomes are extrapolated over a 10 year time horizon, relevant costs during the 10 year period should also be considered.

Extrapolating Time to Event Data

For economic evaluations of cancer interventions, time to event data such as PFS or overall survival, often need to be extrapolated in order to estimate mean survival. Mean survival is calculated as the area under the Kaplan-Meier survival curve and this may involve extrapolation beyond the point of the last observed event (eg. death or progression) in each trial arm. Extrapolation requires that assumptions be made about the shape of the survival curve and the extent of any treatment effect that may continue to apply beyond that observed in the trial. Both of these assumptions may significantly affect the estimates of difference in mean survival between the intervention and comparator treatments, and hence the relative cost-effectiveness of the alternatives, especially when relatively large proportions of patients remain event free at the end of the study and a substantial amount of extrapolation is required.

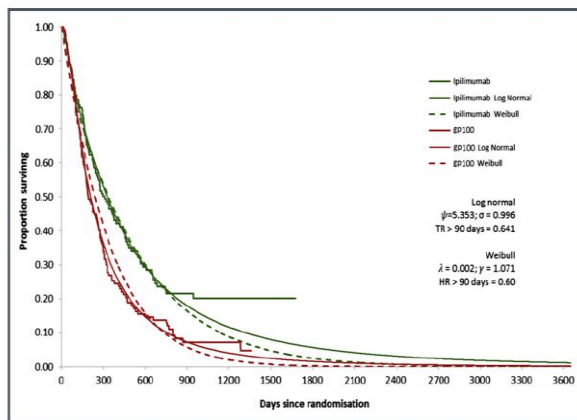
Kaplan-Meier survival curves may be extrapolated by fitting a parametric function (eg. exponential or Weibull function) to the trial data or by using data from non-randomised studies to estimate death rates in the post-trial period.³ Once the therapy has ceased (eg. following a fixed number of cycles

of chemotherapy), it may be appropriate to assume no additional efficacy (i.e. a hazard ratio of one) for the extrapolated period. A more conservative assumption would be to assume a hazard ratio of greater than one so that the survival curves merge.

Example: Extrapolation of overall survival data for ipilimumab and gp100.

This example is sourced from Davies et al (2012).⁴ A randomised trial compared ipilimumab alone, gp100 alone and ipilimumab plus gp100 in 676 patients with metastatic melanoma whose disease had progressed while they were receiving therapy for metastatic disease.⁵

Figure 2: Extrapolation of survival curves for ipilimumab and gp100 using different parametric functions



The comparison of ipilimumab alone and gp100 alone is presented. Patients were followed for up to 55 months. The Kaplan-Meier estimates of the proportion of patients alive at the end of the follow-up period were 20.1% for ipilimumab and 4.7% for gp100. The median survival and mean survival estimated by fitting different parametric functions (log-normal distribution and Weibull distribution) are presented in Table 1. The trial Kaplan-Meier curves and fitted functions are presented in Figure 2. The log normal function results in lower death rates in the extrapolation period and a higher estimate of the incremental survival.

Table 1: Estimated survival for ipilimumab and gp100 based on the Hodi et al 2010 trial⁵

Approach to estimate survival	Ipilimumab	gp100	Difference
Median survival	10.1 months	6.4 months	3.7 months (HR = 0.66, P=0.003)
Mean survival, restricted to 48 months (1440 days) of follow-up	18.87 months	11.27 months	6.3 months
Mean survival, gp100 arm extrapolated by fitting a log-normal distribution; ipilimumab arm extrapolated using efficacy estimates from the trial	18.5 months	11.5 months	7 months
Mean survival, gp100 arm extrapolated by fitting a Weibull distribution; ipilimumab arm extrapolated using efficacy estimates from the trial	Not reported	Not reported	5.7 months

Source: Davies A, Briggs A, Schneider J et al. The Ends Justify the Mean: Outcome Measures for Estimating the Value of New Cancer Therapies. *Health Outcomes Research in Medicine* (2012) 3, e25-e36

Patients switching or crossing-over from their allocated treatment to another trial treatment, or a non-trial treatment, can complicate the extrapolation of Kaplan-Meier survival curves. In the majority of cases, these switches are non-random and are related to disease progression. For example, if some patients in the control arm switch to receive the trial treatment, this is likely to result in an underestimate of the incremental survival. Statistical methods such as the Rank Preserving Structural Failure Time (RPSFT), and Inverse Probability of Censoring Weighting (IPCW) are available to adjust for the effects of cross-over.⁶ However, cross-over will result in the within-trial and extrapolated survival estimates being more uncertain.

Transformation Issues

Often, the outcomes measured in trials are clinically relevant but are not suitable for use in an economic evaluation. For example, PFS or changes in tumour volume may be measured in the trial whereas an estimate of overall survival may be required for the economic evaluation.

In this case, the trial outcomes are considered to act as surrogates for the final patient-relevant outcomes. To establish the relationship between a surrogate and final outcome, the guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) recommend the following steps

(<http://www.pbac.pbs.gov.au/>):

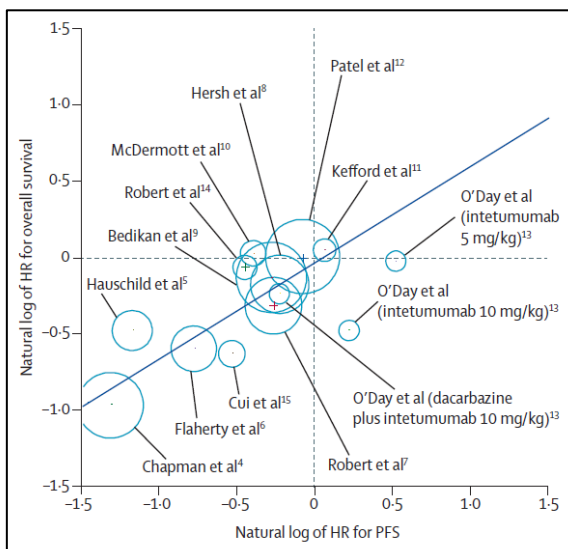
- Step 1 — Present a systematic review of the literature to examine whether epidemiological evidence and biological reasoning has established that there is a relationship between the surrogate outcome and the final outcome independent of any intervention.
- Step 2 — Present a systematic review of the literature to examine whether randomised trial evidence using other interventions has shown that there is a basis to conclude that a treatment effect on the surrogate outcome has satisfactorily predicted a treatment effect on the final outcome. Based on this evidence, quantify the relationship between a change in the surrogate outcome and a change in the final outcome.
- Step 3 — Explain why the relationship is likely to apply to the proposed intervention.

In a cost-utility analysis, quality of life and overall survival are incorporated into a single measure, quality adjusted life years (QALYs). This may require transforming the outcome(s) measured in the clinical trials to value them in utility terms. The sourcing of utility weights is discussed in the CREST FactSheet entitled, “How Oncology Studies Obtain QALY Weights: a Literature Review.”

Example: Transforming PFS to overall survival in malignant melanoma.

Flaherty et al 2014⁷ examined the relationship between PFS and overall survival in metastatic melanoma. Twelve randomised controlled trials were identified that used dacarbazine as the control arm and measured both PFS and overall survival. Figure 3 presents a plot of the natural logarithm of the hazard ratio for PFS versus the hazard ratio for overall survival. The size of the circles is proportional to the sample size for each trial. The Pearson correlation coefficient, weighted by trial sample size, was 0.89 (95% CI 0.68-0.97) suggesting a strong correlation between the 2 measures.

Figure 3: Correlation between treatment effects on overall survival and PFS



In order to estimate overall survival from PFS the relationship between PFS and overall survival needs to be quantified. The regression line in Figure 3 quantifies the relationship eg. with an observed hazard ratio for PFS of 0.5 (natural log of 0.5 = -0.69), the estimated hazard ratio for overall survival would be 0.625 (natural log of 0.625 = -0.47). The relationship has been established using trials with a dacarbazine control arm and therefore it is unknown if this relationship holds when alternative agents, such as immunotherapeutic agents, are used.

Source: Flaherty K, Henning M, Lee S et al. Surrogate endpoints for overall survival in metastatic melanoma: a meta-analysis of randomised controlled trials. *Lancet Oncology* (2014) 15(3):297-304

For More Information

For more information on any part of this factsheet, please contact:

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7. Flaherty KT, Hennis M, Lee SJ, et al. Surrogate endpoints for overall survival in metastatic melanoma: a meta-analysis of randomised controlled trials. *The Lancet Oncology* 2014;15:297-304.

Other Titles in the CREST FactSheet Series:

- [Discounting in Economic Evaluations in Health Care: A Brief Review](#)
- [How oncology studies obtain QALY weights: a literature review](#)
- [Sample size calculation in economic evaluation](#)
- [Economic evaluations in cancer clinical trials - why would I do an economic evaluation as part of my clinical trial?](#)
- [Medicare Australia data for research: an introduction](#)
- [Health related quality of life for economic evaluations in cancer - why do clinical trials need economic evaluation-specific quality of life measures?](#)
- [Step by step guide to economic evaluation in cancer trials](#)
- [Command Files to Generate EQ-5D Weights for Australia - EQ-5D TTO DCE Weights](#)
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