

**Checklist for the Design and Protocols to
Collect Economic Data Alongside Clinical
Trials in Australia**

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July, 1997

ISSN 1325-0663

ISBN 1 875677 49 6

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ACKNOWLEDGMENTS

The following checklist for incorporating economic evaluation alongside clinical trials was developed as a result of materials presented at workshops on this topic held in Melbourne on 27 July 1995 and in Sydney on 3 and 4 August 1995. We gratefully acknowledge feedback provided by the workshop participants both at the workshop and to early draft guidelines,

The authors of this checklist would also like to thank Ms Julie Nutting (Sandoz Australia), Ms Vicki Stynes (SmithKline Beecham Pharmaceuticals), Mr David Grainger (Eli Lilly Australia), and Dr Michael Ortiz (Glaxo Wellcome Australia Ltd) for their presentations and for leading group discussions at the workshop.

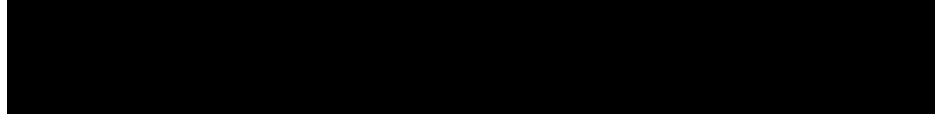


ABSTRACT

There is growing interest in Australia and overseas in the incorporation of economic evaluations alongside randomised clinical trials of new versus existing pharmaceutical products. The most common use of data resulting from such trials will be for the purpose of industry gaining listing under the Pharmaceutical Benefits Scheme (PBS) for specific drugs. Other uses of data include: applications for hospital formulary listing; post-marketing support for price justification; and publication of study findings in academic journals.

When designing a clinical trial with an economic component a number of considerations need to be taken into account. These include: from whose perspective are the costs and outcomes to be measured (eg. societal, governmental, personal); which costs are to be included (eg. treatment, complications, retreatment, disease sequelae, indirect costs); the choice of outcome measures (short, intermediate or long-term outcomes); the appropriate duration of the trial necessary to measure the important costs and key outcomes. Decisions about each of the above can have a significant influence on study design.

A multi-disciplinary approach is required to ensure appropriate study design. Direct input from clinician investigators, clinical research associates, economists, marketing personnel and statisticians is important at the early stages of protocol development. This is necessary to ensure an appropriate trial design, and to minimise the potential for key data not being collected alongside the trial.



1 Introduction

Economic issues have become an important element in the overall acceptance of new drugs. Funding bodies and providers of health care have to function within a constrained budget and have to consider not only safety and therapeutic effectiveness, but also the value for money of new pharmaceutical products. Governments at all levels, hospital formulary committees, prescribing doctors and practising pharmacists have to assess not only whether a new drug offers a potential health improvement, but also whether that improvement comes at the expense of greater potential health gains if resources were directed elsewhere in the community. For this reason governments and other purchasers of pharmaceuticals are increasingly interested in evidence of the cost effectiveness of new products. Australia has been one of the first countries to introduce formal economic evaluation of pharmaceuticals (Henry 1992; Drummond 1995). Guidelines have been developed and refined (Evans et al 1992; DHHS 1992 & 1995), and all new drugs submitted for listing on the Pharmaceutical Benefit Scheme (PBS) must include a formal economic evaluation.

(i) Why Collect Economic Data Alongside a Trial?

There are advantages in collecting economic data on drug-related resource use and health outcomes alongside randomised clinical trials. The principal reason is that it allows for timely collection of information on treatment costs and health outcomes specific to patients eligible for the drug. Such information may not be available at any other time, and is therefore best collected prospectively. Such prospective measurement of costs and outcomes under the same conditions and for the one patient population within a single study is not only more efficient, but may be less expensive overall than performing a later retrospective study to estimate costs (Drummond 1995). In addition, in clinical trials this process allows comparison with the cost of alternative drug treatment(s), placebo or in some cases standard non-drug management.

Most economic evaluations alongside clinical trials in Australia have traditionally been added on to an established clinical trial either prospectively or, in many cases, involving a retrospective analysis of trial data. Often secondary data sources are used in a modelling exercise to supplement trial data. A limited number of clinical trials have been designed to prospectively incorporate the collection of economic data. Such prospective cost-effectiveness trials may be undertaken in Phase II-III clinical development or subsequently

in the post-marketing phase. It is more feasible in post-marketing studies to introduce a naturalistic design to more appropriately reflect clinical practice.

(ii) Purpose of Checklist

All clinical trials are subject to numerous biases and there are well established approaches to minimising these biases by careful choice of trial methodology, study parameters, and measurement instruments. In the case of a clinical trial involving economic analysis, the range of choices open to investigators on trial methodology, study parameters and measurement instruments are potentially greater (Drummond et al 1987; DHHS 1995). Choices include:

- from whose perspective are the costs and outcomes measured (eg government, other funding bodies, personal, institutional);
- which costs are to be included (eg complications, retreatment, disease sequelae, indirect costs);
- appropriate prices to attach to resource utilisations;
- the appropriate time period of the study.

The purpose of this working paper is to provide general guidelines to assist clinical research professionals from the pharmaceutical industry in designing protocols to incorporate economic data alongside clinical trials. In Australia, the most common use of data resulting from such trials will be for the purpose of listing under the Pharmaceutical Benefits Scheme (PBS). However, the principles of the checklist are applicable to uses of economic evaluation other than PBS listing, including hospital formulary listing, post-marketing support for price justification, and publication of study findings in academic journals. The guidelines are also relevant for the evaluation of non-drug technologies (eg surgery, diagnostic procedures). It should be emphasised that the checklist does not cover all aspects of designing clinical trial protocols, but rather highlights areas of importance when the trial is being designed to incorporate economic data.

The working paper is presented in four sections. Section 2 of the paper outlines general principles relevant to incorporating the collection of economic data alongside clinical trials. This is followed in Section 3 by the checklist for the design of the trial. Section 4 of the paper provides a detailed bibliography of articles on both economic evaluation methodology and more specifically on issues relating to incorporating economic data alongside clinical trials. While less emphasis is given specifically to data analysis of trial results and modelling of the results to usual clinical practice in this checklist, it is useful for readers to gain an understanding of the issues involved in the economic analysis of trial data. Important issues include issues of time preference and discounting future cost and benefits, and how to deal with uncertainty regarding key cost and outcome assumptions in the trial. Key references on these important areas are provided in the bibliography.

2 General Principles

(i) Importance of a Strategic Planning Approach

When designing a clinical trial with an economic component, a pharmaceutical company may have a number of objectives in mind. The results of the trial may be used for a number of different purposes. These may include: regulatory approval; PBS listing; institutional purchasing; and consumer and clinician acceptance of the drug. Direct input from clinical investigators, economists, marketing and statisticians is important at the early stages of protocol development. This helps to minimise the chances of key data (eg important cost categories) not being collected alongside the trial, or inappropriate sample size or statistical analyses being used. In the case of insufficient sample size, invalid conclusions can be drawn about potentially important differences in treatment cost and effectiveness. This last issue is discussed in more detail in Section (iv) below.

If working for a multi-national company, it will be necessary to resolve any differences between local and head office priorities (eg suitable comparator, appropriate dosage and formulation in Australia) prior to commencing the trial. The purpose of the study (eg for Therapeutic Goods Administration (TGA) registration, PBS listing or market support) will influence the choice of comparator (eg placebo versus active comparator, most widely prescribed versus highest dollar market share competitor). Data collected alongside Phase II clinical trials can be used to supplement other key information (eg cost-of-illness or economic forecasting as a part of early product planning) to gain a better insight into the potential market for the product.

(ii) When is it Appropriate to Incorporate an Economic Evaluation Alongside a Trial?

The more naturalistic the trial setting, the greater the benefits from conducting the economic analysis alongside the trial. That is to say, economic evaluation is best performed using data on comparative costs and outcomes in 'usual' clinical practice rather than in the special setting of a clinical trial.

However, it may be inappropriate to include an economic component to a trial if the choice of comparator is so atypical of usual practice that generalisations cannot be made. While some of the necessary data can be grafted on to the analysis using modelling at a later stage, the closer the trial is to providing policy relevant information to clinical practice then the more useful it will be. Such data may be more appropriately collected outside the trial protocol in special circumstances. For example, specific surveys could be undertaken to collect cost or resource utilisation data from patients or health care providers alongside trials.

(iii) Purpose of the Study

Economic evaluation can be undertaken from a number of different viewpoints or perspectives. The most comprehensive perspective is the societal one in which all costs and outcomes are identified and valued in the analysis regardless of who bears the cost, who receives the benefits or who provides the resources. This broad societal perspective is generally regarded as the appropriate primary viewpoint for economic evaluations.

Different Perspectives

Although the societal viewpoint is relevant for overall resource allocation decisions, it may not be relevant to particular individuals or organisations making decisions about participating in, providing, or paying for a treatment. Accordingly one or more additional viewpoints could be included in the study (Torrance 1996). For example, whilst the PBAC guidelines recommend that the societal perspective be considered in submissions, they also require that the financial implications to the Commonwealth (PBS and other implications) are estimated.

The perspective of the economic evaluation can have a substantial influence over the study design. It may determine in part the choice of comparator, the study population, the types of costs and outcomes measured, and may even influence the type of economic evaluation to be performed.

In general the broader the perspective the wider the range of costs and outcomes which need to be collected. Consider which costs and resource utilisations need to be collected given the purpose of the economic evaluation. For example, for marketing purposes, indirect costs such as employee absenteeism may be more important an issue than for PBS listing (refer to the checklist in Section 3 for a list of cost categories).

In some circumstances however costs specific to a single payer may be of more interest than those of the government which balances costs to all groups. An example is lost earnings. If treatment produces a change in paid work force status this will impact on individual income and possibly disability insurance payments. However if there is no actual lost production, for example if a previously unemployed individual takes on the vacant job, there is no net cost of overall lost earnings. One person's loss is another's gain from a societal perspective in economic evaluations. The guidelines for submissions to the PBAC discourage the inclusion of productivity losses or gains in economic evaluation (DHHS 1995).

Study Comparator

For PBAC purposes, the most appropriate comparator to use in Phase II-III trials is the drug(s) most likely to be replaced in practice by the new product. This is clearly outlined in the PBAC guidelines (DHHS, 1995). If the proposed drug is in a therapeutic class for which a drug is already listed on the PBS, the appropriate comparator will be the analogue most widely prescribed on the PBS. If the proposed drug is of a new therapeutic class, but there are other drugs listed to treat that condition, the main comparator will be the drug most widely prescribed for that indication. If no currently listed drug is available, the choice of comparator will be current medical or surgical management where the new drug represents a potential alternative to such management. It is also important to ensure that the drug dosage and formulation of the comparator are appropriate for Australia.

In certain circumstances it may be appropriate to include a comparator which, while not currently the most widely prescribed drug, is expected to reach this status by the time the new drug will be listed on the PBS. It may be advisable to convene an expert panel or conduct interviews with key opinion leaders to clarify this or to consult with the PBAC Secretariat prior to commencing the trial. Overseas drug utilisation trends may give some indication of future drug use in Australia, particularly if the new drug to be listed on the PBS or its main comparator gains early marketing approval in some countries.

For Phase II or early Phase III studies for registration purposes, a placebo may be the more relevant comparator in some therapeutic areas, or may be included as one of the comparison groups in the trial.

The appropriate comparator may also be influenced by the viewpoint of the study. A third party payer or funder will be interested in the change in revenue from replacing existing practice with the new drug, where they may or may not pay the full cost of current treatment.

The protocols for clinical trials in Australia are often determined by factors outside of the control of local investigators and company affiliates, and the comparator chosen may reflect external clinical or market forces.

(iv) Trial Design

The most informative pharmacoeconomic analyses are incremental prospective 'usual care' cost effectiveness studies that include all relevant direct medical costs and relevant outcomes (Hillman & Leveque 1996). While there are obvious advantages in including economic data collection and analysis alongside a clinical trial, Phase II-III trials are often protocol-driven and the care given during a trial may not reflect actual clinical practice because of careful patient selection, the extent of patient follow-up and trial site characteristics (eg trials are often conducted in major teaching hospitals with highly trained specialists as research investigators). It is important that resource utilisation and associated protocol-driven costs are separated from those utilisations and costs that would occur in usual practice, when generalising results to the wider clinical setting.

When designing the trial methodology there are a number of specific issues that need to be considered if economic data collection is to be included. Such issues include sample size calculations, intention to treat approaches, and duration of the trial.

Sample Size

Careful consideration must be given to estimating sample size. At present this is usually based on clinical endpoints only. Sample size is influenced by power considerations, likely patient variance in clinical outcomes, the required significance level and expected number of patient withdrawals. Patient quality of life and resource consumption have been shown in many cases to have larger variances around the mean compared to clinical endpoints, thus increasing sample size requirements. It might be inferred from this that a trial with quality of life as an endpoint or which is concerned with cost per endpoint as a primary objective may require a larger sample size than that suggested by clinical considerations alone. It is important to note however that it is not clear what is meant by 'economic' significance. Significance in cost effectiveness analysis presumably refers to a test of the statistical significance of the *ratio* of costs to outcomes, with the test set to find some meaningful change in the cost effectiveness ratio. Whether a change is meaningful will depend on the type of outcome. A difference of \$50 per life saved may not be very significant. However, a difference of \$50 per pain free day may be very significant if it continues over a long period. It is unlikely however that a study primarily designed to study clinical efficacy would have its sample size increased in order to provide enough data for economic significance.

However, in the future some consideration may have to be given to estimating sample size based on variances of quality of life or resource utilisation data, particularly for late Phase III or Phase IV trials. This issue is discussed extensively in the health economic literature (Drummond & Davies 1991; Mullahy & Manning 1995).

Intention-to-Treat Approach

The most appropriate perspective for economic evaluation is intention-to-treat (ITT), since economic evaluation needs to relate to practice in the real world rather than practice under ideal conditions. That is, treatment 'effectiveness' rather than treatment 'efficacy' is more relevant for the purposes of an economic evaluation. The study needs to consider not only the costs and outcomes for patients who complete the trial, but also the costs and outcomes of individuals who entered the trial and who withdrew from the treatment for any reason.

Some researchers interpret ITT in the strict sense of analysing every patient randomised into a particular treatment group. This is reasonable for the purpose of evaluating drug safety. However, for evaluating clinical effectiveness in an economic evaluation, a practical definition would be to include in the analysis all patients randomised, who received at least one drug dosage, and who received at least one measurement of clinical outcome of interest in addition to a measure of resource usage after baseline (Gillings & Koch 1991). An ITT methodology requires a significant amount of effort to be invested in following up patient withdrawals. It has been suggested in the literature that ITT is only applicable to small numbers of subjects lost-to-follow-up (eg < 5%). Large loss numbers threaten the validity of study data analysis (Gould 1980; Gillings & Koch 1991). Appropriate statistical analysis will need to be applied to estimate potential costs and outcomes for patients lost to follow-up.

It is necessary to establish at least that patients who withdraw from treatment do not have significantly higher health costs or worse health outcomes than patients who remain in the trial during the relevant follow up period. Many clinical trials have a short term follow up and so it may be necessary to have further data collection in addition to the protocol, particularly for those who drop out, in order to capture any significant economic resource costs during the period of the trial, the follow up period and possibly beyond the period of the trial.

Duration of Trial

Capturing health related costs and quality of life which extend beyond the period of the trial suggests setting a defined follow up period for all treatment groups. In some cases, however, the very success or failure of the treatment may reduce or increase the necessary time horizon. A pragmatic limit to the time of follow up may be necessary as a balance between capturing the truly important costs and health effects directly relevant to the treatment, compared to the collection of longer-term costs which may bear little relationship to the original disease or treatment (Drummond & Davies 1991).

(v) Health Outcome Status Measures

Clinical Endpoints

Drug effectiveness for economic evaluation should be determined by the measurement of change in either a direct health status consequence of treatment (eg final outcome indicator such as death or cure) or an intermediate outcome indicator which can be translated into such a health status measure (eg % reduction in systolic blood pressure or bone mass below a critical level). In many cases it will not be practical to measure final outcomes (eg. mortality) due to the long time frames required to capture such data. The PBAC guidelines provide advice on appropriate use of intermediate or final outcome measures (DHHS, 1995).

Standard statistical procedures are required when analysing trial outcomes. Quote 95% confidence intervals for the mean estimate for specific outcome measures in preference to standard deviations in conformity with the PBAC guidelines. In addition it may be advisable to statistically allow for multiple comparisons if a number of endpoints are considered. These should be fully described in the methodology and study report. It is preferable, as a rule, to have fewer endpoints of major importance rather than a multiple list of endpoints of lesser importance.

Quality of Life Measures

Ideally, data on quality of life (QoL) should be incorporated into a clinical trial where the treatments are likely to have differential effects upon patients' *physical, psychological or social functioning*, and/or if there is likely to be a trade-off between a patient's quantity and quality of life.

There are three levels at which quality of life can be measured, and, ideally, data should be collected at each level. These levels are discussed below. It is particularly important that regardless of the instrument used, that the instrument is reliable, valid and sensitive. This should be ascertained by a comprehensive review of the literature and discussions with experts in the field.

Disease Specific

Disease specific instruments provide very specific information about those aspects of quality of life directly affected by the illness. Other more general aspects of quality of life may not be measured.

These data are not generalisable to other illnesses, and as such the findings cannot be readily used in comparative studies across several diseases. These data are not suitable for use in a cost utility analysis.

Health Profile

This is a multi-dimensional health profile and provides information about aspects of life such as mobility, pain, affect, social or cognitive functioning. As such, these measures provide information about most or all aspects of life, including those aspects of life or symptoms directly affected by the illness or treatment as well as those of a more general nature.

While less sensitive than disease specific measures, these data can be compared across other illnesses and their treatments. They do not, however, provide any single index of health-related quality of life, nor are they suitable for use in an economic evaluation. Examples of health profile instruments are the SF-36 (Ware et al 1993) questionnaire, which is widely used both in Australia and overseas, and the Nottingham Health Profile (Hunt et al 1989).

Generic Measures

These instruments, often termed *multi-attribute utility scales*, involve collecting generalised data on quality of life that is not specific to any particular disease. Usually data are collected on a number of aspects of health-related quality of life, often referred to as 'domains' or 'dimensions' of life, which are then aggregated to provide a single utility score.

Generic general QoL indices allow direct comparison between different illnesses and treatments. This occurs through obtaining QoL indices, which may be either a measure of health-related quality of life or

computation of quality-adjusted life years. Examples of QoL instruments which collapse to a single index are the 15-D (Sintonen 1993), the Rosser-Kind Scale (Rosser 1993) and the EuroQoL (EuroQoL Group 1990). The major limitation of general quality of life instruments with a single index is that they may not be as valid, reliable or sensitive as a health profile or disease-specific measures.

A recent book edited by Spilker (1996) titled 'Quality of Life and Pharmacoeconomics in Clinical Trials', contains a comprehensive overview of the various methods of quality of life assessments, and their application to pharmacoeconomic evaluations alongside clinical trials.

(vi) Data Collection for Costs

It is useful to think of three steps in evaluating the cost of a drug treatment:

1. *Identification* is the task of deciding which cost categories and resource uses are relevant and need to be collected for the analysis;
2. *Measurement* is the process of counting those resource uses which have been identified;
3. *Valuation* is the placing of a monetary value on resources used.

The checklist has a focus on identification and measurement issues. Issues in the valuation of specific cost categories are discussed in references found in the bibliography section of this paper under the heading 'Measuring and Valuing Costs'.

Identification of Costs and Resource Uses

For comparative cost-effectiveness the major interest in a trial is in differences in resource use between treatment groups. This is termed the *incremental cost* between treatment alternatives. It is hard to know ahead of the trial whether certain unrelated costs may somehow in fact be related to the intervention and may differ between groups. If the data are not gathered this will never be known. It is important to clearly identify the full range of costs that could potentially vary between treatment alternatives.

In practice, trial design is a compromise between the desire to gather information on all resource utilisation no matter how seemingly unrelated to the treatment under study, and the desire to be efficient and reduce the burden on investigators and subjects by not gathering excessive amounts of irrelevant information. A common situation is to gather all major events (deaths, hospitalisations) regardless of cause, and all other events that can reasonably be attributed to the disease under study or to the treatment (Torrance 1996).

Relevant economic cost data relate to resource use associated with the drug intervention, the control therapy, any associated adverse events, and any condition-related resource use. The type of data collected will depend on the purpose of the study (eg PBS listing, hospital listing), the condition being treated, interventions included in the analysis, and the trial setting (eg hospital outpatients, general practice). For PBAC purposes, identification and measurement of direct costs are required. Indirect costs (eg effect on productivity) can be measured but should be included as supplementary data in a PBAC submission. Indirect costs may be more relevant for marketing purposes and for certain conditions (eg cancer, flu). It is less relevant to the overall societal perspective if days lost by a worker are easily replaced by another worker with little change in total productivity and total social income.

Measurement of Resource Utilisation

Measurement takes place during the trial and follow up period. Resources used should be collected in naturally occurring physical units as well as in monetary values (eg days in intensive care, and cost per day in intensive care; number and type of pathology tests ordered and the cost per unit; hours of nursing time and cost per hour). This ensures that the study can be replicated and alternative dollar costs attached at other times in other places.

It is preferable to measure the direct costs associated with treatment from existing Case Report Forms (CRFs) being used for the study. Where this is not possible (eg due to constraints on CRF in multi-national companies), consideration should be given to using other data collection instruments including questionnaires (either administered at medical consultation or by telephone or mail), or patient diaries. Any data collection instrument to be used in the study should be mentioned in the protocol itself.

Indirect costs refer to production (or output) losses to society due to patients and/or their family (or friends) losing time from work as a direct result of the treatment process. Measuring such indirect costs will require detailed information including number of days when employment was not possible, changes in activities of daily living, employment status of patient (or family/caregiver), number of days off paid employment, and gross wage rates. Including indirect costs is clearly relevant to a third party payer who is liable for compensation or whose customers are employers.

Indirect costs are usually measured using either patient diaries or questionnaires.

Valuation of costs

Valuation of costs is usually done outside of the clinical trial since cost data on individual patients can often be estimated subsequently as long as utilisation data is collected alongside the trial. The PBAC encourages the use of standardised resource costs for specific healthcare utilisations as specified in its Manual of Resources. For example, for hospital stay, the PBAC recommends that resource weights developed as part of the National AN-DRG costing study be used for specific hospital episodes of care rather than the prospective collection of costs alongside the trial. In certain circumstances, (eg when a specific DRG weight may not capture the full extent of the real cost of a hospital episode) some companies may prefer to collect patient specific resource costs as part of the trial itself. General cost information on resource usage is best collected from a number of investigational sites participating in the study, to increase generalisability given the potential variation in prices unrelated to resource use variation. For example, clinician salaries may differ from state to state in Australia.

(vii) Some General Issues in the Design of Clinical Trials With Economic Analysis

Pooling Data

Care may be necessary when pooling data on resource utilisation from different hospitals, states, or countries where disease patterns, cultures, physiological traits or medical practices differ noticeably. This is not so important for protocol-driven resource utilisation, but is very relevant for the management of patient withdrawals where usual clinical decision-making applies.

Different styles of medical practice may also operate in public and private hospitals compared with specialist clinics or general practice settings.

If resource utilisation for a particular condition is considered appropriate for pooling across several countries, it is crucial for PBAC purposes that Australian costs only are applied to all resource items. There may also be

a different incidence or prevalence rate or prognosis for a condition across several countries, which may need to be considered when pooling data and analysing results.

Interim Analysis

If an interim analysis is performed which demonstrates a marked difference in efficacy of one treatment over the other at an early stage in a study, this may require cessation of the trial on clinical grounds due to early termination criteria. Care should be taken that an interim analysis does not affect the final data collection and analysis. It may be appropriate for an independent researcher to undertake the analysis. It may be difficult to justify to Institutional Ethics Committees that the study be continued solely for the purpose of obtaining economic information.

Low Frequency Events

If a low frequency event occurs (eg a serious adverse event occurring in less than 1% of the study population), then this may highly skew the results if it is only found in one of the treatment groups in a comparative study, and is associated with high costs of management. In such cases:

- (a) Fully report the event according to Good Clinical Research Practice (GCRP) and regulatory requirements, and thoroughly document it in all study reports.
- (b) In the resulting economic analysis, either:
 - report, and include it in the primary analysis at the observed frequency rate in the study group; or
 - report, but exclude the event in the primary analysis because it is an outlier. It can be included in a secondary sensitivity analysis.

For option (b) above it is important to obtain as much information as possible from corporate head office, national drug monitoring systems, and the published literature, in order to arrive at a probable frequency range (eg 0.1%-3%) for use in the sensitivity analysis.

3. The Checklist

This checklist is intended to provide general guidance in developing a protocol to incorporate economic data collection. The focus for most clinical studies will be PBS listing of the new product in question. The checklist is applicable, however, to a broader range of pharmacoeconomic objectives. It should therefore be of widespread use in the design of clinical trials for cost-effectiveness evaluations.

The checklist does not attempt to deal with all the issues which are relevant when designing a clinical trial protocol. Rather, it covers key issues relating to the collection of economic data. Special attention is given to establishing the purpose of the study and the perspective from which costs are to be considered. Of fundamental importance in designing any cost-effectiveness trial, is to define the likely market positioning of the new product, thereby allowing a judicious choice of the main comparator(s) for evaluation.

It is also vital to define outcomes, or clinical endpoints, in a way which is appropriate to economic evaluation, particularly as expressed in the PBAC guidelines. An intention-to-treat approach should be followed as far as possible, with follow-up data being obtained on both outcomes of resource utilisations for withdrawn patients to the extent that this is possible.

Although the checklist mentions sample size estimates based on variation in costs and quality of life outcomes, this subject is somewhat controversial, and is not to be considered as mandatory at the present time.

(i) Purpose of the Study

Target Audience

Is the purpose of the study for:

| | YES | NO |
|----------------------------|-----------------------|-----------------------|
| TGA approval | <input type="radio"/> | <input type="radio"/> |
| PBS listing | <input type="radio"/> | <input type="radio"/> |
| Hospital formulary listing | <input type="radio"/> | <input type="radio"/> |
| Market support | <input type="radio"/> | <input type="radio"/> |

Study Perspective

| | YES | NO |
|---|-----------------------|-----------------------|
| (a) Has the viewpoint of the analysis been stated explicitly? | <input type="radio"/> | <input type="radio"/> |
| (b) What is the viewpoint of the analysis? | | |

| | | |
|---|-----------------------|-----------------------|
| Societal | <input type="radio"/> | <input type="radio"/> |
| Commonwealth Government (including PBS) | <input type="radio"/> | <input type="radio"/> |
| Hospital formulary | <input type="radio"/> | <input type="radio"/> |
| Other _____ | <input type="radio"/> | <input type="radio"/> |

Study Comparators

(a) If the trial is a Phase II trial will there be a comparator in the study?

If yes, what will be the comparator?

| | | |
|----------------------------------|-----------------------|-----------------------|
| Placebo | <input type="radio"/> | <input type="radio"/> |
| Active comparator, specify _____ | <input type="radio"/> | <input type="radio"/> |
| Standard medical care | <input type="radio"/> | <input type="radio"/> |
| Other _____ | <input type="radio"/> | <input type="radio"/> |

(b) If the trial is a Phase III or IV trial and a drug analogue is already listed on the PBS, what will be the comparator?

| | | |
|----------------------------------|-----------------------|-----------------------|
| Placebo | <input type="radio"/> | <input type="radio"/> |
| Most widely used analogue on PBS | <input type="radio"/> | <input type="radio"/> |
| Other _____ | <input type="radio"/> | <input type="radio"/> |

| | YES | NO |
|--|-----------------------|-----------------------|
| If the new drug is in a new therapeutic class but other drugs are listed on the PBS to treat the condition, what will be the comparator? | | |
| Placebo | <input type="radio"/> | <input type="radio"/> |
| Most widely prescribed drug on PBS for indication | <input type="radio"/> | <input type="radio"/> |
| Other _____ | <input type="radio"/> | <input type="radio"/> |
| | | |
| If no currently listed drug is available, what will be the main comparator? | <input type="radio"/> | <input type="radio"/> |
| Placebo | <input type="radio"/> | <input type="radio"/> |
| Standard medical or surgical management | <input type="radio"/> | <input type="radio"/> |
| Other _____ | <input type="radio"/> | <input type="radio"/> |
| | | |
| (c) Have you checked that the drug dosage and formulation of the comparator is appropriate for Australia? | <input type="radio"/> | <input type="radio"/> |

(ii) Trial Design and Study Outcomes

Sample size

| | YES | NO |
|---|-----------------------|-----------------------|
| Has the sample size estimation taken into account expected variability in costs and quality of life outcomes within study groups? | <input type="radio"/> | <input type="radio"/> |
| If yes above, is the estimated sample size larger than estimates based on clinical endpoints? | <input type="radio"/> | <input type="radio"/> |

Intention-to-Treat Approach

| | | | |
|-----|---|-----------------------|-----------------------|
| (a) | Does the study take an ITT approach to assessing patient costs and outcomes? | <input type="radio"/> | <input type="radio"/> |
| | If yes, has a practical definition of ITT been specified in the study protocol? | <input type="radio"/> | <input type="radio"/> |
| (b) | Have the study protocol and CRF been planned to collect <i>health care and other resource use data</i> for all patient withdrawals for the duration of the protocol treatment period (including 'poor responders' and 'early successes')? | <input type="radio"/> | <input type="radio"/> |
| (c) | Have the study protocol and CRF been planned to collect <i>outcome data</i> for all patient withdrawals for the duration of the protocol treatment period? | <input type="radio"/> | <input type="radio"/> |

(iii) Health Outcome Status Measures

Clinical Endpoints

| | YES | NO |
|---|-----------------------|-----------------------|
| (a) Is the endpoint(s) measured in the trial a final outcome indicator (eg number deaths occurring or averted)? | <input type="radio"/> | <input type="radio"/> |
| OR | | |
| Is the endpoint(s) an intermediate outcome indicator (eg % reduction in cholesterol)? | <input type="radio"/> | <input type="radio"/> |
| (b) Is the endpoint a time-to-event or discrete health outcome? | <input type="radio"/> | <input type="radio"/> |
| OR | | |
| Can it be translated into one (eg % of patients who are 'cured', or number of days free of symptoms?) | <input type="radio"/> | <input type="radio"/> |

Quality of Life Measures

If you are planning to use a quality of life instrument for measurement of health status, is your chosen measure:

| | | |
|---|-----------------------|-----------------------|
| (a) Reliable, valid and sensitive | <input type="radio"/> | <input type="radio"/> |
| (b) Capable of generalisation across diseases | <input type="radio"/> | <input type="radio"/> |
| (c) Validated in Australia | <input type="radio"/> | <input type="radio"/> |
| (d) Specific for the disease in question | <input type="radio"/> | <input type="radio"/> |
| (e) Collapsible to a single index | <input type="radio"/> | <input type="radio"/> |
| If (c), have you considered complementing this measure with a general quality of life measure? | <input type="radio"/> | <input type="radio"/> |
| If cost-utility analysis is the economic methodology used in the study is your measure of utility a well validated multi attribute utility scale? | <input type="radio"/> | <input type="radio"/> |
| Does the QoL instrument require direct measurement of utility from interviews specifying health state scenarios and measuring utility directly from patients? | <input type="radio"/> | <input type="radio"/> |

(iv) Data Collection for Costs

Identify the Various Elements of Data Collection on Health Care Resource Utilisation

Have you included the following broad cost categories in the protocol design?

| | YES | NO |
|--|-----------------------|-----------------------|
| (a) Direct costs of medical or associated procedures | <input type="radio"/> | <input type="radio"/> |
| (b) Direct medical costs of adverse effects | <input type="radio"/> | <input type="radio"/> |
| (c) Direct non-medical costs | <input type="radio"/> | <input type="radio"/> |
| (d) Indirect costs | <input type="radio"/> | <input type="radio"/> |

Identification of Cost Categories

Does the trial design allow for the collection of the following data on resource utilisation?

Direct Costs

| | | | | |
|-----|-------|---|-----------------------|-----------------------|
| (a) | (i) | Dose and cost of drugs and comparator cost per day, per dose, per tablet, number of doses per day, per week, per episode | <input type="radio"/> | <input type="radio"/> |
| | (ii) | Ancillary costs (eg nursing care, dietary or other supplements, usage and cost) | <input type="radio"/> | <input type="radio"/> |
| | (iii) | Drug monitoring (usage and costs), eg haematology tests | <input type="radio"/> | <input type="radio"/> |
| | (iv) | Hospitalisation rate and hospital-based cost per day and per event or episode, number of days in hospital by disaggregate data on days in ICU, ward, tests carried out, surgery performed, ICD code, DRG code | <input type="radio"/> | <input type="radio"/> |
| | (v) | Number of outpatient visits by medical specialty | <input type="radio"/> | <input type="radio"/> |

| | YES | NO |
|---|------------|-----------|
| (vi) Home visits by medical, nursing or allied health staff - number, type | O | O |
| (vii) Medical consultations (protocol and ex-protocol) | O | O |
| (viii) Allied health consultations | O | O |
| (ix) Diagnostic tests (post-randomisation) | O | O |
| (x) Concomitant medication | O | O |
| (b) Management of adverse events: numbers (i) - (x) as above | O | O |
| (c) Travel and other direct costs of patients (including ambulance, public transport, car travel) <ul style="list-style-type: none"> • distance travelled • cost per \$km, trip | O | O |
| (d) Palliative care, (length of stay by type of institution and cost per day) | O | O |
| (e) Number of episodes of community assistance, eg meals on wheels, other municipal help and cost per service | O | O |

Indirect Costs of Lost Output

Does the trial design allow for the collection of the following data on lost production?

| | YES | NO |
|--|-----------------------|-----------------------|
| (a) Time lost from work for patient being treated | <input type="radio"/> | <input type="radio"/> |
| (b) Time lost from work for family member/friend accompanying the patient whilst being treated | <input type="radio"/> | <input type="radio"/> |
| (c) Informal (or non-paid) caregiver costs | <input type="radio"/> | <input type="radio"/> |

Measurement of Costs

What data collection methodology will be used to collect information on **direct** costs?

| | | |
|---|-----------------------|-----------------------|
| (a) Case Report Form (CRF) | <input type="radio"/> | <input type="radio"/> |
| (b) Patient diary | <input type="radio"/> | <input type="radio"/> |
| (c) Patient questionnaire, administered by: | | |
| (i) at protocol visit | <input type="radio"/> | <input type="radio"/> |
| (ii) by mail | <input type="radio"/> | <input type="radio"/> |
| (iii) by telephone | <input type="radio"/> | <input type="radio"/> |

If **indirect** costs are being measured, will they be collected by use of:

| | | |
|---|-----------------------|-----------------------|
| (a) Case Report Form (CRF) | <input type="radio"/> | <input type="radio"/> |
| (b) Patient diary | <input type="radio"/> | <input type="radio"/> |
| (c) Patient questionnaire, administered by: | | |
| (i) at protocol visit | <input type="radio"/> | <input type="radio"/> |
| (ii) by mail | <input type="radio"/> | <input type="radio"/> |
| (iii) by telephone | <input type="radio"/> | <input type="radio"/> |



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