

Protocol

Adherence of Health Economic Evaluations to Country Specific Guidelines: A Protocol for Systematic Review

Running Title: Economic Evaluation Adherence To Guidelines: Systematic Review Protocol

Deepshikha Sharma, Arun Kumar Aggarwal, Akashdeep Singh Chauhan, Shankar Prinja

Dept. of Community Medicine and School of Public Health, Post Graduate Institute of Medical Education and Research

Corresponding Author: Prof. Arun Kumar Aggarwal

Email: aggak63@gmail.com

Abstract

Background & Objectives: Over the years, an increasing number of developed and developing countries have formulated guidelines for the conduct of economic evaluations. However, their relevance to the analysts has rarely been evaluated. It is unclear whether the analysts adopt a particular set of guidelines while undertaking economic evaluations, and if yes to what extent are these followed. We propose to undertake a systematic review to assess the adherence of the published economic evaluations to the existing country specific guidelines for three countries. Depending on the availability of a published guideline in English language, we randomly selected one country each in the high income, upper-middle income and lower-middle income group namely Canada, South Africa and Egypt. *Methodology:* A systematic literature search will be undertaken using three databases, which include PubMed, EmBase and York CRD to identify health economic evaluations pertaining to Canada, South Africa and Egypt. Two reviewers will independently undertake title and abstract screening followed by full-text screening to identify studies that are full economic evaluations, pertaining to the health sector and published one year after the publication of the country specific guideline. Data will be extracted on key principles of economic evaluation. Adherence to the recommendations made in the country specific guidelines will be scored equally to calculate mean adherence scores. Quality will be assessed using Drummond's checklist. *Conclusion:* The findings of this review will help to assess the mean adherence to the guidelines. In addition, we will be able to identify individual principles showing poor adherence and factors responsible. The findings will aid revision of existing guidelines and development of new guidelines.

Keyword: Economic evaluation, Health Technology Assessment, Guidelines, Cost-effectiveness analysis, Pharmacoeconomics

Introduction

Healthcare decision makers often face the dilemma to allocate finite resources against infinite demands. Health Technology Assessment (HTA) is an informative tool to support such resource allocation decisions [1]. Economic evaluations are the most important component of HTA. The quality of economic evaluations has remained questionable. Hutter *et al* reported that about 76 methodological reviews were undertaken from 1990 to 2010, to assess the quality of economic evaluations [2]. These reviews identified important gaps in the basic conduct of economic evaluations. Numerous efforts have been undertaken to standardize the methods of economic evaluations which include development of reference case and standard methodological guidelines.

U.S. Panel on Cost-Effectiveness in Health and Medicine in 1996 had proposed the first ever Reference Case [3]. In 2016, the Second Panel released the revised version of the Reference Case [4]. This Panel Reference Case was developed for use by researchers in the United States. International Decision Support Initiative (iDSI) developed similar document for low and middle-income settings [5]. European region and other high-income countries have also developed their own guidelines for economic evaluations [6]. The overall objective of these guidelines is to define best practices and guide the analysts on how to design, conduct and report economic evaluations. Compliance to these guidelines or reference cases would ultimately produce better quality economic evaluations.

Over the years, an increasing number of countries have developed guidelines, however, the relevance of these guidelines to the analysts has rarely been evaluated. It is unclear whether the analysts adhere to these guidelines and if yes to what an extent? In the late 1990s, experiences and

applicability of the early versions of the Canadian and Australian guidelines were reviewed [7,8]. Such evaluations are largely missing for other country specific guidelines. We thus propose to undertake a systematic review to assess the adherence of the published economic evaluations to existing country specific guidelines.

Methodology

Around 44 countries have published guidelines for the conduct of economic evaluations either as part of HTA or for pharmacoeconomic evaluation [6]. Out of these 44, around 31 guidelines are available online in English language. Majority of the guidelines (26) belong to high-income countries, only five are from middle-income countries. Further, none of the low-income countries has developed a guideline. We randomly selected, one country each from the high income, upper-middle income, and lower-middle income group having pre-developed guidelines namely Canada, South Africa and Egypt.

Objectives

The primary objective of the systematic review will be to estimate the adherence of the published economic evaluations to the principles of economic evaluation as elaborated in the country specific guidelines. The secondary objective will be to identify individual principles showing poor adherence. In addition, independent factors affecting the adherence will also be identified.

The systematic review will be undertaken in accordance to the systematic review guidelines given by the Cochrane Collaboration for Reviews and Centre for Reviews and Dissemination (CRD) [9].

Literature Search

A comprehensive literature search will be carried out to identify all health economic evaluations pertaining to Canada, South Africa and Egypt. The searches will be

be performed using the following databases: PubMed, EMBASE and York CRD and the individual websites of the HTA agencies the three countries. Further, bibliometric search of included articles will also be undertaken to identify any additional studies.

These databases will be searched from one year after the publication of the country specific guidelines. The latest version of the guidelines for Canada, South Africa and Egypt have been developed in April 2017 (fourth version), December 2012 (first version) and August 2013 (first version) respectively [10-12]. Accordingly, the searches for economic evaluations will be undertaken from April 2018 for Canada, December 2013 for South Africa and August 2014 for Egypt.

The potential search terms will include those relating to economic evaluations and the selected countries such as 'cost-effectiveness analysis'; 'cost-benefit analysis'; 'cost-utility analysis', 'cost-minimization analysis'; 'pharmacoeconomic evaluation'; 'health technology assessment'; economic evaluation'; 'incremental cost effectiveness ratio' and 'Canada'; 'Egypt' and 'South Africa'.

Study selection

Two reviewers (DS, ASC) will independently screen title and abstract of individual studies. If considered appropriate full-texts of the selected studies will be screened to check if they meet the inclusion criteria.

A study would be included if it meets the following inclusion criteria:

1. Full economic evaluation that is evaluating both costs and consequences of two or more interventions
2. Economic evaluations pertaining to the health sector

3. Economic evaluation undertaken in any of the three selected countries- Canada, South Africa and Egypt
4. Economic evaluations published one year after the development of the country specific guideline.

A study will be excluded if:

1. It is a partial economic evaluation- cost analysis, cost comparisons, effectiveness studies will be excluded
2. Economic evaluation for non-health related sectors will also be excluded
3. Economic evaluations published in countries other than Canada, South Africa and Egypt will be excluded
4. Economic evaluations published before April 2018 (for Canada), December 2013 (for South Africa) and August 2014 (for Egypt) will also be excluded since we assume that it would take at least one year for the researchers to apply to a particular guideline in their economic evaluation and then publish it.

Quality Appraisal

The quality of the included studies will be assessed by two reviewers (DS, ASC) using Drummonds checklist [13]. This checklist is one of the most widely used checklist for appraising the quality of economic evaluations [14]. It contains a total of 38 criteria divided into 10 main criteria and 28 sub-criteria. The responses to these criteria are to be marked as yes, no, not clear or not applicable.

Data Extraction

A specific data extraction form will be developed to collect general and methodological data. The general information section will include: i) year of publication ii) disease area of the study, iii) type of intervention (pharmaceutical, public health programme, service delivery

etc.), iv) author details and v) funding details. The methodological section will include: i) type of economic evaluation, ii) study design, iii) intervention and comparator(s) iv) characteristics of target population v) the perspective adopted vi) study time horizon used vii) discount rates used to discount costs and outcomes, viii) types of costs included ix) outcome measures x) key model parameter if a model was used and xi) Incremental cost-effectiveness ratios (ICERs) and presentation of results.

Three separate adherence questionnaires will be designed for Canada, South Africa and Egypt based on the recommendations provided in the respective country-specific guidelines. Table 1 illustrates some of the key principles and recommendations given by the three guidelines.

Data Analysis

Microsoft Excel will be used for data entry and analysis. Descriptive statistical analysis, including frequency and percentages, will be used to describe the characteristics of the studies. All principles of the economic evaluation will be weighted equally. A score of '1' will be given if the economic evaluations adheres to the recommendation as specified in the guideline, alternately a score of '0' will be given for non-adherence. Total adherence score will be calculated by adding individual scores. Further, individual

variables showing poor adherence will be identified.

Independent variables such as type of disease, type of intervention, type of economic evaluation, background and affiliation of the lead author and the source of funding which could possibly impact the adherence to the national guidelines will be identified. The difference between mean adherence score for these variables will be tested using one-way ANOVA.

Conclusion and Policy Implications

Economic evaluations are useful to inform policy decisions, however their applicability is highly dependent on their quality. In order to produce high quality and methodologically sound economic evaluations, researchers attempt to comply with standard best practices as elaborated in the country-specific guidelines. The aim of the proposed systematic review is to assess the adherence of the researchers to three such guidelines developed for Canada, South Africa and Egypt. The findings of our systematic review will help to identify the extent to which these guidelines are accepted among the users, and additionally highlight independent factors, which affect compliance. This in turn would have important implications for countries that are targeting to develop new guidelines or revise their existing guidelines in the near future.

Table 1: Summary of recommendations on key principles of economic evaluation as specified in the country-specific guidelines of Canada, South Africa and Egypt

S.No.	Principle	Canada	South Africa	Egypt
1.	Type of Economic Evaluation	CUA	CMA or CUA or CEA or CBA (should be justified)	CMA or CEA or CUA depending on research question (should be justified)
2.	Comparators	Current care	Standard of Care	Widely used and Reimbursed alternative
3.	Perspective	Publically funded health care payer perspective	Third party payer (funder) perspective	It should be relevant to the research question and adapted to benefits gained by the health care system
4.	Time Horizon	Long enough to capture all relevant differences in future costs and outcomes	Based on the natural course of the disease and likely impact of the treatment	It should be ensured that the chosen outcome and the resource consumption of the treatment alternatives are observable in this period
5.	Discounting	1.5% for both costs and outcomes	5% for both costs and outcomes	3.5% for both cost and outcomes
6.	Health outcome	QALYs	Final outcomes such as deaths prevented, life-years gained, or QALYs gained are preferred	Primary outcome measures are the first choice. CEA, where the intermediate marker is chosen, must have a validated, well-established link with an important hard end point. In CUA, outcomes are measured in QALYs gained
7.	Costs	All relevant resources and costs based on the perspective	Only costs relevant to the third-party payer perspective.	Direct medical costs as well as additional costs, savings, or other benefits when data are

		of the publicly funded health care payer.		available
8.	Sources of Costs	Estimate Canadian resources and costs using data that reflect the jurisdiction(s) of interest	Resource use should be based on South African practice and adjusted to local setting if based on international practice. Cost data source must be systematically identified that are relevant to the study perspective.	Primary data collection; if unavailable, secondary data sources may be used. Official sources of unit cost data for products (e.g., tender lists) are preferable.
9	Uncertainty Analysis	Scenario based Analysis, DSA and PSA	One-way, two-way sensitivity analysis, PSA	DSA is required, PSA is optional
10	Incremental Cost-effectiveness Ratios	Should be reported	Should be reported	Should be reported
11	Equity	Weight all outcomes equally regardless of the characteristics of people receiving, or affected by the intervention in question	Not applicable	All lives, life-years, or QALYs should be valued equally irrespective of socio-economic characteristics of the population

CBA: Cost-benefit analysis; CEA: Cost-effectiveness analysis; CMA: Cost-minimization analysis; CUA: Cost-utility analysis; DSA: Deterministic sensitivity analysis; PSA: Probabilistic sensitivity analysis; QALY: Quality adjusted life year

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