

Decision analytic modelling: The need for disease specific model standardization

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Abstract *The design of health economic decision models, including the choice of disease states they incorporate, is based on a variety of assumptions that can significantly impact conclusions. Separate studies addressing the same research question may consequently provide estimates of incremental cost-effectiveness that are beyond reconciliation. Although efforts have been made to standardize both the approach to modelling and the process of Health Technology Assessment across EU member states, to date there has been little attention paid to the standardization of the models which lie at the heart of economic evaluations and decisionmaking. This paper argues that an increased focus on health economic model standardization would be beneficial to both users and producers of economic evidence, while providing more robust and reliable conclusions.*

Economic evaluations are performed in many EU member states prior to the public reimbursement of new health technologies. Methodological guidance on these evaluations between countries varies widely, eg. regarding perspective of analysis, sensitivity analyses and costing (Box 1). A recently published draft guideline from the European network for Health Technology Assessment (EUnetHTA) aims at setting up a general framework for conducting economic evaluations among EUnetHTA members (Draft methodological guidelines, EUnetHTA, 2014). One of the main recommendations was that, when methodologically appropriate, the analysis should be based on a decision analytic model. However despite their central importance in decision-making, recent research has found that such models are prone to a range of problems due to heterogeneity of design.

Differences in modelling approaches and assumptions can lead to dramatically different conclusions. For example, in eleven economic evaluations of two hormonal breast cancer therapies (anastrozole and tamoxifen) total life years gained varied between 0.16 and 0.550 leading to ICERs varying between approximately EUR 4,000 and 120,000 per QALY (Frederix et al. 2012a). Although it is well known that differences in outcomes can be caused by country differences in perspective, unit costs and valuations of quality of life, the major cause of this variation was the variety in methods used to extrapolate the same clinical trial over longer time periods as well as structural differences in Markov models applied.

Despite the existence of quality guidelines (Box 2), the methods and structures of several of the studies reviewed in the example of breast cancer did not adhere to one of the most important characteristics of decision analytic modelling: inclusion of a correct reflection of disease progression. Investigators made their own choices regarding length of time horizon, hazard rate for recurrence, incidence of recurrence and inclusion of carry over effects. Time horizon, the time period over which costs and effects are taken into account, varied between studies from 10 years to lifetime. In hormone receptor-positive breast cancer, relapse can occur even after 20 years, indicating that a

time horizon of 10 years is too short. Moreover, structural differences varied between for instance the inclusion of one metastatic health state compared to various metastatic health states and inclusion of constant time parameters for having metastasis compared to time dependent parameters.

To improve quality of future economic evaluations disease specific recommendations for breast cancer were made aiming to improve reflection of disease progression in breast cancer models (Frederix et al. 2014;Frederix et al. 2012b). Similar efforts have been undertaken eg. in the fields of rheumatology (Gabriel et al. 2003) and fall prevention (Davis et al. 2011), but the problem of widely varying structures and methods is prevalent in many other disease areas such as lung cancer and HIV (Bongers et al. 2012;Colchero et al. 2012).

Although there is academic value in taking different perspectives and approaches to a problem, the building and rebuilding of different models with varying structures aiming to answer similar questions is not likely to be an efficient use of resources and ultimately leads to widely varying conclusions which do not necessarily represent reality. Publishing disease specific modelling guidance after the development and publication of a wide range of heterogeneous models resembles the expression “after meat, mustard”. Duplication of effort could be avoided, not only within academia but within companies submitting economic evidence for the appraisal of their products and within the agencies responsible for evaluating the appropriateness of these models on a case-by-case basis. Consequently there is a case for coming up with solutions and developing guidance for end users at an earlier stage of model development in order to generate standardized models that are acceptable across countries and stakeholders. Such standardized models should be developed by consensus between all relevant stakeholders and experts and adhere to high quality general guidance such as recently published by EUnetHTA. Ongoing projects at the EU level and internationally are actively pursuing standardization of economic evaluation methods and models (Box 3) with the intention of making resulting models directly transferable between countries.

At a more general level, initiatives have also been undertaken to enhance standardization of how health economic models are built. In 2012, a collaboration between the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making (SMDM) published guidance for modelling good practices (Caro et al., 2012). Based on discussion with expert members of both societies, several reports were published, each dealing with a different aspect relating to the application of modelling techniques to the area of health care decision making: conceptualizing a model, state-transition modelling, discrete event simulation, dynamic transmission modelling, model parameter estimation and uncertainty, model transparency and validation.

These guidelines show the current, state-of-the-art best practices in health economic decision modelling. Since the modelling techniques for medical and economic decision modelling are continuously advancing, the authors recognize that it may not be possible to follow the entire set of recommendations in every modelling exercise. The guidelines are not intended for use as a checklist to be followed unthinkingly and modellers who believe that they should not, or cannot, follow a particular recommendation are encouraged to document this divergence, its rationale and likely consequences. (Caro et al., 2012). Importantly, these guidelines are intended to inform the *approach* to health economic decision modelling, and therefore do not necessarily result in standardized outcomes.

The present suggestion for disease specific standardization goes a step further compared to current guidance regarding decision analytic modeling presented within national guidelines and outlined by

EUnetHTA. Standardization of disease specific models would focus on uniform modelling methods, structures and also parameterization which would represent the consensus knowledge and uncertainty about states and events relating to the disease progression based on the best available evidence. Development and open source sharing of disease specific models could ultimately lead to an increase in quality and validity of economic evaluations and even improved efficiency across member states of the EU.

Recommendations for research:

- Establishment of a platform or network to coordinate and implement standardized disease-specific models for health economic evaluation, representing consensus on the most appropriate model structures, clinical parameters and other inputs which are not country or context specific.

Box 3 Standardization of guidelines for health economic evaluations

Economic evaluation: a local business

Economic evaluation (EE) is for a large part local. Demographics, absolute and relative prices, epidemiology, and the organization of the health system may all be different between jurisdictions (Vemer & Rutten-van Mólken, 2010). There are also differences in methodological choices, such as the choice of perspective (societal or health care payer) of an EE, the discounting rate and a threshold willingness-to-pay (WTP) for a quality-adjusted life year (QALY). Such choices are made by local health care decision making bodies or other local experts.

Many countries around the world have published recommendations or guidelines for health economic research to formalize these choices. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has collected pharmacoeconomic (PE) guidelines for 41 countries (Nov 2014), and publishes both a comparative table of 33 key features of each guideline, and hyperlinks or full text of the guidelines (ISPOR, 2014). The guidelines are categorized into three groups and the differences between countries in methodological choices are immediately clear from this categorization. For the United States and China for example, only recommendations published by experts are available, with no official status, whereas England and Australia require a specific EE section in each reimbursement submission and have published official guidelines for this section.

Within the guidelines, many differences are also apparent. For example, some countries use differential discounting (e.g. The Netherlands and Scotland), which means that a different discount rate is used for health outcomes than for costs. Discount rates range from 1.5% to 6%, with some countries requiring no discounting as a scenario. All 33 key aspects identified by ISPOR can differ between countries.

Box 4 Standardization of modelling

Standardizing the quality of models

Several tools have been published in the past few years dealing with the assessment of the quality of health economic decision models. As such, these checklists attempted to create a consensus on what can be considered a “good” model. The Drummond (Drummond & Jefferson, 1996), Consensus on Health Economic Criteria (CHEC) (Evers et al., 2005), Philips (Philips et al., 2006), Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (Husereau et al., 2013) and Caro (Jaime Caro et al., 2014) checklists can all be used to judge the quality of HE decision models.

Standardizing validation efforts

Since decisions based on the outcomes of these models can have extensive consequences, it is important that these models and their outcomes are credible. Validation is a crucial step in establishing credibility. Several guidelines and publications exist on the issue of model validity, both for simulation models in general (Ingalls et al., 2004; Peters et al., 2001; Law & Kelton, 2007) and for HE decision models specifically (Caro et al., 2012; Philips et al., 2006; Jaime Caro et al., 2014). However, they present ideals rather than feasible acceptability criteria, are written to support model development not model evaluation, and are often necessarily general and not geared towards validating HE models. Current work is being done to create a tool that standardizes validation efforts (Vemer et al., 2013). This tool, called Assessment of the Validation Status of Health-Economic decision models (AdVISHE), will also explicitly improve insight for model users in the validation status of a HE decision model, while reducing model users' workload, without reducing the validation status of models. (Vemer et al., 2014)

Box 5 Existing efforts to standardize economic evaluation

Several projects have been initiated to standardize the methodology of EE. The World Health Organization "CHOosing Interventions that are Cost-Effective" project (WHO-CHOICE) was developed in 1998 to perform generalized cost-effectiveness. One of the goals was to define an optimal set of interventions, taking into account setting-specific factors. Amongst others, WHO-CHOICE proposed an alternative WTP, stating that health technologies costing less than three times the gross domestic product per capita for each disability adjusted life year (DALY) averted represent "good value" (WHO, 2001).

Within the EU 7th Framework Programme (FP7), both the "Dynamic model for Health Impact Assessment" project (DYNAMO HIA, <http://www.dynamo-hia.eu/>) and the "Economics of Chronic Diseases" project (EConDA <http://www.econdaproject.eu>) use a generic, flexible model, to quantify the health impact of interventions. Both models are adaptable to the health determinants and outcomes relevant for the policy in question. DYNAMO-HIA has built a dynamic cohort model, which is applicable throughout the European Union (Lhachimi et al., 2012), and EConDA is currently building a flexible microsimulation model for four chronic diseases, which allows for a standardized evaluation of interventions in several European countries. Jurisdiction specific methodological choices and data are necessary when evaluating the cost-effectiveness of interventions that prevent, screen and treat these chronic diseases (Divajeva et al., 2014).

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