

THE ECONOMIC EVALUATION OF HEALTH CARE INTERVENTIONS

Opportunities for Cooperation

between the Division of Health Economics at DKFZ &
Clinical Researchers (at U of Heidelberg, NCT, DKTK)

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Executive Summary

We propose to fully use the potential of clinical studies to generate information not only on clinical efficacy, but also to enable trial-based economic evaluations. This will require data on patient-relevant outcomes and health-related quality of life, as well as resource utilization and cost. Beyond academic interest, such data are increasingly necessary for technologies to be positively evaluated for reimbursement, and thus for successful **translation** of research and development (R&D) into clinical practice.

The Division of **Health Economics at the DKFZ** (under the leadership of Michael Schlander, professor of health economics at the University of Heidelberg with 15 years of experience in clinical R&D management) offers collaboration spanning:

- early consultation in the planning phase of clinical trials, supporting design of protocol and data collection processes in order to maximize opportunities for meaningful health economic evaluations;
- cooperation with statisticians in order to help optimize design and sample size in view of power considerations and evidence expectations of official Health Technology Assessment (HTA) bodies;
- participation in investigator meetings and clinical trial management in order to help ensure high quality data collection, meeting the standards of official HTA agencies;
- cooperation with clinician scientists and biostatisticians in the evaluation of clinical trial data;
- guiding the costing part of study evaluation, considering the most appropriate perspectives to be chosen for economic analysis;
- executing trial-based health economic evaluations, including decision analytic modelling and sensitivity analyses;
- reporting, presenting, and publishing the results of economic evaluations jointly with the clinical study leaders.

Not all of the above will always be needed. Often, **a relatively small extra effort** will suffice to add substantial value, primarily by collecting relevant data on patient-relevant clinical outcomes, health-related quality of life, and resource utilization.

In addition, our **Heidelberg Health Economics Summer School** may be of particular interest to clinician scientists and clinical researchers, as it offers an accessible, tailor-made opportunity to gain insight into the principles and practice of the economic evaluation of health care programs.

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“Hand clapping for science is now inextricably linked to hand wringing over affordability.”¹

1. Background and Rationale

In most cases, medical research and development will bring about health benefits to patients only if (and when) the resulting products and procedures will be adopted as components of routine care. In an increasing number of jurisdictions, this will include the need to be accepted for reimbursement by statutory health insurance or by a national health scheme.

Thus successful **translation** of innovative research from bench to bedside will rest on a positive evaluation of the new methods by regulatory agencies *and* by official Health Technology Assessment² (HTA) agencies (cf. Fig. 1, below). Health technologies³ are then required to meet a number of criteria, which exceed the proof of clinical efficacy, safety, and the consistent fulfilment of high quality standards (i.e., the traditional criteria applied by regulatory authorities tasked with granting marketing authorization for new products, such as the U.S. FDA and the European EMA).

¹ P.B. Bach (Memorial Sloan Kettering Cancer Center, New York, NY), (November 05, 2015). New Math on Drug Cost-Effectiveness. *New England Journal of Medicine* 373 (19) 1797-1799.

² The World Health Organization (WHO) defined Health Technology Assessment (HTA) HTA as “the systematic evaluation of properties, effects and/or impacts of health technologies and interventions. It covers both the direct, intended consequences of technologies and interventions and their indirect, unintended consequences.” (cf. WHO: 2015 Global Survey on Health Technology Assessment by National Authorities. Geneva, 2015. Available for download at www.who.int).

³ SwissHTA defined health technology broadly “as a comprehensive concept including (without any claim to being an exhaustive list) all interventions proposed and performed by health professionals and aiming at the improvement of the health of individuals and populations, e.g., medicines, medical devices, diagnostic measures, medical and surgical procedures, complex clinical care pathways and organizational and administrative settings.” Source: M. Schlander, C. Affolter, H. Sandmeier, U. Brügger, C. Cao, T. Cueni, E. Kraft, G. de Pouvourville, A. Faller, P. Gyger, A. Hebborn, D. Herren, S. Kaufmann, R. Leu, P. Suter, (March 13, 2012). Swiss HTA Consensus Project: Guiding Principles. Basel, Bern, Solothurn and Wiesbaden. Available for download at www.swisshta.org.

To be listed for reimbursement, demonstration of “value for money” will be needed.⁴ While the specific data requested by official Health Technology Assessment (HTA) agencies vary internationally, most systems demand robust information on the comparative clinical and cost effectiveness of the new medical intervention. In many health care systems, benchmarks for cost effectiveness will be applied to determine the acceptability of cost benefit ratios.

The implementation of official HTAs as a tool to assist decisions on formulary listing, pricing and reimbursement of health programs has been an asynchronous and heterogeneous process, beginning in Australia in 1992 and Canada in 1994. HTAs are now a mandatory step in the process leading to market access in European jurisdictions. These HTAs are driven by assessments of comparative clinical effectiveness and some variant of health economic evaluation. Usually, HTAs – like clinical guidelines – have an expiry date and need to be revisited and updated after a certain period of time, and re-evaluations may be linked to a reconsideration of prior pricing and reimbursement decisions (cf. Fig. 1).

Whereas clinical trials have always addressed questions of clinical efficacy and safety, the potential of clinical studies to produce economic information has been used less consistently. We believe the time is ripe for improvement of this situation, in order to maximize (a) the scientific insights gained from clinical research and (b) the generation of information expected by health care policy makers responsible for making decisions regarding reimbursement and, as a consequence, who is to have access to innovative medicines.

⁴ This holds true not only for biopharmaceutical products. Recently, standards for medical devices have also been raised. For an overview of the current situation in Germany, cf. summary presented to MedTech Dialogue Meeting, Mannheim, March 23, 2017. Available at www.michaelschlander.com, or downloaded directly at the following [link](#).

Cost Value Analysis of Health Care Programs

Traditional Regulatory Review and HTAs

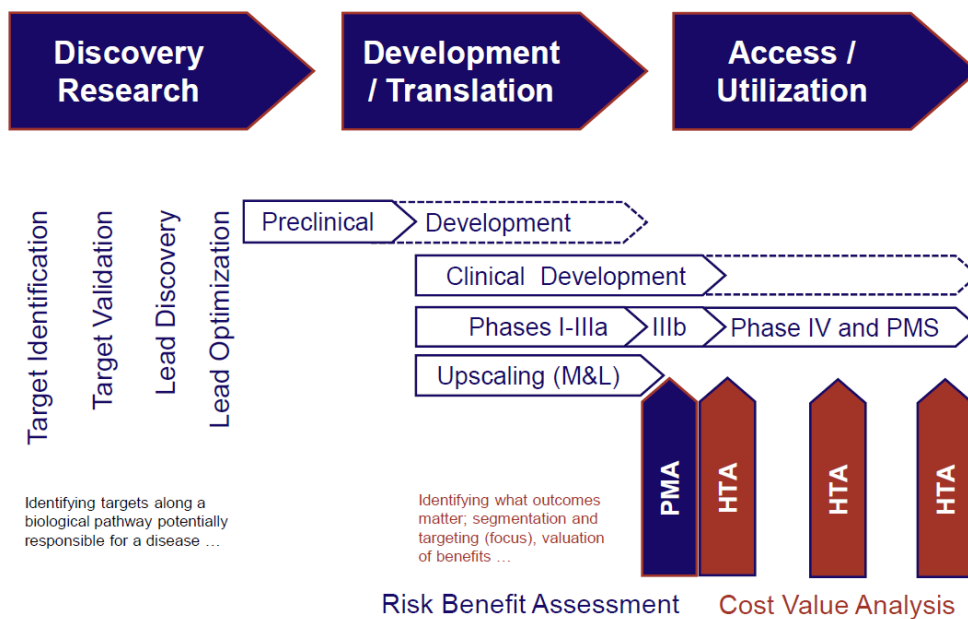


Fig. 1: Health Technology Assessments (HTAs): HTAs are complementary to traditional regulatory reviews that focus on medical risk benefit assessments. The implementation of official HTAs as a tool to assist decisions on formulary listing, pricing and reimbursement of health programs has been an asynchronous and heterogeneous process, beginning in Australia in 1992 and Canada in 1994. HTAs are now a mandatory step in the process leading to market access in European jurisdictions. These HTAs are driven by assessments of comparative clinical effectiveness and some variant of health economic evaluation. Usually, HTAs – like clinical guidelines – have an expiration date and need to be revisited and updated after a certain period of time, and re-evaluations may be linked to a reconsideration of prior pricing and reimbursement decisions. Abbreviations: PMA, Product Marketing Authorization; PMS, Post-Marketing Surveillance.

2. Opportunities for Cooperation

Health economists and HTA specialists at the DKFZ Division of Health Economics now offer a broad range of options for collaboration, ranging from:

- educating at introductory and intermediate levels of applied health economics,
- training courses in health economic modelling,
- consulting during the planning and study design phase of clinical trials,
- selecting appropriate instruments to collect data on resource utilization, patient-relevant clinical outcomes, health-related quality of life, and valuation of resource use and clinical effectiveness outcomes,
- conducting economic evaluations based on clinical trial data, using mixed-design synthesis and modelling approaches, including probabilistic sensitivity analyses,
- reporting, presenting, and publishing economic results based upon clinical trial data.

In order to maximize impact, health economists should be involved as early as possible, i.e., as of one of the initial steps in study planning and preparation of grant applications. Experience has shown that grant applications are generally more successful if they incorporate a systematic evaluation of the anticipated societal impact of the technologies investigated. In practice, that will often include high-level incorporation of health economic evaluation strategies.

As an aside, this approach has been established practice in the research-based biopharmaceutical industry for more than two decades, which is easily explained by the market entry hurdles faced by the manufacturers of medicinal products.

2.1. Study Design

Typically, a number of trial characteristics demand special attention. Among those that increase the relevance of trial-based economic evaluations, the following feature prominently. From an idealistic perspective, these should be reflected in the planning and design phase of clinical studies:

- definition of the patient population for study inclusion so as to minimize selection bias, i.e., considering representativeness for routine clinical care;

- definition of a comparator that is both clinically effective and cost effective that reflects current standards of care for the condition in question – ideally minimizing protocol-mandated standardization;
- choosing the most relevant perspective for economic analysis (e.g., social, societal, payers', etc.);
- collecting relevant data on resource use (expressed in natural units), capturing a sufficiently broad set of medical services;
- identifying and collecting relevant data on direct non-medical and indirect resource use and opportunity cost;
- identifying, and keeping separate from utilization, unit costs using information on tariffs, charges, and list prices, in order to separately determine transfer and opportunity costs;
- definition of study endpoints (clinical outcomes) deemed to be patient-relevant by HTA agencies;
- indirect measurement of utility using validated health-related quality of life instruments (taking into account their sensitivity to different dimensions of health, their foundation in multi-attribute utility theory, and their acceptance by policy makers and HTA agencies);
- considering direct utility measurement by means of other preference-based generalizable measures of benefit;
- considering the appropriateness of capturing other dimensions of benefit, such as well-being, capabilities, and non-medical outcomes.

Other considerations include the identification of data needs for subsequent decision analytic modelling, estimating the number of patients to adequately power the trial, the handling of uncertainty and of censored and skewed data, adoption of sufficiently long patient follow-up periods, extrapolation issues with regard to the transferability of results across settings and jurisdictions, among others.

In an ideal world, all of the above criteria would be met, in order to make clinical study data amenable for economic evaluation and relevant for health care policy makers. Obviously, this will rarely be the case. It has been an old hobbyhorse of health economists to engage in debates about the distinction between the internal and external validity of clinical studies (cf. Tab. 1, below).

Tab. 1: Some limitations of randomized controlled clinical trials (RCTs) – external versus internal validity from a health economics perspective. The table relates to caveats of randomized (phase III) clinical trials for economic analysis and is inspired by a lecture delivered by Suzanne Wait at Bristol-Myers Squibb on December 14, 2001. Note that also non-randomized (and phase II) clinical trials may generate information useful for subsequent economic analyses.

- **Focus on intermediary as opposed to long-term outcomes**
 - efficacy/safety versus effectiveness
 - validity of surrogate outcome parameters (e.g., progression free survival / overall survival)
- **Over-reporting of non-clinically relevant events**
 - protocol-defined events may include those that are mild, which usually require observation only
- **Experimental context often not representative of actual practice**
 - highly selected, narrowly defined patient populations
 - cautionary approaches due to the blinding of interventions
 - protocol-driven costs and effects
 - high prevalence of specialized centers
 - rarely a priori specified subgroups for analyses
- **As a result, high internal validity, but often questionable external validity.**

Based on the above limitations, it might seem virtually impossible to conduct meaningful economic evaluations on the back of a clinical study. However, such a conclusion could hardly be more inappropriate since policy makers concerned with the evaluation of new technologies have to make decisions in the absence of perfect information. Thus, economic evaluation designed to provide timely information to health care policy makers is not a matter of black and white, all or nothing. Rather, keeping in mind the constraints of feasibility, the challenge is to provide evidence that supports real-world decisions, while acknowledging the limitations and uncertainty that result from the fact that we do not operate in an ideal world with perfect information. Thus, to find a balance between the desire for perfect information and feasibility considerations in the clinical trial setting

requires a good sense of judgment and experience. Modelling techniques are an established tool to bridge the gap between empirical data and economic analysis.

Given this background, Henry A. Glick and colleagues (2015)⁵, nevertheless, suggest considering six sets of issues at the early stages of planning a clinical study:

1. preplanning, which consists of identifying an appropriate length of follow-up for economic endpoints; sample size considerations, which may be complex for incremental cost effectiveness ratios (ICERs) and have not been consistently applied to date; identifying the types of resource use by study patients; and feasibility considerations;
2. selection of medical services to be measured (cf. below); decisions on types (e.g., disease-related) and settings of resource use for which data will be collected, and of persons to be included in data collection (e.g., caregivers);
3. level of aggregation of resource utilization data (e.g., micro-costing approaches versus use of aggregated measures such as DRGs or number of visits);
4. unit prices – and perspectives of the economic evaluation (e.g., societal or else) – to be applied, which will have implications for the level of aggregation acceptable for analysis;
5. naturalistic study designs versus protocol-driven resource use, costs and effects, handling of study patient selection (inclusion / exclusion) criteria, intent-to-treat versus per protocol analyses and handling of patients lost to follow-up;
6. planned extrapolation of costs and effects beyond the trial period.

Not all of these salient aspects are unique to the economic component of a clinical study, but their consideration will need to reflect the specific trial objectives and regulatory requirements, notably including expectations of key HTA agencies.

⁵ cf. H.A. Glick, J.A. Doshi, S.S. Sonnad, D. Polsky, (2015). *Economic Evaluation in Clinical Trials*. 2nd edition. Oxford: Oxford University Press.

2.2. Data Collection

Data for Costing

Data for costing will usually be collected as a part of study Case Report Forms (CRFs), which capture use of medical and non-medical services, as well as indirect costs, if deemed relevant.

In a separate step, resource use data need to be transformed into cost data, which are commensurate with the unit of benefits defined by the objectives and perspective of the intended economic evaluation.

As a rule, the latter step will be handled by health economists familiar with the theory and practice of resource valuation. This translation is commonly being done by identifying the relevant cost categories, and multiplying the units used by their appropriate price weights. Depending on the perspective chosen, these price weights (or “unit costs”) may differ greatly from list prices, fees, tariffs, and official charges. Sometimes price weights will be available only at the level of program costs. Unit prices will also be different by jurisdiction, and in any case, will apply at defined time points only, hence requiring adjustments for inflation and time preference (usually expressed as discount rate).

Data for Effectiveness Assessment

In principle, clinical investigators should strive to collect data on patient-relevant outcomes (PROs) irrespective of plans for subsequent economic evaluation. Such data may enable cost consequence and cost effectiveness analyses, both using clinical events as the unit of benefit.

If economic evaluation is intended to inform decisions about rational health care resource allocation, it should be designed to meet the expectations of HTA agencies. Then, typically, a preference-based measure of benefit will be needed. Abstracting from cost benefit and social cost value analyses, the units commonly of interest will be length and (health-related) quality of life. Economic evaluation will be based on calculating the ratio between the absolute difference in relevant costs and the absolute difference in effect – the so-called incremental cost effectiveness ration (ICER), (see below). In the case of economic cost utility analyses, the standard measure of benefit will usually be QALYs (“quality-adjusted life years”), which

combine length and quality of life (the latter weighted by individual preferences for health states) in one single metric.

Ways how to define and measure progression-free and overall survival are well-established in clinical cancer research. In contrast, there is more uncertainty with regard to the measurement of patient-relevant outcomes (PROs), health-related quality of life (HRQoL), and functional outcomes, including their potential to be used for economic analysis and their acceptance by HTA agencies and policy makers.

Scales to measure HRQoL (see Tab. 2, below) differ greatly. Disease-specific instruments are often developed using psychometric methods and produce a profile of scores. They are not preference-based and do not generate severity ratings on a cardinal scale, as needed for conventional cost effectiveness analyses. For some instruments, mapping studies have been done that may allow transformation of scores into “utilities” required for the computation of QALYs.

To put the “Q” into the QALY, generic preference-based “multi-attribute utility” (MAU) instruments should be used. Currently, there are four instruments that were developed to meet the criteria of von Neumann Morgenstern utility theory. These are the AQoL-8D, the EQ-5D (in its latest iteration, “EQ-5D-5L”), the SF-6D, and the HUI-3.⁶ Despite having been developed to measure the same construct, these instruments differ greatly in terms of their descriptive systems and their scoring algorithms – and, as a consequence, in their sensitivity to the various dimensions of HRQoL and their relative performance in capturing differences between health states.⁷

⁶ cf. J. Brazier, J. Ratcliffe, J.A. Salomon, A. Tsuchiya, (2017). *Measuring and Valuing Health Benefits for Economic Evaluation*. 2nd edition. Oxford: Oxford University Press.

⁷ The low level of convergent validity described in international studies was recently confirmed in a large German population sample (n=1,269, including 115 cancer patients) using survey data from the German arm of the “multi-instrument comparison (MIC) study.”

Source: M. Schlander, M. Schlander, M.A. Khan, A. Iezzi, A. Maxwell, O. Schwarz, J. Richardson, (2013). The Measurement of Health-Related Quality of Life: German Findings from the Multi-Instrument Comparison (MIC) Study. *Value in Health* 16 (7) A330.

Tab. 2: A typology of commonly used instruments to measure health-related quality of life (HRQoL) in clinical studies in oncology

- **Generic instruments based upon multi-attribute utility theory (excluding 15-D and QWB)**
 - AQoL-8: Assessment of Quality of Life / 8 Dimensions
 - EQ-5D-5L: EuroQol 5 Dimensions Index / 5 Levels
 - HUI-3: Health Utilities Index / Version 3
 - SF-6D: Short Form / 6 Items
- **Generic instruments / not preference-based (examples)**
 - NHP: Nottingham Health Profile
 - PROMIS: Patient-Reported Outcomes Measurement Information System
 - SF-36: Short Form / 36 Items
 - SIP: Sickness Impact Profile
 - WHOQOL-100: WHO Quality of Life
- **Cancer specific instruments (examples)**
 - FACT-G: Functional Assessment of Cancer Therapy - General
 - FLIC: Functional Living Index / Cancer
 - QLQ-C30: EORTC Quality of Life Questionnaire
 - Cancer site specific instruments (examples)
 - FACT-L: Functional Assessment of Cancer Therapy – Lung
 - QLQ-BR23: EORTC Quality of Life Questionnaire – Breast

In practice, the choice between instruments can present difficult trade-offs⁸ - which will be most effectively addressed by a team of clinician scientists, biostatisticians, and experienced health economists.

Sometimes it may be necessary to complement the application of carefully selected MAU instruments with a direct measurement of the utility associated with defined health states. There are well established choice-based methods to accomplish this, most often using the standard gamble or time trade-off technique. In contrast, rating scales should not be used to generate weights for use in economic evaluation.

⁸ cf. K. Hernandez-Villafuerte, J. Ubels, D. Hernandez, M. Schlander, (2018). Efficacy of the multi-attribute utility instruments to reflect quality of life of cancer patients. *International Journal of Technology Assessment in Health Care* 34 (S1) 103.

2.3. Study Evaluation

As a rule, the objectives, the perspective adopted, comparators, primary outcomes criteria, and analytical methods (including critical assumptions and types of sensitivity analyses) of any clinical trial based economic evaluation should be pre-specified in the study protocol.

Most often, standard health economic evaluations of health care interventions based on clinical trial data will report incremental cost effectiveness ratios (ICERs), supplemented by a range of deterministic and probabilistic sensitivity analyses. Given that cost data will often be highly skewed, and the nature of the ICER as a ratio of two distributions, the computation of ICER confidence intervals is not straight-forward, and uncertainty is often graphically represented by scatter plots on the cost effectiveness plane and by cost effectiveness acceptability curves. The availability of patient-level data from a clinical study can enable the use of nonparametric methods that may greatly enhance the precision of probabilistic sensitivity analyses.

This way, it will be possible to support translation of clinical research into routine use by providing health care policy makers, HTA experts, and decision-makers representing the perspective of payers, with information contributing to cost value assessments and ultimately reimbursement in a collectively financed health scheme (cf. Fig. 2, below).

Health Economic Evaluation Principles

The Logic of Cost-Effectiveness – Questions Asked:

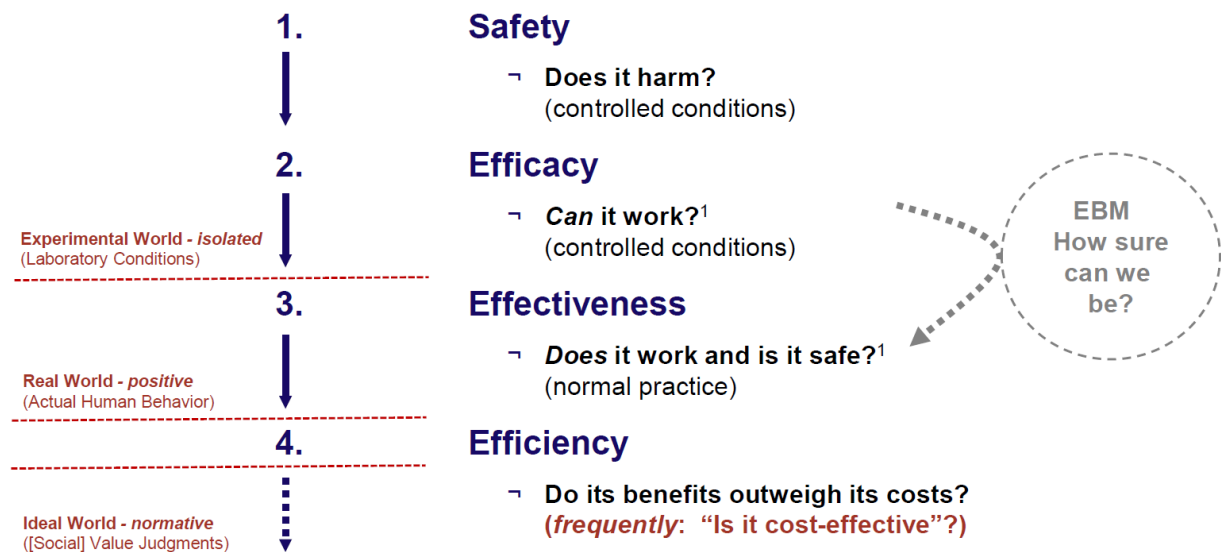


Figure 2: Health economic evaluations may help answering critical questions of health care policy makers; establishing the links between efficacy, clinical effectiveness and cost effectiveness often requires both experimental data from clinical trials and other sources of information, and their combination by way of decision-analytic and economic modelling. Abbreviations: EBM, Evidence-based medicine.

¹cf. D. Schwartz, J. Lellouch, (1967). Explanatory and pragmatic attitudes in therapeutical trials. *Journal of chronic diseases* 20(8) 637-648.

3. Education & Training

The Division of Health Economics is committed to offering clinician scientists opportunities for gaining insights into and familiarity with the application of health economic methods – ranging from an introduction to the way of thinking of economists to standard concepts and their application. Beyond this, opportunities will be provided to review the appropriate use of economic evaluation methods in oncology, insights generated, as well as limitation – including open discussion of normative and ethical implications.

In this context, please consider giving clinician scientists the opportunity to attend our **Health Economics Summer School (website link)**.

The Summer School introduces basic concepts of health economics and address practical issues faced by health care decision makers responsible for allocating scarce resources. For further information on Introductory Lectures and Open Seminars – often held by senior scientists from leading health economic institutions – please visit the **Division's website** at: <https://www.dkfz.de/en/gesundheitsoekonomie/index.php>

Heidelberg, October 03, 2019

List of Abbreviations

EBM	evidence-based medicine
HRQoL	health-related quality of life
HTA	health technology assessment
ICER	incremental cost effectiveness ratio
MAU	multi-attribute utility (theory)
MIC	multi-instrument comparison (study)
PMA	product marketing authorization
PRO	patient-relevant outcomes
QALY	quality-adjusted life year

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