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Early Stage Healthcare Technology Assessment

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Healthcare Technology

The term "Healthcare Technology" is used to describe any intervention that may be used for safe and effective prevention, diagnosis, treatment, and rehabilitation of illness and disease, for instance:

1. drugs (from an engineering perspective, this relates to drug delivery, enabling control of the drug release, absorption, distribution, and elimination rates);
2. medical devices, as defined by the European Directive 93/42/EEC (medical devices in general)
3. procedures (e.g., surgical techniques, acupuncture, medical advice);
4. secondary care (e.g., hospitals, outpatient);
5. health programs (e.g., screening programs, public health).

Health Technology Assessment (HTA) is a scientific, multidisciplinary, and multidimensional decision-making process that enables benchmarking of the positive and negative effects of such technologies. The purpose of HTA is to holistically consider a variety of alternatives and select the best technology that addresses the identified medical (and non-medical) needs in order to support health policy decisions at all levels.

However, satisfying such needs in the healthcare domain is quite challenging since improving or maintaining a health state depends only partly on technology action. Furthermore, the technology contribution itself is also often complex and may be difficult to measure and evaluate. A widely deployed scheme that summarizes the production process of National Health Services (NHS) and other concomitant factors that affect people's health is shown in Figure 8.1.

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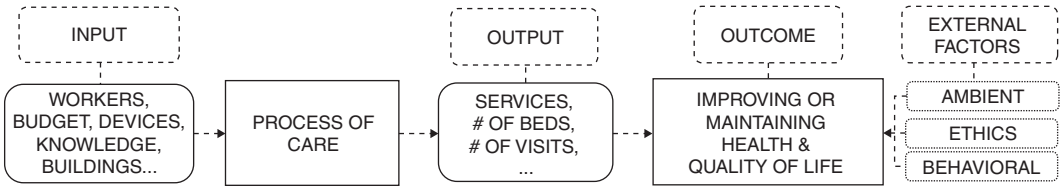

FIGURE 8.1 Production process in health.

In accordance with Figure 8.1, it is worth considering three concepts (Anthony and Young, 2003):

1. $Efficacy = \dfrac{Output}{Input}$
2. $Efficiency = \dfrac{Outcome}{Output}$
3. $Performance = Efficacy * Efficiency = \dfrac{Outcome}{Input}$

Taking in account those three concepts introduced using a system engineering approach, we can say that the purpose of HTA is to identify the technology with the best performance. HTA is thus the decision-making process through which a decision can be made whether to adopt a new technology in health care, based on its efficacy and efficiency with respect to alternatives (Craven, 2007).

In order to maximize its impact, it is important to consider such variables early on, before a new biomedical technology arrives on the market and, where possible, during the research and development phase of the technology. The World Health Organization (WHO) emphasizes that technology assessment may be perceived as an obstacle that slows down the introduction of innovative technologies in health systems; however, one of the reasons identified by the WHO is that the "assessment problem" is considered only when the technology is entering the market (Health technology assessment of medical devices, 2011). The growing importance of HTA for the biomedical engineering profession is increasingly clear. For example, European projects aiming to train biomedical engineers (CRH-BME Curricula Reformation, 2008) have for the first time (in 2010) included HTA in teaching foundation for biomedical engineering courses (Jarm et al., 2012; Pallikarakis et al., 2011). Furthermore, on a global scale, the International Federation of Medical Engineering and Biomedical (IFMBE) created the HTA Division, to minimize this problem (IFMBE, 2012).

Health Technology Assessment: Standard *De Facto*

Depending on the evaluation purpose and the available resources and time, HTA can take various formats. However, HTA reports published in respected international scientific journals generally have a very regular structure, which defines a *de facto* standard of methods and tools for HTA. The basic structure of many HTA reports can be summarized as:

1. definition of the medical goal and decision problem;
2. assessment of consequences using clinical evidence;

3. resource assessment using cost analysis;
4. analysis of incremental cost versus consequences.

In literature, several algorithms summarize the main steps of an HTA. Figure 8.2 shows a general diagram along with a brief description of the individual steps (Pecchia et al., 2009a,b,c).

Definition of the Medical Goal and Decision Problem

Different scenarios can affect the definition of the medical problem, which is often determined by contingencies depending on the size of the problem itself. Therefore, it is not always easy to identify a standard method for the choice of the medical problem. Although many authors suggest assessing the consequences of a health technology in several dimensions (economical, technical, ethical, etc.), the majority of studies are focused mainly on the clinical and the economical dimensions. While this is in theory a limitation, these two dimensions are sufficient for the majority of HTA studies. Later on we will consider other dimensions of HTA.

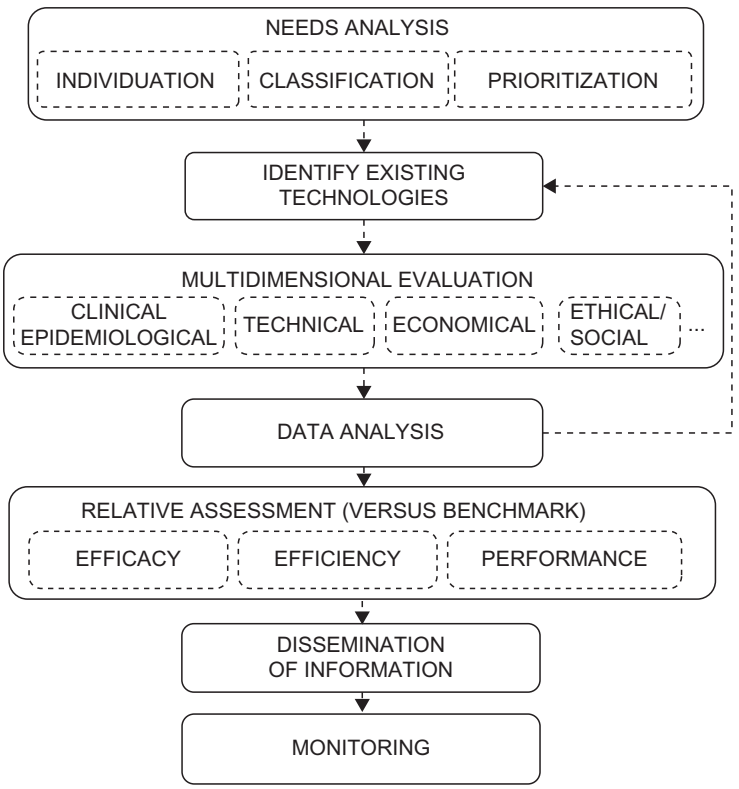

FIGURE 8.2 HTA process. *(Pecchia et al., 2009a,b,c).*

Needs Analysis

In order to carry out an HTA, the first step is to formally define the medical problem (usually clinical or epidemiological) that the technology in question must meet, through a detailed analysis of needs. In this case, the analysis includes: identification of needs; their organization into classes (e.g., clinical, economic, technological); the attribution to each need and each class a weight that reflects its relative importance. In other words, the relevance and importance of each identified need must be quantified. The quantification process is crucial for selecting the best performing technology and should be completely transparent and structured (weighted) *a priori*. Moreover, since the quantification process is based on underlying qualitative information, it should be carried out as objectively as possible in order to make the evaluation reproducible (Pecchia et al., 2011a,b). Several methods have been used in the literature for scientific needs assessment, such as *Conjoint Analysis* (CA) (Bridges et al., 2012), *discrete choice experiments* (de Bekker-Grob et al., 2012), *best–worst scaling* (Gallego et al., 2011) and *Analytic Hierarchy Process* (AHP) (Pecchia et al., 2011a,b).

At the end of this step, the most important needs to be met should be known and the most significant dimensions of the analysis (e.g., clinical/epidemiological, economic, technical) should be identified and quantified with their relative importance.

Technology Identification

In this step, potential technologies that can help meet the needs are identified. It is good practice at this stage to not consider *a priori* partial information on technology performance. However, the major difficulty is to include all the technologies that might contribute to meet the identified needs. For example, technology identification is undoubtedly affected by the selected assessment scale, which differs between national, regional, or institutional levels, and according to the scale chosen, there are different HTAs: macro-, meso-, and micro-HTA. For example, a medical device assessment for a health institution (e.g., hospital) may be mainly aimed at optimizing the purchase of new equipment to fulfill a specific treatment objective in that institution alone, whereas an assessment at a regional or national level may have as its ultimate objective the optimization of strategic health outcome within the territory, which would broaden the range of technologies to be considered.

Resources and Consequences Evaluation

Resources and consequences are generally considered as the two fundamental dimensions of HTA considering both economic cost and clinical/epidemiological outcome (including quality of life or other quantified benefits). In the following section, we also consider ethical/social and the technical dimensions of HTA.

The Economic (Cost) Dimension

Along with the clinical dimension, the economic (cost) dimension is most often considered in HTA processes. In fact, some HTA processes are limited to cost alone (cost studies).

At this step of the analysis, the costs of all the economic resources used for the provision of technologies, taken in consideration, need to be identified.

Without going into details of specific methods, the purpose of this step is to assign an economic value to each resource used directly (or in some analyses, indirectly) in the production of the provided health service. By resources, it is meant: human resource complexity, environment, technologies, supplies, depreciation, cleaning, insurance, and so forth.

In this chapter, we mainly consider direct costs which are the costs of delivering the treatment by the institution, health service, or insurer (payer's costs) and do not include indirect costs, e.g., travel costs to individuals or mainly productivity losses to society caused by the health problem or disease (although see later with respect to cost−benefit analysis which may include consideration of indirect monetary benefits). Within direct costs, it is useful to distinguish between fixed cost and variable cost. Fixed costs are costs that are independent of the amount or number of good/service provided whereas the variable costs are costs that vary with it. For example, cost of buildings rent is generally independent of the number of services provided which is a fixed cost, whereas a surgical procedure may incur a variable cost due to staff wages, facility time, and consumables used each time, which are carried out. Often, capital equipment can be considered as a variable operating cost, divided into the number of procedures per year.

Economic (cost) analysis is divided in three steps: identification of necessary resources, the classification of the same, and monetization of their value. Further complexity is introduced when the analysis is carried out over a longer period (time horizon); in which case, discounting is generally used to account for the value of money in subsequent years, and price or currency changes may also need to be modeled.

The Clinical/Epidemiological Outcomes Dimension

This is another crucial step for HTA. In this step, the technology clinical/epidemiological effects are evaluated through the outcome measurement. Of course, the outcome varies according to various factors as before, including: the assessment scale (e.g., institutional, regional, national), the type of technology that is being analyzed (e.g., equipment, medication, health process, surgical technique), the purpose of the technology (e.g., diagnosis, care, treatment, prevention, screening), and the type of patients concerned (e.g., age, medical specialty). It is very common to classify a study according to the method chosen to measure the technology effect. Classic examples of measurement of technologies effects are effectiveness, utility, and benefits estimation.

By effectiveness, it is meant the measure of how technology meets a specific clinical outcome (e.g., reduced mortality, pain, or maintenance/improvement of a "natural" biomedical parameter such as blood pressure). The main limitation of this analysis is that it may measure outcome in a one-dimensional manner, although several one-dimensional outcomes can be combined, with the added difficulty of deciding which outcomes are most important. In general, considering costs against such outcomes is called a cost-effectiveness analysis (CEA), where the appropriate parameters of effectiveness are specified. Sometimes, instead of attempting a weighting, the result may be presented to decision-maker as a side-by-side

table of costs and outcomes in the HTA report, in which case it is called a cost-consequences analysis (CCA). See later for a summary of the different types of analysis. Utility is a measure of health state, considering simultaneously multidimensional functions of several clinical outcomes, used to estimate the quality of life. It is common to measure the effect of a technology-supported treatment by its contribution to improvement in quality of life. Here the outcome is estimated as a function independent dimension as: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; the absence of pain. A common example of the utility function is the one used by QALY (Quality Adjusted Life Years), which weights the years of life gained with a quality index that takes value 1 for a year of life in perfect health, and a value between 0 and 1 for years with less quality. These values are then added together in order to assess the overall value of the QALY in the observation period. As an example, this method equates two years lived at 50% of perfect health with one year lived in perfect health. This is a somewhat indirect measure because it estimates the global health state based on preferences gained from interviews with people in the wider society (not only patients who have the disease). The main methods are:

1. Time trade-off (TTO), interviewees choose between being ill for a number of years or be healed and restored to a healthy condition, but having a minor life expectancy;
2. The standard gamble, in which interviewees choose between remaining in the current conditions or to undergo treatment, through which the patient is likely to die or be restored to good health;
3. Rating scales, such as the visual analogue scale (VAS), where interviewees are asked to assign a value between 0 (death) to 100 (health) to the different health states.

The major limitation of this method is in the way a specific status is defined. This assessment is often subjective and difficult to generalize. There are also other structured methods for self-assessment of health status. Unfortunately, no scale proposed so far has reached consensus and is thus universal which is a limitation of the use of utilities and QALYs, although there are agreed data sets used in some regions such as the EQ-5D value sets which are based on TTO and VAS (Oppe et al., 2007). The type of analysis comparing costs and QALYs is called a cost-utility analysis (CUA).

Another way to address the problem is by a cost−benefit analysis (CBA). Benefit is the effect of a health outcome expressed in monetary terms (we note, it is common to hear the term “benefit” used to express the more general concept of clinical outcome, generating some confusion). Monetary quantification of the value of health can be carried out with the two widely used techniques:

1. Human Capital, HC;
2. Willingness To Pay, WTP.

The HC standard method estimates the value of an individual’s life through their future potential productivity to society, calculated as the value of the remuneration of the planned work, reported at present value. This method is implicitly based on the maximization of such productivity as the goal. The main problem with this approach is the reduction of the

individual health to only include the value that a person provides to Gross Domestic Product (GDP), neglecting the intangible value of life itself. In fact, in a country with a public NHS and with a constitution that emphasizes the equality of all citizens, regardless of how much they contribute to GDP, which is still a questionable indicator of the wealth of a country, this method is still not favored in many countries.

The WTP standard method estimates, in the case of a pathology, how much a society would be willing to pay to avoid contracting the disease. In other words, it estimates the aggregate value that a population at risk would invest on programs that save lives statistically, or the sum of the amounts that individuals would be willing to pay *ex ante* to reduce the probability of their death. An example may help to illustrate this point. Suppose that every person in a population of 100,000 inhabitants is willing to pay 25 pounds ($25 \times 100{,}000 = 2.5$ pounds) for a program that is expected to reduce the overall probability of death from 0.09% to 0.08%. Since this is equivalent to a reduction in the mortality rate from 90 per 100,000 to 80 per 100,000, the implied value for each of the 10 lives saved is 250,000 pounds (2.5 million divided by 10 lives saved). Of course, whether a life is worth more or less than this figure is a difficult question for society.

The Ethical and Social Dimension

The consideration of these dimensions in the HTA reports is very limited (Sacchini et al., 2009). For more information, please refer to specific texts (Reiser, 1988). However, it is useful to recall the pattern of Heitman (1998) suggesting to organize ethical dimension in five categories:

1. aspects of concepts and definitions of the process of HTA itself;
2. aspects related to diagnostic procedures (e.g., limits, risks, employment.);
3. aspects related to preventive strategies (e.g., the management of the risk of pathologies) and therapies (e.g., evidence, efficiency, appropriateness);
4. aspects related to research (e.g., protection of subjects enrolled in the studies, informed consent);
5. aspects related to the resource allocation (e.g., distributive justice, rationing mechanisms, economic evaluations).

The Technical Dimension

As far as the technical dimension is concerned, this is related predominantly to technological aspects, which affect only partially or indirectly the economic or clinical dimensions. It includes, for example, aspects related to the drug administration that do not impact directly on the patient (preparation, archiving, etc.). Moreover, the technological asset of an institution affects the technical dimension. For example a hospital linked to a university which develops technologies may be more comfortable with the deployment of new technologies such as robotic surgery or may be able to provide it at minimal cost, for example, if linked to research activities funded externally, making its introduction more attractive.

Data Analysis: The Meta-Analysis

Data analysis presents the next step. This includes data collection, processing, synthesis, and representation. The most common method used to collect clinical data for HTA is from meta-analysis (Sutton, 2000). This method uses statistical tools for harmonizing and combining results from different study to identify significant patterns. Therefore, the main aim is to aggregate information in order to achieve a higher statistical power for the measure of interest, as opposed to a less precise measure derived from a single study. Although this analysis has several limitations, it enables to conduct studies on large number of patients and on different case studies, decreasing for instance the economic concern. The studies' identification is usually performed by independent researchers through structured approaches. Subsequently, their results are compared in order to reach consensus on what studies accepting to the next step of the analysis, namely, the elaboration of the latter. The inclusion criteria, used to define which studies are worth elaborating, are defined *a priori*, by choosing the appropriate criteria, including the choice of scientific studies with a high evidence level. For instance, the randomized controlled trials (RCTs) are included as first, pseudo-randomized trials as second, and finally the cohort studies (prospective, prospective with retrospective control group, retrospective) or the retrospective studies (Guyatt et al., 1995). After having identified the studies, the analysis proceeds with the classification and weight of the studies in order to extrapolate the results. Finally, the results of individual studies are aggregated, weighing them on the basis of the study importance. This importance depends on the number of cases handled and the accuracy of the results. These results are then presented in graphic form, to be communicated to the larger number of decision-makers, which may not be very confident with advanced mathematical methods. Figure 8.3 shows the results of a meta-analysis carried out on a biological drug to evaluate its effects on life quality between patients assuming the drug (treatment group) and control group.

This meta-analysis was conducted on five studies (one per line) (Furst et al., 2003; Van de Putte et al., 2003; Weinblatt et al., 2003; Keystone et al., 2004; Van de Putte et al., 2004). In each study, the effects were observed in a treatment group, with a sample of N_t subjects

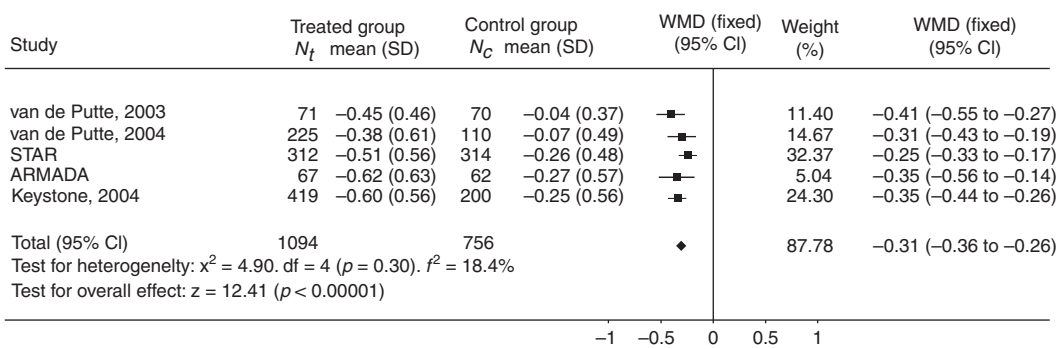

FIGURE 8.3 Mean difference of adalimumab effect on HAQ, in the control group and the treatment group. In the first five rows, are reported the results of other studies. The end result is shown in the bottom line.

(from 67 to 419 per study), and compared with a control group of N_c subjects (from 62 to 314 per study). The quality life of a subject has been measured in the individual studies, by the Health Assessment Questionnaire (HAQ), which measures the outcome for clinical trials, and it is widely used before and after treatment in the two groups (treatment and control group). HAQ values, indicating an improvement of health status, are shown in the second and fourth columns, respectively, for the treatment and control groups, respectively; the mean and standard deviation values are reported in parentheses. In the penultimate column, the relative weight of each study is shown. The weight increases with the number of subject of the two groups (N_c and N_t) and decreases with the magnitude of the standard deviation (SD) of the effect. In fact, the study of Keystone (fifth line) conducted on 619 subjects (419 + 200), and with an SD of 0.56 in both control and treated group, has a relative weight, normalized to percent of 24.30, which is less than the relative weight of the STAR study, conducted on a larger number of subject but with a less SD value, at least in the control group. For instance, the STAR recruited 626 patients (312 + 314) and reported an SD of 0.56 in the treated group, but an SD of 0.48 in the control group. Finally, the last column shows, for each study, the mean difference between groups (control against treated) and in brackets the confidence interval of 95%. In the last row, Weighted Mean Difference (WMD) is presented; it shows the difference that would have been achieved if the study had been conducted only one study of 1094 patients treated with the drug and 756 patients for the control group. Similar statistics on dichotomous variables can be found in Sutton (Sutton, 2000). Many examples of meta-analysis can be found in the existing literature (Castaldo et al., 2015; Bracale et al., 2012a,b). The second of the last two studies (Bracale et al., 2012b) is a network meta-analysis, which represents one of the possible generalizations of the meta-analysis (Lumley, 2002).

Cost and Consequences Assessment

In practice, it never happens that a new technology overcomes the other existing in all the dimensions of the analysis. Therefore, it is crucial to understand which dimensions need to be prioritized, according to the objective of the analysis. This decision may depend strongly on the analysis scale. For example, a Local Health Authority may consider as priority the maximization of the efficiency, while in a highly specialized hospital it may consider as priority the maximization of the efficacy, and in particular certain outcomes. As discussed in previous sections, the majority of studies consider the economic and clinical dimensions in terms of efficacy, utility, or benefit. In the literature (Nord, 1999), four methods to analyze the efficacy of a health technology are Cost Minimization Analysis (CMA); Cost-Effectiveness Analysis (CEA), which may also include Cost-Consequences Analysis (CCA); Cost-Utility Analysis (CUA); and Cost−Benefit Analysis (CBA). Table 8.1 summarizes the main characteristics, advantages, and limitations of these four methods. In addition, in Figure 8.4 the algorithm, to choose the most suitable type of analysis, is described.

There may be three conditions, as summarized in Table 8.2 (in which the efficacy is treated in the same way as the utility), during the evaluation of the costs and the outcomes/consequences of a new technology compared to a widely used technology.

Table 8.1 Comparison of Different Methods Used to Analyze the Cost/Result

	CMA	CEA	CUA	CBA
Costs	Monetary units	Monetary units	Monetary units	Monetary units
Consequences	Equal in both programs	Clinical outcomes	QALY	Monetary units
Measuring	Differences in costs (DC)	ICER	ICUR	ICBR
Advantage	Direct measurement	Direct measurement	Indirect measurements	Indirect measurements
	Necessary for the other	Uniform clinical outcomes	Mixed clinical outcomes Multidimensional analysis	Mixed outcomes Multidimensional analysis
Limits	No consequences	One-dimensional analysis	Indirect measurement	Indirect measurement
		Data table missing in many national health services	Data table missing in many national health services	Monetization of value of life Ethical limits

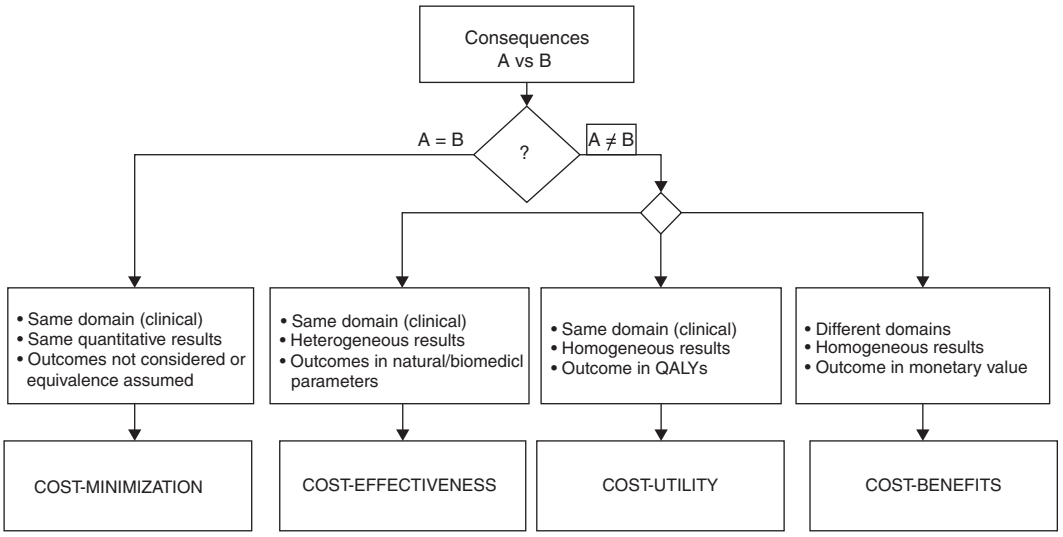

FIGURE 8.4 Algorithm for the choice of health economic analysis.

If a new technology (Technology A) proves to be less effective and more expensive compared to a benchmark (gold standard—technology B), as represented in the first case of Table 8.2, it is rejected without further analysis, unless there is a high degree of uncertainty in the data (in this case, further experiments are needed). On the other hand, a technology is a good candidate, if it is more effective and less costly (the second case of Table 8.2). In the third case, the achievement of a greater efficacy is related to an additional cost, therefore the

Table 8.2 Possible Results of a Cost-Effectiveness Analysis

Costs	Consequences	Result
$C_A \geq C_B$	$X_A < X_B$	DOMINANCE. A is more expensive and less effective/utile than B. B continues to be the standard.
$C_A \leq C_B$	$X_A > X_B$	A IS COST SAVING. A is less expensive and more effective than B. The new technology A is introduced gradually in the NHS.
$C_A \geq C_B$	$X_A > X_B$	INCREMENTAL ANALYSIS IS REQUIRED. A is more expensive and more effective/utile than B. The new technology A may be introduced gradually in the NHS if the cost for unit of effectiveness/utility is less than the last one introduced into the NHS.

technology requires an evaluation of the Incremental Cost-Effectiveness (or Utility) Ratio (respectively ICER or ICUR) expressing the cost of a unit improvement in outcome. This third case is a common situation; since the price of a new technology includes the manufacturer's recouping of design and prototyping costs, they can be much higher (especially with low volume production of devices) than a product already on the market. An ICER over a given threshold may suggest that the new technology is more cost-effective, and therefore its adoption is justified since the expected outcomes are considered to be worth the costs incurred. In the United Kingdom, it is generally considered that for the adoption of a new drug or device-related treatment, a threshold of between £20 K and 30 k pounds per QALY gained is acceptable. In other words, it is considered worth spending up to 30 k pounds for 1 year of life gained or for 2 years of life lived to at 50% of perfect health compared with no intervention or intervening with a benchmark treatment.

Standard Method Limitations and Weaknesses

Most HTA methods, which have been effectively used for evaluation of drugs, may straggle when applied to the assessment of medical devices. In fact, there are some differences between drugs and medical devices, which have a significant impact on the assessment (Table 8.3).

Furthermore, HTA methods are not very accommodating of the reality of research and development process for medical devices. For example, in the research phase, there are generally no RCTs that are sufficiently large or numerous for a proper assessment of the consequences. Nevertheless, it is important to aim to collect information for HTA at a very early stage of research, preferably during the conception of the idea, together with a reliable estimation of the probability of return on investment or of the needs of the market to which the technology aims to (Ijzerman and Steuten, 2011).

Finally, standard HTA methods do not directly identify the priorities among the needs of individual users or subgroups. For example, the weighting of utility in value sets is not

Table 8.3 Comparison between Drugs and Medical Devices

Devices	Drug
Principal action	
Other than principally drugs	Pharmaco/Immunologic/Metabolic
Mechanical/Electromagnetic/Materials	Chemical based
Product life cycle	
Short life cycle	Long life cycle
Constantly evolving components/parts	Unchanging compound
Clinical evaluation	
Difficult to blind (no placebo)	Easy to blind
Multiple end users	Usually one end users
Long learning curve	Short learning curve
Strongly dependent by settings/users	Less dependent by settings/users
Complex to standardize for RCT	Easy to standardize for RCT
Use issues	
User-dependent efficacy	Efficacy is less user-dependent
Often require intensive training	Usually do not require training
Complication decrease with use	Complication increase with use
Diversity	
Mainly small companies/few large co.	Mainly large multinationals
Diagnostic or therapeutic	Therapeutic
Costs	
Varying overheads/slow return	High overheads with quicker return
Higher distribution costs	Lower distribution costs
Higher maintenance/installation costs	No maintenance/installation

(Adapted from Craven, 2007).

reflective of age so dimensions pain and mobility are averaged in one country and are the same for people with different aspirations. Therefore, stratification by age and other factor is possible in principle (Kind et al., 1998).

Early Stage HTA (eHTA)

Recent studies try to overcome some of the limitations described in particular: does the assumption that the device, on which the research is to be carried on, work exactly as demonstrated by the experimental data and provide benefits or cost savings (or both) more than the existing technology (and is therefore reimbursable by the NHS)? This is exactly the question that the early stage HTA tries to answer scientifically. In this section, some of these methods are introduced.

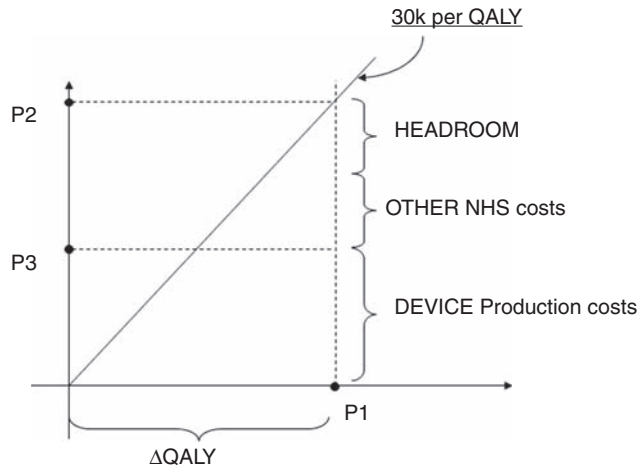

FIGURE 8.5 Headroom method.

Headroom Analysis

In order to answer the aforementioned question in an appropriate way, outcomes should be quantified and expressed in terms of QALYs and compared to a reference threshold for the incumbent technology whether to be considered cost-effective, as discussed previously. As stated previously the NHS generally considers appropriate a reimbursement of up to £ 30,000 per QALY gained, for one patient undergoing a novel treatment versus an existing alternative (which may include no treatment). The Headroom method tries to answer the above question on the supply side (i.e., from the manufacturer's perspective) (Cosh et al., 2007) by evaluating the technology's cost-effectiveness through the ICUR, according to the best hypothesis. Therefore, since the evaluation is carried out, according to the most favorable assumptions, the results do not guarantee that the device will be successful, but it may exclude ideas being not successful. The method consists of the following steps (Figure 8.5):

1. assume that the device actually improves the estimated ΔQALY (Step 1);
2. calculate the maximum cost that the NHS is willing to spend on such ΔQALY (Step 2);
3. subtract the cost of the device production (Step 3);
4. subtract the costs that the device does not reduce (e.g., administration);
5. calculate the maximum profit margin for the product.

If the final gain presents a sufficient margin, the R&D could reasonably continue. Otherwise further research investment would be better spent elsewhere. Having this knowledge at a very early stage in the applied research is very useful.

Cost-Utility Evaluation in a Preliminary Phase: Markov Models

As introduced in previous sections, cost analysis assigns a monetary value to each resource used in the care process. This analysis can become more complex when the needed

resources for each patient vary according to disease evolution (for instance, deterioration may require additional resources). At the beginning of an analysis of a typical long-term or chronic health condition, patients in the same study population may be in different early stages of the disease. Subsequently, each state may vary: the probability of having an exacerbation, severity of exacerbation (mild, moderate and severe), the probability of moving from one state to another (e.g., mild becoming moderate). Such phenomenon can be modeled using a Markov model (Sonnenberg and Beck, 1993). These models assume that a patient is always attributable to one of a finite number of discrete health states called Markov states (nodes into the model). All the events are represented as transitions from one state to another (edge), with a given probability "p." A marginal cost "ΔC" is associated to each event (transition) "k", representing the total amount of required resources for that event, including costs for normal treatment, treatment of exacerbations, and so forth.

Since some consequences can vary over a time period, Markov models can be used to perform an incremental health economic analysis (Sonnenberg and Beck, 1993) in the evolving patient population.

In this case, the following steps are usually performed:

1. Each status "k" of a pathology (including the initial one) is associated to a cost (ΔC_k), which represents the total amount of required resources such as trading patients in such status, and a marginal consequence, which may be a marginal effectiveness variation (ΔE_k) or a marginal utility (ΔU_k).
2. The transition from one state to another is associated with a probability.
3. The expected exacerbations from each state are associated with a probability, for each kind of exacerbation (e.g., mild or severe).
4. The total path costs for each final state and the total path effectiveness (or utility) are combined representing the total costs (C) and total consequences (E or U) for groups of patients in each final state.
5. The model is then evaluated dynamically (often with a Monte Carlo simulation).

This generates a distribution of Cost-Utility points (C, U) j, with $j = 1, \ldots, N$ (number of simulations carried out), as shown in Figure 8.6.

In the case of a comparison between a new technology (A) and a benchmark (B), this procedure is repeated with the same Markov model, but with probability, cost and consequences resulting from the use of the new technology in order to calculate the costs and consequences of each one ($\Delta = A - B$). In this case, the cost-consequences plane has on the x-axis the consequences difference (ΔE or ΔU) and on the y-axis the costs difference (ΔC) (Chapman et al., 2000).

In the development of a new device or a technological breakthrough, it can be difficult to obtain data that enables stratification of patients according to risk factors or previous interventions (if any), or to consider the whole range of outcomes that may occur. However, it may be sufficient in a preliminary stage to consider the main outcomes and to limit the patient stratification to a small number of sub-groups. One of the most common analytical approaches is based on the use of Markov models with a small number of states and

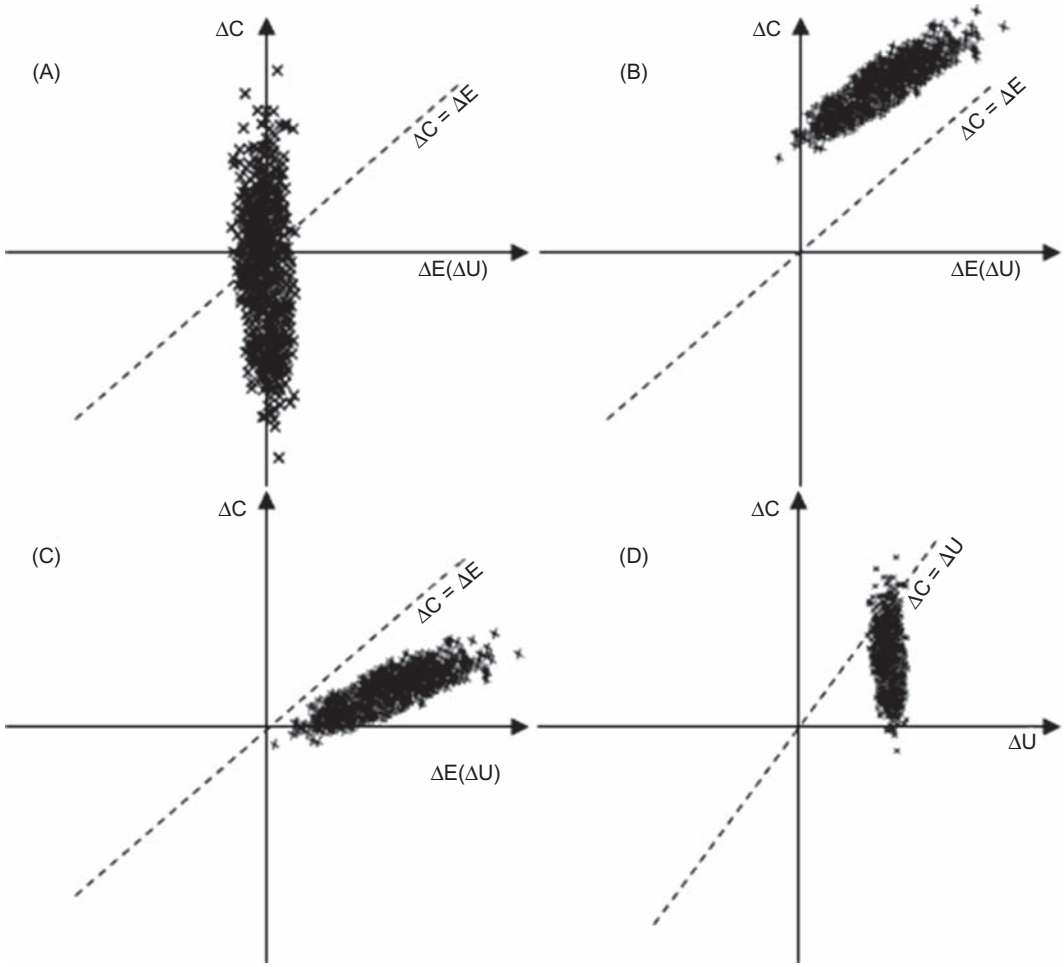

FIGURE 8.6 (A) Equivalence between the efficacy of two technologies (symmetry with respect to the vertical axis); (B) new technology less cost-effective than the benchmark; (C) new technology more cost-effective compared to the benchmark as all points of the simulation are below the line of willingness to pay; (D) uncertainty: the new technology seems to be more effective in the 80% of the simulation.

transitions according to the availability of data. This approach was applied by Dong and Buxton (Dong and Buxton, 2006) to compare a new computer-assisted technology and the standard procedure for total knee replacement (TKR). The number of patients who had a primary TKR was limited to three groups, according to risk: the absence of complications, minor complications, and serious complications. Patients with complications may require revision surgery or other treatments. The model required a number of different variables, such as the transition probabilities between states, the various additional complications or death, which were extracted from the literature or estimated ad hoc. The comparison was made with a model with nine states, proving that the assessment in the early stage offered

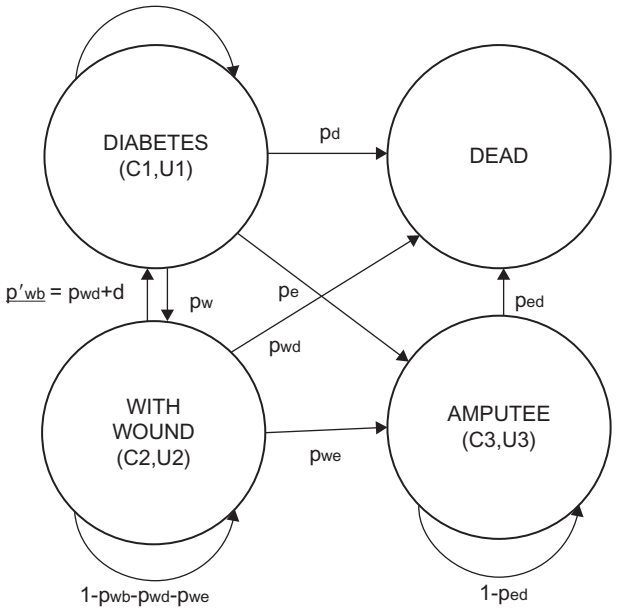

FIGURE 8.7 Evaluation model in the early stage via Markov model.

sufficient knowledge of effectiveness long before an RCT or meta-analysis were available in the literature. In a subsequent study (Craven and Morgan, 2011), a model with four states was used for what-if analysis regarding a device promoting healing of diabetic foot ulcers. The model included four states: absence of injury, the wound (ulcer), amputation, and death. This is a simplification of a more sophisticated model that included classification in high and low risk and considered more types ulcerations and amputations with different probabilities. The value of the device was examined by assuming that the probability of transition between two states (return from ulcerated foot to the absence of wound) was improved by the use of the device in question, as illustrated in Figure 8.7.

The Needs Analysis and Benchmarking via AHP

As introduced previously, several methods have been proposed for the analysis of the HTA needs, including Conjoint Analysis (CA) (Bridges et al., 2012), discrete choice experiments (de Bekker-Grob et al., 2012), best−worst scaling (Gallego et al., 2011), and recently the Analytic Hierarchy Process (AHP) (Pecchia et al., 2011a,b). According to (Scholl et al., 2005), the AHP method proved to be more suitable than the CA for complex decisions involving many factors. Mulye (1998) has suggested that AHP is more effective than CA, since more than six attributes are considered. Ijzerman (Ijzerman et al., 2008) concluded that AHP, compared with CA, is shorter, more flexible, and easier to implement in questionnaires, although inconsistencies can be generated and other methods may benefit of a more holistic approach. This section briefly describes the method and its application to eHTA.

AHP is a decision-making method aiming to solve multifactorial and multidimensional problems. This method is particularly effective in quantifying the users' opinions based on their personal experiences and in taking a coherent decision. AHP is based on the classification of a hierarchy of elements; therefore, questionnaires are showed at each user, which, through pairwise comparisons, assess the relative importance of the elements. By asking redundant questions, it is possible to assess the consistency of the respondent. Applying this iterative method, it is possible to estimate: the relative importance of each need in its category, the relative importance of each category, and the absolute importance of each need compared to all the other. A detailed explanation of the AHP method applied to user need elicitation can be found in Pecchia et al. (2009a,b,c) and Pecchia et al. (2011a,b). This method has been successfully applied to detect the user needs in previous studies, to identify the best care model for chronic heart failure (Pecchia et al., 2009a,b,c) for the choice of a maintenance contract based on the location of the hospital and the services offered (Pecchia et al., 2009a,b,c) for the identification of risk factors for falls in the elderly (Pecchia et al., 2011a,b), or the purchase of a computed tomography scanner (Pecchia et al., 2013) and for the definition of a life quality scale for the well-being of the elderly (Pecchia et al., 2011a,b).

The method consists of five steps:

1. identification of the needs that new biomedical devices aim to satisfy;
2. design of a need tree with nodes (categories) and leaves (needs);
3. development and presentation of a questionnaire to detect users' needs;
4. weights quantification; and
5. assessment of multiple technologies.

The needs' identification (first step) is generally conducted revising the scientific literature and through focus groups, involving domain experts (e.g., medical specialists, clinicians, biomedical engineers), potential users of the device (medical personnel, patients), and one AHP expert. In the second step, the needs, identified previously, are reorganized in a tree structure. Three main categories are included in most tree models: clinical needs, economic needs, and technical needs (Pecchia et al., 2009a,b,c).

The third step is based on the development of questionnaires, by which respondents compare the relative importance of each need against the others of the same category. For example, for each pair of needs (i, j), each respondent is asked: "Based on your experience and according to the specific evaluation objective, how do you rate the need i against the need j?" The expert chooses one of the suggested choices, relating to the question. A weight is then assigned to each judgment using a numerical scale. Several scales have been proposed, including the natural scale, proposed by the same inventor of the method Prof. Saaty (Saaty, 1977), which consists in assigning a numeric value to positive choice, e.g., from 3 "more important" to 5 "very more important". A value of 1 is assigned to the choice "equally important." The reciprocal values are attributed to the remaining choices: for 1/3 "less important", 1/5 if "much less important." The natural scale of Saaty provides nine possible choices, (1, equally important; 9, extremely important) (Saaty and Vargas, 2001). The fourth step involves a series of numerical calculations aiming to find the relative weight, reflecting

the relative importance, of each element (need or category), compared with all the other in the same father node. Details can be found elsewhere (Pecchia et al., 2010; Saaty, 1982).

Finally, the same algorithm is applied to compare device under development with existing technologies (Fifth step). In other words, the question posed this time is, "how much the technology A, in comparison with the technology B, is meeting the need *i*?" Using the same weights as described above, it is possible to obtain a vector $\underline{E}$ (with m elements, where m is the total number of identified needs) that describes the efficacy of the technology in the development phase, compared to all others. The summary analysis that represents the overall performance of the device in question compared to other existing technologies is estimated by calculating the scalar product of this vector with the vector GW introduced earlier. Examples of such applications applied to technologies may be found in the literature in various stages of development (Pecchia et al., 2009a,b,c; Ijzerman and Steuten, 2011; Pecchia et al., 2007; Liberatore and Nydick, 2008; Sloane et al., 2003).

Conclusion

In this chapter, after briefly recalling some key concepts such as efficacy, efficiency, and health performance, some HTA methods were introduced. These methods are very useful and their widespread distribution is highly desirable. However, they have historically been developed to evaluate drugs and have limitations of applicability when they are used to evaluate new medical technologies, particularly to estimate the potential for sustainability in development, research, or even conception (early stage).

In the last few years, evaluation methods designed precisely for the early stage of HTA biomedical technologies have been developed; they aimed to answer the following question: "Assuming that the device on which you are carrying out the research work exactly as demonstrated by experimental data, which benefit will this technology give to the patient more than the technologies currently on the market ?" In this chapter, three of these methods were presented. In this period, assessments are particularly difficult for several reasons, including the nonavailability of adequate data. However, it would be helpful to have an assessment, albeit preliminary, to decide whether and how to invest resources. In fact, in the research and development process, great results in terms of sustainability of the technology itself are obtained with small changes. In recent years, the biomedical international community has begun to show more interest in HTA, due to applicability of these methods also to research. Moreover, the use of these methods may speed up the commercialization of devices.

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