Università degli Studi del Piemonte Orientale

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Dipartimento di Scienze del Farmaco

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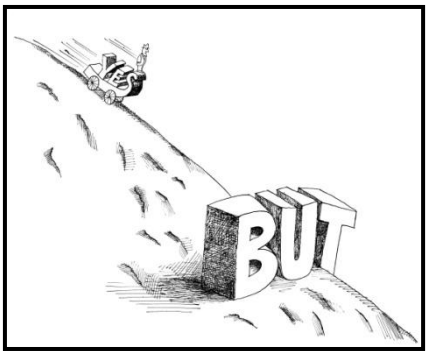
Budget Impact Analyses: are studies consistent with guidelines?



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Budget Impact Analyses: are studies consistent with guidelines?

Margherita Battista

Supervised by Prof. Claudio Jommi

PhD program co-ordinator Prof. Menico Rizzi

To my family

Non ti arrendere mai,
neanche quando la fatica si fa sentire,
neanche quando il tuo piede inciampa,
neanche quando i tuoi occhi bruciano,
neanche quando i tuoi sforzi sono ignorati,
neanche quando la delusione ti avvilisce,
neanche quando l'errore ti scoraggia,
neanche quando il tradimento ti ferisce,
neanche quando il successo ti abbandona,
neanche quando l'ingratitudine ti sgomenta,
neanche quando l'incomprensione ti circonda,
neanche quando la noia ti atterra,
neanche quando tutto ha l'aria del niente,
neanche quando il peso del peccato ti schiaccia...
Stringi i pugni, sorridi e ricomincia!

(San Leone Magno)

Content

1. Introduction

1.1 The economic evaluation in health care

In the last decades there has been a growing consciousness on the increasing need of health on the one hand and the paucity of resources on the other.

The economic evaluation aims at assessing whereas a new health technology provides value for money and, ultimately, if the available budget is efficiently allocated, i.e. if we are reaching the maximum level of health with the available budget.

The economic evaluation has been defined as *"the comparative analysis of alternative courses of actions in terms of both their costs and consequences"* (1).

The economic evaluation can help the decision maker to choose among a possible wide range of alternatives of resources use (2), paying particular attention to the "opportunity cost" which refers to the loss of health benefits that would have been created if the resources were used in another course of action (3).

Thus, health economics and economic evaluation can be considered as a "link" between economics and healthcare in which the discipline of economics is applied to the topic of health (4).

The economic evaluation is a component of the Health Technology Assessment (HTA).

Health technology assessment (HTA) is *"a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient-focused and seek to achieve the best value"* (5).

HTA aims at evaluating new technologies (i.e. drugs, medical devices, procedures, settings of care and screening programmes) (6), to determine their efficacy, clinical safety, indication for use, economic impact and ethical, social and legal implications too (5).

Economic evaluation, compares two alternatives, looking at their costs and consequences (fig.1).

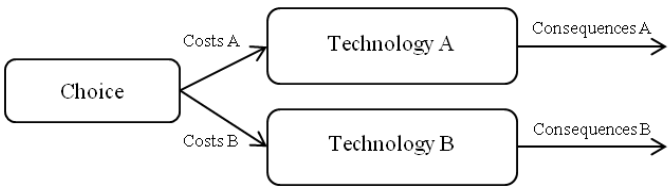

Figure 1: Comparison of alternatives in economic evaluation (3).

Depending on how benefits are measured, economic evaluation can be classified as:

i. Cost Efficacy/Effectiveness Analysis (CEA), should there be an important benefit measured in physical units (e.g. life expectancy, years of life saved, progression free survival, etc.) (7).
ii. Cost Utility Analysis (CUA), should the improvement in quality of life be an important impact of the treatment; in CUA benefits are measured as life years saved weighted by the quality of life after

treatment (ranging from 0 to 1), i.e. QALY (Quality Adjusted Life Years saved) (7).

iii. Cost Benefit Analysis (CBA): in this analysis benefits are measured in monetary units (7).

Whereas economic evaluations consider both costs and benefits, Budget Impact Analysis (BIA) is carried out to estimate the financial burden for the health care payer caused by the adoption and diffusion of a new technology (8).

The following sections will briefly describe / analyse the most important characteristics of cost effectiveness analysis (CEA), cost utility analysis (CUA) and cost benefit analysis (CBA) (table 1). Afterwards, the analysis will illustrated the difference between a BIA and an Economic Evaluation.

Type of analysis	Evaluation of costs	Outcomes measure
CEA	Monetary units	Physical units (years of life saved, progression free survival)
CUA	Monetary units	QALY
CBA	Monetary units	Monetary units

Table 1: CEA, CUA and CBA

1.2 Cost-Effectiveness Analysis

In cost-effectiveness analysis (CEA) two different alternatives are compared as to their costs and benefits in terms of year of life saved, life expectancy, progression free survival etc. This kind of analysis is a complete one (1) since it is performed taking into consideration both the costs and the consequences deriving from the adoption of a new technology.

It worth mentioning the difference between the term "efficacy" and "effectiveness". The efficacy is the extent at which an intervention fulfils its intended effect in a perfect setting of care, while the effectiveness is the effect of one intervention in the real world practice.

The additional cost that one program imposes compared to the additional benefit it delivers is expressed by the "Incremental Cost-Effectiveness Ratio" (ICER), which is calculated by dividing the incremental cost of the new intervention by the incremental change in effectiveness (3).

$$ICER = \frac{C_A - C_B}{E_A - E_B}$$

Where: C_A is the cost of the new intervention

C_B is the cost of the comparator

E_A is the effectiveness of the new intervention

E_B is the effectiveness of the comparator

The ICER measures incremental costs over incremental benefits (e.g. 10,000 Euros per Life Years Saved), due to the adoption of the new programme.

The outcome of a CEA (i.e. the ratio between incremental costs and incremental benefit), may be represented using the cost effectiveness plane (CEP) (fig. 2) (3).

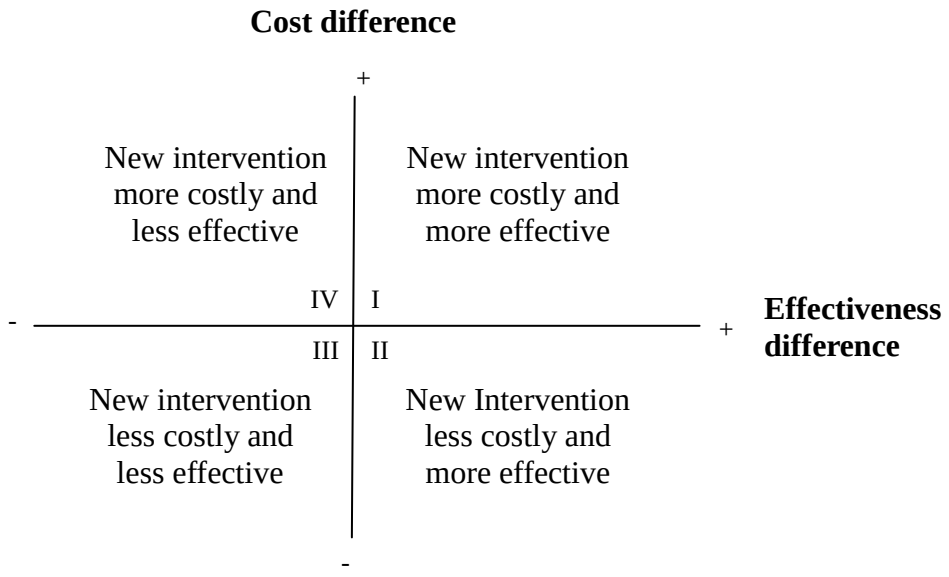

Figure 2: The cost effectiveness plane (3).

If we are either in the quadrant II or in the quadrant IV, one intervention "dominates" the other one. Since in the quadrant II the new intervention is less costly and more effective, it dominates the other. On the contrary, if it falls in the quadrant IV, the new alternative will generally be rejected since it would be more costly and less effective (3).

If the intervention falls in the quadrant I (more effective but more costly), or in the quadrant III (less effective but less costly) the ICER should be calculated.

The final decision to adopt or not adopt the new intervention will depends on the maximum ICER (threshold) the decision-maker is available to pay, the level of priority assigned to the target (disease) and the available resources (3).

Costs included in the analysis depends on the perspective used. The perspective may be that of healthcare payer, the single hospital, the patient or the society as a whole (1).

Costs may be classified as direct health care costs, other direct costs and costs generated by loss of productivity (short-term, long-term or permanent absence from work; premature mortality before retirement) (6).

Evidence on efficacy and effectiveness may derive from single trials / observational studies, systematic reviews and meta-analyses (1, 6, 7), and experts panel (6). Experts opinion may be collected through the Delphi technique (7), where the opinions are gathered through a double-blinded "round" series (9).

1.3 Cost Utility Analysis

The CUA is used when the quality of life is an important outcome, i.e. when both morbidity and mortality are affected by the intervention (1, 3, 7). The final outcome (i.e. the utility) is generally reported as the cost per quality-adjusted life year (QALY) (3) which allows to combine the effects on survival and health related quality of life (HRQoL), enabling comparison among different areas (10).

Various methods can be used to measure utility, i.e. a parameter ranging 0 (death or vegetative status) through 1 (perfect health).

Direct methods include the time trade-off (TTO) and the standard gamble (SG) (3, 6, 10), whereas indirect methods rely on multi-attributes questionnaires, like the Health Utilities Index mark 3 (HUI-3), the EuroQol five-dimension (EQ-5D), the six-dimensional health State short Form (SF-6D), derived from the Short Form 36 health survey (3).

Using a TTO, the interviewee is asked to choose between two alternatives: to remain in a certain health status for a determined period of time *"t"* or to be in a perfect health status for a time *"x"* less then *"t"*, followed by death (fig 3). The amount of years of life the interview is available to give up for a perfect quality of life in the remaining years measures the utility score (6, 7).

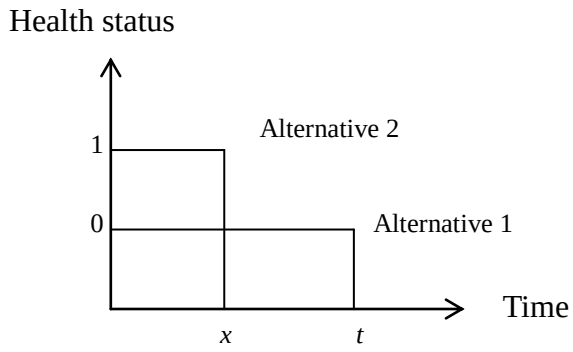

Figure 3: Time trade-off (3).

In the SG technique the interviewee is asked to choose between a treatment with an uncertain efficacy but a high number of QALYs and a certain treatment with fewer QALYs (6). In the SG the probability to obtain a determined outcome are continuously changed until for the patient there is not any difference between the two alternatives, i.e. participating in a lottery that makes him / she having a higher quality of life (with probability p) and probability p-1 to die immediately or remain for a certain number of years in the same condition.

Among the indirect methods the HUI investigates eight health domains, with a preference scoring system based on standard gamble utilities measured from the general public (11, 12).

The EQ-5D contains five attributes: mobility, self-care, usual activity, pain/ discomfort, and anxiety / depression. Each attribute has three possible states which provides 245 possible health states. Utility scores were measured for each health state using the TTO technique (13).

The SF-6D is based on the Short-Form 36 (SF-36) and Short form 12 (SF-12) and it consists of six attributes which use data from either 11 items from the SF-36 or eight items from the SF-12. Utility values on 249 potential health states were calculated (14).

Figure 4 illustrates QALYs. Without the intervention, a patient HRQoL would deteriorate following the lower curve (grey area), and he would die at time death 1. With the intervention the patient's health would deteriorate more slowly, he would live longer, and die at time death 2. The area between the two curves measures the number of QALYs gained by the adoption of the intervention. This area can be divided into two portions, A and B. The first one is represented by the QALYs gained due to a better quality of life and the second represents the QALYs gained due to the extension of the quality (extension of life) (1, 3).

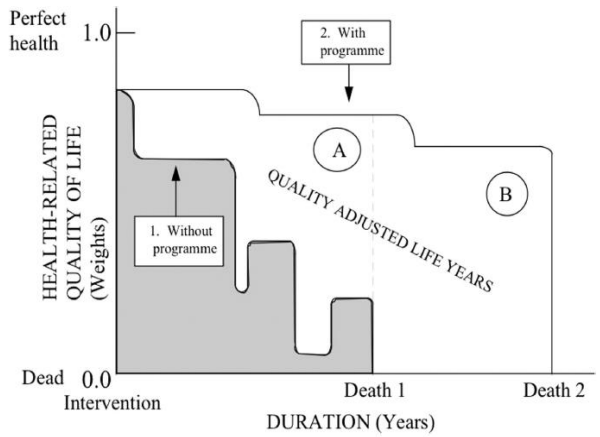

Figure 4: The QALY (3).

1.4 Decision analytical models

Economic evaluations compare the expected costs and consequences of two alternatives in the long-run or at least since the two alternatives have produced the most relevant costs and consequences. Evidences on the long-run impact of a technology and clinical pathways are generally not available.

The main objective of a decision analytical modelling is to provide economic evaluations with long-run extrapolations starting from the clinical

evidence (15) and to make explicit the process associated with the decision to implement a new intervention in healthcare (16).

The simplest form of decision model is represented by a decision tree: alternative options are represented by pathways or branches (fig. 5).

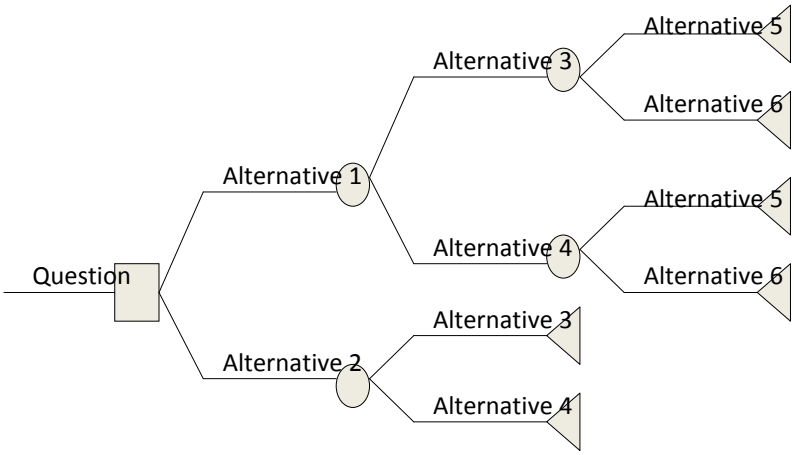

Figure 5: Decision tree

The decision tree starts with a decision node (square) which corresponds to the decision point between two (or more) alternative options (3, 17, 18). Following the different branches, a chance node (circular symbol) is reached. The alternatives following a chance nose are mutually exclusive and the probability to occur of all the possible alternatives, which spring from a single chance node, should sum exactly to one (17).

The end points of each pathway are denoted by terminal nodes (triangular symbols) with the relevant values or pay-offs, such as costs, life years, or QALYs, assigned. By rolling back through the branches of the decision tree it is possible to calculate the expected values (costs) for each option (3, 17).

Decision trees are useful for their simplicity and transparency, but they lack of any explicit time horizon, making problematic dealing with time dependent elements of an economic evaluation. Recursion or looping within the decision tree is also not allowed, so that decision-making in chronic diseases with recurring events may be not adequately represented by decision trees.

The Markov model is more appropriate for these situations (fig. 6). Markov models allow for managing more complex processes including many variables into the model (17, 18). Such models have been extensively used in the evaluation of screening programs (19), diagnostic technologies (20), and therapeutic interventions (21).

Figure 6 illustrates a generic Markov model in which there are three different health status A, B, C and death. The arrows indicate that patients can move from one status to another or remain into the same health status over a discrete period of time (cycles), but they cannot return in a previous health status.

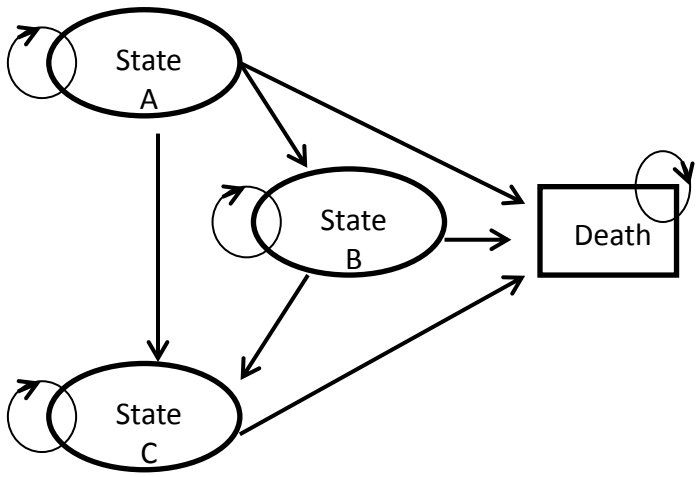

Figure 6: The Markov Model

Despite the Markov model allows to face complexity, it shows diverse pitfalls: transition probabilities depend only on the current health status, it is not possible to understand where patients come from, and it is not possible to determine the time at which the transition take place. These limitations can be overcome by introducing temporary states and introducing time dependency into transition probabilities (17, 18).

1.5 BIA vs. Economic evaluation

Economic evaluation provides evidence on the value for money of a new technology, but does not give information on its sustainability, i.e. whether the available budget is sufficient to cover the expected expenditure, which is a crucial information for payers.

For this reason, economic evaluation has been integrated by BIA. Since affordability has become one of the most important priorities, the BIA is increasingly required by payers to make a new technology eligible for reimbursement and to negotiate its price, both at central and local levels. As a consequence, the interest in the BIA of both scientific community and payers has increased.

The BIA compares two scenarios: the scenario with (A) and without (B) the new technology. The budget impact is the difference between expected spending in Scenario A and Scenario B (8). Whereas economic evaluation may use the societal perspective, the BIA is carried out taking the payer's perspective. The budget impact is calculated in the short-term (three to five years), whereas cost-effectiveness should incorporate all costs and benefits, till they are different between the two interventions under comparison. A budget impact is calculated for the whole target population, whereas an economic evaluation is performed on an hypothetical cohort population. For both economic evaluation and BIA a sensitivity analysis should be carried

out to assess the robustness of the results: in CEA a probabilistic sensitivity analysis usually integrates one-way analyses. In the BIA a one-way (or two-way) deterministic sensitivity analysis is preferred.

ITEM	CEA	BIA
Purpose	Value for money	Affordability
Comparator	Comparison between two alternatives	Scenario analysis
Perspective	Society	Payer
Time horizon	The most appropriate for the disease	Suggested 3-5 years but can go over lifetime
Data source	RCT	Real world data
Population	Not specified. The analysis is mad for a single patient representing the whole population with the pathology for which the alternative is evaluated	Open population
Costing and discounting	Intervention costs	Direct and indirect costs
Sensitivity analysis	Probabilistic	One or two way deterministic

Table 2: Comparison between CEA and BIA

1.6 Guidelines for the Budget Impact Analysis

Both the scientific community, including scientific networks (International Society for Pharmacoeconomics and Outcomes Research – ISPOR (8)) and individual researchers (Italy 22), and payers (Belgium 23, Canada 24, Ireland 25, and Poland 26) have recently issued guidelines on BIA.

All these guidelines investigated the most critical issues in carrying out a BIA, including:

- the perspective used: according to most guidelines the perspective should be the one of the budget holder. Only one guideline has suggested to adopt a societal viewpoint. The Canadian guidelines states that the drug perspective should be adopted, thus providing for a budget silos approach;
- the scenarios to compare: all guidelines stresses the importance to rely on real world data to describe the current mix of treatments and to consider

the future scenario as the scenario where either the new treatment does not exist or it is not listed and covered by public funds;

- the population to consider: according to some guidelines, the target population should be the population which could generally benefit from the intervention; other guidelines explicitly consider the population covered by public funds the target of the BIA;
- the time horizon, which ranges from 1 to 5 years: only one guideline has suggested a possible longer time horizon, until the technology reaches a steady state;
- costing and discounting: most guidelines recommends (i) to include all relevant resources used (including drugs, patients follow-up, complications and adverse events); (ii) to use real world evidence on clinical pathway; (iii) to assess unit costs considering the financial flows for the payer (hence, not using the notion of opportunity cost). Only few guidelines suggest to discount costs, using a 5% rate;
- sensitivity analysis. This analysis is strongly suggested to validate results, demonstrating their robustness. A deterministic sensitivity analysis (DSA) is generally considered sufficient, whereas a probabilistic (PSA) one is strongly suggested for cost-effectiveness analysis.

ISPOR (8)	
Perspective	The recommended perspective is that of the budget holder.
Scenarios	The reference scenario should be the current mix of interventions without the new technology. The future scenario should be the current mix of interventions with the new technology.
Population	The population to be included in a BIA should be all patients who might benefit from the adoption of the new intervention.
Time horizon	Budget impact analyses should be presented for the time horizon of most relevance to the budget holder.
Costing and discounting	The steps in costing are: identifying the resource use that may change, estimating the amount of change, and assessing these changes. It is not necessary to discount the costs.
Sensitivity analysis	Various forms of sensitivity analysis (univariate, multivariate, probabilistic, etc.) may be carried out. The analyst should compute a range of results that reflect the plausible range of circumstances the budget holder will face. It is useful to consider both a most optimistic and most pessimistic scenario.

ITALY (22)	
Perspective	Budget holder specifying if national, regional or local.
Scenarios	Should start from the current treatment mix in the analysed context (national, regional or local)
Population	It is necessary to identify the size of the target population to be treated in the analysis setting.
Time horizon	Maximum 3 years
Costing and discounting	All direct medical costs, that may change between the new technology and the current mix, should be included. Discounting is not necessary.
Sensitivity analysis	Analysis of best and worst case scenario to evaluate the maximum variation range

BELGIUM (23)	
Perspective	BIA should be carried out from the healthcare payer's perspective.
Scenarios	The intervention in the BIA is the same as in the economic evaluation, the comparator is the usual daily practice without the add-on treatment.
Population	The target population should be consistent with the population defined in the reimbursement request.
Time horizon	The time horizon of the BIA depends on the time needed to reach a steady state. The analyst should calculate the yearly country-specific budget impact up to this steady state
Costing and discounting	Direct healthcare related costs are included in the reference case. It is recommended to calculate both the global budget impact and consequences for the different health care payers. The Belgian guidelines recommend not to discount costs
Sensitivity analysis	One- or multiple-way sensitivity analysis can be performed on the most important variables such as the price of the intervention or the diffusion rate.

CANADA (24)	
Perspective	Public drug plans participating in the Common Drug Review (CDR) process have explicitly requested that the analytic framework should be developed from the perspective of the drug plan.
Scenarios	The reference scenario is a forecasted version of the current market, in which the new drug is assumed not to obtain formulary listing. The new drug scenario is forecasted in a manner similar to that used for the reference scenario; however, in this case, the new drug is assumed to be granted formulary listing.
Population	The target population comprises individuals who are insured by the public drug plan of interest and have the condition of interest. All drug plan beneficiaries who are expected to be diagnosed and treated for the condition(s) of interest and are eligible to use the new drug be included in the BIA.
Time horizon	A time horizon of 3 years is recommended.
Costing and discounting	The price of a treatment strategy should be adjusted to consider the mark-ups, inventory allowances, business related costs to the pharmacy covered by the drug plan, dispensing fees and/or patient co-payments as requested by the drug plan. All other premiums and deductibles should be excluded. Discounting should not be factored into BIAs because discounted costs do not reflect the actual amount that a drug plan can be expected to pay in a given year
Sensitivity analysis	Deterministic sensitivity analysis, which includes one-way, multi-way and analysis of extremes, should be reported.

IRELAND (25)	
Perspective	The BIA should be conducted from the perspective of the publicly-funded health and social care system (HSE) in Ireland.
Scenarios	The technology should be described in sufficient detail to differentiate it from its comparators and to provide context for the study. The preferred comparator for the reference case is 'routine care', that is, the technology or technologies most widely used in clinical practice in Ireland.
Population	The target population should be defined based on the approved indication for the technology. Stratified analysis of subgroups (that have been ideally identified a priori) is appropriate.
Time horizon	The core analysis should estimate the annual financial impact over a minimum timeframe of five years.
Costing and discounting	The costs included should be limited to direct costs associated with the technology that will accrue to the publicly-funded health and social care system.
Sensitivity analysis	Scenario analyses for a range of plausible scenarios and sensitivity analysis must be employed to systematically evaluate the level of uncertainty in the budget estimates due to uncertainty associated with the model and the key parameters that inform it.

POLAND (26)	
Perspective	The study perspective should be that of the public purchaser—the key audience for such analyses.
Scenarios	NA
Population	The target population for BIA is defined based on the approved indication(s).
Time horizon	Ideally, time horizon for the BIA should be until the proposed drug is predicted to have achieved a peak or stable market share. Annual financial implications to the health-care budget, for drugs as well as total, to this time horizon or for at least 2 years after the date of listing on the reimbursement list should be estimated.
Costing and discounting	The approaches to measurement and evaluation of costs vary along a spectrum of specificity. Micro-costing and gross-costing can be used within a single analysis. This analysis should use a 5% discount rate. The costs in BIA should be estimated in terms of the payments actually made or the savings actually realized by the public purchaser.
Sensitivity analysis	The analyst should conduct one-way sensitivity analyses to determine where uncertainty or lack of agreement about some key parameter's value or the functional form of the model could have a substantial impact on conclusion. Furthermore the analyst should conduct multi-way sensitivity analyses for important parameters.

Table 3: Guidelines on BIA

Despite some agreement on general topics, most guidelines do not discuss more specific but important issues, i.e. whether (i) the new intervention is expected to raise awareness on the disease, thus increasing the proportion of the eligible population actually treated (inducement effect), (ii) off-label use of drugs should be included, in the case off-label is currently used, (iii) avoided unit cost should be based on fixed or variable unit cost, (iv)

transaction costs should be considered when fee-for-service is used as a proxy for unit costs.

These topics are covered by the ISPOR guidelines that we consider, as other authors did (e.g. Orlewska and colleagues (27)) the reference guidelines in our analysis.

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2. The outline of the thesis

HTA is a discipline aimed at evaluating new technologies (i.e. drugs, medical devices, procedures, settings of care and screening programmes), to determine their efficacy, safety, indication for use, economic impact and ethical, social and legal implications.

Economic evaluation, as part of the HTA, assesses the benefits and the costs of a new health care programme compared with the existing alternative(s) for the same disease.

This comparison provides an indicator – the ICER (Incremental Cost Effectiveness Ratio) which measures incremental costs over incremental benefit (e.g. 10,000 Euros per Life Years Saved), due to the new programme.

Depending on how benefits are measured, economic evaluation can be classified as:

(i) Cost Efficacy/Effectiveness Analysis (CEA), should there be an important benefit, measured in physical units (e.g. life expectancy, years of life saved, progression free survival, etc.);

(ii) Cost Utility Analysis (CUA), should the improvement in quality of life be an important impact of the treatment; in CUA benefits are measured as life years saved weighted by the quality of life after treatment (ranging from 0 to 1), i.e. QALY (Quality Adjusted Life Years saved);

(iii) Cost Benefit Analysis (CBA), which measures added benefit in monetary units.

Economic evaluation measures value for money of a new technology, but does not provide data on its sustainability. The impact on budget of a new technology is assessed by the Budget Impact Analysis (BIA). The BIA, looking at additional expenses, i.e. the cost due to the technology, and

avoided expenses due to its adoption, may help payers to understand whether the new technology is sustainable.

Economic Evaluation and Budget Impact Analysis have been growing their importance in the last years. In fact, they are supporting decision making (recommendation to end-users, coverage, price), because resources are scarce and should appropriately allocated.

Since affordability has become one of the most important priorities, the BIA is increasingly required by payers to make a new technology eligible for reimbursement and in price negotiation, both at central and (possibly) local levels. As a consequence, the interest in the BIA of both scientific community and payers has increased.

My PhD program has been focused on two topics.

I have firstly analysed the role of economic evaluation and budget impact analysis in drugs price and reimbursement in the most important EU countries (England, France, Germany, Italy, Scotland, Spain, and Sweden). The results of this descriptive analysis have not been published and are illustrated in Chapter 4.

The second part of my Phd Program has been focused on BIA. More specifically, I have investigated the consistency of published Budget Impact Analyses with the relevant ISPOR guidelines, which are widely accepted and recognised as the leading ones. The results of this analysis has been submitted to a peer-reviewed international journal.

Review of budget impact studies: are they consistent with Ispor guidelines?

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Abstract

Budget impact analyses (BIAs) are playing an increasingly important role in health care payers' decision making. The interest in BIAs is apparent from the growing number of published studies and discussions about methodological issues. Many guidelines on BIAs have been published to date, but the guideline created by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) is the most complete.

The objective of this paper is to review published BIAs and determine whether they are consistent with the ISPOR guideline.

We carried out a search for BIAs by combining "budget", "impact", and "analysis" with the Boolean operator "AND" in Medline, Embase, and Web of Science for the period from January 2008 to June 2013. We included only original papers. We retrieved 1891 studies, of which 119 were selected for the analysis.

We found that the studies were consistent with some aspects of the ISPOR recommendations: the researchers adopted a short time horizon, considered relevant costs for the budget holder, and performed a sensitivity analysis. However, in many other ways, they did not fully comply with the ISPOR guidelines. Few studies were based on an open-population model, many did not illustrate market share in current and future scenarios, and very few

explicitly mentioned that all available treatments were considered. Other minor issues (e.g., the inclusion of off-label use of drugs) were never mentioned.

We may conclude that BIAs should be performed with more accuracy, considering their growing role in the decision making of health care payers.

Introduction

Budget constraints and allocative efficiency are major issues in health care systems. Health technology assessments (HTAs) have increased in importance in the decision-making processes used by regulatory authorities and payers (1). HTA covers the full spectrum of health technologies (i.e., drugs, medical devices, procedures, settings of care, and screening programs) and their impacts (clinical, economic, organisational, ethical, and social impact) (2).

Economics and management contribute to HTAs. They assess value for money by performing economic evaluations (3) of health technologies, their sustainability (using budget impact analysis, BIA) and their organisational impact.

A BIA compares two scenarios: the scenario with (A) and without (B) the new technology / intervention. The budget impact is the difference between expected spending in Scenario A and Scenario B (4). BIAs are populated with real world data about the target population and the expected additional and avoided costs attributable to the new technology.

Because affordability has become one of the most important priorities in health care systems, a BIA is increasingly required by payers to make a new technology eligible for reimbursement and increasingly used in their price negotiations both at central and local levels (5). As a consequence, interest in BIAs has increased both in the scientific community and among payers.

The scientific community, including scientific networks (International Society for Pharmacoeconomics and Outcomes Research – ISPOR (4)), individual researchers (Italy (8)), and payers (Belgium (6), Canada (7), Ireland (9), Poland (10)) have recently issued guidelines on BIA.

All of the guidelines addressed the most critical issues in BIAs, including the following:

- The perspective used. According to most guidelines, the perspective should be that of the budget holder (4, 6, 8, 10). Only one guideline suggested adopting a societal viewpoint (9). The Canadian guidelines (7) stated that the drug perspective should also be adopted, thus providing for a budget silos approach.
- The scenarios to compare. All of the guidelines stressed the importance of relying on real world data to describe the current mix of treatments and considering a future scenario where either the new treatment does not exist or it is not listed and covered by public funds.
- The population to consider. According to some guidelines, the target population should be the population that could generally benefit from the intervention (4, 8-10); other guidelines explicitly consider the population covered by public funds as the target of the BIA (6, 7).
- The time horizon, which ranges from 1 to 5 years. Only one guideline suggested using a longer time horizon until the technology reaches a steady state (6).
- Costs and discounts. Most guidelines recommended (i) including all relevant resources used (drugs, patient follow-up, complications and adverse events); (ii) using real world evidence about the clinical pathway; and (iii) assessing unit costs considering the financial flows for the payer (i.e., not using the notion of opportunity cost). Only one guideline suggested discounting costs, using a 5% rate (10).
- Sensitivity analyses. A sensitivity analysis is strongly suggested to validate the results by demonstrating their robustness. A deterministic sensitivity analysis is generally considered sufficient, whereas a probabilistic one is strongly suggested for cost-effectiveness analyses.

Although they agree on general topics, most guidelines do not discuss the more specific but important issues covered only by the ISPOR guidelines (4), i.e. whether (i) the new intervention is expected to raise awareness of the disease, thus increasing the proportion of the eligible population actually treated (inducement effect), (ii) off-label use of drugs should be included in cases where off-label uses are present, (iii) the avoided unit cost should be based on fixed or variable unit costs, and (iv) transaction costs should be considered when fee-for-service is used as a proxy for unit costs.

Research question and methods

This article aims to understand whether the published BIAs are consistent with the ISPOR guidelines. A similar analysis was published in 2009 by Orlewska and colleagues (5). The authors reviewed *"BIAs published to date in peer-reviewed bio-medical journals with reference to current best practices and discusses where future research needs to be directed".*

We have adopted the following search strategies. Only BIAs were investigated. Economic analyses other than BIAs - i.e., cost of illness, cost description, cost-outcome description, cost analyses, cost-effectiveness, cost-utility, cost-benefit - were excluded unless they were performed together with a BIA. We included only studies published in English. The period covered was January 2008 - June 2013; the previous review on BIA by Orlewska and colleague (5) covered the period of time between January 2000 and November 2008. Original papers were included; conference papers, abstracts, case reports, letters, comments, editorials, and review papers were excluded. The PubMed / Medline, Embase, and Web of Science databases were used. The search terms were "budget", "impact", "analysis", and "model". The terms were combined using the Boolean operator "AND". Following Cochrane recommendations, the "NOT" Boolean operator was not used. We did not carry out any assessment of methodological quality because of the absence of standards for quality assessment of BIAs and the descriptive nature of the article.

Starting from the ISPOR guidelines, a checklist was compiled (Table 1).

Table 1. BIAs checklist

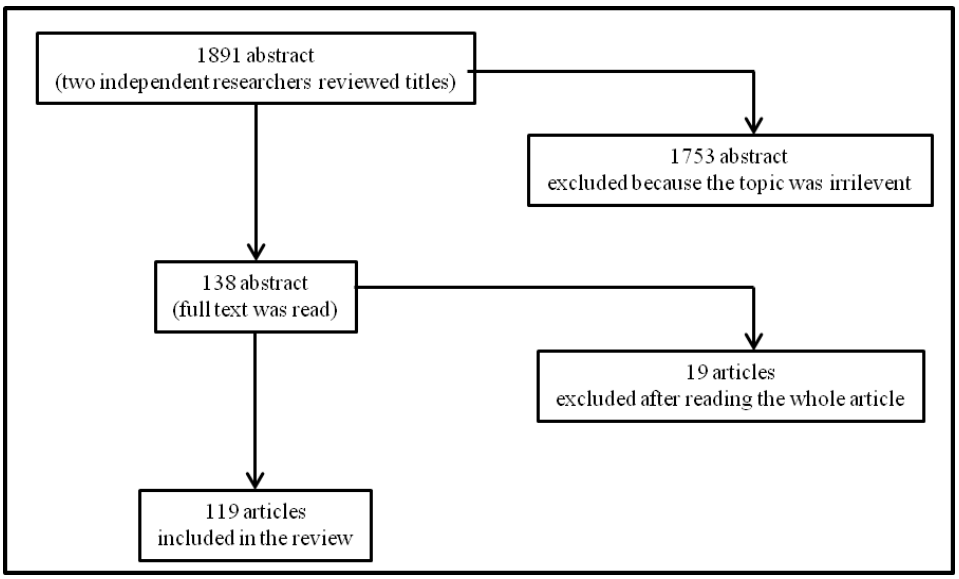
Item	Checklist
Perspective	Which perspective is adopted in the study? Which cost categories have been included?
Scenarios to compare	Are the two scenarios well specified? Does the reference scenario include all the available treatment alternatives? Are market shares illustrated? Do the scenarios include off-label drug use? [a] Are the assumptions about the current and future scenarios identified and justified?
Population & subgroups	Does the analysis include all of the patients who are expected to be eligible from the perspective of the payers? Does the study consider an open population (i.e., individuals enter or leave the population depending on whether they currently meet the analyst's criteria for inclusion) or is it a cohort-based analysis? Does the analytical framework allow for subgroups to be considered? Is there any hypothesis of inducement? [a]
Time horizon	What is the time horizon used for the analysis? Are any extensions of the time horizon considered? [a]
Resource consumption and unit costs	What information source is used for resource consumption? How are the unit costs for health services estimated? Are fixed costs considered in the long run? [a] Are transaction costs included? [a] Is any rebate applied? [a]
Sensitivity analysis	Is a sensitivity analysis carried out? Which sensitivity analyses have been carried out?
Discounting	Is any discounting applied to the costs? What discounting rate is used?

[a] These items, which are included in the ISPOR guidelines, will not be discussed in the "Results" section because they were considered in very few studies.

Results

Using the above-mentioned criteria, 1891 articles were retrieved. A total of 1753 articles were excluded after reviewing the title and the abstract: 976 because they were focused on sectors other than health care (e.g., the environment); 777 discussed the role of BIA in decision-making, they only mentioned the budget impact issue within a cost-effectiveness (CEA) or cost-utility (CUA) analysis, or they were not published in English. The remaining 138 articles were fully read, and 19 were excluded because they were not BIAs despite the information included in the title and the abstract. Hence, 119 articles (11-129) were analysed (Figure 1).

Figure 1. Search strategy: articles retrieved from the databases.



The selected BIAs were carried out in the US (34 studies), the UK and Spain (15 studies each), France and Italy (9 studies each), Canada (7 studies), Germany (6 studies), Belgium (4 studies), Japan and Thailand (3 studies each), Denmark, Bulgaria, Sweden, the Netherlands, Uganda and Austria (2

studies each), Ireland, Greece, Switzerland, Finland, Portugal, Czech Republic, New Zealand, South Africa, Brazil, Colombia and India (1 study each). We also found five multi-country studies (33, 56, 109, 116, 117).

The diseases covered included cancer (24 out of 119) and chronic diseases (23 out of 119). The other areas of interest were cardiovascular diseases (14 out of 119), viral infections (13 out of 119), central nervous system disorders (10 out of 119), bacterial infections (6 out of 119), gastrointestinal diseases (5 out of 119), and rare diseases (4 s out of 119). Most BIAs addressed drugs or vaccines (92 out of 119). A minority considered the impact of prevention or screening programs on health care budgets (18 out of 119), and in nine studies a BIA was carried out for a device or a surgical procedure.

Although the ISPOR guidelines suggest considering the population under treatment (i.e., individuals entering or leaving the treatment group depending on whether they meet the analyst's criteria for inclusion), most of the retrieved BIAs relied on a cohort-based population. Of the studies, 13% adopted an open-population approach, 50% (most of them integrated with an economic evaluation analysis) adopted a virtual cohort population (e.g., 1,000 patients), and 37% adopted a fixed cohort-based population estimated using prevalence data. It is worth mentioning that seven studies also performed analyses for subgroups (32, 44, 58, 61, 68, 101, 113).

The ISPOR guidelines state that BIAs should adopt the perspective of the budget holder, who should be identified as a national, regional or local payer. Sixty-three studies adopted the national health care payer perspective (i.e., a national health service / system, a national social insurance system, or Medicare for the US), thirty-eight assumed the local health care payer perspective (i.e., a regional health service / system, hospitals, private

insurance, or managed care organisations for the US), one study adopted both a national and local health payer perspective, six studies adopted a societal perspective, seven adopted both the societal and the health care perspective and four studies did not specify a perspective (Table 2).

All of the selected studies included direct health care costs (Table 2). Drug costs were always included, except in one study that focused on prevention. Twenty-two studies included drug costs exclusively, thirty-nine studies included the cost of treatment and also the cost of drugs used to treat adverse events and twenty-six studies that focused on injectable drugs considered administrative costs. More than 50% of BIAs incorporated the patients' clinical pathway, thus estimating the (avoided or incremental) costs of inpatient services (51% of studies) and outpatient services (42% of studies).

Table 2. Perspectives used and categories of direct health care costs included

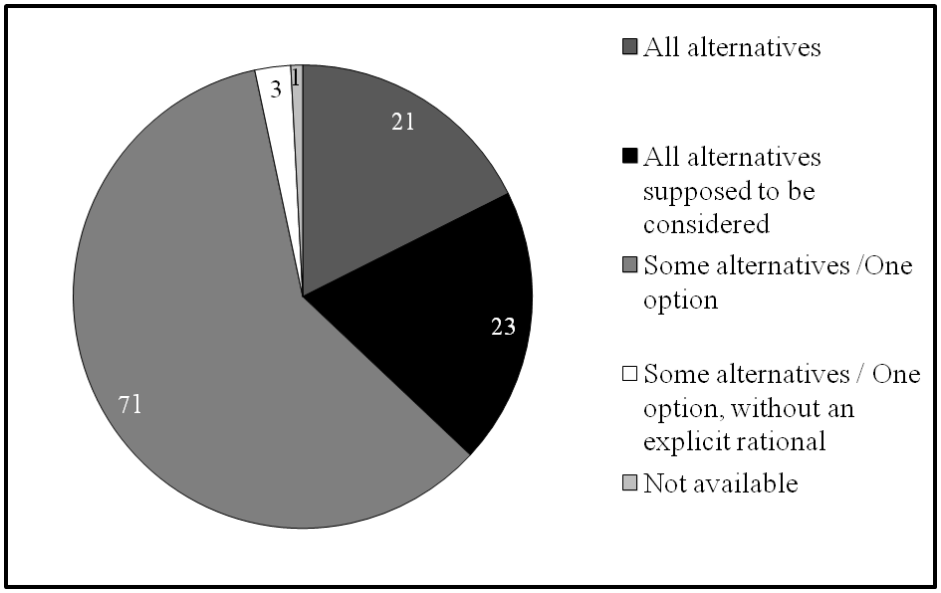
Perspective	Number of studies	Direct costs considered	Number of studies
National health care payer	63	Drug / Other health technologies	118[a]
Local health care payer	38	Inpatient services	60
Society	6	Outpatient services	49
National and local health care payer	1	Adverse events	39
National health care payer and society	6		
Local health care payer and society	1	Drugs administration costs	26
Not available	4		

[a] One study [74] focused on a prevention program and only outpatient services were included.

Most of the BIAs did not include all available options in the analyses of the scenarios: 74 studies considered only one or some of the options

available, and the majority of these studies (71 studies) gave an explicit rationale for this choice. In 21 studies, the authors considered all available treatments in the reference scenario. In 23 BIAs, although it was not explicitly declared by the authors, we assumed that all available treatments options were considered. In 1 study (110) the data were not available (Figure 2).

Figure 2. Interventions considered in the reference scenario

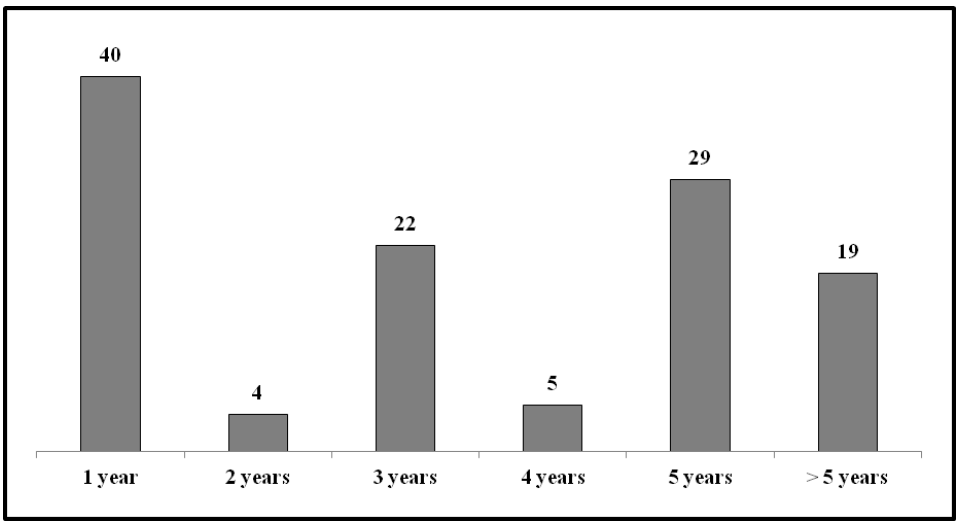


In 29 studies, the market share changes over time, reflecting the gradual market uptake of the new therapy, whereas in 16 studies the market share is fixed over time. In the remaining 73 studies, the market shares for the interventions considered by the author were not mentioned. One study (81) illustrated the budget impact with both fixed and variable market shares.

The time horizon in the selected studies ranged from 1 year to lifetime (i.e., over 15 years) as shown in Figure 3. The ISPOR guidelines suggest

using the time horizon that has the *most relevance to the budget holder*; other guidelines explicitly state that the time horizon should range from 3 to 5 years. Thus, in our analysis, the studies adopted an appropriate time horizon: in more than 80% of the studies, it was less than 5 years.

Figure 3. Time horizon adopted in the BIAs



Most of the studies used multiple data sources to determine resource consumption. The existing literature was the most common source (75 studies relied on data from the literature), and 39 studies relied on an expert panel, which is considered the weakest information source. Many studies (47 out of 119) used primary information, including clinical records, insurance claims and other administrative databases. The unit costs for inpatient and outpatient services were estimated from fee-for-service information (46% of studies), the literature (33%), primary data (18%) and expert opinion (5%). In most studies, the costs were not discounted, which is consistent with the ISPOR guidelines. An average 3% discount was applied in 21 studies, most of which integrated the BIA with a CEA / CUA.

A sensitivity analysis was carried out in 80% of the studies. Consistent with the ISPOR guidelines, most of the sensitivity analyses are deterministic (72 out of 119 studies), showing the robustness of the results to variations in one or two parameters, or they were scenario-based (17 studies). In a few studies (29 out of the 119 retrieved publications), a probabilistic approach was adopted.

Discussion and conclusion

Despite the growing interest in sustainability, the number of BIAs published in peer-reviewed publications is still limited, according to our review. This result may be explained by the following circumstances: (i) economic evaluations are more interesting for the scientific community, and BIAs are more interesting for the payers; (ii) many BIAs are presented as posters at conferences and may not be published as articles; (iii) BIAs are mostly published at the national level; and (iv) allocative efficiency has been considered more important than affordability by the scientific community.

Previous reviews (5) have shown that BIAs follow some major aspects of the guidelines, including the perspective adopted, the categories of costs included, the interventions considered in the two scenarios and the data sources used. For a few topics (i.e., the population and time horizon), the consistency between the studies and the guidelines was lower. We found similar results for (i) the perspective used, which was that of the budget holder, with a few exceptions represented by some studies that adopted a societal perspective, and (ii) the population, with many studies relying on a cohort-based approach and only seven studies performing subgroup analyses (32, 44, 58, 61, 68, 101, 113). With regard to other crucial issues, our results are different from the results of the previous review. As for cost categories, only half of the studies included all health care services, whereas many of them focused on drug costs. With regard to market share, ISPOR recommends considering the actual market share of each intervention as the starting point for future scenarios and taking into consideration that the market penetration rate of the new intervention could be gradual over time. In 62% of the studies, market share was not considered. On the contrary, whereas the previous review found that studies were not consistent with the

guidelines in terms of the time horizons used, our review found that the time horizon was less than 5 years in most of the studies retrieved.

Our analysis also found that the methodological requirements were partially met by the reviewed studies. For example, the BIAs mostly relied on the literature to design and populate the clinical pathways in BI models (primary information was only used in 39% of the studies) and on fee-for-service information to estimate the unit costs for inpatient and outpatient services.

It is also worth mentioning that some minor aspects addressed by the ISPOR guidelines have been completely disregarded by the published studies. No studies reported the off-label use of drugs in the current treatment mix or considered the hypothesis that the new intervention might raise awareness of the disease, thus increasing the proportion of the eligible population that is actually treated. The extension of the time horizon was never justified because a steady state is reached after five years, as one guideline suggested, but it would have been justified on the grounds of the chronic nature of certain diseases (HIV (22, 40), diabetes complications (126), Alzheimer's disease (108), chronic pain (117)). Transaction costs, which may be considered when fee-for-service is used as a proxy for unit costs, were never investigated. Although the ISPOR guidelines suggest considering the fixed costs only in the long run, most of studies did not distinguish between fixed and variable costs and of those that did (11, 13, 15, 20, 38, 43, 54, 62, 85, 107, 114, 126) only one study (38) had a time horizon of 10 years. Finally, rebates on the cost of drugs were rarely considered, even though actual costs (not list prices) should be used in BIAs.

Our review has one main limitation. We included many studies in which a BIA was integrated with a CEA or a CUA rather than being carried out alone. This may imply that the CEA / CUA drove some of the methodological choices for the BIA, e.g., (i) the consideration of a single therapy / technology (as for the CEA) rather than all current therapies and (ii) the use of a cohort-based population.

Despite this limitation, this review indicated that further steps should be taken to improve the rigour of BIAs, thus increasing their usefulness for payers' decision-making processes. For this reason the new Task Force created at ISPOR, which aims at updating the previous principles of good practice, may represent an important further step towards a more rigorous application of the BIA methodology (130).

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4. Unpublished result

Economic evaluation and BIA in P&R

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Summary

Value for money and sustainability have become crucial for payers in their decision-making process.

In this work I have investigated the role of cost effectiveness analysis (CEA) and budget impact analysis (BIA), in pharmaceutical pricing and reimbursement policies across the five major European countries (France, Germany, Italy, Spain, and UK) and Sweden.

In addition, I have investigated the consistency among decisions taken by the HTA Agencies: the analysis has been focused on the French (Transparency Commission) and the Scottish (Scottish Medicine Consortium) appraisal for drugs which have not been recommended by the National Institute for Health and Care Excellence.

Finally, the evidence on the impact of P&R procedures on market access delays is illustrated.

Introduction

The process which takes place before a new drug is introduced into the market is long, risky and complex.

This process is illustrated by the Figure 1 (1) and starts with the pre-discovery phase in which researchers focus on the unmet medical need of a disease and identify and validate a new target. After that, trough different processes (nature, de-novo, high-throughput screening and biotechnology), a new promising molecule (lead compound), that could become a new drug, is identified. The discovery phase usually terminates with the pre-clinical laboratory and animal testing during which the safety of the new compound is investigated and assessed.

The development phase is composed by three different steps: phase I, II, III, in which the new drug is tested on a small group of healthy volunteers, on a small group of patients and on a large group of patients respectively.

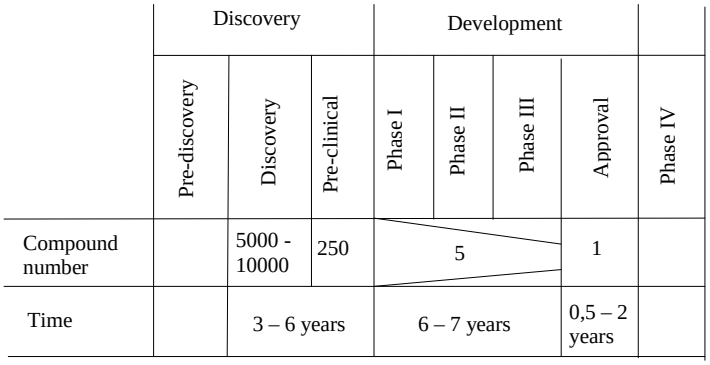


Figure 1: Research and development process

Only one out of 5000 / 10000 compounds reaches the market, after a period of time of nearly 15 years (2).

In Phase IV safety profile in real-world and effectiveness are investigated.

Once the pre-marketing phase has been completed, the new drug is assessed to get marketing approval. In the European Union (EU) the centralized procedure (3) is mandatory for human medicines for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases; medicines derived from biotechnology processes; advanced-therapy medicines; and orphan medicines. For other drugs which are intended to be marketed in more than one EU countries, the relevant company may apply for a decentralised procedure or mutual recognition (3).

Marketing approval makes the product marketable. Further steps are needed to get reimbursement and price. These steps are usually referred as the fourth hurdle for market access, because, besides efficacy, safety (and quality in the production process), economic impact is usually considered (4, 5). More specifically, the role of economic evaluation and budget impact in this process, has been investigated in the main EU countries and Sweden.

Research questions

My research has been focused on three aspects.

Firstly, I have investigated the assessment and appraisal processes of new drugs for reimbursement and price. The analysis involved the following agencies: HAS (Haute Autorité the Santé (6)) for France, IQWIG (Institute for Quality and Efficiency in Health Care (7)) for Germany, AIFA (Italian Medicine Agency (8)) for Italy, ISCIII (Instituto de Salud Carlos III (9)) for Spain, NICE (National Institute for Health and Care Excellence (10)) and SMC (Scottish Medicines Consortium (11)) for England and Scotland respectively (UK) and SBU (Swedish Council on Health Technology Assessment (12)) for Sweden.

Secondly, I have scrutinised differences across the assessments/appraisals, comparing NICE, HAS and SMC.

The last topic investigated was the impact of the price and reimbursement on the market access delays. The whole process does not take place simultaneously in different countries and the time required for each agency to deliver its decision, often causes delays for the market access of new products.

The HTA agencies decision-making process

The decision-making process of the main HTA agencies in Europe and requirements for price and reimbursement process are illustrated in Table 1.

In England there is the most important HTA agency in Europe, named NICE (National Institute for Health and Care Excellence). Technical assessment and appraisals (recommendations bases upon assessment) are carried out following an early identification of new products, through horizon scanning and referred by Ministers, following advice from an expert panels (13). Recommendations for the NHS usually take into consideration the clinical evidence and the incremental cost effectiveness ratio (ICER) where the benefits are measured through the quality adjusted life-years (QALY) gained. Generally NICE recommends an intervention with an ICER under £30,000 per QALY (14). The relevant documentation (Single or Multiple Technology Appraisal - STA/MTA) is fully available (15). These appraisals are often used by other European HTA organisations to perform their own assessments.

In Scotland, the Scottish Medicines Consortium (SMC) informs the Regional Health Board and the related Area Drugs and Therapeutic Committee (ADTC) on clinical evidence and cost-effectiveness of new drugs, like the NICE does. However, in Scotland there is not any official threshold for the ICER (16). To get a positive recommendation pharmaceutical companies are requiring to complete a New Product Assessment form, which includes the following sections: registration details, alternative treatments, efficacy, comparative safety, clinical effectiveness, economic evaluation, resource implications (budget impact). Like in England, the SMC may take the decision to recommend, not recommend or recommend with restrictions for use (in Scotland) (17).

In France, the assessment of new drugs is performed by the French National Authority for Health (Haute Autorité de Santé – HAS). More specifically, the assessment is carried out by the Transparency Commission (TC). This assessment is focused on clinical evidence (18). The absolute benefit is firstly (SMR - Service Médical Rendu) evaluated looking at the disease severity, the efficacy and the impact on public health. This assessment is used by the social insurance system to decide whether the new products should be covered by the Social Insurance System and level of co-payment. Secondly, the TC performs a comparative assessment to identify the added value (ASMR - Amélioration du Service Médical Rendu). This can lead to an ASMR level I (Major), II (Important), III (Moderate), IV (Minor) or V (None). ASMR is a parameter used in price negotiation carried out by the Economic Committee (19, 20).

In Germany there are several actors which play a role in the HTA process; among those the most important are: the Federal Joint Committee (G-BA), the Institute for Quality and Efficiency in Health Care (IQWiG), the German Institute for Medical Documentation and Information (DIMDI) and the statutory health insurance (SHI). The IQWiG, on the behalf of G-BA and Ministry of Health (MoH), is responsible for the assessment of new pharmaceutical products, but its evaluation is not mandatory for the final decision, which is taken by the G-BA. The DIMDI collects information about new intervention and the DAHTA@DIMDI performs HTA to support health policy, but not to determine the benefit package, i.e. the list of reimbursable drugs (21).

In Italy a central role is played by the Italian Medicine Agency (AIFA). AIFA, through two committees (CTS – Scientific Committee; CPR – Price-Reimbursement Committee) assesses new drugs according to the clinical (comparative) evidence (22). In principle, AIFA uses CEA for ‘very

innovative' products and orphan drugs, but CEA has been usually disregarded, because of the existence of a drug budget (23).

In Spain the NHS is composed by the Ministry of Health and the Regional Health Departments both coordinated by the National Health System Interterritorial Council. The latter one is responsible for providing the benefit package for the whole population. Drugs, medical technologies and procedures are assessed through both at the central level by the Instituto de Salud Carlos III (ISCIII) and at the local level by the regional HTA agencies. The HTA process is aimed at assessing costs, efficiency, effectiveness, safety and health care utility of a new intervention for its introduction into the benefit package, as well as the exclusion of those already provided (24, 25).

In Sweden the NHS together with the 18 Country Councils, which are present in the respective regions, provides healthcare to the whole population. On the territory there are several organisations which cooperate in the assessment of new interventions, but the most important are the Swedish Council on Health Technology Assessment (SBU) and the Dental and Pharmaceutical Benefits Board (TLV). SBU performs a complete HTA and gives recommendations to TLV which requires a CEA with a societal perspective and an estimate of the total impact on burden of disease using quality adjusted life years (QALYs) as measure of outcomes (26, 27).

Table 1 summarizes for each country the criteria used to assess a new drug, guidelines on comparators, and the usage of ICER and BIA.

COUNTRY	INSTITUTION	OUTCOME INDICATORS										COMPARATORS	ICER	BIA
		FINAL ENDPOINTS	SURROGATE ENDPOINTS	COMPOSITE ENDPOINTS	QoL	UTILITIES	DISEASE SPECIFIC QoL	SAFETY DATA	CONTRA-INDICATIONS	EASE OF USE	EXPERIENCE			
UNITED KINGDOM	NICE	QALYs	YES	YES	YES	YES	YES	YES	YES	YES	YES	Best standard care, not only pharmaceuticals. Sources: the product sponsor, experts, clinical guidelines and international methodological guidelines.	YES	BIA is used by NICE only as a tool-kit but only as a decisional parameter.
FRANCE	HAS	Mortality Morbidity	YES	YES	YES	NO	YES	YES	YES	NO	YES	All technologies for a specific indication and all pharmaceuticals within a therapeutic class. Best standard care. Not only pharmaceuticals. Sources: indication by the product sponsor, experts, clinical guidelines and international methodological guidelines. Indirect comparators.	NO	Evaluation of the impact on the market share for the pharmaceutical expenditure.
GERMANY	IQWIG	Mortality Morbidity HRQL	YES	YES	YES	NO	YES	YES	YES	NO	NO	All technologies for a specific indication and all pharmaceuticals within a therapeutic class. Not only pharmaceuticals. Sources: clinical guidelines and international.	NO	IQWIG does not use the BIA but the efficacy frontier
ITALY	AIFA	Mortality Morbidity	YES	YES	YES	NO	YES	YES	YES	YES	YES	All pharmaceuticals within a therapeutic class. Not only pharmaceuticals. Sources: experts, clinical guidelines and international methodological guidelines. Indirect comparisons.	NO (?)	Evaluation of the impact on the market share for the pharmaceutical expenditure.
SWEDEN	TLV and SBU	Mortality Morbidity QALYs	YES	YES	YES	YES	YES	YES	YES	YES	NO	All technologies for a specific indication and all pharmaceuticals within a therapeutic class. Whatever is used in registration trials. Sources: indication by the product sponsor, experts, clinical guidelines and international methodological guidelines.	YES	NO

Table 1: Parameters used in price and reimbursement negotiation (28).

Drugs prices and reimbursement in Europe

United Kingdom. Prices are freely determined by the pharmaceutical companies, after the marketing authorisation has been granted. Since drugs prices do influence cost-utility ratio, a too high price will make the cost-effectiveness overcoming the threshold. Besides threshold on cost-effectiveness, prices are indirectly regulated through the PPRS (Pharmaceutical Price Regulation Scheme). A more explicit value-based pricing is going to be introduced in 2014. In the United Kingdom reimbursement is not influenced by the assessment: any drugs is automatically reimbursable unless it is put on the 'national negative list'. Reimbursement is mostly decided relying on efficacy/effectiveness, safety, severity of disease, cost-effectiveness, value for money and ease of use for patients (29).

France. Prices are set by the Economic Committee for Health Products considering, among others aspects, the ASMR level. Products with an insufficient SMR level do not receive reimbursement. The level of reimbursement and co-payment is decided by the National Insurance (20).

Germany. Prices are freely set by the companies, but subject to (a) a therapeutic reference pricing, should they are not innovative, in comparison with the existing alternatives and (b) according to the jurisdiction introduced in 2011, to a rebate should they are covered by the social insurance system and consistently with their added value. (30).

Italy. Price and reimbursement are both and simultaneously negotiated by AIFA. In Italy a positive and a negative lists co-exist: in the first one medicines reimbursed by the National Health Service are listed, in the second pharmaceuticals such as non-prescription or life-style pharmaceuticals are not subject to reimbursement evaluations (22).

Spain. After marketing authorisation, both pricing and reimbursement are managed by the Directorate of Pharmaceutical and Healthcare Products (DGFPS). The inclusion in the national reimbursement list is mandatory throughout the country, but many regions (Comunidades Autonomas) have their own independent HTA agency, which may decide additional hurdles to market access for drugs (31).

Sweden. Price negotiation and reimbursement for drugs are both managed by TLV: prices are freely set by the manufacturer but, since the proposed price is an element in the assessment of the cost-utility ratio, a too high price will make the cost-efficacy of a medicine unacceptable. The reimbursement process takes into account the cost-effectiveness assessment as well as the principles of human value, need and solidarity. Reimbursement levels are progressive (from 0% to 100%), depending on previous consumptions (32).

Appraisal: which differences across agencies?

Assessment/appraisals across countries have been compared if publicly available. England, France and Scotland were the unique countries were complete appraisals were published on the website of the relevant HTA agency (33-35) (table 2). At present, also the appraisal / assessment by G-BA and IQWIG, within the new P&R process, are published.

. NICE appraisals were firstly investigated: in October 2011 31 drugs were not recommended, 68 were recommended for particular use and 65 recommended, out of 165 Single Technology Appraisal (STA). Negative appraisal are mostly motivated by a high cost/effectiveness ratio (over acceptable threshold), an insufficient clinical evidence anthe circumstance that the manufacturer did not provide the documentation, to avoid a possible negative judge.

Negative recommendations by NICE seem to be consistent with the assessment of the two other agencies investigated. The ASMR score in France were very low for drugs non recommended by NICE

The Scottish Medicine Consortium has accepted 2 of the 31 drugs not recommended by NICE and 7 drugs were accepted for restricted use, whereas 15 pharmaceuticals were not recommended for use within the Scottish NHS.

Table 2: Drugs not recommended by NICE: evaluation in France and Scotland (continue)

INDICATION	DRUG	NEGATIVE RACCOMANDATIONS BY NICE	ASMR LEVEL	SMC
Thrombocitopenic purpura	Eltrombopag	High cost/effectiveness ratio	2	Accepted for restricted use
Brain tumor	Carmustine implants	Documentation not provided by the manufacturer	4	Accepted
Breast cancer	Bevacizumab	Documentation not provided by the manufacturer	4	Not recommended (lack of submission to SMC)
	Paclitaxel	Lack of clinical evidence and high cost/effectiveness ratio	4	Not recommended (lack of submission to SMC)
Colorectal cancer	Raltitrexed	Lack of clinical evidence	N/A	N/A
Metastatic colorectal cancer	Bevacizumab+oxaliplatin+fluoruraci	Lack of clinical evidence	4	N/A
	Bevacizumab+oxaliplatin+capecita			N/A
	Bevacizumab+5-fluoruracil+folinic	High cost/effectiveness ratio		Not recommended (economic case not demonstrated)
	Bevacizumab+5-fluoruracil+folinic			Not recommended (not sufficiently robust economic analysis)
	Cetuximab+irinotecan			Not recommended
	Cetuximab	Documentation not provided by the manufacturer	3	Accepted for restricted use
Gastrointestinal stromal tumor	Imatinib	Lack of clinical evidence	3	Accepted for restricted use
Chronic lymphocitic leukaemia	Ofatumumab	High cost/effectiveness ratio	5	Not recommended (high cost in relation to health benefit)
Leukaemia	Fludarabine	High cost/effectiveness ratio	5	Accepted for restricted use
Head and neck	Cetuximab+platinum-based	Lack of clinical evidence	3	Not recommended (lack of submission to SMC)
INDICATION	DRUG NOT APPROVED BY	MOTIVATION	ASMR LEVEL	SMC
Hepatocellular carcinoma	Sorafenib	Lack of clinical evidence and high cost/effectiveness ratio	4	Not recommended (not sufficiently robust economic analysis and high cost in relation to health benefit)
Lung cancer	Bevacizumab	Documentation not provided by the manufacturer	5	Not recommended (lack of submission to SMC)
	Pemetrexed	High cost/effectiveness ratio	5	Accepted for restricted use
	Gefitinib	Documentation not provided by the manufacturer	5	Not recommended (not sufficiently robust economic analysis and high cost in relation to health benefit)
Mantle cell lymphoma	Temsirolimus	Documentation not provided by the manufacturer	4	N/A
Lymphoma non-Hodgkin's	Bendamustine	Documentation not provided by the manufacturer	3	Not recommended (lack of submission to SMC)
Urogenital cancer	Denosumab	Documentation not provided by the manufacturer	N/A	N/A
Renal cell carcinoma	Bevacizumab	High cost/effectiveness ratio	4	Not recommended (lack of submission to SMC)
	Sorafenib		4	Not recommended (cost effectiveness not demonstrated)
	Sunitinib		3	Not recommended (economic case not demonstrated)
	Temsirolimus		2	N/A
Ulcerative colitis	Infliximab	High cost/effectiveness ratio	2	Not recommended (economic case not demonstrated)
Heptitis B	Telbivudine	High cost/effectiveness ratio	5	Accepted
Macular degenetation	Pegaptanib	High cost/effectiveness ratio	3 and 5	Accepted for restricted use
Osteoporosis	Raloxifene	Lack of clinical evidence and high cost/effectiveness ratio	2	N/A
Asthma	Omalizumab	Lack of clinical evidence	4	Accepted for restricted use

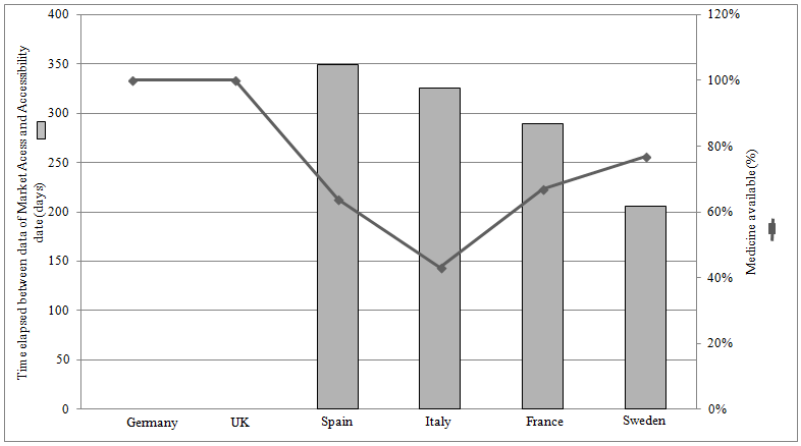
Price and reimbursement: which impact on market access delays

An evaluation of market access delays has been carried out by the European Federation of Pharmaceutical Industries and Associations (EFPIA), with the collaboration of IMS Health. For such a purpose, the Patient Waiting to Access Innovative Therapies (W.A.I.T.) indicator has been developed (36). The W.A.I.T. indicator shows the rate of availability of medicines and the average time between marketing authorisation and patient access (i.e.. completion of post-marketing authorisation, including pricing and reimbursement processes).

Figure 1 shows W.A.I.T. indicators for major EU countries and Sweden. UK and Germany have in principle an immediate market access, because they have not any positive list. However, as I mentioned before, in UK recommendations by NICE are binding: if a drug is not recommended, it cannot be used at the expense of the NHS.

For other countries delay between marketing approval and marketing authorisation ranges from 206 days for Sweden to 349 days in Spain.

Figure 1: Days between market access and availability of a new drug and % of available drugs.



Conclusions

Economic evaluation (CEA) and Budget Impact Analysis are becoming an important component of drugs price / reimbursement negotiation.

This is particularly true for the CEA. Our analysis on the most important European Countries (France, Italy, Germany, Spain and the UK) and Sweden, has shown that CEA is explicitly used by most of them. The budget impact is not explicitly mentioned in some countries, even if it is actually used to understand the sustainability in all countries investigated.

The methodological framework for comparative efficacy / effectiveness and economic evaluations is very complete: there are many guidelines, which have been developed by scientific societies, networks of HTA agencies, and single countries. The circumstance that this common general framework is demonstrated by a high level of consistency among clinical assessments (and innovativeness ranking).

Several national guidelines have been published also for budget impact studies. The most complete is represented by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [see Chapter 3]. However, there are still huge variations in the perspectives used in budget impact analysis provided to the HTA Agencies. In some countries (e.g. the UK), a health care budget impact analysis may be used. In other countries, where "silos budgeting" prevails (such as in Italy), the budget impact is required for drugs.

Hence, despite a general trend towards a higher consensus over comparative effectiveness and economic evaluation, there is a high uncertainty around the way BIA should be carried out.

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Conclusion

In the last years there has been a huge increase in the interest in Economic Evaluation and Budget Impact Analysis (BIA) by the scientific community and the payers. This interest is motivated by an increasing pressure of budget constraints and the opportunity to understand the value for money of a new technology and the existing ones.

The role of economic evaluation in decision making is very different across countries. In some countries (England, Scotland, Sweden among countries I have investigated, together with Australia and The Netherlands) cost-efficacy (cost-utility) plays an important role, whereas in other countries economic evaluation is either disregarded or does not play a crucial role.

On the contrary, in all countries budget impact is explicitly or implicitly used by payers, both at national and regional levels (if any).

This interest in the BIA is witnessed by a growing number of guidelines and publications on this topic. One of the most complete guidelines has been published in 2007 by ISPOR. These guidelines have been recently updated, but the final version of the new guideline is not available so far.

Despite this growing interest, the number of BIAs published in peer-reviewed articles is still limited, according to our review. The limited number of published results may be motivated by the perception that the discipline is not sufficiently mature and methodologically supported. Another reason is that economic theory shows greater interest in allocative efficiency than in budget-impact analysis.

Our analysis covers all BIAs retrieved from the literature and published after 2007. Studies are more aligned to guidelines as for time horizon (less

than 5 years), costing (resource consumption and unit costs), sensitivity analysis (performed nearly in every study considered) and discounting (generally not applied). As for scenarios to compare, market shares and eligible population, published studies are less consistent with guidelines. Generally speaking, it seems that BIAs are not structured as they should be to influence decision-maker, together with other indicators.

Despite the limitations of published studies, we expect a further increase in the interest in Budget Impact Analysis in the future. This growing interest will be supported by payers and it is likely that researchers will move that direction.

List of publications

- **Review of budget impact studies: are they consistent with Ispor guidelines?**
  Margherita Battista, PhD Candidate, Arianna Iorio, MSc, Claudio Jommi
  This article has been submitted to Pharmacoeconomics.

- **Economic evaluation and BIA in P&R**
  Margherita Battista, PhD Candidate
  Unpublished results

Appendix

This section illustrates the checklist (extraction template) for budget impact analyses and the whole database

Checklist used for the analysis of the articles.

Item	Checklist
Perspective	Which is the perspective adopted in the study?
	Which categories of costs have been included?
Scenarios to be compared	Are the two scenarios well specified?
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?
	Are the market shares assessed?
	Do the scenarios include of off-label drugs use? *
	Are the assumptions on the current and future scenarios identified and motivated?
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?
	Is the population open (individuals enter or leave the population depending on whether they currently meet the analyst's criteria for inclusion)or is it a cohort-based analysis?
	Does the analytical framework allow for subgroups to be considered?
	Is there any hypothesis of inducement? *
Time horizon	Which is the time horizon considered in the analysis?
	Are some extension of the time horizon considered? *
Costing	Which is the information source used for resource consumption?
	How are estimeted the unit costs for health services?
	Are fixed costs considered in the long-run?*
	Are transaction costs included?*
	Is any rebate applied?*
Sensitivity analysis	Is a sensitivity analysis carried out?
	Which sensitivity analyses have been carried out?
Discounting	Is any discounting applied to costs?
	Which is the discounting rate considered?

*: Those items, included only in the ISPOR guidelines, were initiallly investigated but they will not be discussed in the results since they have been considered in few studies.

Database of the reviewed studies

Item	First author	Anaya	Thorlund	Pfeil	Rønborg	Xie
	Reference number	11	12	13	14	15
Perspective	Perspective adopted	Insurance	NA	Health Care + Society	Danish NHS	NHS
	Categories of costs included	Direct medical costs (drug costs, physician and nurse staffing costs, laboratory costs, and costs of therapy associated with differing levels of disease progression)	Direct medical costs (drugs costs, costs for handling adverse events, costs of clinical visits, cost during follow-up period)	Direct costs (hospital costs, nursing home costs, outpatients nursing costs, physicians costs, medicatione costs, costs for the memory clinics) **Informal care**	Direct medical costs (drug costs, physician vistis) Direct non medical costs (transport) Loss of productivity	Direct medical costs (pharmacy costs - drugs; medical costs -inpatient, emergency room, and outpatient services)
	Is the perspective the one of the budget holder?	No	Not specified	Yes	Yes	Yes
Scenarios to be compared	Are the two scenarios well specified?	REFERENCE SCENARIO Mantain baseline HIV testing rate program FUTURE SCENARIO Increase HIV testing rate to 15%	REFERENCE SCENARIO PEGylated interferon + rivabirin (standard of care) FUTURE SCENARIO SOC+Boceprevir and SOC+Telaprevir both in treatment naïve and treatment experienced patients	REFERENCE SCENARIO Monotreatmente with cholinesterase inhibitor or memenatine FUTURE SCENARIO Combinatione treratment of cholinesterase inhibitor and mamantine	REFERENCE SCENARIO and FUTURE SCENARIO Subcutaneous immunotherapy (SCIT) or Allergy immunotherapy tablets (AIT)	REFERENCE SCENARIO Failure of letrozole or anastrazole (L/A) therapy, Second line therapy with exemestane, Fulvestrant, Tamoxifen FUTURE SCENARIO Failure of letrozole or anastrazole (L/A) therapy, Second line therapy with exemestane, Fulvestrant, Tamoxifen, EVEROLIMUS
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	Some options considered	Some options considered	Some options considered	Some options considered	Some options considered by the author. . Commonly recommended treatment options for postmenopausal women with HR+, HER2- ABC include hormone therapy with anti-estrogens (tamoxifen, fulvestrant) and the third-generation aromatase inhibitors (letrozole, anastrozole, and exemestane).
	Inclusion of off-label drugs use	No	No	No	No	No
	Are the assumptions on the current and future scenarios identified and motivated?	Yes	No	Yes	Yes	Yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?					
	Inducement hypothesis	No	No	No	No	No
	Open-population versus cohort-based analysis	Hypotetical cohort	Hypotetical cohort	Cohort from general population	Hypotetical cohort	Hypotetical cohort
	Subgroups	No	No	No	No	No
Time horizon	Time horizon	2 years	1.5 years	5 years	5 years	5 years
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	No	Follow up period of 24 weeks	No	No	No
Costing	Information source used for resource consumption	Expert panel	Adverse events from literature, Other clinical data such as frequency of clinical visits and necessary testing were derived from interview with expert panel	Medical resource use and costs were assessed using aggregate data from publicly available databases (top-down) as well as survey data and expert opinions (bottom-up).	Health care utilization was calculated based on data collected from review of RCT and standard treatment in Denmark (according to SPC). Where data were limited , these were validated by medical experts.	Drug use estimated using SPC, medical costs derived from literature
	Do the unit costs reflect the value attached by payers to resources?	database and literature	Unit cost were obtained from clinical experts interview	Medical resource use and costs were assessed using aggregate data from publicly available databases (top-down) as well as survey data and expert opinions (bottom-up).	Unit costs were obtained from established Danish public sources, including the Danish federal statistical office (Statistics Denmark), fees for service remuneration, and product list prices.	Medical costs inputsMedical service costs associated with non-progression and progression disease states were obtained from a study that estimated medical charges for inpatient, emergency room, and outpatient services incurred 6 months before and after a distant recurrence of metastasis among breast cancer patient. Drug costs were obtained from Ready Price [9] (Drug topics red book software) .The pharmacy cost was calculated based on the average wholesale acquisition cost (WAC), treatment duration, dispensing fees, and co-payment.
	Are fixed costs considered in the long-run?	nurse staffing costs	No	nursing home costs, outpatients nursing costs.	No	NA
	Are transaction costs included?	No	No	No	No	
	Is any rebate applied?	No	No	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	Yes	No	Yes	Yes	Yes
	Which sensitivity analyses have been carried out?	One way	-	-	One way	Two ways
	Are ranges presented on realistic scenarios?					
Discounting	Is any discounting applied to costs?	No	No	Yes	Yes	No
	Which is the discounting rate considered?	No	-	In the base-case cost-utility analysis, costs and benefits were discounted at a rate of 3%.	In accordance with Danish guidelines a discount rate of 3% per year was applied to account for treatment duration of 3–5 years.	-

Item	First author	De Cock	Jiang	Benjamin	Averinou	Martinez-Raga
	Reference number	16	17	18	19	20
Perspective	Perspective adopted	Public Health Care	Public Health and Economic Perspective	Health insurance	NHS	NHS
	Categories of costs included	Direct medical costs (device cost and procedural costs)	Direct medical costs (vaccine, management of IPD, NBPP and post-meningitis sequelae, inpatient e outpatient cost, meningite cost)	Direct medical costs (outpatient physician consultation, specialist and general practitioner, clinical examinations before treatment initiation and for monitoring treatments, chemotherapy sessions, and medical transportation) Direct non medical costs (transport)	Health care direct costs (aquisition, monitoring, administration costs, supportive care, outpatient visits, and hospitalization)	Direct medical costs (drug, logistic, dispensing, staff involvement, counseling, laboratory test)
	Is the perspective the one of the budget holder?	No	Yes	Yes	Yes	Yes
Scenarios to be compared	Are the two scenarios well specified?	REFERENCE SCENARIO Bare-metal stents (BMS) FUTURE SCENARIO Zilver PTX stent progressively relace BMS	REFERENCE SCENARIO Vaccination with PPV2 FUTURE SCENARIO Vaccination with PPV23 and PCV13 or PCV13 alone	REFERENCE SCENARIO Still TBT after diesase progression FUTURE SCENARIO L+C after disease progression	REFERENCE SCENARIO Biological agents without ustekinumab FUTURE SCENARIO Biological agents + ustekinumab	REFERENCE SCENARIO Methadone FUTURE SCENARIO B/N combination
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	Some option (or one option) considered.	All options considered by the author. Currently, there are two types of vaccines available in Germany: PPV23 and PCV.	Some option (or one option) considered. Two drugs are currently approved for the treatment of HER2-positive metastatic breast cancer (MBC): Tratuzumab and lapatinib for use in combination with capecitabine.	All options considered by the author. Currently available systemic treatments for moderate to severe psoriasis include conventional drug therapies (cyclosporine, methotrexate, retinoids, and phototherapy) and biologic agents (infliximab, etanercept, adalimumab, and ustekinumab). In this analysis only biologis were considered while conventional drugs have been excluded.	Some option (or one option) considered. Different types of medications are used in the management of opioid dependent patients, including opioid agonists and partial agonists, opioid antagonists and alpha (2)-adrenergic agonists. Agonist opioid treatment (AOT) is the most common intervention for heroin dependence. Methadone, is the most widely used and well researched pharmacotherapy for heroin dependent patients since the 1960s. However, other agonists alone or in combination with antagonist compounds are increasingly used. Buprenorphine, and a buprenorphine/naloxone (B/N) combination.
	Inclusion of off-label drugs use	No	No	YES Trastuzumab is often used off-label	No	No
	Are the assumptions on the current and future scenarios identified and motivated?	NA	Yes	Yes	Yes	Yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?					
	Inducement hypothesis	No	No	No	No	No
	Open-population versus cohort-based analysis	Cohort from general population	Cohort from general population	Open population	Cohort from general population	Cohort from general population
	Subgroups	No	Yes	No	No	No
Time horizon	Time horizon	5 years	5 years	3 years	5 years	3 years
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	No	No	No	No	No
Costing	Information source used for resource consumption	RCT, expert opinion and literature	Literature	Literature and database	Medical resource use from interview with dermatologists.	Literature and expert opinion.Drug use based on DDD by WHO and expert opinion. A previous published [24] budgetary impact model using Microsoft Excel 2003 following the international recommendations [25-28] has been updated to estimate healthcare costs of the approval of B/N
	Do the unit costs reflect the value attached by payers to resources?	Direct medical costs for inpatient treatment were based on the reimbursement tariffs for both private and public hospitals, according to the French Groupe Homogène des Malades (GHM, a national diagnosis-related group system)	Costs of administration and treatment of pneumococcal disease were retrieved from German sources or updated from previous German studies	Physicians consultation fees were drawn from published conventional fees, clinical examination from NABM and CCAM (database), treatment cost from BDM. Public hospital costs (oncologist, drugs, outpatient hospitalization for chemotherapy) derived from conventional fee.	Prices of the biologics were taken from officially published price bulletins from the Ministry of Development. Tariffs from the largest social health insurance fund were used to assess monitoring, administration and inpatient costs.	Resource unitary costs were collected from literature
	Are fixed costs considered in the long-run?	No	No	Yes	No	Yes
	Are transaction costs included?	No	NO	No	No	Yes
	Is any rebate applied?	No	YES. Unit prices of the vaccines took into account the mandatory rebate on ex-factory prices to the third-party payer by manufacturers (16% of the ex-factory price) and by pharmacies (€2.05 per pack).	No	No	The 7.5% reduction of ex-factory price required by Health Authorities was applied to B/N combination.
Sensitivity analysis	Is a sensitivity analysis carried out?	Yes	Yes	Yes	Yes	Yes
	Which sensitivity analyses have been carried out?	One way	Scenario analysis	One way	Three ways	One way
	Are ranges presented on realistic scenarios?					
Discounting	Is any discounting applied to costs?	No	No	No	No	No
	Which is the discounting rate considered?	-	-	-	-	-

Item	First author	Lee	Simpson	Thongprasert	Dee	Chanjaruporn
	Reference number	21	22	23	24	25
Perspective	Perspective adopted	Hospital Pharmacy	NHS	Thay Payer Perspective	Health Service Executive Insurance	Hospital budget perspective
	Categories of costs included	Drug cost	Direct costs (drugs and adverrse events)	Direct medical costs (acquisition costs, administration and monitoring and adverse event management)	Cost of current DMTs (drugs, adverse events , relapses)	Drug cost
	Is the perspective the one of the budget holder?	Yes	Yes	Yes	Yes	Yes
Scenarios to be compared	Are the two scenarios well specified?	REFERENCE SCENARIO Independent calculations were performed to determine the number of patients treated with rapid-acting insulin analogue and short-acting human insulin FUTURE SCENARIO Reallocations of the current rapidacting insulin analogue and shortacting human insulins administered to patients were used to create a hypothetical future scenario.	REFERENCE SCENARIO and FUTURE SCENARIO: LPV/r vs. ATV+RTV for ART-naïve o ART-experienced patients	REFERENCE SCENARIO Docetaxel FUTURE SCENARIO pemetrexed, erlotinib, gefitinib	REFERENCE SCENARIO Standard DMTs (disease modifying treatments - interferon and glatiramer) FUTURE SCENARIO Natalizumab	REFERENCE SCENARIO Docetaxel FUTURE SCENARIO Pemetrexed
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	Some option (or one option) considered	Some option (or one option) considered	Some option (or one option) considered	All options considered by the author	Some option (or one option) considered
	Inclusion of off-label drugs use	No	No	No	No	No
	Are the assumptions on the current and future scenarios identified and motivated?	Yes	Yes	Yes	Yes	Yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?					
	Inducement hypothesis	No	No	No	No	No
	Open-population versus cohort-based analysis	Cohort from general population	Hypotetical cohort	Hypotetical cohort	Open population	Open population
	Subgroups	No	No	No	No	No
Time horizon	Time horizon	From 3 months to 3 years	Lifetime	2 years	3 years	5 years
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	No	No	No	No	No
Costing	Information source used for resource consumption	Data from the Randomized Study of Basal-Bolus Insulin Therapy (RABBIT 2), clinical trial were used as the basis for estimating insulin use.	RCT and primary data. UK healthcare cost data were based on CD4þ T-cell group-specific resource utilization rates recorded for 5766 patients from 2004–2006, obtained from the National Prospective Monitoring System–HIV Health-economic Collaboration (NPMSHHC) cohort.	Administration and monitoring, including standard outpatient visits and chemotherapy outpatient visits, were based on the standard cost list for health technology assessment (HTA), the health technology assessment program (HITAP), Ministry of Public Health, Thailand. For adverse event management costs, resource use was derived from expert opinion.	Natalizumab use and other DMTs from administrative databases and literature	Assumption and estimate for the parameters in the model were derived from the hospital database and the literature
	Do the unit costs reflect the value attached by payers to resources?	The Average Wholesale Price were obtained from Analy- Source Online (database)	Adverrse events cost were based on Fee	Administration and monitoring costs were based on reference prices of medical services published by Ministry of Public Health.AE unit costs were based on the standard cost list for HTA and HITAP, Ministry of Public Health, Thailand.	Costs of DMT from primary care reimbursement service, natalizumab cost from review, adverse event (PML) from literature, cost of a MS relapse from Health Atlas Ireland (database)	
	Are fixed costs considered in the long-run?	No	No	No	Yes	No
	Are transaction costs included?	No	No	Yes	No	No
	Is any rebate applied?	Yes: actual price paid by hospitals	Yes	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	No	Yes	Yes	Yes	Yes
	Which sensitivity analyses have been carried out?	-	One way	One way	One way	One way
	Are ranges presented on realistic scenarios?	NA				Yes
Discounting	Is any discounting applied to costs?	No	No	Yes	No	No
	Which is the discounting rate considered?	-	-	Discounting was undertaken with a 3% annual discount rate, as recommended in the guideline of health technology assessment in Thailand	-	-

Item	First author	Simoens	Colin	Benucci	Purmonen	Ishiguro
	Reference number	26	27	28	29	30
Perspective	Perspective adopted	Belgian NHS	The French Sickness Fund	Italian NHS perspective	Hospital	Societal perspective
	Categories of costs included	Drug cost	Direct medical costs (ART drugs, hospitalization, day hospital, hospital consultation, non ART costs)	Direct medical costs (drug acquisition, administration, premedication and monitoring costs)	Direct costs allocated to the hospital district (drug cost, included the administration and preparation costs)	All costs
	Is the perspective the one of the budget holder?	NA	Yes	Yes	Yes	Yes
Scenarios to be compared	Are the two scenarios well specified?	REFERENCE SCENARIO World without lacosamide FUTURE SCENARIO World with lacosamide	REFERENCE SCENARIO Without darunavir FUTURE SCENARIO With darunavir	REFERENCE SCENARIO anti-TNF-α cycling, ABA as third biological line, ABA as second biological line FUTURE SCENARIO RTX as third biological line, RTX as second biological line	REFERENCE SCENARIO Adjuvant treatment without trastuzumab , that includes hormonal treatment: tamoxifen or aromatase inhibitor FUTURE SCENARIO Trastuzumab in addition to standard breast cancer treatment	REFERENCE SCENARIO Second generation adjuvant chemotherapy regimens without prophylactic use of G-CS FUTURE SCENARIO Third-generation regimens with prophylactic use of G-CS
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	All options considered by the author	All options considered by the author	All options considered by the author	All options considered by the author	Some option (or one option) considered
	Inclusion of off-label drugs use	No	No	No	No	No
	Are the assumptions on the current and future scenarios identified and motivated?	Yes	Yes	Yes	Yes	Yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?			Yes, patients with RA who were eligible for a second-line biological DMARD	Elegible population is represented by patients with early or metastatic breast cancer HER2- positivetry.	Postoperative patients with primary breast cancer at high risk of recurrence
	Inducement hypothesis	no	No	No	No	No
	Open-population versus cohort-based analysis	Open population	Cohort from general population	Cohort from general population	Open population.	Cohort from general population
	Subgroups	No	No	No	No	No
Time horizon	Time horizon	5 years	3 years	5 years	4 years	5 years
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	No	No	No	No	No
Costing	Information source used for resource consumption	Drug use derived from SPC	FIHD (French Hospital database in HIV) database	Dosing schemes were derived from the Summaries of Product Characteristics of the considered drugs and Italian guidelines. The other resources were derived from the literature.	The treatment mix and costs of breast cancer therapy are based on current clinical practice in the treating hospital (database).	Costs were estimated by developing a treatment model and using data from the relevant literature and expert opinion.
	Do the unit costs reflect the value attached by payers to resources?	Reference prices for generic products	Medication, consultation and visits costs were based on 2008 prices. Inpatients costs from national sample of French hospitals. Drugs cost based on pharmacy tarifs	The value used for Administration and Monitoring cost is not specified.Drug acquisition costs were computed considering the least costly package, or, in case of multiple identical alternatives, the package consistent with the recommended dosage. Ex-factory price was applied to all drugs (because of exclusive hospital use) except MTX (distributed in territorial pharmacies), for which the public price was considered.	Activity-based costing was used as the costing method (in 2008 euros, VAT excluded).	Costs were calculated using prescription drug prices as of 2006, with the exception of the cost of palliative care in the last month of life (data from Kondo et al32) and National medical care fee schedule for others direct cost.
	Are fixed costs considered in the long-run?	No	NA	No	No	No
	Are transaction costs included?	No		No	No	No
	Is any rebate applied?	No	NA	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	Yes	Yes	No	Yes	No, only for the CEA.
	Which sensitivity analyses have been carried out?	One way	One way	-	Scenarios analysis	-
	Are ranges presented on realistic scenarios?	No			These extreme scenarios were assumed to reflect the range of circumstances that the budget holders may face.	
Discounting	Is any discounting applied to costs?	No	NA	No	No	No
	Which is the discounting rate considered?	-	NA	-	-	-

Item	First author	Martinez-Raga	Mar	Anselmino	Kondo	Ho
	Reference number	31	32	33	34	35
Perspective	Perspective adopted	Spanish Regional Healthcare System	Healthcare and Social perspective.	Hospital	Japan's Health System	Hypothetical Health Plan with 1 million members
	Categories of costs included	Healthcare costs	Direct medical costs **Informale care**	Direct medical cost (preoperative assessment, laparoscopic GBP and AGB surgical operations, follow-up, and the treatment of complications)	Drug cost	Direct pharmacy cost
	Is the perspective the one of the budget holder?	Yes	NA	Yes	NA	Yes
Scenarios to be compared	Are the two scenarios well specified?	REFERENCE SCENARIO Methadone FUTURE SCENARIO Methadone + Buprenorphine/Naloxone	REFERENCE SCENARIO no treatment FUTURE SCENARIO Thrombolysis	REFERENCE SCENARIO: conventional treatment (The continuation of medically guided diet during 1 year in spite of previous failure FUTURE SCENARIO: adjustable gastric banding (AGB) and gastric bypass (GBP)	REFERENCE SCENARIO: No prophylaxis FUTURE SCENARIO Prophylaxis with tamoxifen at age 35 and 50 and with raloxifene at age 50 and 60 years.	REFERENCE SCENARIO : market without ixabepilone (set of interventions) . FUTURE SCENARIO: market with ixabepilone
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	Some option (or one option) considered. Two pharmacotherapies were considered in the present analysis: methadone, the medication widely used in AOT in Spain, and the alternative of B/N . Naltrexone, an opioid antagonist also licensed to reduce heroin relapse as part of a maintenance treatment program, was excluded from the analysis due its limited acceptance among both patients and clinicians.	Some options considered by the author. Thrombolysis, , is the only specific treatment for the acute event that improves the prognosis in patients	Some option (or one option) considered. The reference scenario represented by the conventional treatment doesn't include the pharmacologic therapy with orlistat	Some options (or one option) considered by the author without an explicit rational	All options considered by the author. The model includes all chemotherapeutic treatment options for MBC pre-ixabepilone
	Inclusion of off-label drugs use	No	No	No	No	No
	Are the assumptions on the current and future scenarios identified and motivated?	Yes	Yes	Yes	Partially	Yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	Three likely target population groups were considered: (1) patients in medically assisted withdrawal (MAW) programs (patients undergoing a MAW prior to entering a relapse prevention program, not in AOT); (2) high-threshold programs (HTP) (patients with no physical or psychological impairment, but with difficulty in remaining abstinent; these patients generally show good adherence to AOT, they should require intermediate or high methadone doses, and need a high level of supervision), and (3) low-intermediate-threshold programs (LITP) (patients with physical and/or psychological impairment and with poor treatment adherence to AOT; these patients have less supervision, should require higher doses of methadone and the majority are poly-substance (e.g., cocaine, alcohol, ...) abusers).	Flow of patients with stroke in the Spanish population.	Yes The hypothetical cohort of obese patients (BMI at least 35 kg/m2) with T2DM who had not responded to at least 1 year of well-conducted medical treatment.	Women at high risk of developing the disease, women with a history of atypical hyperplasia (AH) or lobular carcinoma in situ (LCIS).	The target study population for ixabepilone treatment is female MBC patients who are aged 20 years or older and are anthracycline and taxane pretreated (AT-p) or anthracycline, taxane, and capecitabine pretreated (ATC-p).
	Inducement hypothesis	NO	No	No	No	No
	Open-population versus cohort-based analysis	Cohort from general population	Open population	Hypothetical cohort	Cohort from general population	Hypothetical cohort
	Subgroups	No	Yes	No	No	No
Time horizon	Time horizon	3 years	16 years	5 years	25 years	3 years
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	No	No	No	No	No
Costing	Information source used for resource consumption	The resource use were obtained by expert opinion and doses of medications were based on the SPC	The health care resource derived from literature	Expert panel	Results of insurance claims review for 1 year of 400 early-stage breast cancer cases in various stages during follow-up care at Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital.	The annual pharmacy resouce was established by the SPC. The median cycle lengths of all drug therapies were based on expert opinions.
	Do the unit costs reflect the value attached by payers to resources?	Resources components identified, were quantified assigned them a unit costs, but the source of this value is non specified.	The health care cost derived from previous studies. Costs of formal and informal care were calculated following a bottom-up approach and a diary survey methodsWe retrieved the cost of the drug Alteplase (Actilyse, Boehringer Ingelheim, Ingelheim, Germany) (€1295) and the cost of a 1-day stay in the intensive care unit (€1399) from the literature.	Unit costs were obtained from published sources when available or from coauthors' institutions otherwise. Cost inputs for AGB and GBP initial hospital admission in 2009 are: the Lombardy diagnostic-related group (DRG) tariff in Italy, the average service-based hospital tariff (Leistungsorientierte Krankenanstaltenfinanzierung, LKF) in Austria, and microcosting estimates from two hospitals in Madrid (Hospital Clínico "San Carlos" and Fundación Hospital Alcorcón) in Spain.		Drug costs were based on wholesale acquisition cost
	Are fixed costs considered in the long-run?	No	No	No	No	No
	Are transaction costs included?	No	No	No	No	No
	Is any rebate applied?	No	No	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	Yes	No	Yes	No	Yes
	Which sensitivity analyses have been carried out?	One way	-	Scenarios analysis	-	PSA
	Are ranges presented on realistic scenarios?					
Discounting	Is any discounting applied to costs?	No	No	Yes	No	No
	Which is the discounting rate considered?	-	-	The annual discount rate for costs is 3.5%.	-	-

Item	First author	White	Chau	Milne	Chiao	Simpson
	Reference number	36	37	38	39	40
Perspective	Perspective adopted	Third-party payer in the US	BC Cancer Agency	Societal, Healthcare (Government plus patient) and Government (Ministry of Health and Pharmaceutical Management Agency) perspectives	Managed-Care Organization in US	Managed-Care Organization in US
	Categories of costs included	Direct medical costs (ED visits, outpatient visits, hospitalizations, substance abuse treatment, opioid abuse drug treatment, injection-related disease, non-RxO prescription drug use)	Drug cost	Direct medical cost (vaccine acquisition cost per dose, hospitalization, emergency department and GP consultation) Direct non medical costs (transport) Informal care and loss of productivity	Direct medical cost (acquisition costs, administration costs, monitoring costs and relapses cost)	Direct costs (drug cost, ambulatory cost and hospital admission cost).
	Is the perspective the one of the budget holder?	Yes	NA	Yes	Yes	Yes
Scenarios to be compared	Are the two scenarios well specified?	REFERENCE SCENARIO: existing RxOs (Prescription opioid) FUTURE SCENARIO: existing RxOs + ADO (abuse-deterrent opioid)	REFERENCE SCENARIO: androgen deprivation therapy (ADT) FUTURE SCENARIO: Combined androgen blockade (CAB)	REFERENCE SCENARIO: No treatment FUTURE SCENARIO: Vaccine Immunization Program	REFERENCE SCENARIO and FUTURE SCENARIO both of them include: natalizumab 300 mg administered intravenously The two scenarios differ for the natalizumab market share, which is 1% in the current and 9% in the adjusted.	REFERENCE SCENARIO: Lopinavir/Ritonavir FUTURE SCENARIO: Atazanavir+Ritonavir
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	All options considered by the author.	• Some option (or one option) considered. Based on the 2005–2006 data, cyproterone and nilutamide accounted for less than 2% of antiandrogens used. Therefore, cost predictions were simplified by assuming that only flutamide and bicalutamide would be used and that their use would not differ between the ADT and CAB groups.	Some option (or one option) considered	All options supposed to be considered. The model includes the four disease-modifying therapies (DMTs) available for the treatment of MS: three interferon beta (IFN) therapies (intramuscular [IM] IFN -1a [Avonex®], IFN -1b [Betaseron®], and subcutaneous [SC] IFN -1a [Rebif®])3–5 and glatiramer acetate (GA; Copaxone®).	Some option (or one option) considered.
	Inclusion of off-label drugs use	No	No	No	No	No
	Are the assumptions on the current and future scenarios identified and motivated?	Yes	Yes	Yes	Yes	Yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	NO. The analysis includes patients with privately insurence aged 12–64 years. To simplify the analysis, cost data were obtained from claims data for privately insured individuals from national employers. While the privately insured population accounts for approximately 60% of the US population,costs and abuse patterns for smaller employers as well as Medicaid and uninsured individuals may be different.	Eligible population is : Patients were received their first prescription of an LHRH agonist for prostate cancer in 2005–2006 from a regional or community cancer centers of the BC Cancer Agency.	The birth cohort for 5 years and the ages eligible for vaccine is: 6 Weeks to 12 Weeks	The population of interest consisted of patients with relapsing forms of MS (relapsing-remitting MS and secondary progressive MS with relapses) who were candidates for treatment with a DMT.	Treatment -Naïve individuals HIV-1-infected with plasma HIV-1 RNA levels >5000 copies/mL at baseline .
	Inducement hypothesis	No	No	No	No	No
	Open-population versus cohort-based analysis	Cohort from general population	Cohort from general population	Cohort from general population	Hypotetical cohort	Cohort from general population
	Subgroups	No	No	No	No	No
Time horizon	Time horizon	1 year	1 year	10 years	2 years	10 years
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	Yes. This study presented annual estimates, although savings from an ADO could be realized over the lifetime of an abuser.	No	No	No	Yes, lifetime cost savings are estimated too.
Costing	Information source used for resource consumption	Medical and prescription drug claims were dentified from claims database (Ingenix Employer Solutions). The number of abuse-related episodes and the the healthcare costs of non-clinical abusers relied on expert opinion.	The resource use reflected the prescription data.	The hospital resource use was estimated form literature. The drug use was estimated from the New Zealand Pharmaceutical Schedule. Work loss by the caregiver was estimated from UK data in the large randomized clinical trial	Primary data and literature	Literature
	Do the unit costs reflect the value attached by payers to resources?	Unit costs associated with RxO abuse, dependence and misuse were calculated using claims data. The potential cost offsets associated with switching to the new ADO, the costs for branded and generic formulations of ER RxOs were derived from IMS National Prescription Audit and National Sales Perspectives data.	The study considered only drug cost. The therapy cost is determinated using 2007 drug prices (Hospital List Price).	Mean hospitalization costs to the Government were calculated using diagnosis-related group (DRG). The drug cost is calculated from the PHARMAC (pharmaceutical management agency of new zealand) .The GP consultations is estimated with the notional charge to the Government at the time. The median pretax cost of work loss per person per day is calculated based on the median income for female wage and salary earners 30 to 34 years of age of $33,000 per year and 70% workforce participation.The marginal cost of travel to the hospital's ED was estimated at $4.00 based on one 20-km return trip at $0.20 per kilometer.	The costs per package, monthly drug costs, and 2-year drug costs were determined based on wholesale acquisition cost (WAC) as published in Medispan's drug pricing database. Drug administration and routine monitoring costs were obtained from published 2008 physician fee schedules	The cost per AIDS event is recorded for Medicaid outpatient payment data for ambulatory treatments, and for all-payer discharge data for patients with AIDS events who are treated in a hospital. The CHD (coronary heart disease) cost is estimated based on the analysis of all-payer hospital discharge data).
	Are fixed costs considered in the long-run?	No	No	No	No	No
	Are transaction costs included?	No	No	No	No	No
	Is any rebate applied?	No	No	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	Yes, scenarios analysis	No	No, only for the CEA	No, only for CEA	Yes
	Which sensitivity analyses have been carried out?	Scenario analysis	-	-	-	Multiple ways
	Are ranges presented on realistic scenarios?					
Discounting	Is any discounting applied to costs?	No	No	No	No	No
	Which is the discounting rate considered?	-	-	-	-	-

Item	First author	Neyt	Hadker	Huang	Montouchet	Merchant
	Reference number	41	42	43	44	45
Perspective	Perspective adopted	Insurance + Society	German Payer perspective	Hospital	Managed Care Organization	US health plan
	Categories of costs included	Direct medical cost	Direct medical cost (diagnosing, treating, managing preeclampsia)	Direct medical costs (drug, administrating, monitoring and hospitalization)	Direct medical costs (drug , administration, monitoring)	Direct healthcare cost (drug cost, physician office visit, emergency department, hospitalization, telephon calls, surgery, diagnostic tests, management of AE).
	Is the perspective the one of the budget holder?					
Scenarios to be compared	Are the two scenarios well specified?	REFERENCE SCENARIO: Standard breast cancer tratment without trastuzumab FUTURE SCENARIO: Treatment with trastuzumab for 1 year or 9 weeks	Yes, The reference scenario includes standard practise as currently followed by Germany physician in diagnosing PE (preeclampsia) involves using a combination of test to diagnose PE, including serum uric acid, urine tests to screen for proteinuria, blood pressure, end uterine artery Doppler ultrasounds. The new scenario includes Novel PE test in addition to the existing armamentarium of diagnostic PE test.	Yes, Reference scenario: Vancomycin plus aztreonam and other vancomycin regimens vs New Scenario: Ceftaroline fosamil, Vancomycin plus aztreonam and other vancomycin regimens	Yes, in the reference scenario all patient were initiated on simvastatin or atrovastatin and titrated to a higher dose or switched to atrovastatin (if initiated to simvastatin) or rosuvastatin; in the new scenario the 50% of high risk patient were initiated on rosuvastatin.	Yes, the reference scenario includes: Oxicodone CR (controlled elease), Morfine sulfate ER (extended release), morfine sulfate / naltrexone hydrochloride ER, Hydromorphone ER.Oximorphone ER, Fentanyl transdermal. The new scenario assumed a 10% formulary share of tapentadol ER with a 10% decrease of oxycodone CR.
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	All options considered by the author	All options considered by the author.	All options considered by the author. The author considered not only vancomycin +aztreonam as comparator in the phase III registration trial , but also other vancomycin combination frequently used.	No• Some option (or one option) considered	Yes. All options considered by the author. The model includes all formulary short and long acting opiod options.
	Inclusion of off-label drugs use	No			No	No
	Are the assumptions on the current and future scenarios identified and motivated?	Yes	Yes. Compared to current diagnostic practise, the new diagnostic test has the potential to decrease the number of false negative patients and also to decrease the likelihood of complications among these patients as thry benefit from early detection and are subsequently appropiately managed.Improved clinical detection and management can have important and direct economic implication on healthcare payers.	Yes. Ceftaroline is the first antimicrobial drug approved by FDA for the treatment of ABSSSIs (acute bacterial skin and skin structure infections),caused by susceptible isolates gram + e - microrganism, including S. aureus. The current treatment guidelines identify vancomycin as the standard of care for ABSSSIs.	Yes.Initiating and maintaining patients with higher risk of cardiovascular disease on rosuvastatin could increase their likelihood of reaching their LDL-C goal and thereby decrease the clinical burden and cost of switching from less effective treatments with potential downstream clinical and economic benefits through reduced CV events and associeted costs.	Yes. Randomized clinical trials have consistantly demonstrated that tapentadol extended release (ER) effectively reduces moderate to severe pain with superior tolerability compared with oxycodone controlled release (CR) at equianalgesic doses
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?		Yes	Yes, hospitalized adult patient with an ABSSSIs (Acute bacterial skin and skin structure infections)	Yes, a hypotetical 1 000 patients, aged >18 years, elegible to be initiated on statins with an average LDL-C level of 189 mg/ dL.	Yes, chronic noncancer pain patients.
	Inducement hypothesis	No	No	No	No	No
	Open-population versus cohort-based analysis	Cohort from general population	Hypotetical cohort of 1000 pregnant women	Hypotetical cohort	Hypotetical cohort	Open population. The model included an initial cohort of both incident and prevalent patients and incident patients were addede each quarter over the course of 1 year.
	Subgroups	No	Yes, True positive, true negative, false positiv	No	Yes. The results are presented for the 3 risk group of cardivascular disease: high, moderate, low.	No
Time horizon	Time horizon	Lifetime	< of 1 year (from week 12 to week 40)	3 years	3 years	1 year
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	No	no	No	No	No
Costing	Information source used for resource consumption	Data were collected from several sources: literature, expert opinion, breast cancer data from a national survey (5254 breast cancer patients), a small patient sample from a university hospital in Belgium, and cost data from the Belgian national health insurance	Public databases, expert opinions, SPC. Interviews were conducted to validate resource utilization inputs, that were obtained through data from published literature and public databases such as Germany drug and healthcare cost database (GOA).	Public databases and literature,	RCT, Literature , Primary data.	Primary data, RCT, Literature. Formulary allocation percentages, drug costs, and daily average consumption were obtained from the IMS National Prescription Audit
	Do the unit costs reflect the value attached by payers to resources?	For ambulatory and hospital health care, data from the Belgian reimbursement scheme and standard fees for regularly insured patients are used. Based on simulations relying on literature data and information from the University Hospital Ghant, we calculated the cost for MBC treatment. **Expert opinion** was used to evalute the cost of mastectomy and radiotherapy, cost of follow up based on expert opinion and guidelines **(literature)**	Yes. PE assesment and management cost were derived from fee and expert opinion.The cost of new test was defined by manufacturer.	The cost of antimicrobial administration and drug monitoring was based on published literature. The cost of hospitalization were derived from a chort study using comprehnsive clinical records. Wholesale acquisition costs data for all drugs were obtained from First DataBank.	Yes. The cost associated with physician visit was based on the cost of outpatient visit as the Centre for Medicare and Medicare Services Physician Fee Schedule.Wholesale acquisition cost is based onmarket research.Wholesale acquisition is considered for all drug, and are applied also a dispensing fee and a copayments.	The medical resource costs were obtained from Fee **Schedule and Statitical Brief.(literature)**
	Are fixed costs considered in the long-run?	Yes (lifetime horizon)	No	Yes, Hospitalization cost includes also nursing and hospital room	No	No
	Are transaction costs included?		No		No	No
	Is any rebate applied?	Yes	No	No	Yes, for rosuvastatin is considered a rebate (41%)	No
Sensitivity analysis	Is a sensitivity analysis carried out?	Yes	Yes	Yes	Yes	Yes
	Which sensitivity analyses have been carried out?	PSA	Scenarios analysis	Scenarios analysis	One way and scenarios analysis	One way
	Are ranges presented on realistic scenarios?		Yes	Yes	Yes	
Discounting	Is any discounting applied to costs?	Yes	No	No	No	No
	Which is the discounting rate considered?	3% costs; 1.5% effects (in CEA)				

Item	First author	Parades	Kuhlmann	Bergh	De Salas-Cansado	Nita
	Reference number	46	47	48	49	50
Perspective	Perspective adopted	Spanish Public healthcare system	Statutory Health Insurance (Germany)	South Africa private healthcare setting	Spanish NHS	Brazilian private health system
	Categories of costs included	Direct heathcare cost (cost of vaccinations and outpatient and inpatient cost of pneumococcal desease)	Direct heathcare cost (outpatient and inpatient treatment cost)	Direct heathcare cost (drug, follow up, monitoring and management of stroke, systemic embolism, transient ischaemic stroke and AE)	Direct heathcare cost (drug, administration, inpatient follow up)	Direct cost (The BIA considered only the cost relating to the **purchase of medicine**, since other medical costs are not significantly different among the comparators).
	Is the perspective the one of the budget holder?					
Scenarios to be compared	Are the two scenarios well specified?	Yes. Reference scenario: not vaccination vs New scenario: 13-valent pneumococcal conjugate vaccine (PCV 13)	Yes. The reference scenario includes surgery and sclerotherapy. The new scenario includes surgery, sclerotherapy and Closure Fast.	Yes. The reference scenario includes only warfarin for stroke prevention in AF patients. The new scenario includes warfarin and dabigatran.	Yes. The reference scenario includes only fasciectomy in patient with Dupuytren . The new scenario includes fasciectomy and Collagenase Clostridium Histolycum (CCH)	Yes. The reference scenario includesMetformine + Pioglitazone or Rosiglitazone . The new scenario includes Metformin + Saxagliptine
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	No. Some option (or one option) considered.	All options considered by the author. Although the author mentionated both interventional and non interventional treatments, he considered only interventional reimbursed procedures.	No . Some option (or one option) considered	No (there is also the fasciotomy). Some option (or one option) considered	All options supposed to be considered
	Inclusion of off-label drugs use			No	No	
	Are the assumptions on the current and future scenarios identified and motivated?	Yes. In 2010, a new 13-valent conjugate vaccine (PCV13) that widened the spectrum of the former 7-valent conjugate was licensed to reduce the incidence of pneumococcal disease in children. An adult indication for the prevention of pneumococcal disease caused by the serotypes included in the vaccine has recently been approved. At present, there is no evidence available regarding the cost-effectiveness of adult pneumococcal immunization in the Spanish population.	Yes.Several interventional and non-interventional treatments of varicose veins exist and are approved for treatment in Germany. Despite the growing popularity of new minimally invasive endovenous treatments for varicose veins surgery still represents the standard intervention in Germany , since endovenous thermal ablations aren't covered by the general benefits catalogue of the Statutory Health Insurance (SHI) Recently, a new endovenous thermal ablation named ClosureFast, was introduced in the USA. This improved version of the ClosurePlus device promises reduced pain, improved Quality of Life (QoL) and a faster recovery after treatment in comparison to surgery.In addition, since ClosureFast is mainly performed in an outpatient setting, treatment costs may be reduced by avoiding costly inpatient procedures. Hence, an inclusion of ClosureFast in the general benefits catalogue of the German SHI should be considered.	Yes. Dabigatran is an oral anticoagulant with direct thrombin inhibitory action and was registered in SA in September 2012 for the prevention of cardioembolic stroke in patients with non-valvular AF. The Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY)[8] trial was a non-inferiority trial with 2-year follow-up, comparing the use of dabigatran with warfarin in patients with AF who were at risk of stroke.In SA, the daily cost of dabigatran is significantly more than the cost of warfarin.	Yes, the Fasciectomy, a surgical treatment, is the gold standard, to treat the Dupuytren disease.Injectable collagenase Clostridium histolyticum (CCH), Xiapex1, is the first licensed nonsurgical treatment for adult patients with Dupuytren's contracture with a palpable cord	Yes. The current scenario is obtained from a Brazilian study of clinical outcomes and cost of DM2 on the private health system. The new drug Saxagliptine, whose safety and efficacy have been estabilished in randomized studies, is available in Brazil, but its cost effectivness in schemes haven' yet been demostrated.
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	No. The target population for the vaccination programme is the 65 year old cohort, but consequences were measured in the population >50 years of age.	Yes , patients with varicose veins	Yes patient with AF	Yes, the target population is calculated from the 5100 fasciectomies performed inn 2009 in Spain	Yes. Patients with Diabetes Mellitus type 2 (DM2) treated with metformin without glycemic control
	Inducement hypothesis	No	No	No	No	No
	Open-population versus cohort-based analysis	Cohort from general population	Cohort from general population	Hypotetical Cohort	Open population (5% increase rate of fasciectomies).	Hypotetical Cohort
	Subgroups	No	No	No	No	No
Time horizon	Time horizon	5 years	5 years	5 years	3 years	3 years
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	No	No	No	No	No
Costing	Information source used for resource consumption	Literature, primary data.	Primary data, expert opinion, literature, official handbooks.Input parameters were derived from a systematic literature research. In addition, two medical experts in the field of varicose veins were contacted to provide expert opinions on present and future market shares of initial and secondary interventional treatment of varicose veins as well as resource use	Primary data.	RCT, Literature, expert opinion.FSC data was obtained through a retrospective, observational, local study that included 123 patients treated by selective FSC in three public hospitals.Consumption of CCH per joint and per patient were assumed to be similar to those observed in the main clinical trials.	Literature , Primary data.
	Do the unit costs reflect the value attached by payers to resources?	The unit costs derived from literature. The cost of vaccination programme was calculate using the official price of PVC 13.The costs associated with pneumococcal disease, in euros for the year 2010, were determined according to published data in the Spanish population	Yes. The inpatients stays are evaluated with **DRG Catalogue** while outpatient setting with Official German Oniform Valuation Scheme. For the evaluation of resource use is taking also into consideration patient copayment and discounts for medications given by manufacturer and pharmacies	Yes . Event costs used to populate the model were estimated using 2007 medical scheme claims data.The cost of dabigatran was supplied by Boehringer Ingelheim SA.The cost of ischaemic stroke (IS) was estimated by calculating the total claimed amount for any hospitalisation during which a patient had a claim reflecting stroke.Owing to a lack of robust data, it was assumed that intracranial haemorrhage (ICH), haemorrhagic stroke (HS) and IS all incurred the same cost.	Yes. Unit costs were obtained from **local database** e-SALUD for procedures, visits, and tests [33] and BOT for drug ex-factory price	The annual cost data inserted in the model are related to the purchase of medicinal products, control of adverse events and treatment of complications for DM2. Medication costs were obtained from official lists and the mean doses of the DIAPS79 study. The source of cost data related to micro and macrovascular complications was also the DIAPS79 study,
	Are fixed costs considered in the long-run?			No	No	No
	Are transaction costs included?	No		No	No	No
	Is any rebate applied?	No	For the evaluation of resource use is taking also into consideration discounts for medications given by manufacturer and pharmacies	No	Yes. A 7,5% discount of CCH drug price was applied due to the mandatoryrebate imposed by the Spanish Ministry of Health since 2010	No
Sensitivity analysis	Is a sensitivity analysis carried out?	Yes	Yes	Yes	Yes	Yes
	Which sensitivity analyses have been carried out?	Scenarios analysis	One way and probabilistic analysis	Scenarios analysis	Scenarios analysis	Univariate SA
	Are ranges presented on realistic scenarios?	Yes	Yes	Yes	Yes	Yes
Discounting	Is any discounting applied to costs?	Yes	No	No	No	Yes
	Which is the discounting rate considered?	3%			No	5%

Item	First author	Rubin	Mar	Tosteson	Noskin	De Salas
	Reference number	51	52	53	54	55
Perspective	Perspective adopted	US health plan perspective	NA	Healthcare system perspective (U.S.)	National perspective	Spanish National Healthcare System
	Categories of costs included	direct medical costs (including acquisition and administration costs)	Cost of thrombolysis intervention, cost of autonomous patient, cost of disabled patient	Direct medical costs: hospitalization (acute inpatient, rehabilitation/short-stay, and readmission), physician visits, emergency department visits, home healthcare, disability/dependence, nonmedical home care, and outpatient, nursing home, and other longterm care costs.	Direct costs (cost of: nurse minutes to obtain a nasal swab sample, diagnostic test to hospitals, S.aureus infections).	Direct medical costs
	Is the perspective the one of the budget holder?	Yes	NA	Yes		
Scenarios to be compared	Are the two scenarios well specified?	darbepoetin alfa every3 week (Q3W) vs. epoetin alfa every week (QW)	Thrombolysis vs. standard care	Risedronate therapy compared with alendronate, ibandronate, and PTH (parathyroid hormon) for the treatment of women with PMO at high fracture risk.	Yes. The refernce scenario is the standard care. In the new scenario was added the preadmission rapid testing for nasal carriage of S. aureus and subsequent decolonization therapy.	Yes. The refernce scenario includes antihypertensive drugs. The new scenario includes antihypertensive drugs plus the fixed combination Amlodipina+Atorvastatin.
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	Some option (or one option) considered. The ESA regimens compared in this analysis were taken from registration studies referenced in the package inserts and published literature.	Some options considered to the author.	All options considered by the author. The bone-specific osteoporosis treatments evaluated in the model include risedronate, alendronate, ibandronate, and PTH. These reflect current practice patterns, capturing those treatments that are used most frequently..	• Some options (or one option) considered by the author without an explicit rational. (the model focuses on using advanced rapid diagnostic testing to identify S. aureus colonization. Less expensive, more traditional nasal culture techniques are available)	All options supposed to be considered.
	Inclusion of off-label drugs use	No	No	No	No	
	Are the assumptions on the current and future scenarios identified and motivated?	Yes. Darboepoetin alfa and epoetina alfa are erythropoiesis stimulating agents that are approved by US FDA in the treatment of anaemia due to effect of chemiotherapy. Although the most common regimens for darbepoetin alfa are every 1 or 2 weeks, the recent approval every 3 weeks may be advantageous as it allows for synchronism of patients' anaemiatreatment with ongoing cancer treatment , which may have implications not only for patients but also for health plans.	yes	Yes	yes. Providing preadmission rapid screening for S. aureus carriage and subsequent short-term decolonization therapy for colonized patients shows the potential to be a more specifically targeted approach to reducing the rate of in-hospital S. aureus infections than performing no screening or providing blanket decolonization treatment.	Yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	Yes	Yes	Yes: women aged 65-84 with low bone mineral density	Yes. All patients scheduled for elective surgery	Yes. Hypertensive patients with 3 or more concomitant CVRF (cardiovascular risk factor), normal or slightly elevated cholesterol levels and no clinical evidence of coronary disease.
	Inducement hypothesis	No	No	No	No	No
	Open-population versus cohort-based analysis	Cohort (from general population)	Open	Open	Cohort from general population	Open
	Subgroups	Patients with chemotherapy induced anemia	No	4 risk groups were evaluated: women aged 65 years with and without a prevalent vertebral fracture, and women aged 75 years with and without a previous vertebral fracture. The main subgroup was women aged 65 years with low BMD (low bone mineral density) and a prior vertebral fracture	No	No
Time horizon	Time horizon	16 weeks	15 years	3 and 10 years	1 year	3 years
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	No	No	No	No	No
Costing	Information source used for resource consumption	Data from RCT and published literature.	Cost source: literature	Published data sources and clinical experts.	Literature, primary data, expert opinion	Literature, expert opinion
	Do the unit costs reflect the value attached by payers to resources?	Cost of an office visit: Mediacre fee schedule. Drug costs: AWP based on Red Book (fee); c	NA	Yes. Unit cost for hospitalization, physician visits, emergency department ecc derived from literature and were update to year 2005 using the medical care component of the consumer price index.	yes. The 2003 charges derived from the NIS analysis were converted to 2004 US dollars by use of the medical care component of the Consumer Price Index.	Yes The cost of complication CV were quantified using the results from the ASCOT study. . The mean daily costs of the FC treatment were estimated using retail price and VAT established by the Catalogue of Spanish Pharmaceutical Colleges General Council
	Are fixed costs considered in the long-run?	No	No	No	Yes. The median earnings for a registred nurse in a US Hospital.	No
	Are transaction costs included?	No	no	no	No	No
	Is any rebate applied?	No	no	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	Yes	No	Yes	Yes	Yes
	Which sensitivity analyses have been carried out?	Deterministic one-way and probabilistic SA	NA	Deterministic one-way and probabilistic SA.	PSA	Univariate
	Are ranges presented on realistic scenarios?	Yes	NA	Yes	Yes	Yes
Discounting	Is any discounting applied to costs?	No	No	No	No	Yes
	Which is the discounting rate considered?	No	No	No	No	Isn't specified. ("... Onche the pharmaceutical costs of the introduction of the FC were calculated for SNHS, the pharmaceutical costs of the treatments that are substituted by the FC ...must be discouted).

Item	First author	Pedretti	Iannazzo	Dimitrova	Borg	Annemans
	Reference number	56	57	58	59	60
Perspective	Perspective adopted	NHS	Italian National Healthcare System	Clinical Centre of healthcare budget for AIDS	Healthcare perspective in Sweden	Belgian NHS
	Categories of costs included	Direct medical costs (Implantable Cardioverter Defibrillator, ICD national implantation reimbursement rate)	Direct medical costs (acquisition and administration of the vaccines, visits and pharmaceutical treatments for influenza and hospitalizations)	Direct medical costs (Drugs, physician's consultation, follow-up, hospitalization, clinical and paraclinical monitoring, viral load)	Direct medical costs (Costs evaluated are cost of surgery plus the excess treatment costs that an obese patient has over and above the treatment costs of a normal-weight patient.	Direct health care cost (antipsychotic drug , hospital utilisation and concomitant medication)
	Is the perspective the one of the budget holder?					
Scenarios to be compared	Are the two scenarios well specified?	No. The authors to estimate in a 5-year timeframe the annual incremental rate of ICD implantation procedures necessary to treat all eligible patients, according to international guidelines, in Italy and the USA, and the budgetimplications from the perspective of each country's government.	Yes. The reference scenario includes the traditional vaccine or the absence of vaccination. The new scenario icludes the MF59 adjuvanted vaccine	Yes. The reference scenario includes all antiretroviral medicines on current practise while the new scenario includes also the antiretroviral biotechnology medicines (tenofovir, disoproxil, emtricitabin and darunavir).	Yes. The reference scenario is no surgical operation. The new scenario is surgical intervention for obesity in tree different possibilities: 3000 operations in person with BIM > 40, 4000 operations in person with BIM > 40 and 5000 operations in person with BIM >38.	Yes. The reference and the new scenario include the same mix treantment: Depot neuroleptics, Conventional oral neuroleptics, aripiprazole, clozapine, amisulpiride, quetiapine, olazapine, oral risperidone and long acting risperidone (RLAI). The future scenario represents a further market penetration of RLAI.
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	NA	All options supposed to be considered	All options supposed to be considered	Some option (or one option) considered	All options considered by the author
	Inclusion of off-label drugs use		No			No
	Are the assumptions on the current and future scenarios identified and motivated?		Yes. The MF59 adjuvanted vaccine (Fluad®) is authorized in European countries since 1997, for the seasonal influenza vaccination. Results of several clinical trials demonstrate a significant immunological superiority of this vaccine with respect to the traditional vaccine in the elderly population	Yes. As part of the centralized European procedure all of the antiretroviral medicines are authorized for sale in Bulgaria which makes them available for the therapy of AIDS patients (lamivudine, zidovudine, abacavir, lopinavir, ritonavir, efavirenz, etc.). Recently the newest antiretroviral drugs like tenofovir disoproxil, emtricitabine and darunavir have been authorized.	Yes. There are basically three different treatment options for obesity: diet and exercise therapy, pharmacological therapy and surgery. Following great improvement in safety and efficacy of surgery as an alternative for obesity treatment, the demand for surgery has in recent years increased rapidly. Obese surgery is, however, quite expensive and this has raised concern in Sweden about budgetary impacts of an increased demand for surgical treatment of obesity	Yes. A belgian Cost effectviness analysis has indicated that RLAI represents a favourable first line strategy for patients with schizophrenia requiring long term maintenance therapy, being more effective and less costly from the public healthcare payer perspective than either olanzapine or depot haloperidol. However despite acquisition costs than conventional depot agents and oral antipsychotic agents has ensured that : is treating patients with RLAI affordable?
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	Yes. The sample considered in the analysis comes from the registry of the (ALPHA) study and acoording to selection criteria of international guidelines were defined patients as eligible for an ICD.	Yes. Italian elderly population.	yes. HIV patients treated in Sofia Centre	Yes. A population of overweight and obese persons (BIM>25) is sampled from a data set representing the adult Swedish population (>15 years old)	Yes. Patients with schizophrenia.
	Inducement hypothesis		No	No	No.	No
	Open-population versus cohort-based analysis	Open poulation	Cohort from general population	Open population	Cohort from general population	Cohort from general population
	Subgroups	No	No	Yes. Patients in I and II line.	No.	No
Time horizon	Time horizon	5 years	Influenza season	1 year	10 years	3 years
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	No	No	no	No.	No
Costing	Information source used for resource consumption	Primary data	Literature, primary data	Primary data, expert opinion, literature. The information about the treatment algorithms was gathered from the university clinic on the basis of the analysis of patient records for the current state therapy and expert opinion about the new state therapy. It was also revised and the international guidelines on antiretroviral therapy and compared with the established practice and expert opinion.	Literature.	Literature , Primary date.
	Do the unit costs reflect the value attached by payers to resources?	FEE	Yes. Vaccine cost was valorized by the mean value of the bid prices in public tenders in years 2006-2009. The administration cost was considered equivalent to the cost of one GP outpatient visit plus the incentive granted by the Italian SSN to the GP to improve the diffusion of the influenza vaccination among the elderly people. Hospitalization costs for the Italian SSN were calculated considering national Diagnosis Related Group (DRG)	Cost of consultation and hospitalization derived from National Framework Contratct	To capture the costs as experience by Swedish health care providers, we use data from a study that have analysed the development in costs of treatment of obesity related diseases.	Unit costs, outpatient and hospital costs were taken from the **belgian Health Care System**.Data for the mean dose per day of antipsychotic agents were taken from the Belgian e STAR study.
	Are fixed costs considered in the long-run?	no	No	no	No.	no
	Are transaction costs included?	no	No	No	No.	no
	Is any rebate applied?	no	No	No	No.	no
Sensitivity analysis	Is a sensitivity analysis carried out?	yes	Yes	No	No.	Yes
	Which sensitivity analyses have been carried out?	Univariata	One way, scenario			Scenario analysis
	Are ranges presented on realistic scenarios?	yes	Yes			Yes
Discounting	Is any discounting applied to costs?	yes	No	No	No.	No
	Which is the discounting rate considered?	3%				

Item	First author	Langill	Martin	Savova	Gordon	Ballali
	Reference number	61	62	63	64	65
Perspective	Perspective adopted	Hospital perspective	healthcare system perspective	Payer perspective	Society	Local health payer (Veneto region)
	Categories of costs included	Direct medical costs (consumable materials associated with fecal management, treatment of complications)	Direct medical cost (Infusion supplies, registered nurse, unit clerk, scheduling clerk, ward aid)	Direct costs (drug and adverse events)	Direct and indirect costs (Hypoglycemia releted, training and education, medications, medical service, Inpatient admission, outpatient service, emergency room ; family/carer time, Time off work and copayment)	Drugs costs and administration (chemotherapy)
	Is the perspective the one of the budget holder?					Yes
Scenarios to be compared	Are the two scenarios well specified?	Yes, the reference scenario includes traditional fecal management methods. The new scenario includes modern fecal management system (FFMS).	Yes. The reference scenario includes the IVIG (intravenous immunoglobulin). The new scenario includes IVIG 50% and SCIG 50%(subcutaneous immunoglobulin)	Yes, The reference scenario includes : desatinib+ imatinib. Teh new scenario includes: desatinib+ imatinib+ nilotinib.	Yes . Both the reference scenario and new scenario include Human Insulin and analog insulins (current 39% human vs 59% analog; hypotetical 100% human vs 0% analog)	SCENARIO 1) First line treatment with trastuzumab + paclitazel. SCENARIO 2) First line treatment with paclitaxel alone. SCENARIO 3) Second line tratment with lapatibin + capecitabine after filure of first line tratmetn with trastuzumab + paclitaxel
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	All options supposed to be considered	Some option (or one option) considered	All options supposed to be considered	Some option (or one option) considered	Some options considered
	Inclusion of off-label drugs use		No	No		NA
	Are the assumptions on the current and future scenarios identified and motivated?	Yes. Traditional methods of fecal management re labor- and resource-intensive. In terms of minimizing secondary complications associated with fecal incontinence and mitigating risks for spread of infectious organisms, it is well recognized that more effective measures are needed.Modern methods of fecal incontinence management include devices specifically designed to divert fecal waste to collection bags, thus reducing soiling and the spread of infectious microrganism and preserve skin integrity. One of this is the FFMS, approved in US by FDA and that was shown to be safe and effective in diverting fecal waste.	Yes . Immunoglobulin can be administered by intravenous or subcutaneous infusion. Intravenous immunoglobulin (IVIG) infusion is typically performed on a monthly basis in an outpatient setting (hospital), whereas subcutaneous immunoglobulin (SCIG) infusion can be self-administered one or more times a week by the patient at home. Similar efficacy in preventing infections has been reported between SCIG and IVIG with no difference in severity and length of infections . Although these two treatment options are associated with similar efficacy and safety profiles, switching from hospital-based IVIG to home-based SCIG was shown to significantly improve healthrelated quality of life (HRQoL) of adult PID patients.	Yes. The introduction of imatinib mesylate as a standard treatment of CML is associated with high response rates and improved overall survival, especially when used in the chronic phase However, CML patients sometimes become resistant to imatinib. Options for those patients include either increasing the imatinib dose or using second-generation tyrosine kinase inhibitors—dasatinib or nilotinib. Both drugs may not only produce complete hematologic and cytogenetic responses, but also increase the overall survival in patients with imatinib-resistant or intolerant CML.	Yes	NA
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	Yes, patients with fecal incontinence	Yes. Adult PID (primary immune deficiency) patients.	Yes, patients with CML in accelereted or chronic phase who are resistant or intolerant to imatinib.	Yes. Patient with type 2 diabetes in UK	YES
	Inducement hypothesis	No	No	No	No	NA
	Open-population versus cohort-based analysis	Cohort from general population	Cohort from general population	Cohort from general population	Cohort (from general population)	Cohort population
	Subgroups	The results for 1 hospital are presented for 2 groups: average and complex intensive unit care patients	No	The results are presented for the two groups: accelereted and chronic phase.	No	NA
Time horizon	Time horizon	1 year	3 years	3 yr	1 year	3 years divided into 6 months periods (6 periods)
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	No	No	No	No	NA
Costing	Information source used for resource consumption	Primary date, SPC, questionnaire.Data were input to the BIM by a health economics researcher from the FFMS manufacturer. T	Primary data,	Primary date, SPC, RCT.	Literature	Literature
	Do the unit costs reflect the value attached by payers to resources?	Unit cost of consumables were obtained from the hospital's Purchasing Department or Detailed Managementr Report.he budget impact and nursing time of implementing FFMS were based on data obtained for 2009 from the Ottawa Hospital-Civic Campus (TO H-CC), Ottawa, Ontario, Canada, and the Hamilton Health Sciences (HHS), McMaster University Campus, Hamilton, Ontario, Canada	Yes. Unit costs for resources were obtained from St Paul's Hospital and the Adult SCIG home infusion program	All available treatmentoptions and costs were calculated according to carriage **and insurance paid price** in the national currency.	Literature	NA
	Are fixed costs considered in the long-run?	Annual nursing time was not included in the overall cost calculation but reported separately	yes	No	No	No
	Are transaction costs included?	no	no (nurse, manager, assistent...)	No	No	No
	Is any rebate applied?	No	no	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	No	Yes	No	No	NA
	Which sensitivity analyses have been carried out?		Scenario analysis			NA
	Are ranges presented on realistic scenarios?		Yes			NA
Discounting	Is any discounting applied to costs?	No	no	No	No	NA
	Which is the discounting rate considered?					NA

Item	First author	Pollock	Simoens	Gregory	Malavaud	Kuan
	Reference number	66	67	68	69	70
Perspective	Perspective adopted	NHS	Belgian NHS	Payer perspective	NHS	US NHS
	Categories of costs included	Direct costs (drug, surgery, medical consultation, complications)	Drugs costs and hospitalization	Inpatient, outpatient, physician, emergency room, pharmacy	Direct costs: PB cost (prostate biopsy), PCA3 testing costs, complications costs	Costs for physician's fees, laboratory tests, and endoscopies and medication costs.
	Is the perspective the one of the budget holder?	Yes	Yes	Yes	Yes	Yes
Scenarios to be compared	Are the two scenarios well specified?	Standard management of obesity vs. laparoscopic adjustable gastric binding	Azithromycin vs. placebo	Yes: high risk percutaneous coronary intervention (HR-PCI) with IABP (intra-aortic balloon pump) and HR-PCI with pVAD (percutaneous cardiac assist device)	Yes: reference scenario current practice vs. RAM+PCA3	Yes: compare patients receiving: (1) single-tablet ibuprofen/famotidine; (2) chronic NSAID treatment plus any GI-protective agent; and (3) chronic NSAID treatment without a GI-protective agent.
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	Some options considered	Some options considered	Some options considered	Some options considered	Some options considered
	Inclusion of off-label drugs use	No	No	NA	NA	NA
	Are the assumptions on the current and future scenarios identified and motivated?	Yes	No	NA	Yes	Yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	Yes	Yes	Yes	Yes	Yes
	Inducement hypothesis	No	NA	No	No	No
	Open-population versus cohort-based analysis	Cohort	Cohort population	open	Cohort	Cohort
	Subgroups	No	NA	cardiogenic shock population	No	
Time horizon	Time horizon	5 years	1 year	30 months	1 year	3 years
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	No	No	No	No	No
Costing	Information source used for resource consumption	Literature	RCT and literature	Database	Literature	Literature
	Do the unit costs reflect the value attached by payers to resources?	Literature and fees	NA	NA	Literature	Fees and wholesale acquisition costs
	Are fixed costs considered in the long-run?	No	No	No	No	NA
	Are transaction costs included?	No	No	No	No	
	Is any rebate applied?	No	No	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	Yes	Yes	YES	No	Yes
	Which sensitivity analyses have been carried out?	One-way and multi way SA and PSA	?	univariate	No	Univariate
	Are ranges presented on realistic scenarios?	Yes	NA	Yes	No	Yes
Discounting	Is any discounting applied to costs?	Yes	No	NA	No	No
	Which is the discounting rate considered?	3,50%	No	NA	No	

Item	First author	Yen	Aubry	Freijer	Lotan	Ariza
	Reference number	71	72	73	74	75
Perspective	Perspective adopted	US's payer perspective	Hypothetical commercial health plan	The perspective of this study is that of the compartment of patients living at home with assistance of home care and patients living in residential homes being the community setting. The perspective of the study was a limited societal perspective, because indirect costs due to productivity loss were not included, as the study population concerns elderly people, most likely to be retired.	French payer and society in 2010.	Colombian NHS
	Categories of costs included	Medication and Inpatient admissions cost, Emergency department cost, Office visit cost, Other outpatient /ancillary visit cost, Non–UC-related pharmacy cost	Direct costs of screening procedure, complication, repetition of PSA testing	The incremental cost difference was based on the costs associated with the cost of ONS (oral nutritional supplement) and the cost of illness of DRM (disease related malnutrition). All health care costs other than use of ONS and costs of DRM are not included in the model.	Including direct medical costs and also indirect costs due to lost productivity. We focused on the costs associated with nephrolithiasis, treatment related complications and CKD. The incremental cost difference is based on: (i) a difference in costs associated with nephrolithiasis and its complications (acute and long term), and (ii) a difference in costs associated with high and low water intake.	Three types of direct costs were considered in the model analysis: 1) drug acquisition cost, 2) cost of maintenance therapy and 3) cost of exacerbation.
	Is the perspective the one of the budget holder?	Yes	Yes		Yes	Yes
Scenarios to be compared	Are the two scenarios well specified?	2 scenarios: (1) the base case scenario, in which all UC patients were distributed among the 5-ASA drugs based on formulary share; and (2) the new formulary scenario, in which all DRM patients were switched to MMX mesalamine, while formulary share for the remaining 2 drugs remained the same. The model allowed users to create 2 health plan formulary scenarios (ie, base case and new scenario) and compare total all-cause direct costs associated with UC patients under each scenario.	Yes: In the reference scenario, the model uses current clinical patterns of care to simulate the treatment of men at risk of prostate cancer in the reference scenario; a molecular assay was not utilized for prostate cancer detection. In the new scenario, men at risk for repeated biopsy are evaluated with the epigenetic assay, and those with a negative DNA methylation test result are spared a repeat of the biopsy, thereby reducing the number of unnecessary rocedures.	The study population is based on a comparison of the use of ONS versus "no use" of ONS due to DRM in elderly patients of 65 years and over (>65 years) in the community setting.	Yes: increased water intake vs. standard care to treat nephrolithiasis	Two different CE analyses were performed: Indacaterol vs. formoterol/budesonide and indacaterol vs. salmeterol/fluticasone. A second analysis was based on a head-to-head trial of indacaterol vs. open-label tiotropium.
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	All options considered by the author	Some options considered	All options supposed to be considered by the author	All options supposed to be considered by the author	All options supposed to be considered by the author
	Inclusion of off-label drugs use	No	NA	NA	NA	NA
	Are the assumptions on the current and future scenarios identified and motivated?	Yes	NA	YES: The model is based on the assumption that the use of ONS only has an impact on re-/hospitalization due to DRM.	Yes	Yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	Yes	YES	Yes	Yes	Yes
	Inducement hypothesis	No	No	No	No	No
	Open-population versus cohort-based analysis	Cohort	cohort	cohort	hypothetical cohort of persons	Cohort
	Subgroups	Adults patients (≥ 18 years) with newly diagnosed or relapsing mild to moderate UC (ulcerative colitis)	Yes The model's base-case analysis was conducted for a hypothetical plan using patient age-groups between ages 40 and 64 years	Elderly patients of 65 years and over	No	NA
Time horizon	Time horizon	1 year	1-year time horizon	1 year	BIA 5 years	5 years
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	No	No	No	CEA follow-up up to 25 years	No
Costing	Information source used for resource consumption	Literature	Literature	RCT and literature	Panel	Primary data
	Do the unit costs reflect the value attached by payers to resources?	Literature	Literature and fees	Fees	Fees	Primary data
	Are fixed costs considered in the long-run?	NA	NA	No	No	No
	Are transaction costs included?	No	NA	No	No	No
	Is any rebate applied?	No	NA	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	Yes	Yes	Yes	Yes	Yes
	Which sensitivity analyses have been carried out?	Univariate - one way	?	Univariate	Univariate	Probabilistic
	Are ranges presented on realistic scenarios?	Yes		Yes	NA	Yes
Discounting	Is any discounting applied to costs?	No	NA	No	Yes	Yes
	Which is the discounting rate considered?	No	NA	NA	3%	5%

Item	First author	Sicras-Mainar	Kohli	Mohseninejad	Atkins	Mills
	Reference number	76	77	78	79	80
Perspective	Perspective adopted	community-treated setting perspective	Health care system	We adopted the Dutch healthcare perspective in our analyses	UK and Wales NHS	NHS ministry of health
	Categories of costs included	the direct health care costs considered were: medical visits (primary and specialist care), hospitalization days, emergency room visits, diagnostic tests and referrals to rehabilitation and physiotherapy due to neuropathic pain. The indirect costs considered were related to absenteeism (number of days of sick leave).	The total annual cost from the perspective of the budget holder (i.e. the Department of Public Health) was calculated using the cost of vaccine purchase and administration. The total cost of each strategy included the health care costs incurred by those receiving vaccination plus cervical cancer screening as well as those receiving cervical cancer screening only.	Only direct health care costs are considered (i.e. relevant testing and treatment costs were taken into account, and these were estimated bottom-up. Costs of serological tests, endoscopy, complications, IBS care, and gluten free diet were distinguished). The costs of a gluten free diet were also taken into account.	Vaccine costs and hospitalization costs	Treatment cost and adverse events costs
	Is the perspective the one of the budget holder?	No	yes	Yes	yes	yes
Scenarios to be compared	Are the two scenarios well specified?	Standard care for PNP + gabapenting vs. standard care for PNP + pregabalin	The model simulates the effect of adding vaccination to the current screening program, where two cohorts of 100,000 12-year-old females were followed over a lifetime, one cohort vaccinated with the HPV-16/18 AS04- adjuvanted vaccine and the other with the HPV-6/11/16/18 vaccine.	1. Catch up Scenario: Screen all prevalent IBS cases with IBS-D/mix type symptoms at the beginning and then continue with screening of new incident cases in the following years. 2. Gradual Scenario: Start screening new incident cases and continue this annually.	Administration of rotavirus vaccine concomitantly with childhood vaccination or separetly	Expand the ART treatment to patients with 350 CD4+ cells instead to treat only patients with CD4+ cell count of 200 per microliter.
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	Some options considered by the author	All options supposed to be considered by the author	Some oprion considered by the author	Some option considered by the author	All options supposed to be considered by the author
	Inclusion of off-label drugs use	NA	NA	NA		no
	Are the assumptions on the current and future scenarios identified and motivated?	yes	Yes: As vaccine coverage rates do not impact the cost-effectiveness ratios estimated with a static model, a coverage rate of 100% was assumed. This analysis assumed lifelong protection against all HPV types, including crossprotection against non-vaccine types. Both of the vaccines were assumed to cost $100 per dose plus an administration fee of $10.97, and it was assumed that 3 doses were given for both. For the costeffectiveness analysis, it was assumed that the entire cohort received all doses (100% coverage).	Yes: we assumed that patients with a General Practitioner (GP) diagnosis of IBS-D/mix will be screened for CD.	yes	yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	yes	yes	Yes	yes	yes
	Inducement hypothesis	No	No	No	no	no
	Open-population versus cohort-based analysis	cohort	cohort	cohort	cohort	cohort
	Subgroups	adult population only	No	No	undere 5 years of age	age >14 years, $CD4^+$ count cell: 142 per microliter
Time horizon	Time horizon	3 years	lifetime	10 years	1 year	5 and 30 years
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	no	NA	No	no	yes
Costing	Information source used for resource consumption	NA	Literature and primary data	Literature	Literature	Literature and panel
	Do the unit costs reflect the value attached by payers to resources?	Primary data	Fees	Fees, panel and literature	Fees	Literature
	Are fixed costs considered in the long-run?	No	No	no	yes	No
	Are transaction costs included?	No	No	no	No	No
	Is any rebate applied?	No	No	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	Yes	yes	yes	yes	yes
	Which sensitivity analyses have been carried out?	Descriptive-univariate/bivariate sensitivity analysis	One and two-way deterministic sensitivity analysis, multivariate probabilistic sensitivity analysis	Both one-way and probabilistic sensitivity analyses were performed.	probabilistic SA	deterministic SA
	Are ranges presented on realistic scenarios?	NA	yes	yes	yes	yes
Discounting	Is any discounting applied to costs?	NA	yes	NA	no	yes
	Which is the discounting rate considered?	NA	3%	NA	no	3%

Item	First author	Yan	Geitona	Gruss	Gidwani	Chapa
	Reference number	81	82	83	84	85
Perspective	Perspective adopted	French Social Security perspective	NHS	NHS	VETERANS ADMINISTRATION EMERGENCY DEPARTMENTS	NA
	Categories of costs included	Cost of primary and secondary dressing	Economic data included all the expenses incurred in running all the OST programmes for 2008. (1) personnel, (2) drugs/consumables, (3) medical consultations/diagnostic investigations, (4) maintenance of equipment and buildings, and (5) overheads.	Drug acquisition costs and procedural costs	Costs of Rapid Testing include both program implementation and treatment of disease. Costs of Usual Care include disease-treatment costs only, but health care utilization is more intensive in this population due to late identification of disease. Treatment costs were calculated for the following budgets: inpatient, outpatient, pharmacy, and global. Cost per disease-severity category was determined by examining utilization patterns of HIVpositive patients and allocating VA-specific direct medical cost values to this utilization.	The base case model used a conservative rate of $50/minute of operating room time, length of stay, the cost of Gynecare Interceed (device)
	Is the perspective the one of the budget holder?	yes	yes	Yes	yes	
Scenarios to be compared	Are the two scenarios well specified?	Scenario 1 used forecasted annual market shares for alginate, generic or brand (Algosteril®, Brothier) and Hydrofiber® (AQUACEL®) dressing to simulate a situation where the Hydrofiber® dressing would continue to gain a slight market share over time; scenario 2 used fixed market shares to simulate a situation where Hydrofiber® and alginate market shares remain constant at 2010 levels.	bupenorphine (comprising buprenorphine-naloxone combination) vs. methadone treatment	Yes: sodium picosulphate with magnesium citrate +sodium biphosphate/sodium phosphate vs. PEG+ASC	We forecast the costs of two Emergency Department-based HIV testing programs in the Veterans Administration: 1) implementing a non-targeted screening program and providing treatment for all patients thusly identified (Rapid Testing); and 2) treating patients identified due to late-stage symptoms (Usual Care); to determine which program was the most financially feasible.	use of the device to avoid adesion during cesarean surgery or not
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	Some option considered by the author	All options considered by the author	Some options considered	All options supposed to be considered	Some options (or one option) considered by the author without an explicit rational
	Inclusion of off-label drugs use	NA	No	No	no	no
	Are the assumptions on the current and future scenarios identified and motivated?	NA	YES Since the administration of buprenorphinenaloxone was initiated in the last 3 months of 2008, economic and outcome assessment data on buprenorphine-naloxone were not yet available. The cost for the 620 buprenorphine-naloxone participants was therefore included in the buprenorphine treatment arm. The assumption of equal cost was based on the fact that participants, whether receiving buprenorphine monotherapy or buprenorphine-naloxone combined therapy, received the same clinical management, e.g., drug administration, medical/psychological consultations, personnel support, and use of equipment and buildings per week, and that both are currently administered three times a week and in the same way.	Yes	YES: To summarize, the following assumptions were made in conducting these analyses: 1. Patients can be properly stratified into four CD4+ count categories. 2. All health care utilization, and therefore cost, is contingent upon CD4+ count at diagnosis. 3. Utilization patterns of patients identified through these programs can be modeled using utilization data from past HIV-positive patients treated at the same location. 4. All persons diagnosed are immediately linked to treatment. 5. All patients identified by Rapid Test would be diagnosed an average of 1.25 years later in the Usual Care program.	yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	The number of patients with VLU in France was estimated from the published literature. The number of patients was fixed over the 5 years.	yes	Yes	yes	yes
	Inducement hypothesis	No	No	No	no	no
	Open-population versus cohort-based analysis	Cohort	cohort	Cohort	cohort	cohort 1000 patients
	Subgroups	no	No	Yes: inpatients, outpatients, frail outpatients	no	no
Time horizon	Time horizon	5-year time horizon	1 year	1 year	7 years	1 year
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	no	No	No	no	no
Costing	Information source used for resource consumption	literature and panel	Literature	Panel	Primary data-database.	Literature
	Do the unit costs reflect the value attached by payers to resources?	Unit costs	Literature	Fees	NA	Literature
	Are fixed costs considered in the long-run?	No	No	No	No	yes: operating room cost
	Are transaction costs included?	No	No	No	No	No
	Is any rebate applied?	No	No	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	yes	yes	Yes	yes	yes
	Which sensitivity analyses have been carried out?	One-way sensitivity analysis and Probabilistic sensitivity analyses	deterministic sensitivity analysis and probabilistic sensitivity analysis	DSA	Probabilistic sensitivity analyses	deterministic two-way sensitivity
	Are ranges presented on realistic scenarios?	yes		Yes	yes	yes
Discounting	Is any discounting applied to costs?	no	No	No	NA	No
	Which is the discounting rate considered?	NA	NA	NA	NA	No

Item	First author	Fragoulakis	Hoshi	Bilir	Léon-Justel	Lau
	Reference number	86	87	88	89	90
Perspective	Perspective adopted	The perspective of the economic evaluation was that of sickness funds (payers) in Greece.	the perspective of a municipality, which is responsible for providing the routine vaccination	A payer-perspective	perspective of the hospital budget impact	hospital medication budget impact associated with
	Categories of costs included	Only direct health care costs reimbursed by payers were considered. Direct costs are those associated directly with the medical care of patients.included direct medical costs: the total treatment cost accounted for the cost of drugs, routine examinations, and resources expended in the management of acute myocardial infarction, stroke, and death.	we will consider the treatment costs of children who are covered by the National Health Insurance only	direct medical costs	direct cost due to the need for two days of hospitalization to evaluate MSC, and compared the cost of using the new protocol which substitutes MSC for MSVC, that does not require hospitalization	drug costs
	Is the perspective the one of the budget holder?	no	yes	yes	yes	yes
Scenarios to be compared	Are the two scenarios well specified?	comparing rosuvastatin atorvastatin, simvastatin, and pravastatin in the primary and secondary prevention of CVD among high-risk patients in Greece	We defined four vaccination programmes with same vaccination schedule, which is a three dose primary series over 6 months followed by a fourth dose in the second year: two levels of copayment,i.e., none or ¥1000 per shot (US$13; US$1 = ¥80, based on the average exchange rate of 2011 instead of purchasing power parity); and two scenarios of the uptake of PCV-7, i.e., vaccinated alone or co-vaccinated (simultaneously inoculated with other vaccines). Combinations of these produced four different designs of vaccination programmes. These programmes were compared with no programme scenario, respectively.	2 scenarios: 1) BIS (bioimpedance spectroscopy)testing performed routinely during post-BC follow-up visits; 2) current standard (CS) assessments are employed	The study participants were patients under the suspicion of having CS and patients that were referred to our institution (tertiary universitary hospital) to manage proven CS. Option A (UFC×2, MSC, LDDST): urinary free cortisolx2, midnight serum cortisol, low-dose dexamethasone suppression test Option B (UFC×2, MSVC, LDDST):urinary free cortisolx2, midnight salivary cortisol, low-dose dexamethasone suppression test	conversion from IV to PO medication for the 4 targeted IV medications, each representing a different class of drug, when patients were clinically eligible for PO medication intake. (Clorothiazide, Levetiracetam, Voriconazole, Pantoprazole)
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	Some options considered	All options supposed to be considered	All options considered by the author	All options supposed to be considered	Some option considered
	Inclusion of off-label drugs use	no	No	No	no	no
	Are the assumptions on the current and future scenarios identified and motivated?	yes	yes	NA	yes	yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	yes	yes	yes	Yes: participants were patients under the suspicion of having CS and patients that were referred to our institution (tertiary universitary hospital) to manage proven CS.	yes
	Inducement hypothesis	no	no	no	no	no
	Open-population versus cohort-based analysis	cohort	cohort	cohort	cohort	cohort
	Subgroups	no	no	no	no	no
Time horizon	Time horizon	lifetime	5-year programme	1-year	1 year	1 year
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	no	no	(literature suggests a longer time frame)	no	no
Costing	Information source used for resource consumption	Panel	Literature	Literature and panel	SPC	Primary data-database
	Do the unit costs reflect the value attached by payers to resources?	Fees	Literature	Fees	Fees	NA
	Are fixed costs considered in the long-run?	No	No	No	No	No
	Are transaction costs included?	No	No	No	No	No
	Is any rebate applied?	No	No	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	yes	yes	yes	yes	NA
	Which sensitivity analyses have been carried out?	The model was set to provide deterministic and probabilistic analyses	one-way sensitivity analyses	uni/multi-variate	deteeministic (one-way)	NA
	Are ranges presented on realistic scenarios?	yes	yes	yes	yes	NA
Discounting	Is any discounting applied to costs?	yes	yes	no	no	NA
	Which is the discounting rate considered?	3,50%	Costs and outcomes were discounted at a rate of 3%	no	no	Na

Item	First author	Nichol	Stauffer	Saadi	McLellan	Mueller
	Reference number	91	92	93	94	95
Perspective	Perspective adopted	NHS (adding to the health plan the new test)	hyospital Bylor Medical Center Garland (BMCG)	U.S. payer perspective assuming fixed fee-reimbursement (Mediacre)	NHS	German statutory health insurance (SHI)
	Categories of costs included	direct mediacl costs (visits, lab test, screening test)	costs and reimbursement experience from the intervention: total direct cost, revenue (from reimbursement) and contribution margins (difference from direct costs and revenue)	all direct costs (procedure, comprisingdevice, and re intervention)	direct medical and non medical costs (specialist visit, consultant, scan test, patients records, patients transport)	cost of screening, treatmente costs and fracture costs, as well as general healthcare costs in added years of life, were taken into account.
	Is the perspective the one of the budget holder?	yes	yes	yes	yes	yes
Scenarios to be compared	Are the two scenarios well specified?	three testing strategies were compared: 1) PSA (prostate-sspecific antigen); 2) %fPSA (freePSA) 3) index (prostate cancer risk index) Strategy 1 and 2 are reference scenario in the model.	interventional patients (which receive TCP(transitional care program) by APN (advanced practice nurce)) vs. non-interventional patients	comparison of 4 drug eluting stent (DES) in diabetic patients: Cypher, Endeavor, Taxus and Xience	FLS (fracture liaison service) vs usual care (non FLS: mixture of no identification or assessment along opportunistic hospital or GP assessment)	Secondary + tertiary prevention vs. tertairy prevention alone for osteoporosis.
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	All option supposed to be considered	Some option considered	Some option considered	All option considered by the author	Some options considered
	Inclusion of off-label drugs use	no	no	Yes because DES did not receive FDA-approval for diabetic patients	no	NA
	Are the assumptions on the current and future scenarios identified and motivated?	NA	NA	Yes , they assumed a use of 100% for each DES	yes	yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	no	No	no	yes	no
	Inducement hypothesis	no	No	no	no	no
	Open-population versus cohort-based analysis	cohort	cohort	cohort	cohort	cohort
	Subgroups	man 50-75 years old	patient of 65 yeras alnd older discharged from hospital at Augut 24, 2009	diabetic patients	50 years old or older with fragility fracture	post-menopausal women and only insured by SHI of 50 - 60 - 70 and 80 years old.
Time horizon	Time horizon	1-year	8 months(from August 24, 2009 to April 30, 2010	1 year	1 year	lifetime the CEA and 1 year the BIA
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	no	no	no	no	no
Costing	Information source used for resource consumption	Literature	Primary data	Primary data database	Primary data database (West Glasgow)	Literature
	Do the unit costs reflect the value attached by payers to resources?	Fees	Unit cost	Fees	Fees and unit costs	Literature
	Are fixed costs considered in the long-run?	No	No	No	No	No
	Are transaction costs included?	No	No	No	No	No
	Is any rebate applied?	No	No	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	yes	No	yes	yes	yes
	Which sensitivity analyses have been carried out?	DSA	no	deterministic	detreministic and probabilistic	one way and probabilistic
	Are ranges presented on realistic scenarios?	yes	no	yes	yes	yes
Discounting	Is any discounting applied to costs?	no	no	no	yes	yes
	Which is the discounting rate considered?	no	no	NA	3,50%	3%

Item	First author	Arlandis	Olchanski	Carlson	Sweet	Indinnimeo
	Reference number	96	97	98	99	100
Perspective	Perspective adopted	Spanish NHS	The analysis perspective is that of a hospital administrator	US health plan	UK NHS	Italian NHS
	Categories of costs included	the analyses considered direct health-care costs only, and these were expressed in 2008 Euro values. Costs comprised health-care resources used at treatment initiation (preprocedure costs), during treatment (procedure and drug costs), during follow-up, for adverse events, and after treatment failure.	total direct medical costs (eg, hospitalization, treatment of MRSA infections, individual isolation, and MRSA testing)	drug, administration and AE costs	screening, diagnosis and treatment costs	direct medical costs
	Is the perspective the one of the budget holder?	yes	yes	Yes	Yes	yes
Scenarios to be compared	Are the two scenarios well specified?	long-term cost-effectiveness of treatment with SNM (sacral neuromodulation) therapy in refractory idiopathic OAB-wet (overactive bladder) patients compared to repeat BoNT-A (botulin neurotoxin A) injections or optimized medical treatment (OMT) consisting of continued drug and pad use.	Our understanding is that many hospitals with active surveillance programs test only high-risk patients; therefore, we focused on this type of screening for the test option comparison analysis. Results were estimated for the base-case analysis, using five population screening approaches: (1) all admissions, (2) high-risk admissions only, (3) ICU admissions only, (4) patients with a history of MRSA positivity only, and (5) no program	Erlotinib MTx vs. altrnative MTx treatment	Yes:1) Biennal fecal occult blood test (FOBT) as current screening 2)Biennal FOBT with CTC (CT colonography) follow up of positive result 3) Five-yearly CTC	treatment of fecal inconinence with or without sacral neuromodulation (SNM)
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	All options supposed to be considered	Some options considered	Some option considered	All options supposed to be considered	Some options considered
	Inclusion of off-label drugs use	yes Injection of the bladder wall with BoNT-A, although currently not licensed for use for the idiopathic OAB indication Europe, is often used to treat refractory idiopathic OAB in Spain.	no	No	no	NA
	Are the assumptions on the current and future scenarios identified and motivated?	yes	yes	Yes	yes	yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	yes	patient population: ICU patients only, all high-risk patients, patients with a history of MRSA colonization or infection, or all patients admitted to the hospital.	Yes	no	yes
	Inducement hypothesis	no	no	No	no	no
	Open-population versus cohort-based analysis	hypothetical cohort of OAB patients	cohort of patients admitted to the hospital	Cohort	cohort	cohort
	Subgroups	yes female population older than 45	no	No	over 50 years patients	no
Time horizon	Time horizon	10-year time frame for CEA and four consecutive years for BIA	1 year	1year	10 years	5 years
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	no	no	No	no	no
Costing	Information source used for resource consumption	Literature, panel	Literature	Literature and RCT	Literature and panel (personal communication)	Panel and literature
	Do the unit costs reflect the value attached by payers to resources?	Unit cost	Literature	Fees	NA	Fees and literaturre
	Are fixed costs considered in the long-run?	No	No	No	No	No
	Are transaction costs included?	No	No	No	No	No
	Is any rebate applied?	No	No	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	yes	yes	Yes	yes	yes
	Which sensitivity analyses have been carried out?	Probabilistic and deterministic sensitivity analyses	probabilistic multivariate	Scenario and DSA	univariate sensitivity analysis	probabilistic and multivariate deterministic S
	Are ranges presented on realistic scenarios?	yes	yes	Yes	yes	yes
Discounting	Is any discounting applied to costs?	yes in the CEA	no	No	no	yes for the CEA
	Which is the discounting rate considered?	3% per annum	no	NA	no	3%

Item	First author	Martin	Guest	Leelahvarong	Ladabaum	Sladkevicius
	Reference number	101	102	103	104	105
Perspective	Perspective adopted	US NHS (medicare, medicaid and Ryan White entitlement)	the perspective of the publicly funded healthcare system	Thai societal perspective	regional government as (local NHS Aragon, Spain)	hospital pharmacies' perspective
	Categories of costs included	The testing cost calculations also include the cost of screening non-infected individuals. We tracked HIV-related treatment costs for all adults, including the elderly	direct medical costs (screening, visits, treatment)	direct medical costs, direct non-medical and indirect costs for CEA; direct medical costs only for BIA	direct medical costs in Aragón (Colonoscopy, Colonoscopy with lesion removal, Endoscopy complication). For BIA: We first made estimates considering only costs related to CRC screening, testing, complications and cancer care	drug costs, tecnician salary, nurse salary
	Is the perspective the one of the budget holder?	yes	yes	yes	yes	yes
Scenarios to be compared	Are the two scenarios well specified?	We examined two testing strategies: current practice (defined by completing a test, on average, every 10 years) and expanded screening (defined by completing a test, on average, every five years).	agalsidase alfa and agalsidase beta. It was estimated that there are approximately 60 adult Fabry patients in Norway of whom 23% are treated with agalsidase alfa, 30% with agalsidase beta and 47% are not on ERT. Additionally, it was estimated that there are four new patients per annum of whom 23% would be treated with agalsidase alfa, 30% with agalsidase beta and 47% do not receive any ERT.	was performed to evaluate and compare the costs and health outcomes for related and unrelated HSCT (Hematopoietic stem cell transplantation) compared with BT-ICT (blood transfusions combined with iron chelating therapy).	We compared Natural History, colonoscopy every 5 years, and colonoscopy every 10 years.	use of generic docetaxel vs. branded docetaxel
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	Some options considered	All options considered by the author	All options considered by the author	Some options considered	Some options considered
	Inclusion of off-label drugs use	NA	no	no	na	no
	Are the assumptions on the current and future scenarios identified and motivated?	yes	yes	yes	YES	yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	no	yes	yes	yes	yes
	Inducement hypothesis	NA	NA	no	no	no
	Open-population versus cohort-based analysis	open population	cohort	cohort	cohort based on general population	cohort based on general population
	Subgroups	Non elderly (19-64 years old)	no	no	persons ages 40 - 85 years old, with CRC family history	no
Time horizon	Time horizon	5 years	1 year	15 years for BIA; lifetime for CEA	1 year	1 year
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	no	yes Expected annual cost after the first year following diagnosis	no	no	no
Costing	Information source used for resource consumption	Literature	Primary data database	Literature, primary data database (hospital database), interviews to patients and caregiver	Primary data	Literature and panel
	Do the unit costs reflect the value attached by payers to resources?	Literature	Unit costs	Fees	Unit costs	Panel
	Are fixed costs considered in the long-run?	No	No	No	No	No
	Are transaction costs included?	No	No	No	No	No
	Is any rebate applied?	No	No	No	No	no
Sensitivity analysis	Is a sensitivity analysis carried out?	yes	yes	yes	yes	yes
	Which sensitivity analyses have been carried out?	probabilistic SA	Deterministic sensitivity analyses	One-way sensitivity analysis and a probabilistic sensitivity analysis	one way sensitivity analysis	deterministic SA
	Are ranges presented on realistic scenarios?	yes	yes	yes	yes	yes
Discounting	Is any discounting applied to costs?	no	no	yes	no	no
	Which is the discounting rate considered?	no	No	3%	no	no

Item	First author	Manson	Woodward	McNamee	Cicchetti	Gruber
	Reference number	106	107	108	109	110
Perspective	Perspective adopted	US payer perspective	US managed care organization perspective	UK health and socual system	A social perspective	hospital and a socioeconomic perspective
	Categories of costs included	direct costs only, indirect costs and out-of-poket patinets payment considered for secondary analysis	Chronic suppressive treatment drug cost, acute drug costs and annualmedical costs, costs associated with home heath visits and lab monitoring.	Treatment costs (price of cholinesteraseinibhitor medication) and total AD care costs (cholinesterase inhibitors and other long-term resources such as nursing home care)	Absenteeism GP visit Hospital admissions Oseltamivir Zanamivir Vaccine + administration	The hospital perspective considered only relevant direct medical costs. The socioeconomic perspective included indirect costs due to productivity loss caused by work absenteeism.
	Is the perspective the one of the budget holder?	yes	yes	yes	yes	yes
Scenarios to be compared	Are the two scenarios well specified?	primary and secondary events	Tobramycin inhalation solution (TIS) + standard care vs. standarda care alone	1) NICE guideline-mild and moderte (NG-MM) model, where only thiose with a level of MMSE (mini mental state examination) greater than 12 commenced therapy and were withdrawn from therapy when MMSE was no longer grater than 12; 2) a NICE guidelines-moderate (NG-M) model, where individuals with MMSE between 10 and 20 were treated, and were withdrawn from therapy when MMSE fell below 10, 3) NICE-guideines-all (NG-ALL), where all individuals with AD were treated, irrespective of MMSE.	different levels of extention of flu vaccination in poepla aged 50-64 in Italy, France, Germany, Sapin	ultrasound-guided 14-g large core breast biopsy (US-guided LCBB) vs. open surgical biopsy (OSB).
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	Some options considered	All options supposed to be considered	Some options considered	Some options considered	Some options considered
	Inclusion of off-label drugs use	no	no	no	no	no
	Are the assumptions on the current and future scenarios identified and motivated?	yes	yes: assumption developed with key opinion leaders	yes	NA	yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	yes	yes	yes	yes	yes
	Inducement hypothesis	no	no	no	no	no
	Open-population versus cohort-based analysis	cohort	open	cohort	cohort	all 399 evaluated breast lesions.
	Subgroups	no	no	yes patients with mild to moderate AD	people aged 50 - 64	no
Time horizon	Time horizon	10 years	4 years	10 years	1 year	1 year
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	no	no	no	no	no
Costing	Information source used for resource consumption	Literature	Literature	RCT	Literature	Literature
	Do the unit costs reflect the value attached by payers to resources?	Literature and fees	Fees, unit cost (reimbursement code) and literature (for lab moniyoting and health visits)	Literature (RCT)	Literature and unit costs (database)	Fees
	Are fixed costs considered in the long-run?	No	yes: durable medical equipment (DME)	No	No	No
	Are transaction costs included?	No	acquisition costs based on WAC	No	No	No
	Is any rebate applied?	No	No	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	yes	yes	yes	yes	yes
	Which sensitivity analyses have been carried out?	one way	one and two way SA	probabilistic SA	A probabilistic sensitivity analysis	deterministic sensitivity analyses
	Are ranges presented on realistic scenarios?	yes	yes	yes	yes	yes
Discounting	Is any discounting applied to costs?	yes	no	no	no	no
	Which is the discounting rate considered?	5%	No	no	no	no

Item	First author	Gani	Bakhshai	Weber	Jackson	Rose
	Reference number	111	112	113	114	115
Perspective	Perspective adopted	NHS cost perspective	Third party US managed care perspective	Czech statutory health insurance system	NHS perspective	NHS and society perspective
	Categories of costs included	1) Maintenance costs. 2) Exacerbation Costs. 3) Intervention costs	drug and medical costs	direct costs of SMBG (self monitoring blood glucose) and type 2 diabetes-related complications	medication , diagnostic, staffing costs	The base case evaluates only direct medical costs, including those incurred by patients' families or by any public sector entity contributing toward the cost of care. In a secondary analysis from the societal perspective, we also included direct nonmedical costs such as transportation expenses for patients' families and indirect costs such as foregone wages of parents caring for sick children
	Is the perspective the one of the budget holder?	yes	yes	yes	yes	yes
Scenarios to be compared	Are the two scenarios well specified?	comparing combined SAAC/SABA (short-acting anticholinergic/short-acting β2-agonist) therapy, a LAAC (long-acting anticholinergic), and a LABA (long-acting β2-agonist), in patients with COPD (Chronic obstructive pulmonary disease). These were: the SAAC ipratropium; the LABA salmeterol; and the LAAC titoropium.	Natalizumab in MS vs: interferon β-1a, interferon β-1b and glatiramer acetate. Natalizumab in CD vs. infliximab, adalimumab,	patients treated with OAD (oral anti-diabetics) vs. patientes treated with OAD + insulin. In both groups 20% are SMBG users. 5% of SMGB non-users switch annually to SMBG.	Existing clinical practive based on national clinical guidelines and estimates of current clinical practice where patients were assumed to be referred to a weekly outpatients clinic, and a revised care pathway that replicated the treatment protocols of phase II of the EXPRESS study for patiente experiencing TIA (transient ischaemic attack) - ENGLAND, SCOTLAND, WALES, NORTHERN IRELAND AND UK AS A WHOLE	universal vaccination with RIX4414 at the recommended ages of 2 and 4 months35 versus no vaccination (the status quo).
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	Some options considered	Some options considered	Some options considered	Some options considered	Some options considered
	Inclusion of off-label drugs use	no	no	no	no	no
	Are the assumptions on the current and future scenarios identified and motivated?	yes	yes	yes	yes	yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	yes	yes	yes	yes	yes
	Inducement hypothesis	no	no	no	no	no
	Open-population versus cohort-based analysis	cohort	cohort	cohort	cohort	Simulated Indian birth cohort
	Subgroups	no	no	yes: according to age(<55, 55-60, 60-65, 65-70, >70), gender, smoker, fasting plasma glucose at diagnosis	no	birth children
Time horizon	Time horizon	1 year	2 years	5 years	1 year	5 years.
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	no	no	no	no	no
Costing	Information source used for resource consumption	Panel, primary data-database	Literature	Literature (ROSSO study)	Literature and trial	Literature
	Do the unit costs reflect the value attached by payers to resources?	Fees	Literature	Literature	Fees	Literature and fees
	Are fixed costs considered in the long-run?	No	No	No	No	No
	Are transaction costs included?	No	No	No	No	No
	Is any rebate applied?	No	No	no	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	yes	yes	yes	yes	yes
	Which sensitivity analyses have been carried out?	multivariate probability sensitivity analysis	deterministic	univariate	1 way SA	one way SA and probabilistic SA
	Are ranges presented on realistic scenarios?	yes	yes	yes	yes	yes
Discounting	Is any discounting applied to costs?	no	no	no	no	yes
	Which is the discounting rate considered?	no	no	no	no	3%

Item	First author	Paradis	Kumar	Neil	Malmstrom	Giorgi-Rossi
	Reference number	116	117	118	119	120
Perspective	Perspective adopted	System wide perspsctive form Canada to France, Germany, Italy and UK	CanadianNHS and US Medicare and BCBS (blue cross, blue shield) insurer systems	US medicare	Swedish health service	public health service perspective.
	Categories of costs included	Prescription drugs, hospitalization, outpatients services,	We calculated the cost of the initial workup, implantation, annual maintenance, and the mean annual cost of complications per patient implanted during this period.	the annual per-patient cost or payment by dialysis modality,	cost of initial TURB	direct medical expenditures included the costs of the vaccine program (vaccine doses, vaccine delivery, and administrative costs) as well as outpatient and inpatient care for treating vaccine-preventable diseases
	Is the perspective the one of the budget holder?	yes	yes	yes	yes	yes
Scenarios to be compared	Are the two scenarios well specified?	Topiramate, an AED (anti epilectic drug), substitution with generic compound; stable vs. variable topiramate dose, monotherapy vs. polytherapy, number of topiramate generic version used during the study.		in-home versus in-center dialysis. Scenarios were developed in which the PD (peritoneal dyalisis) share of total dialysis was varied to estimate the impact on total Medicare dialysis costs.	WLC (white light cystoscopy) alone, HAL (hexaminolevulinate)-guided cystoscopy for TURB (transurethral resection of the bladder)	vaccinating infants with conjugated pneumococcal vaccine (PCV-7) compared to the costs (in and outpatient) of treating the disease
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	Some options considered	Some options considered	All options supposed to be considered	Some options considered	Some options considered
	Inclusion of off-label drugs use	yes	NA	no	NA	no
	Are the assumptions on the current and future scenarios identified and motivated?	yes	yes	yes	yes	yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	yes	yes	yes	yes	yes
	Inducement hypothesis	no	no	no	no	no
	Open-population versus cohort-based analysis	cohort	cohort	cohort	cohort	cohort
	Subgroups	no	no	no	no	newborn (we followed the first cohort of newborns for 10 years and the last one only for 1 year.)
Time horizon	Time horizon	1 year	12 years	5-year	5 year	10 years (2005–2014)
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	no	no	np	no	no
Costing	Information source used for resource consumption	Primary data-database	Primary data-database	Primary data-database	Literature and panel	Literature and RCT
	Do the unit costs reflect the value attached by payers to resources?	Fees	Fees	Fees	Literature	Fees
	Are fixed costs considered in the long-run?	No	No	No	No	No
	Are transaction costs included?	No	No	No	No	No
	Is any rebate applied?	No	No	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	no	no	no	yes	yes
	Which sensitivity analyses have been carried out?	NA	no	no	one way	one way SA
	Are ranges presented on realistic scenarios?	NA	no	no	yes	yes
Discounting	Is any discounting applied to costs?	NA	no	no	no	yes
	Which is the discounting rate considered?	NA	no	no	no	3,5% and 0%

Item	First author	Taylor	Launois	Mueller	Lee	Danese
	Reference number	121	122	123	124	125
Perspective	Perspective adopted	National Health Service (NHS) pharmacy perspective.	French health care system.	German SHI (statutory health insurance)	MCO (managed care organisation) US	perspective of a US managed care plan
	Categories of costs included	treatment costs with varenicline and NRT (nicotine replacement treatments) and bupropion	treatment administration, hospitalizations, outpatient visits, concomitant treatments, imaging and tests, hospital-home transport.	cost of screening and diagnosis (including the costs of false positive results and follow-up), medication with alendronate and treatment of fractures, as well as general healthcare costs resulting from added years of life (i.e. costs unrelated to osteoporosis incurred due to life extention).	TOTAL COSTS calculated for: incremental per member per month (PMPM) and per treated member per month (PTMPM) costs were considered	Total costs including the costs of treatment, adverse events (AEs), and administration.
	Is the perspective the one of the budget holder?	yes	yes	yes	yes	yes
Scenarios to be compared	Are the two scenarios well specified?	use of varenicline compared to the world without varenicline	MTX(methotrexate) + RTX(rituximab) 1000 MTX + ETA(etanercept)25 ETA25 alone MTX + ADA (adalimumab)40 ADA40 alone MTX + INF(infliximab)3/8	1 QUS (quantitative ultrasound) 2) No screening, 3) No QUS but DXA (dual x-ray absorptiometry) alone + alendronate	wireless pH capsule vs. catheter -based system to detect pH in the esophageal tract	We compared 2 treatment regiments: (1) erlotinib + gemcitabine and (2) gemcitabine monotherapy
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	Some options considered	Some options considered	Some option considered	All options supposed to be considered	Some option considered
	Inclusion of off-label drugs use	no	no	no	no	no
	Are the assumptions on the current and future scenarios identified and motivated?	yes	yes	yes	yes	yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	yes	yes	yes	yes	hypothetical managed care plan with 500,000 members
	Inducement hypothesis	no	no	no	no	no
	Open-population versus cohort-based analysis	open (population of current, former, and new smokers)	cohort (we assumed that the target population was constant over time)	cohort	cohort	cohort
	Subgroups	no	no	yes women aged 50, 60, 70 and 80	no	no
Time horizon	Time horizon	5 years	4 years	4 years	1 year	1 year
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	no	no	no	no	no
Costing	Information source used for resource consumption	Literature (national health surveys)	Literature	Literature	Panel and literature	SPC
	Do the unit costs reflect the value attached by payers to resources?	Fees	Fees	Fees	Fees and literature	Fees
	Are fixed costs considered in the long-run?	No	No	No	No	No
	Are transaction costs included?	No	No	No	yes AWP	yes WAC
	Is any rebate applied?	No	No	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	yes	yes	yes	yes	yes
	Which sensitivity analyses have been carried out?	one way and probabilistic SA	deterministic SA	one way SA and probabilistic SA	One and nulti way SA	One-way sensitivity analyses
	Are ranges presented on realistic scenarios?	yes	yes	yes	yes	yes
Discounting	Is any discounting applied to costs?	no	no	yes	no	no
	Which is the discounting rate considered?	no	no	3%	no	no

Item	First author	Chuck	Brosa	Duerden	Heeg
	Reference number	126	127	128	129
Perspective	Perspective adopted	Ministry of Health perspective	Spanish NHS	UK NHS	portuguese NHS
	Categories of costs included	Cost of HBOT Annual cost per patientb: Healed, Minor LEA-low extremity amputation (including operation), Unhealed, Major LEA (including operation)	direct mediacl costs	total cost of healthcare for heart failure within the UK.	direct medical cost (medicatione and location costs)
	Is the perspective the one of the budget holder?	yes	yes	yes	yes
Scenarios to be compared	Are the two scenarios well specified?	comparing adjunctive HBOT (Hyperbaric oxygen therapy) + standard care vs. standard care alone.	Currente clinical scenarios without SNM (sacral neuromodulation) vs. a scenario where SNM is offered as first-line treatment in patients with FI (fecal incontinence) with IAS (inctact anal sphinctere) not responding to conservative treatments and as second-line treatment in patients wid SDAS (structurally deficient anal spinctere) not responding to sphincteroplasty.	adding eplerenone to standard care for heart failure resulting from myocardial infarction (MI) vs. standard care alone.	Scenario 1) conventional depot; scenario 2) LAR (long acting risperidone); scenario 3) oral risperidone.
	Does the reference scenario include all the alternatives available on the market for the treatment of the disease?	Some option considered	Some option considered	Some option considered	All options supposed to be considered
	Inclusion of off-label drugs use	no	no	no	no
	Are the assumptions on the current and future scenarios identified and motivated?	yes	yes	yes	yes
Population & Subgroups	Does the analysis include all the patients who are expected to be eligible in the perspective of payers?	no	yes	yes	yes
	Inducement hypothesis	no	no	no	yes
	Open-population versus cohort-based analysis	cohort	cohort	cohort	NA
	Subgroups	65-year-old with DFU	no	no	individual patients
Time horizon	Time horizon	12 years	5 years	3 years	5 year
	Possibe extension of the time horizon, to better reflect what happens when a steady state is reached and no further changes are assumed	no	no	no	no
Costing	Information source used for resource consumption	Primary data-database (prevalence)	Panel	NA	Panel
	Do the unit costs reflect the value attached by payers to resources?	Fees	Unit cost (database) and literature	NA	Literature and fees
	Are fixed costs considered in the long-run?	yes	No	No	No
	Are transaction costs included?	No	No	No	No
	Is any rebate applied?	No	No	No	No
Sensitivity analysis	Is a sensitivity analysis carried out?	yes	yes	yes	yes
	Which sensitivity analyses have been carried out?	one way SA	probabilistic SA	deterministic SA	univariate SA
	Are ranges presented on realistic scenarios?	yes	yes	yes	yes
Discounting	Is any discounting applied to costs?	no	yes	no	no
	Which is the discounting rate considered?	no	3%	no	no

Acronyms

ADTC	Area Drugs and Therapeutic Committee
AIFA	Italian Medicine Agency
ASMR	Amélioration du Service Médical Rendu
BIA	Budget Impact Analysis
CBA	Cost Benefit Analysis
CEA	Cost Effectiveness Analysis
CEP	Cost Effectiveness Plane
CHMP	Committee for Medicinal Products for Human Use
CTS	Scientific Technical Committee
CUA	Cost Utility Analysis
DAHTA	German Agency for Health Technology Assessment
DGFPS	Directorate of Pharmaceutical and Healthcare Products
DIMDI	German Institute for Medical Documentation and Information
DSA	Deterministic Sensitivity Analysi
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EQ-5D	Euro Quality of Life 5 Dimensions
G-BA	Federqal Joint Committee
HAS	Haute Autorité de Santé
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
HUI-3	Health Utilities Index Mark 3
ICER	Incremental Cost Effectiveness Ratio
IQWIG	Institute for Quality and Efficiency in Health Care

ISCIII	Institudo de Salud Carlos III
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LEA	livelli essenziali di assistenza
MoH	Ministry of Health
MTA	Multiple Technology Appraisal
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMB	Net Monetary Benefit
PPRS	Pharmaceutical Price Regulation Scheme
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Years saved
QoL	Quality of Life
RCT	Randomised Controlled Trial
SBU	Swedish Council on Health Technology Assessment
SF-6D	Short-form 6 Dimensions
SG	Standard Gamble
SHI	Statutory Health Insurance
SMC	Scottish Medicines Consorium
SMR	Service Médical Rendu
STA	Single Technology Appraisal
TC	Transparency Commission
TLV	Dental and Pharmaceutical Benefit Board
TTO	Time Trade-Off
W.A.I.T.	Patient Waititng to Access Innovative Therapies Indicator
WTP	Willingness to Pay

Aknowledgements

Probabilmente questa è la parte della mia tesi di dottorato più difficile da comporre. Non ci sono dati da commentare o discutere ma semplicemente mettere nero su bianco ciò che sento dentro di me in questo momento.

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