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ECONOMIC EVALUATION IN HEALTH RESEARCH: COHORT SIMULATION AND APPLICATIONS

Nuria Pérez Álvarez

Thesis Directors:

Guadalupe Gómez Melis, PhD

Departament d'Estadística i Investigació Operativa

Universitat Politècnica de Catalunya, Barcelona, Spain

Roger Paredes i Deirós, MD, PhD

Fundació de Lluita contra la Sida, Badalona, Spain

Institut de Recerca de la Sida IrsiCaixa, Badalona, Spain

Universitat Autònoma de Barcelona, Barcelona, Spain

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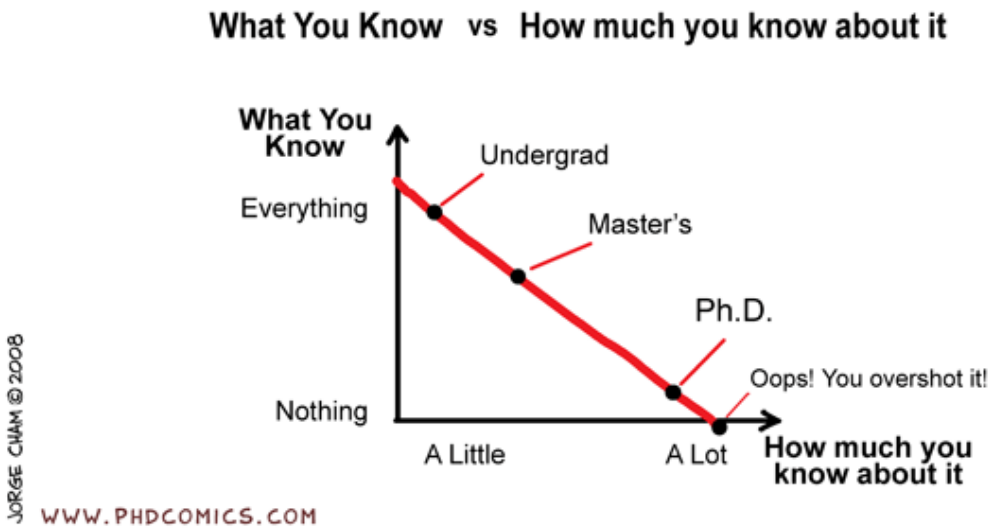
What You Know vs How much you know about it
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ABBREVIATIONS CODE

AEs	Adverse events
AIDS	Acquired immune deficiency syndrome
ANCOVA	Analyses of covariance
ANOVA	Analyses of variance
ART	Antiretroviral
AZT	Zidovudine
BD	Bone densitometry
BF	Bone fracture
BIA	Budget impact analysis
BMD	Bone mineral density
BMI	Body mass index
cART	Combined antiretroviral therapy
CCR5	C-C chemokine receptor type 5
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEACs	Cost-effectiveness acceptability curves
CEP	Cost-effectiveness plane
CI	Confidence interval
CXCR4	C-X-C chemokine receptor type 4
D	Dead health state
DALY	Disabitlity adjusted life year
DALYs	Disability adjusted life years
DFLE	Disability-free life expectancy
EMEA	European Medicines Agency
EUR	Euros
FDA	U.S. Food and Drug Administration
HAART	Highly active antiretroviral therapy
HALE	Health adjusted life expectancy
HE	Health expectancy
HIV	Human immunodeficiency virus infection
HPV	Human papillomavirus
HRQoL	Health-related quality-of-life
ICER	Incremental cost-effectiveness ratio
INB	Incremental net benefit
INHB	Incremental net health benefit
INMB	Incremental net monetary benefit
IQR	Interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LE	Life expectancy
MANCOVA	Multivariate analyses of covariance
MCS	Mental component summary
MD	Medical doctor

MOS	Medical outcomes study
MRV	Maraviroc
NE	North-east
NICE	National Institute for Health and Clinical Excellence
NW	North-west
PCS	Physical component summary
PNH	Paroxysmal nocturnal hemoglobinuria
PPM	Per patient month
PPY	Per patient year
PS	Population sequencing
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QoL	Quality of life
R&D	Research and development
Rc	Ceiling ratio
RCT	Randomized clinical trial
S	Sick health state
SD	Standard deviation
SE	South-east
SERM	Selective estrogen receptor modulator
SF	Short form
SOC	Standard of care
SW	South-west
Trofile-ES	Enhanced Sensitivity Trofile
VL	Viral load
W	Well health state
WHO	World Health Organization
YLDs	Years of life lived with disability
YLLs	Years of life lost

ABSTRACT

Currently, resources that may be spent in health care are limited so it is necessary to rationalize their consumption and prioritise their allocation to the options with higher health outcome and economic sustainability. It is for that reason that economic analyses are increasingly included in medicine research as an instrument for evaluating different therapeutic strategies. In this thesis, both cost and health outcome are separately and jointly evaluated to compare different therapeutic strategies to treat diseases in different and specific health areas. The challenge was adapting and implementing the methods to reflect the assessed health issue.

The analyses require data, and the main sources to obtain them are clinical studies (prospective or retrospective), or simulation models. The use of simulations avoids to experiment directly to the system of interest, these methods imply a smaller time consumption and cost, and any danger can be caused by the experimentation performance. However, the simulated data always is going to be an approximation of real data.

Real data of a clinical trial was used in the assessment of the adherence to antiretroviral treatment promotion program in HIV infected patients. A decision tree was used to study the cost per health gain, measured by means of clinical and health related quality of life outcomes.

The simulation of a Spanish cohort of postmenopausal women and their possible osteoporotic fractures was done to assess the performance of two treatments for the prevention of vertebral and non-vertebral fractures in terms of cost-effectiveness. Simulation by means of a Markov model required that the disease evolution and the related events were simplified using a finite number of health states and the probabilities of moving from one state to another as the time go on.

Markov models were adapted to reflect that the risk of suffering an event can change over time. This analytical model was applied to elucidate whether co-receptors testing is cost-effective to determine patient's suitability to benefit from the use of an antiretroviral treatment that includes maraviroc. All HIV strains require binding to CD4 plus at least one of the 2 co-receptors CCR5 or CXCR4 to enter human cells. Some HIV can use both co-receptors, and some individuals have a mixture of strains. Only patients with exclusively CCR5-tropic HIV are considered eligible to use the CCR5 antagonist maraviroc.

A budget impact analyses to assess the economic effects of introducing eculizumab for treating the paroxysmal nocturnal hemoglobinuria was performed. Direct and indirect costs of this disease treatment were estimated and reported from the perspective of the health care system and from the societal perspective.

Most of the published clinical studies are focused on measuring health in terms of efficacy and/or safety. But, sometimes the health and well-being quantification is not a direct measurement. Here, the calculation of the burden of disease for osteoporotic women who may suffer from fractures done at an individual level was presented in terms of disability adjusted life years (DALYs). Few studies of burden of diseases are available, and even less for Spanish population and performed using individual characteristics.

The pharmacoeconomic studies can be useful in the health resources rationalization, and both budget impact analyses and new health measures are complementary tools. The work performed in this thesis constitutes a good example of methods application and adaptation to answer real clinical questions.

Unesco codes that describe the work done in the thesis:

120806 Markov Processes
120900 Statistics
120903 Data analysis
120904 Decision making procress (see 1207.06)
120912 Statistical association methods
120914 Statistical prediction methods

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Summary Chapter 1. INTRODUCTION

Resources that may be spent in health care are limited so it is necessary to rationalize their consumption and prioritise their allocation to the options with higher health outcome and economic sustainability. Consequently, economic analyses are increasingly included in medicine research as an instrument for evaluating different therapeutic strategies. In this first chapter we explain the data required to complete a pharmacoeconomic study and the techniques available to perform it.

Analyses require data, and the main sources to obtain them are clinical studies (prospective or retrospective), or simulation models. The use of simulations avoids to experiment directly to the system of interest, these methods imply a smaller time consumption and cost, and avoid dangers that could be caused by the experimentation performance. However, simulated data is only an approximation of real data.

The available tools to jointly evaluate the cost and the health outcome are: Cost-minimization, cost-effectiveness, cost-utility and cost-benefit, the incremental cost-effectiveness ratio (ICER), the cost-effectiveness plane and incremental net benefit (INB). For all of their results exist the need of discounting to the present when future values are used. A state of the art of the different approaches used in the health literature is presented.

The aim of this thesis is to assess both cost and health outcome, separately and jointly, to compare different therapeutic strategies to treat diseases in different and specific health areas.

1. INTRODUCTION

This first chapter contains the description of the framework in which the thesis is developed, a summary of the state of the art— containing both the data required and its available sources, and methods of analysis— and the thesis aims and structure.

1.1. Background and motivation

This doctoral thesis attempts to define several tools to assist in the rationalization of expenditure in health care, taking into consideration costs and health benefits. During the learning process, we used various methodologies to answer real questions in a number of health-related areas; these constitute the practical aspect of this work.

The problem of expenditure must be considered in a context that comprises public health management of new medical technologies and emerging drugs, increasing life expectancy of the population, economic and financial circumstances, and existing techniques for joint evaluation of cost and health outcome*.

The main goal of public health is to identify and implement strategies to enhance the well-being of the population by promoting health, preventing disease, and ensuring recovery of good physical and mental status. These goals are achieved by providing health education and reporting the benefits of a healthy lifestyle through the media, schools, and primary

* Health Outcomes are a change in the health status of an individual, group or population which is attributable to a planned intervention or series of interventions, regardless of whether such an intervention was intended to change health status. There are different ways of measuring the outcome such as, death, degree of disability, number of hospitalizations, health related quality of life or any health marker. The treatment and analysis of the health outcome should be chosen according to the type (continuous, discrete…) of the outcome.
[Reference: http://definitionofwellness.com/wellness-dictionary/health-outcomes/]

care centres. Prevention of disease includes primary health interventions such as vaccination campaigns and early detection programmes. The health services—both primary care centres and hospitals—are responsible for a recovery of health in cases where there has been a loss.

Technological progress implies that existing mechanisms of providing health care are continually changing. Moore's law[1] states that the capacity of a computer increases 100% approximately every 2 years. This ongoing improvement generates breakthroughs in science, in general, and in medicine, in particular. These advances include the following:

i) Information gathering techniques, where electronic databases are used to record a patient's medical history and where medical information is shared or searched for using the Internet

ii) Online databases and more precise instruments of measure that improve research procedures

iii) Development of better treatments

iv) More powerful communications tools, e.g., health campaigns launched through social media[2].

Improvements in technology have made health care much more efficient than in the past. Many treatments are cheaper and more readily available to the general population, and previously "untreatable" diseases now have a cure. Sometimes these advances complicate health care. For instance, the possibility of detecting the presence of cancer cells imply that the medical community has to make every effort to treat it. A relevant example of the improvement in health technology is the change in the costs associated with the DNA sequencing of a complete human genome, which decreased dramatically from September 2001 ($95,263,072) to January 2008 ($3,063,820) and again in April 2013 ($5,826), thanks to second-generation sequencing platforms[3].

Information on the human genome makes personalized medicine feasible: the common medical prescription based on summary responses from a broad population is becoming a lifelong health maintenance strategy adapted to a person's unique genetic constitution. It will, therefore, be possible to customize disease-prevention strategies and prescribe treatment that is both more effective and free of side effects. Making personalized medicine available for the general population can reduce the duration, cost, and failure rate of therapeutic strategies and eliminate the inefficiencies arising from empirical treatment that inflate health care costs and undermine patient care.

Nanomedicine is a finding that can also be applied in daily clinical practice. Its goal is to identify the precise targets—cells and receptors—associated with specific clinical conditions and ensure delivery of treatment to achieve the required responses while minimizing side effects and dose, leading to a reduction in health care cost. However, further research is needed on design, nanoscale vehicles for site-specific drug delivery, medical imaging after parenteral administration, and associated side effects[4].

Although some improvements in health care are reflected in cheaper treatment, the rising cost of health care is a reality. Increasing life expectancy in developed countries, active expansion of medical technology, and the cost of using effective clinical services mean that the demand for health resources exceeds supply.

The increase in life expectancy often implies an increase in the prevalence of chronic diseases. The World Health Organization [WHO] defines chronic diseases as "diseases of long duration and generally slow progression"[5]. This type of disease has traditionally included cardiovascular disease, diabetes and asthma or chronic obstructive pulmonary disease. As survival rates and durations have improved many varieties of cancer, HIV/AIDS, mental disorders such as depression,

schizophrenia and dementia, and disabilities such as sight impairment and arthroses are also included[6].

Most morbidity, mortality and health expenses in Europe are due to chronic diseases. They cause 86% of deaths and an expenditure of the 50-80% of the health budget across the 53 member states in the WHO European region[7]. Projections of future mortality and disease show that chronic diseases will continue to be the biggest contributor to mortality and disability in high-income countries, and chronic disease will increase. The Disability Adjusted Life Years (DALYs)* associated with chronic or noncommunicable conditions** in high-income countries is projected to rise from 86% in 2005 to 89% in 2030[6].

Availability of resources is a crucial area in healthcare. The European Union is facing an economic and financial crisis that started between 2008 and 2009 after a period of general growth and stability. In almost all European countries, this crisis has been characterized by a strong increase in government deficit*** and public debt****. Hospitals and health

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* One measure of the overall burden of disease, developed by WHO, is the disability-adjusted life year (DALY). It is designed to quantify the impact on a population of premature death and disability by combining them into a single measure. The DALY relies on the assumption that the most appropriate measure of the effects of chronic illness is time either spent disabled by disease or lost due to premature death. One DALY equals one year of healthy life lost [WHO (2005). Preventing chronic diseases: A vital investment. Geneva, World Health Organization Available from: http://www.who.int/chp/chronic_disease_report/full_report.pdf, accessed 13 May 2014].

** A situation in which outflow of money exceeds inflow. That is, a deficit occurs when a government, company, or individual spends more than he/she/it receives in a given period of time, usually a year. One's deficit adds to one's debt, and, therefore, many analysts believe that deficits are unsustainable over the long-term. [REFERENCE: http://financial-dictionary.thefreedictionary.com/]

*** A non-communicable disease is a medical condition or disease, which by definition is non-infectious and non-transmissible among people. Often, the terms "noncommunicable disease" and "chronic disease" are treated as interchangeable, but given recent advances in treating communicable diseases this use is no longer precise enough. For example, HIV/AIDS treated with modern medicines has become a disease of long duration and generally slow progression (chronic and communicable disease). WHO acknowledge this issue, but nevertheless refer to sources that use noncommunicable disease as a proxy for chronic disease if no alternative high-quality data are available.

**** The total of all bonds and other debt owed by a government. Most of the time, the national debt comes from bonds and other debt securities, but some countries in the developing world borrow directly from international institutions (such as the World Bank). The national debt may be internal, that is, owed to bondholders and banks within the country, or external, that is, owed to foreign governments, institutions, and/or individuals. [REFERENCE: http://financial-dictionary.thefreedictionary.com/]

care services are traditionally the primary source of social expenditure and have been at the core of many measures aimed at reducing costs and increasing efficiency. Some European countries such as Greece, Ireland, Italy, Portugal, and Spain, have reduced healthcare spending and introduced low ceilings on increases in the healthcare budget. Other countries have reduced the operational costs of health services and the prices paid to providers for goods, services, and tangible assets*. Some of these measures directly affect users in terms of payment for treatment, visits, hospitalization, and access to health technologies and drugs**, [8, 9].

Consequently, rationalization of available resources and selection of the most beneficial and sustainable therapeutic strategies have become a priority[10]. It is necessary to evaluate the costs and benefits of available therapeutic strategies when attempting to make major improvements in health care. Indeed, decisions about public health and health care delivery increasingly rely on studies that assess the cost-effectiveness of medical services[11].

It is clear that a standardized set of methodological tools should be developed. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) provides a series of healthcare-specific economic concepts and facilitates a forum for discussion and guidelines for the development of research on healthcare costs and outcomes[12]. Pharmacoeconomics is the scientific discipline that evaluates the clinical, economic, and humanistic aspects of health care interventions in order to provide health care decision makers, providers, and patients with valuable information for allocating resources and obtaining optimal

* Austria, Belgium, the Czech Republic, Denmark, Estonia, Greece, Ireland, the Netherlands, Portugal, Spain, Slovenia, and the United Kingdom.

** The Czech Republic, Denmark, Estonia, France, Greece, Ireland, Italy, the Netherlands, Portugal, Switzerland –and also the private health insurance in the United States -raised user charges.

outcomes. The health care interventions include pharmaceutical products, diagnostic tools, services, programs, and activities to promote, generate, or re-establish health. Pharmacoeconomics incorporates and combines economics, clinical evaluations, risk analysis, health related quality of life, and epidemiology. It uses statistical and computer-based techniques to analyze drugs, medical devices, biotechnology, surgery, and disease-prevention services. In this context, the outcome and impact of different strategies can be examined by taking into account cost and health gain in order to address the following questions:

- Which health care interventions should be included in the clinical care guidelines for a particular disease?
- Which is the best health care intervention for a particular subset of patients?
- Which is the cost per unit of outcome for a concrete health care intervention?
- Will patient health related quality of life be improved by applying a particular health care intervention?

The general aim of this thesis is to assess several methods to answer real clinical questions related to health resources rationalization. An overview of techniques and illustrations on the evaluation of cost and health outcomes to compare different strategies are presented and discussed.

The Spanish health care system

The data discussed here apply to the Spanish population, its health care system, and its expenditure on health care.

In Spain, life expectancy at birth increased by more than two years from 1995 to 2005 and now stands at 80.23 years (76.96 for men and 83.48 for women)[13]. Application of various techniques to project life

expectancy in Spain for 2050 reveal values of 81 to 85.38 years for men and 87 to 91.97 years for women[13–15]. It is important to note that all the estimations in the studies cited indicated an increase in life expectancy.

The increase in survival is linked to a larger number of citizens affected by a chronic disease. At least one over six Spanish adults (15 years old and older) suffers one of them. The lumbar pain (18.6%), arterial hypertension (18.5%), arthroses, arthritis and rheumatism (18.3%), high cholesterol (16.4%) and cervical pain (15.9%) are the most common[16]. A study published on 2002 reported that the Spanish population older than 65 years old suffers a mean of 1.8 chronic diseases (Standard Deviation=1.2, Minimum=0, Maximum=5). Being the hypertension the most prevalent (40.1%), followed by osteoarticular (24.0%) and cardiovascular diseases (18.4%) and sight impairment (16.6%)[17].

In order to gain a perspective of the impact of disease on the cost of the Spanish Health Care System, we analyzed the following 5 groups of diseases: HIV/AIDS, cancer, respiratory diseases, cardiovascular diseases, and neurological diseases. For each group, we used various sources to obtain information on the number of cases and the corresponding costs. The information provided below must be interpreted with caution, as the sources are not homogeneous.

Neurological diseases generate the highest costs for the health care system. During 2004, between 6 and 7.5 million people had a neurological disease; the cost of treatment to the health system was over €10.8 billion[*,18].

This group was followed by cardiovascular diseases, which generated an expenditure of more than €9 billion per year[19]. Cardiovascular diseases have a high impact on mortality and cause 31.7% of deaths[20].

[*] Billion is equivalent to a one thousand million, i.e., 10^9.

As for respiratory diseases, asthma affects 2.5 million people and costs €1.48 billion, and chronic obstructive pulmonary disease affects 4.8 million people and costs €3 billion[21-23].

Every year 162,000 of new cases of cancer—excluding skin cancer and melanoma—are diagnosed in Spain. In 2003, these generated costs of about €1.75 billion (colorectal, breast, prostate, and uterine cancer)[24, 25].

Treatment of HIV/AIDS affects fewer people and costs less than the other disease groups. In 2005, the Spanish health care system estimated the cost of antiretroviral drugs to be €0.423 billion (i.e., 423 million)[26].

1.2. Data sources

Several considerations should be taken into account in an economic evaluation. Data (information on cost and health gain per treatment strategy) are collected from real sources or generated through simulation. The type of the health-economic evaluation performed and the input data required depend on the definitions selected for cost and health outcome.

The information used in the economic evaluation is detailed in subsection 1.2.1. A description of the available methods for obtaining data, namely, by real data collection or analytical models and simulation, is given in subsections 1.2.2 and 1.2.3, respectively. The Section ends with a discussion of the features of the various data sources.

1.2.1. Data requirements

For a model to enable rationalization of resources and thus produce the largest possible gain in health per monetary unit, a series of points must be taken into account. These include the population of interest, the characteristics of the study cohort, the course of the disease under

study, available treatments or health care interventions, treatment efficacy*, adverse events, and cost.

The disease of interest and the cohort characteristics depend on the target population, which can be a subset of the patients affected by the disease.

It is necessary to gain knowledge of disease course, incidence, and guidelines for diagnosis and treatment. The intervention to treat the health problem studied can be a combination of tests, care services, and drugs, and it is of interest to analyze both their efficacy and their side effects. Efficacy should be measured objectively, i.e., it can be expressed in terms of enhanced health related quality of life and self-sufficiency, number of clinical events avoided, number of patients without treatment failure, or even health gain expressed as a monetary value. Apart from disease course and therapeutic options, the model should include the associated costs of each health care intervention, which are expressed in monetary terms. The items and services that are included in the cost calculation should be stated in the study plan (e.g., drugs, health care, and patient's travelling expenses).

The effectiveness (or efficacy) measure chosen and the list of items included in the costs of therapy define the type of the pharmacoeconomic study (described in subsection 1.3.1). Once the therapeutic strategies to be compared have been decided and the terms of the comparison are made, the data collection or generation process is designed.

* The terms Efficacy and Effectiveness are going to be used with the following meaning: **Efficacy** entails how a drug performs in an ideal or controlled circumstance, as in the context of a clinical trial. However, **effectiveness** describes a drug's success in real-world circumstances where the patient population and other variables cannot be controlled, i.e. under usual circumstances of health care practice. [REFERENCE: http://www.contextmattersinc.com/use-of-efficacy-and-effectiveness-often-misleading-and-may-skew-reimbursement-decisions-presented-at-ispor-europe-2012/]

1.2.2. Data collection

The data needed to build a pharmacoeconomic model can come from prospective randomized clinical trials (RCTs) and observational studies, retrospective databases or clinical files, expert panels (expert opinion), patient surveys, published literature, treatment guidelines, and research institute databases, such as those of the World Health Organization[27], the Statistical Office of the European Communities[15], the Instituto Nacional de Estadística[28], or the Institut d'Estadística de Catalunya[29].

The availability, advantages, and disadvantages of the different types of databases are discussed below.

1.2.2.1. Prospective RCTs and observational studies

In prospective RCTs, patients are randomly allocated to the intervention of interest and followed up for a defined period of time. The main goal is to evaluate and compare the health outcome, usually efficacy and/or safety, of the intervention. Within this framework, monetary cost can be easily registered to perform a pharmacoeconomic evaluation[30, 31], but the utility of the data generated is limited owing to homogeneity in patient characteristics, fixed screening and follow-up schedules, and finalization of data collection when patients discontinue the study treatments. The design of RCTs makes it difficult to evaluate the therapeutic strategies for a large variety of patients, since it reduces the chance of unexpected outpatient visits and the need for symptom-driven diagnostic procedures and implies a lack of information when the patient discontinues the study. These restrictions prevent an extrapolation of health cost results for patients in daily clinical practice. This limitation is especially important in the field of prevention and chronic maintenance therapy.

Observational studies assess patients with similar characteristics who differ with respect to the specific factors under study; the health

interventions are not controlled. During the follow-up, changes in the available therapeutic strategies and guidelines for treatment of a disease can vary and invalidate future conclusions, thus leaving them outdated. Observational studies have fewer limitations than the pharmacoeconomic studies associated with clinical trials; however, both are time-consuming and involve cost expenditure. Decision making in healthcare usually requires rapid access to information. The data from previous RCTs and observational studies can be used, but they have the same drawbacks as described above, except for the time and money consumed to obtain results.

1.2.2.2. Retrospective databases and clinical files

Retrospective data analysis measures effectiveness and can provide "real-world" data. Cost-effectiveness analyses based on retrospective databases or clinical files can provide real-time, relevant, and comprehensive decision-making tools. Retrospective analyses are quick and relatively inexpensive to perform. They reflect specific populations that cannot be easily studied using RCTs. Retrospective databases tend to cover more realistic time frames, since they are not constrained by the limitations of a set trial period. Existing databases can provide a set of variables, and analyses of these data can reveal real-world prescribing patterns. The disadvantages of retrospective database analyses used for economic evaluations include the fact that some of the study variables are not directly precisely recorded[32], which reduces the quality of the information.

1.2.2.3. Expert panels

The increase in the number of pharmacoeconomic studies in the last decade has promoted the development of guidelines for the conduct of economic evaluations in many countries. It is noteworthy that different

study designs can impact results. The use of expert judgement in decision analytic modelling is one area where design issues may influence the findings of a study[33]. Several researchers have suggested that expert judgement can be used successfully in pharmacoeconomic studies. Most acknowledge that expert opinion should be used as a last resort in pharmacoeconomic studies. Barr and Schumacher support its use when ideal data are not available and when, together with information from meta-analyses and other trial data, expert opinion can serve as a reasonable approximation[34]. Nuijten et al. also acknowledge the weaknesses inherent in the use of expert opinion, although they report that its application is not forbidden in modelling studies[35]. Evans suggests that the use of expert opinion need not be avoided as long as potential weaknesses are addressed and the techniques are applied appropriately[36]. Similarly, Halpern et al. recognise that expert opinion plays an important role in modelling studies but that it is subject to many errors and biases[37].

Expert opinions can be obtained by means of Delphi panels, modified Delphi panels, and round tables. The Delphi technique is a well-known method for consensus building based on a series of questionnaires delivered using multiple iterations to collect data from a panel of experts[38].

The areas of concern to be considered when obtaining expert opinion include the provision of baseline information or seed algorithms to panellists, the high attrition rate of panels, the criteria for selecting experts, and the definition of consensus[36]. Despite the difficulties and limitations involved in this method, information gathered through an expert panel can cover the lack of appropriate information necessary to perform pharmacoeconomic studies.

1.2.2.4. Patient surveys

Surveys have been used to understand the value that patients place on health care interventions. Understanding patient preferences can help to improve adherence and better predict the corresponding health outcomes. It is widely accepted that adherence is maximised when a treatment or intervention matches the patient's preferences (World Health Organization [WHO][39], National Institute for Health and Clinical Excellence [NICE][40]).

Patient surveys have been used to demonstrate patient tradeoffs between treatment features and outcomes, and to quantify patient values. The approaches used are self-reported adherence and measures such as willingness to pay or maximum acceptable risk. The term "willingness to pay" is the maximum amount a person would be willing to pay, sacrifice, or exchange for a good. The parameter "maximum acceptable risk" was proposed by Johnson[41]. The objective of this approach is to estimate the maximum risk patients are willing to accept in order to achieve the therapeutic benefits of drug therapy. This maximum acceptable risk can then be compared against the actual or expected risk associated with a treatment to determine whether a treatment is acceptable to patients.

1.2.2.5. Published literature

Published literature, treatment guidelines, and research institute databases can provide insight into disease outcome, patient characteristics, recommended treatment, disease prevalence, and treatment efficacy or effectiveness.

1.2.3. Data generation

Analytical models or procedures based on simulations provide data without conducting real experimentation using patients. These methods

do not imply costs or danger in their performance, and the results are obtained relatively quickly.

1.2.3.1. Analytical models

Analytical models are symbolic and yield general solutions to a problem. The model is constructed following specific rules written in terms of mathematical expressions which reflect as closely as possible the real-world problem. A general solution is obtained, and specific cases might be assessed by forcing the variables included in the model to take different values. Both the complication of constructing an analytical model for dealing with a complex problem and the oversimplification of the problem are limitations of this approach. The steps required to define an analytical model departing from a real system and applying the information obtained to solve it are presented in Figure 1.1.

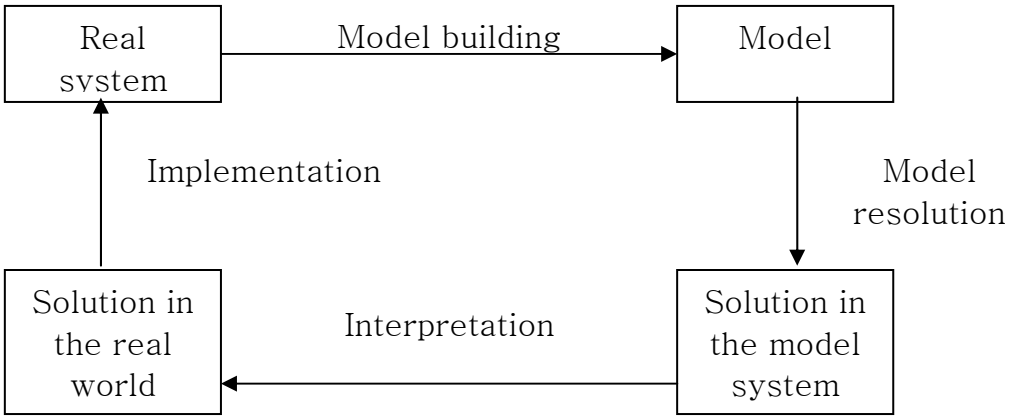


Figure 1.1. The components of an analytical model and the steps required to represent and assess a real system by means of modelling are displayed[42].

The steps required to define an analytical model departing from a real system and applying the information obtained to solve it are presented. The use of these models is advisable when the study is relatively simple.

1.2.3.2. Simulation procedures

Shannon, in 1978, defines simulation as the process of designing a model of a real system and conducting experiments with this model for the purpose of understanding the behaviour of the system and/or evaluating various strategies for the operation of the system[43]. Another way of defining modelling and simulation is by using the concept of "learning by doing" or "experimental learning" introduced by the political scientist Herbert A. Simon (1916-2001). The process of simulation allows the imitation of the operation of a real-world process or system over time. The execution of an operation in a designed model generates a history, which makes it possible to draw inferences concerning the operating features of the real system that is represented[44]. Simulation-based models yield specific solutions and make it possible to test a combination of variables and scenarios that would be impossible to study in real life.

Thus, the simulation provides a means of learning about a system which cannot be observed or experimented with directly.

Simulation-based models require the use of knowledge and data about the real system, and the accuracy of the results depends enormously on the quality of the input parameters and the simplifications of the real system when constructing the model. Different steps can be identified when constructing a simulation model, as follows:

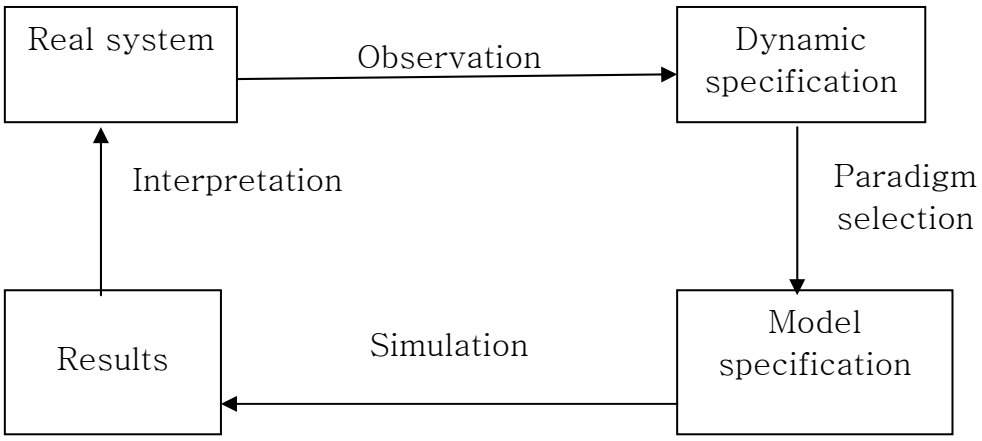


Figure 1.2. The components of a simulation model and the steps required to represent and assess a real system by means of simulation are displayed.

Simulation models can be based on continuous or discrete time[45]. The variables or events that constitute the model can be continuous, discrete, or both. Prescriptive models are built to characterize and optimize the choice of a treatment, whereas descriptive models study the behavior of the disease. Simulation models can be deterministic or probabilistic/stochastic. The deterministic simulation model assumes point values and do not account for variability, whereas the probabilistic model accounts for uncertainty by using random variables to assign the values to the system status and its entries[46]. Autonomous models are those that the system users are initially included in the model and they evolve through the time function i.e., the patients assessed are already

inside the model –also called "closed" models. The non-autonomous models have a paradigm to represent the flux of new "patients" entering in the system –also referred to them as dynamic or "open" models.

The most appropriate models for our cost and health outcomes are discrete time models, since the recurrence of the disease events and medical visits are recorded discretely in a finite number of time points. Decision trees, Markov models, and discrete-event simulation use discrete-time models, which are the most common in the literature.
Further details about discrete-event simulation are given in Annex I.

1.2.4. Some remarks on data sources

The accuracy of model-based pharmacoeconomic estimates depends on the quality of input data, validity of surrogate endpoints, and appropriateness of modelling assumptions, including model structure, length of the simulated time, and ability of the model to differentiate between clinically and economically meaningful outcomes.

It would be desirable to find real data collected for the population and treatments under study to provide the required information about cost and health gain already registered. A prospective study designed with this purpose would require time and money investment. The simulation requires less time and money to be performed but the results obtained have a limited amount of information and are based on assumptions.

Depending on the available means, information can be collected from a single source or multiple sources and be combined in order to answer the question of interest. For the objectives, it is desirable to have the minimum possible data sources that fulfil our cost and efficacy requirements in a cohort with characteristics similar to those of our

target population. The conclusions obtained will be as accurate as the data we use. If the available data cannot answer our question, the gaps can be filled in using assumptions; in this case, the conclusions obtained will be valid under the assumptions we made. Bodrogi et al. stated the following: "These economic evaluation methods are not mutually exclusive: in practice, economic analyses often combine data collection alongside clinical trials or observational studies with modelling. The need for pharmacoeconomic evidence has fundamentally changed the strategic imperatives of research and development (R&D). Therefore, professionals in pharmaceutical R&D have to be familiar with the principles of pharmacoeconomics, including the selection of health policy–relevant comparators, analytical techniques, measurement of health gain by quality adjusted life-years and strategic pricing of pharmaceuticals"[47].

1.3. Techniques for economic evaluation

This section contains the description of several useful tools to jointly evaluate the cost and the health outcome. In the first subsection -1.3.1- four techniques selected depending on the cost and health outcome measurements definition are described, these definitions are the bases for the analysis developed in this thesis. Further calculations and graphical displays combining cost and health outcomes can help to assess the performance of the therapeutic strategies such as the incremental cost-effectiveness ratio (ICER), the cost-effectiveness plane and incremental net benefit (INB) (See subsection 1.3.2).

Finally, in the third subsection, a review of examples of relevant economic evaluation techniques and modelling approaches used in the health literature is presented.

1.3.1. Definitions

The value of one health-care intervention can be compared to another in terms of cost and health outcome. The cost is expressed in monetary terms and the effects can be expressed either in terms of monetary value, efficacy or enhanced quality of life. Depending on which measurement is chosen for the effect, a different type of economic evaluation should be performed. Costs and benefits can be assessed through cost-minimization, cost-effectiveness, cost-utility and cost-benefit analysis.

The **cost-minimization** is the simplest of the pharmacoeconomics tools. It is applied when comparing two drugs of equal efficacy and equal tolerability. When clinical equivalence is previously proved, a simple comparison of cost can suffice to choose between two or more therapeutically equivalent treatment alternatives. The weakness of this approach lies in the difficulty of proving that the compared treatment strategies have the same health impact, or in describing the assumptions under which the bioequivalence of treatments become true.

The **cost-effectiveness** (CE) of a therapeutic or preventive intervention is the ratio of the cost of the intervention to a relevant measure of its effect. Cost refers to the resource expended for the intervention, usually measured in monetary terms such as Euros or Dollars. The measure of effects is the units of health improvement, and this depends on the intervention being considered. For a given therapeutic strategy the number of people cured of a disease, the number of symptom-free days experienced by a patient or the number of illness events avoided can be of interest. The selection of the appropriate health effect quantification

should be based on clinical judgment in the context of the intervention being considered.

A special case of CE analysis is **cost-utility analysis**, where the effects are measured in terms of the number of years that a person lives with "good health", using a measure such as quality-adjusted life years or disability-adjusted life years. The purpose of the cost-utility studies is to estimate the ratio between the cost of a health-related intervention and the benefit it produces in terms of the number of years lived in full health by the beneficiaries. Cost is measured in monetary units. Benefit needs to be expressed in a way that allows health states that are considered less preferable to full health to be given smaller quantitative values. The utility-related measure is often expressed in quality-adjusted life years (QALYs).

A QALY takes into account both quantity and health related quality of life generated by healthcare interventions. It is the multiplication of life expectancy by the measure of the quality of the remaining life-years. Further details about this health measurement are given in Annex II.

The QALY places a weight on time in different health states. A year of perfect health is worth 1; however a year with any health impairment has a score less than 1. Death is considered to be equivalent to 0, some health states might be considered worse than death and have negative scores. These health status scores are known as utilities.

The cost-utility ratio indicates the additional cost required to generate a year of perfect health (one QALY). Comparisons can be made between interventions, and priorities can be established based on those interventions that are relatively inexpensive (low cost per QALY) and those that are relatively expensive (high cost per QALY). However, this approach, as a method for assessing interventions, remains controversial, because methods for scoring health states require a consensus about

how valuations should be made, which valuations should be used, and how the valuations of different individuals should be combined.

The cost-benefit analysis measures the impact of an intervention on monetary units. The costs and also the benefits are assessed in monetary terms, for this reason it is necessary to set money values on health outcomes. The therapies are compared using the ratio Cost/Benefit. The advantage of this method is its simplicity when comparing between treatments; however, the difficulty in setting money values to health outcomes and the ethical issues related to a subjective quantification entail a scarce use of this type of study on health area. The cost-benefit analysis is mainly, but not exclusively, used to assess the value for money of very large private and public sector projects. This is because such projects tend to include costs and benefits that are less agreeable to being expressed in financial or monetary terms (e.g. environmental damage), as well as those that can be expressed in monetary terms.
A small discussion on ethical issues related to the resources allocation is presented in Annex III.

Discounting

Discounting is a procedure that can be applied to all the previous analyses. In fact, the results of the measures described above should be reported indicating if they are discounted or non-discounted.
Costs and health outcomes should be discounted to present values when they occur in the future, to reflect society's rate of time preference. Accordingly, any costs or outcomes occurring beyond one year should be depreciated using standard methods. A common discount rate should be used to ensure the comparability of results across evaluations. The standard rate for the Reference Case is set at 5% per year. A rate of 0% should be used to show the impact of discounting and a 3% discount rate

must be used in a sensitivity analysis* for a comparison with published evaluations in other jurisdictions. The discount rates are expressed in real (constant value) terms, which are consistent with valuing resources in real (i.e., constant, inflation-adjusted) monetary units (Euros, dollars, etc.)[48].

Some countries have developed their own guidelines to perform pharmacoeconomic studies. One of the most complete and frequently used as a good example are the NICE guidelines[49], where the suggestions are to apply a 3.5% of annual discount rate and vary the rate between 0% and 6% for the sensitivity analysis if results are potentially sensitive to the discount rate.

The discounting rate applied in the model should be clearly stated in the results document.

In the assessment of the therapeutic strategies by means of cost and health outcome, both cost and health measurement should be defined and calculated. The following table summarizes the terms of cost and health outcome that can be used to compare a health-care intervention.

* A sensitivity analysis consists in examining the changes in results when the assumptions in the model are varied. Generally an economic evaluation is based on a number of debatable hypotheses, introducing an element of uncertainty. Sensitivity analysis suggests vary the input parameters in different ways to calculate and evaluate the robustness of the results under different assumptions.

Table 1.1. Summary of the techniques of analysis to jointly evaluate health outcome and economical cost. The health outcome units and the calculation required to compare between therapies are characterized.

Method of analysis	Health outcome measurement	Terms used to compare between therapies	Assumptions and comments
Cost-minimization	Any unit	Therapies price	Therapies compared have the same efficacy and tolerability
Cost-effectiveness	Natural health units	Cost/Effectiveness ratio	The health effect quantification should be suitably selected for the assessed therapy
Cost-utility	Utility score such quality-adjusted life years (QALYs)	Cost/Utility ratio	Special case of the Cost-effectiveness analysis. The score per health state can be debatable
Cost-benefit	Monetary units	Cost/Benefit Ratio	The assignation of monetary units to health states can be debatable
Discounting	Should be applied to cost and health outcomes involded in the described methods of analyses when future values should be discounted to present values. The rate of discount should be set up depending on the study aim.		

1.3.2. The ICER, the cost-effectiveness plane and the INB

Well known and widely used calculations and plots to display the results for the cost-effectiveness and cost-benefit analysis are the incremental cost-effectiveness ratio (ICER), the cost-effectiveness plane plot and the incremental net benefit (INB), which facilitate comparing the costs and benefits of new and existing health care interventions.

Incremental Cost-Effectiveness Ratio

In the evaluation of treatments, either by pairs or all of them versus an established therapeutic standard of care (SOC), four situations can be identified in terms of cost and health outcome:

- Cost treatment A<Cost treatment B; Effect treatment A>Effect treatment; Accept the treatment A, as it is both cheaper and more effective than B. It is a situation of dominance.
- Cost treatment A>Cost treatment B; Effect treatment A<Effect treatment B; Reject the treatment A, as it is both more expensive and less effective than B. It is a situation of dominance.
- Cost treatment A>Cost treatment B; Effect treatment A>Effect treatment; the magnitude of the additional cost of treatment A relative to the additional effectiveness should be considered.
- Cost treatment A<Cost treatment B; Effect treatment A<Effect treatment; the magnitude of the cost saving of therapy A relative to its reduced effectiveness should be considered (See also Table 1.2).

Table 1.2. In the comparison of two treatments, 4 situations are possible according to cost (rows) and effect (columns). In two of the combinations, the treatment selection is clear, the unclear ones are marked with a question mark.

Cost A<Cost B	A selected	?
Cost A>Cost B	?	B selected
	Effect A>Effect B	Effect A<Effect B

As a summary of the previous situations, the cost-effectiveness can be expressed as an incremental cost-effectiveness ratio (ICER) defined as the ratio of change in costs to the change in effects.

$$ICER = \frac{Cost\ treatment\ A - Cost\ treatment\ B}{Effect\ measurement\ treatment\ A - Effect\ measurement\ treatment\ B}$$

The ICER value might be considered as the monetary cost of the additional outcome caused by switching from treatment B practice to the treatment A. Assuming that the new treatment is more effective and its price is low enough, the new strategy is considered "cost-effective" or dominant. The ICER value can be directly compared to a pre-specified amount of money which represents the maximum cost health payers would invest to achieve one clinical benefit unit, and this value is defined as the willingness to pay (or ceiling ratio, Rc) benchmark. The advantage of ICER is that different interventions are evaluated in the same units and decision, between interventions, can be based on the cost/unit of result. Its drawback is that the ICER interpretation varies in function on the result of the difference between the effects and between the costs of the compared treatments. Also, there is a limitation on the confidence interval calculations, especially when the the effect of both treatments is close to the same measured value[50].

Cost-effectiveness plane

The incremental cost-effectiveness plane represents the incremental cost and the incremental effect from a treatment A versus a treatment B as coordinates in a plot[51]. The plane is divided into four quadrants: the horizontal axis divides the plane according to the incremental cost (positive above, negative below) and the vertical axis divides the plane according to the incremental effect (positive to the right, negative to the left). The cost-effectiveness plane is presented in Figure 1.3[52].

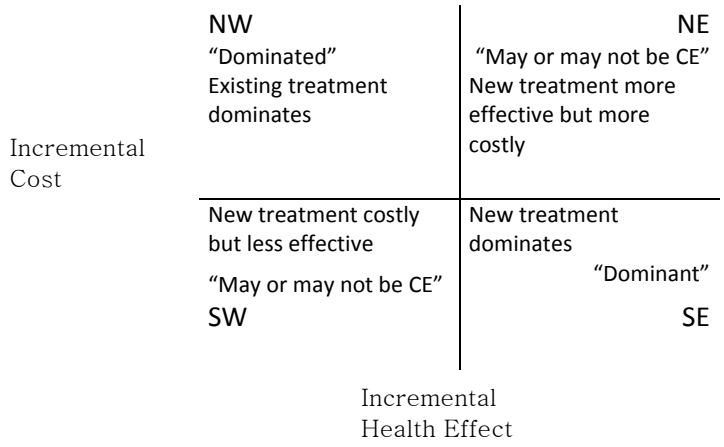


Figure 1.3. The cost-effectiveness plane. In the figure, the label and the decision about the compared treatments corresponding to each quadrant are indicated. NE = northeast quadrant; NW = northwest quadrant; SE = southeast quadrant; SW = southwest quadrant.

Each quadrant has a different implication for the decision:

i) If the ICER is calculated for the new treatment compared to the SOC and it falls in the southeast quadrant, with negative costs and positive effects, the new treatment would be claimed more effective (larger health gain) and less costly than SOC; in this case it can be said that the new treatment 'dominates' the SOC. Interventions falling in this 4th quadrant are always considered cost-effective.

ii) If the ICER is located in the northwest quadrant, with positive costs and negative effects, the new treatment would be more costly and less effective than SOC (i.e., new treatment is 'dominated' by SOC). Interventions falling in the 2nd quadrant are never considered cost-effective.

iii) If the ICER falls in the northeast (or 1st) quadrant, with positive costs and positive effects, or the southwest (also named 3rd) quadrant, with negative costs and negative effects, trade-offs between costs and effects would need to be considered. The 1st and 3rd quadrants represent the situation where the new treatment may be cost-effective compared to SOC, depending upon the value at which the ICER is considered good

value for money i.e.: compared to the maximum amount that the payer is willing to pay for health effects.

For instance, in the UK, the National Institute of Health and Clinical Excellence (NICE) at 2012 uses a threshold between £20,000–30,000 (€24,557–36,835, using the exchange ratio of 1£ = €1.23) per QALY gained when deciding which interventions to approve (interventions costing less than £20,000 (€24,557) per QALY gained are more likely to be approved than interventions costing more than £30,000 (€36,835) per QALY gained)[53]. In Spain an intervention costing less than €30,000 per QALY gained is considered cost-effective[54] and the interventions in the range of €30,000–€45,000 per QALY are also susceptible to be labelled as cost-effective.[55] When a treatment is not dominant, deliberations about the collateral potential benefits and costs gained or lost, in the context of the most efficient use of resources, can help in the election.

When the ICER shows that the new treatment is less costly and more effective than the SOC the concern is to quantify the variability or uncertainty of this result. The ICER is usually calculated from point estimates of costs and effects without taking into consideration their variability. To account for this variability, sensitivity analyses changing the input parameters and probabilistic techniques to generate a range of input parameters can be used to generate a set of possible results which can be taken as a quantification of the uncertainty surrounding the estimates of costs and effects.

There remains considerable debate concerning the presentation of joint uncertainty for estimates of cost-effectiveness. The calculation of confidence intervals can be complex. The possibility that the numerator and/or denominator tend to 0 complicate calculations even more. As a result of these challenges, a number of alternative methods for calculating confidence intervals have been proposed. These methods

include the use of Fieller's theorem and non-parametric bootstrapping[56, 57].

Incremental Net Benefit

The incremental net benefit (INB) can be defined in terms of health gain, known as incremental net health benefit (INHB), or in monetary quantification becoming the incremental net monetary benefit (INMB).

INHBs estimate a treatment's net clinical benefit after accounting for its cost increase versus an established SOC.

Lynd[58] has proposed a framework for calculating the incremental net health benefits (INHB) of different pharmaceutical treatments. Both benefits and adverse events associated with a treatment are quantified using available clinical trial or surveillance published data.

A score reflecting the utility is assigned to each outcome in order to express all benefits and all risks in a common scale. The difference between the sum of the weighted benefits and the sum of the weighted risks of a treatment represent the net health benefits of the treatment. INHB is calculated as the difference between the NHB of the treatment of interest minus the NHB of an alternative treatment or the standard of care. A positive INHB indicates that the net benefits of treatment are larger than its competitor[59]. INMB would be defined analogously.

1.3.3. Outline of the approaches used in health research

Techniques used for pharmacoeconomic evaluations performance in the health area and the ones susceptible to be adapted for application to our real case studies are described. According to the data source, the models were classified in dynamic models, Markov models and models based on real. The main methodological differences among studies were allocated in the data generation/collection; the provenance of the data on costs and

health outcome can be real or simulated using different methods. The data used in the assessment can be collected from clinical records or prospectively in the framework of a clinical study. Another difference is the numerical summaries and graphical displays chosen to be reported, they are based on the research question that should be answered. Some examples of models applied to several health area problems are described in the following.

Dynamic models

These models are useful for studying the nature of epidemics or disease trends over time. They are typically deterministic and non linear over time; they track the changing population and individuals constantly enter the model as they are born and exit the model as they die. The probabilities of suffering health events change with the time. They are difficult to implement and few works used them. Edmunds et al.[60] used a dynamic model for assessing the cost-effectiveness of vaccination programmes on human papillomavirus (HPV).

Markov models

Markov models, also called health-state transition models, are widely used for cohort simulation. In this approach, the transition probabilities between health states do not change with time.

In cancer research, Markov models are often used to simulate the disease evolution. A brief summary of three representative published works is here stated: Van de Velde et al.[61] implemented a state transitions model to assess the effectiveness of HPV vaccine; considering the natural history of infection and disease, the probability of a woman of being tested for HPV and the life-long natural immunity. The aim of this study was to predict the impact of HPV-6/11/16/18

vaccination on the girl's life time risk of HPV infection. Yang et al.[62] used a Markov model to evaluate the cost-effectiveness of two available gene expression profiling test to learn about the breast cancer recurrence and guide the treatment.

Two representative examples of cost-effectiveness studies on coronary heart diseases[63, 64] used Markov models to simulate the health-states previous death. The outcomes measured included costs, life expectancy in quality-adjusted life-years (QALYs), incremental cost-effectiveness ratios, and events prevented.

In the HIV/AIDS cost-health outcome studies, we identified three differentiated cohort simulation models: the implemented by Freedberg et al.[65-68], the developed by Sanders et al.[69] and the developed by Sax et al.[70]. These models have in common a state-transition model framework, but they are based on different clinical assumptions.
Freedberg et al. have developed a mathematical simulation model of HIV disease, using the CD4 cell count and HIV RNA level as predictors of the progression of the disease. The input information used for modelling the course of the disease were the monthly probabilities of clinical events: changes in CD4 cell count, changes in HIV RNA level, development of opportunistic infections, adverse reactions to medications and death. A state-transition model framework was employed; wherein disease progression in a patient was characterized as a sequence of monthly transitions from one health state to another. Outcome measures included life expectancy, life expectancy adjusted for the health related quality of life - scale from 0.0 (death) to 1.0 (perfect health), lifetime direct medical costs, and cost-effectiveness in dollars per quality-adjusted year of life gained.

The simulation model previously described, or slightly adapted, was used in a long list of published papers of cost-effectiveness assessments. Goldie et al.[65] also used it to explore the cost-effectiveness of interventions to improve adherence to combination antiretroviral therapy in patients with HIV infection. Shackman et al.[66] examined the societal cost-effectiveness and the impact on government payers of earlier initiation of antiretroviral therapy for uninsured HIV-infected adults. In the work published at AIDS by Walensky et al.[67], the value of resistance surveillance in influencing recommendations toward effective and cost-effective sequencing of ART regimens in clinical care in Cote d'Ivoire was assessed. In one of the last published works, Morris et al.[68] evaluated the immune response when an immune-enhancing agent was added to the initial antiretroviral therapy.

Sanders et al.[69] used the Decision Maker software (version 2003.11.1. Prat Medical Group) to develop a Markov model that followed a cohort of patients over their lifetime. The HIV infection evolution was defined on the basis of CD4 levels and HIV RNA viral load, the change to another antiretroviral regimen after virological failure and the virus resistances developed. By means of this model, costs, quality of life, and survival associated with an HIV-screening program and current practice were estimated.

Sax et al.[70] defined a state-transition model of HIV disease to determine the clinical impact and cost-effectiveness of genotype resistance testing for treatment-naive patients with chronic HIV infection. By using the hypothetical cohort of antiretroviral-naive patients with chronic HIV infection, the life expectancy, costs, and cost-effectiveness were projected. Results were given in terms of incremental cost-effectiveness ratio and a sensitivity analyses was performed through wide variations in baseline assumptions, including variations in genotype cost, prevalence

of resistance overall and to individual drug classes, and sensitivity of resistance testing.

In a work published by Greeley et al.[71] Markov model simulated data was used to assess the economic impact of adding genetic testing to the clinical routine in permanent neonatal diabetes, which is an example of personalized genetic medicine to other disorders in the future.

Models based on real data

Cost-effectiveness studies can be done prospectively, using data recorded in the framework of a clinical trial or a prospective study; this is more often done in programs which outcome can be measured in a short period of time. For instance, the cost-effectiveness study done for a pulmonary rehabilitation program in which, a cost/utility analysis was undertaken jointly with a randomised controlled clinical trial of pulmonary rehabilitation versus standard care[72].

Hamel et al.[73] performed a prospective cohort study to evaluate the clinical outcomes and cost-effectiveness of initiating dialysis or to continue aggressive care for patients who suffered a renal failure.

It is remarkable the use of decision trees to assess the results of the study. The decision trees are a graphical display that gives a good representation of the health care interventions assessed and their health outcomes. In dental health there are programs and treatments susceptible to be studied as cost-benefit and cost-effectiveness studies. Two examples of them are a prospective study following a cohort of patients during 3 years to compare between implant 2 denture prostheses versus complete dentures[74], and a decision tree to help in the choice of the management strategy for symptomatic, disease free mandibular third molar[75].

Dasbach et al.[76] used **hybrid models**, which are a combination of a cohort model simulation and a dynamic model. In the cohort simulation the probability of transition does not change with time, the dynamic model adds flexibility to the model structure by estimating how the probability of transition would change with the time for the cohort of interest. The complication added by the integration of both models allows reflecting more acurately the real system than when the separated model structures are used.

1.4. Goals and thesis structure

The **aim** of this thesis is to present a set of models that could favour a more rational use of resources in order to achieve the largest gain in health per monetary unit spent on health care in a national health system. The methods are applied to real clinical questions: two on antiretroviral treatment for HIV-infected patients (Decision trees and Markov models in n-stages), two on prevention of osteoporotic fractures (Markov models and techniques for health benefits quantification), and one on the rare disease paroxysmal nocturnal haemoglobinuria (budget impact analysis).

The thesis is organized as follows: This first chapter had the aim to explain the data required to perform a pharmacoeconomic study and the techniques available to carry out an economic evaluation. The next 5 chapters of the thesis are devoted to 5 different approaches of pharmacoeconomic studies; existing methods are adapted, combined and/or developed to be applied into real health problems.

From a methodological perspective Chapters 2, 3 and 4 compare different therapeutic strategies by jointly evaluating cost and health outcome, while Chapters 5 and 6 deal with cost and health outcome separately, by means of a budget impact analysis and the use of techniques to quantify health benefits. Concercing the areas of application, Chapters 2 and 4 are devoted to HIV health issues, Chapters 3 and 6 to osteoporosis disease while Chapter 5 provides an example of study for a rare disease, the paroxysmal nocturnal haemoglobinuria (PNH).

Finally, in Chapter 7 and Chapter 8, we discuss the issues raised and examine indications for new lines of research.

Some details about other technical approaches, data input used in the clinical applications and the program code for the model, and/or statistical analysis —by means of SPSS, R or Microsoft Excel— are provided in the Annexes.

Summary Chapter 2.

TREATMENT ADHERENCE PROMOTION STRATEGY IN HIV INFECTED PATIENTS. DECISION TREES

Real data of a clinical trial was used in the assessment of the adherence to antiretroviral treatment promotion program in HIV infected patients. A decision tree was selected to study the cost per health gain, measured by means of clinical and health related quality of life outcomes. The simplicity of the technique was appropriate to summarize the cost-effectiveness of the adherence promotion program. A small immunological or health related quality of life improvement resulting from the new strategy was observed. It was found that an increment of the treatment cost in €14.53PPM could generate a 1% of additional health outcome.

2. TREATMENT ADHERENCE PROMOTION STRATEGY IN HIV INFECTED PATIENTS. DECISION TREES

Decision trees are used to describe the possible choices and their consequences, in terms of the health outcome and resources expenditure. This method was used to assess an HIV antiretroviral treatment adherence program. The comparison between the intervention group and the standard of care is performed in terms of cost-effectiveness and using real data collected in the framework of a clinical trial.

2.1. Decision trees

A **decision tree** (or tree diagram) is a decision support tool that uses a graph of available options and their possible consequences, including chance event outcomes, resource costs, and utility.

The branches off the initial decision node represent all the therapeutic strategies that are to be compared. A series of probability nodes of each strategy branch can be used to reflect uncertain events, usually within a relatively short time frame. The outcomes at the end of each pathway are values that reflect both the cost and the health effect associated with that pathway. Usually, the outcomes are grouped into health states which are characterized by a utility measure and a monetary measure of cost[84].

Example:

The figure 2.1 is a graphic representation of the context of a decision and its impact on health results. In this case, the potential outcomes are Well, Sick and Dead, which should be defined in such a way that they are exhaustive, but

exclusive, i.e., they cover all possible outcomes, but a patient cannot be in more than one state at a time. The available therapeutic strategies to treat the health problem are A and B. The probabilities of achieving a health outcome for the studied treatments are known and displayed in the diagram (p and q). A logical constraint in the final nodes for the possible health outcomes is that the sum of the probabilities must be 1.

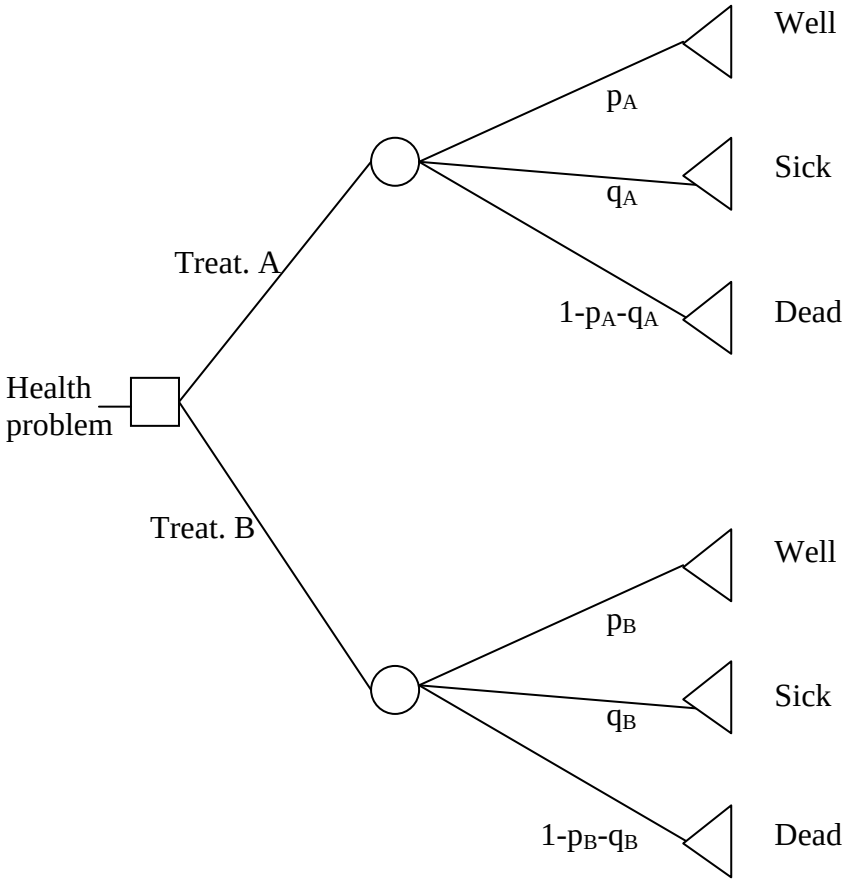


Figure 2.1. *Decision tree structure. This is a graphic representation of the context of a decision and its impact on health results. A and B can be used as a treatment for the health problem assessed. The potential outcomes are Well, Sick and Dead. p and q are the probabilities of achieving the fist two health states, 1-p-q is the probability of Death. The square indicates a decision node, the circles represent the probability of the event, and the triangles indicate a final state.*

Cost-effectiveness (CE) and incremental cost-effectiveness ratio (ICER) can be calculated to compare outcomes between groups. The CE and ICER are calculated at the end of the follow-up as described in subsection 1.3.2, CE is calculated as the cost divided by efficacy and ICER is the difference of cost between the treatment A and treatment B divided by their difference in effects. The decision tree offers a static portrait of a dynamic process. It is relatively easy to construct and use this approach, although it only works for micro-circumstances (i.e., well defined systems, described by few and well characterized features and usually in a bounded time), where the information does not come from different studies or populations, and it is not necessary to adjust for factors. Furthermore, duration of follow-up should be the same for all patients and branches. The difficulty to represent a disease characterized by the repetition of events in the time (such as chronic diseases: complications, recurrence and progression) and the impossibility to assign utility values to the health states and a discount rate to the costs are limitations of this approach.

2.2. HIV infection and a promoting adherence program

2.2.1. Clinical background

HIV infection continues to be a major health epidemic problem. The World Health Organization (WHO) estimated that there were 34.0 million [31.4 million–35.9 million] people living with HIV worldwide at the end of 2011. In 2011, an estimated 2.5 million [2.2 million–2.8 million] new HIV infections occurred and 1.7 million [1.5 million–1.9 million] annual deaths were due to AIDS[77]. The WHO estimated the number of people living with HIV in Spain, among adults aged 15 years and older, to be 150,000

[130,000-160,000], and the prevalence in this setting was 0.4%[0.4-0.5][78].

Significant advances in antiretroviral treatment have been made since the introduction of zidovudine (AZT) in 1987. With the advent of highly active antiretroviral therapy (HAART), HIV-1 infection is now manageable as a chronic disease in patients who have access to medication and who achieve durable virologic suppression[79]. Accessibility to antiretroviral therapies is general because the Spanish health care system provides universal health care free of charge for the patients. Nowadays concern is whether patients take the prescribed medication, as well as they follow the treatment dosage. Poor adherence to combined antiretroviral therapy (cART) has been shown to be an important determinant of virologic failure, emergence of drug resistant virus, disease progression, hospitalizations, mortality, and, consequently health care costs. The challenge is to achieve a high long term adherence and break the barriers to optimal adherence. The obstacles to overcome may be from individual (biological, socio-cultural, behavioural), pharmacological, and societal factors[80].

2.2.2. Study characteristics

A program to promote adherence in HIV naïve patients that start cART was established. The experimental group received the standard care of treatment and a psychoeducational adherence-based intervention consisting in 3 sessions of 1 hour of duration each. The visits were performed in the moment of cART starting, 2 weeks and 4 weeks later. During these sessions the beliefs of the patient about the HIV disease and his/her circumstances that prevent the patient to be adherent to the cART, including conceptual, behavioural and motivational areas, were discussed and the importance of the adherence was emphasized. The control group did not participate in the psychoeducational adherence-

based intervention program. See the chronogram of the study in figure 2.2.

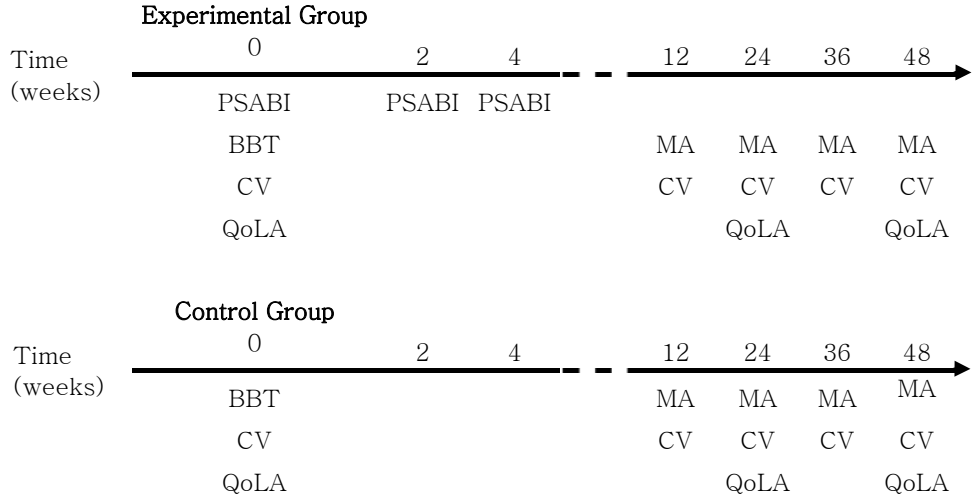


Figure 2.2. Chronogram of the study procedures by branch of health care intervention. Time expressed in weeks (w) of follow-up (48w, considered equivalent to 1 year). PSABI is the psychoeducational adherence-based intervention. BBT is the Baseline blood test, CV is the Clinical visit, MA is the Monitoring analysis and QoLA is Health related quality of life questionnaire assessment.

The performance of the program was evaluated in terms of cost-effectiveness for different health outcomes. Data was collected through a prospective clinical trial designed to evaluate the health outcome in terms of HIV RNA viral load, CD4 cells count and health related quality of life variables at 1 year of follow-up. Forty treatment-naïve participants were randomized to the experimental and control groups. Clinical, economical and health related quality of life variables were assessed from the RCT data base and the direct cost of the hospital medical supplies. The numerical variables were expressed as mean (Standard deviation, SD) or as median and interquartile range (IQR) and compared using the t or Mann-Whitney test. For the categorical variables, percentages and/or number of patients were given and compared using the χ^2 or Fisher exact test (as appropriate). Further

detail on cost and effectiveness input data and calculations are provided in Annex IV and Annex V.

2.3. Results

Participants were all men with a median (IQR) of 35 (30-45) years old, who were infected mainly through sex with other men (90%). The median number of cART changes during the study was 2, with a minimum of 0 and a maximum of 4 changes. Initially, 20 patients were allocated in each treatment group but 5 and 2 were lost to follow up in the control and experimental groups, respectively.

To assess both cost and the clinical and health related quality of life outcomes of interest six decision tree models were built. The first two present the results for viremia control and the immune recovery, the next ones reflect the quality of live improvements (figure 2.3 and 2.4). These models compared the performance of the patients attending the adherence program with the individuals receiving the standard of care.
The mean (SD) cost per patient month (PPM) was €1,252 (460) in the experimental group and €1,139 (275) in the control group. The percentage of patients that reached the end of the study with virological suppression was larger in the experimental group (94.4% versus 86.7%; not statistically different, p-value=0.579). The CE indicates that the cost per 1% more of patients with virological response is slightly larger in the experimental group (€1,326 PPM versus €1,314 PPM). The ICER indicates that, per 1% additional in viral suppression outcome, the incremental cost is €14.53 PPM. The percentage of individuals that show an improvement of 100 or more CD4 cells/mm^3 was larger in the control group (80% versus 72.2%; not statistically different, p-value=0.699).

When this outcome is assessed, the adherence program is not cost-effective (Figure 2.3).

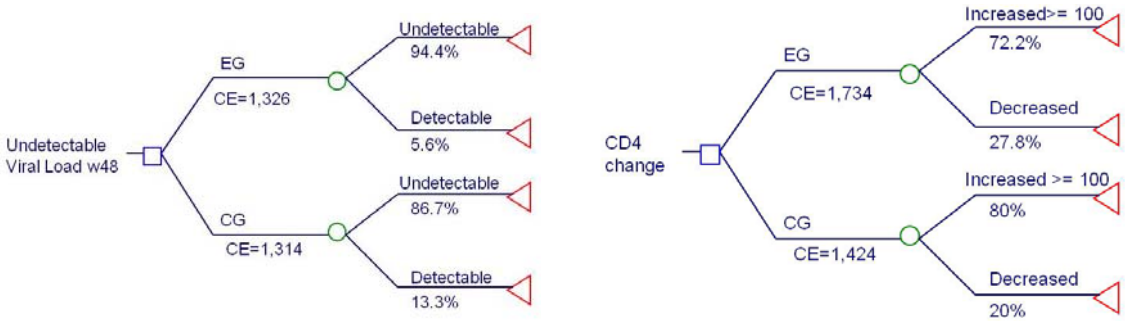


Figure 2.3. Cost-effectiveness decision trees considering clinical variables in experimental (EG) and control groups (CG). The ICER for the Undetectable Viral load marker is €14.53 and €-14.53 for the CD4 change as an incremental cost per 1% of increasement in the health outcome. Decision is represented by the square, the circle is a chance node, and triangle represents a final node.

Mental and psychological, and global health scores were favourable to the experimental group in comparison with the control group; although the differences between groups were not statistically significant for any of the scores. Considering the cost added for the adherence promotion visits, the minimum cost therapeutic strategy should be chosen in this population. The percentage of every outcome and the CE ratios are displayed in Figure 2.4.

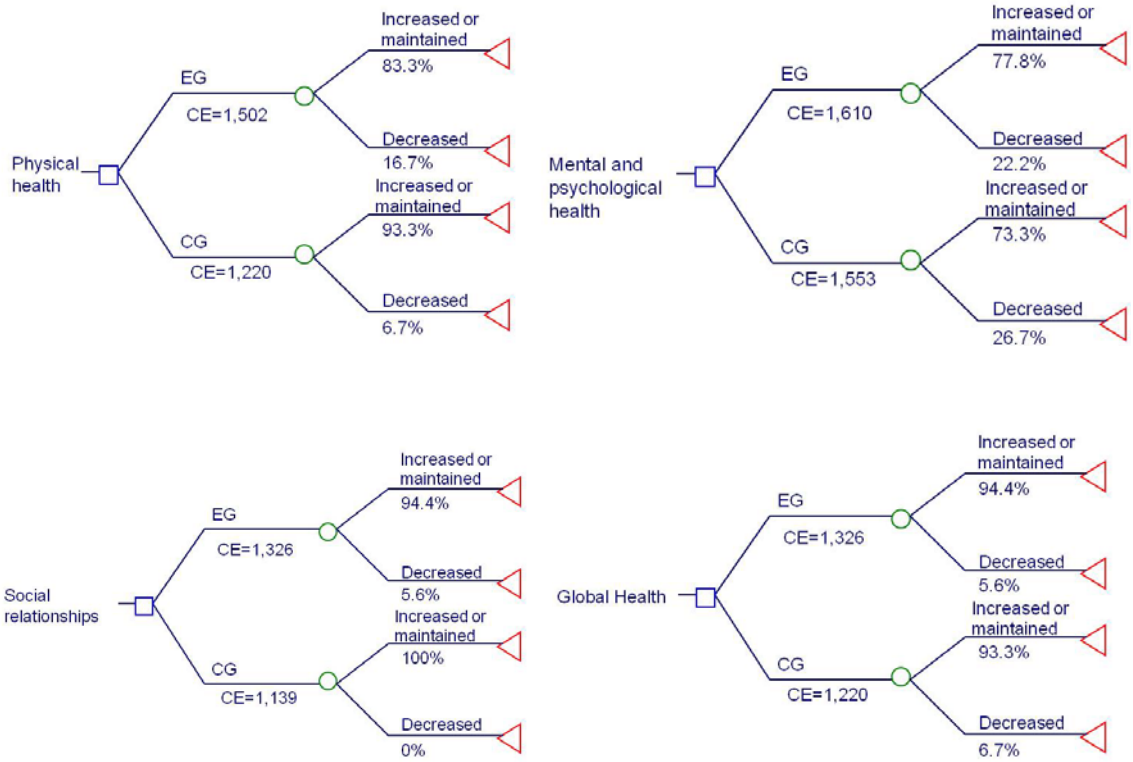


Figure 2.4. Cost-effectiveness decision trees considering health related quality of life variables in experimental (EG) and control groups (CG). The ICERs for the Physical health, Mental and psychological health, social relationships and global health are €-11.30, €25.42, €-20.34 and €101.70 respectively. Decision is represented by the square, the circle is a chance node, and triangle represents a final node.

2.4. Discussion

In our study there were no significant differences in the health outcomes between control and experimental programs. In terms of the trend found on the descriptive analysis it can be said that the patients in the psychoeducational adherence program had a scarce benefit in terms of achieving undetectable HIV viral load, compared with the patients in the control group. The HIV Unit where the trial was performed stresses the need of educating and making the patients aware of the treatment

adherence importance; the standard of care include interventions to help patients to understand the HIV infection, the drugs role and connect these terms with their routine and believings. This might be due to the fact that the adherence in our patients is greater than 80%. Then, it can be supposed that the standard of care in terms of adherence sensitivity is greater than in generalized clinical practice. If the program is implemented in units of care without specific interventions to help the patient to deal with the disease, a larger improvement in adherence, and consequently, in the health outcomes can be expected.

Increasing the follow-up would be valuable to quantify the changes in immunological and health related quality of life scores and characterize the program effects in the long term. The health resources used were registered using the clinical files and some information on visits and prescribed drugs done out of the HIV unit could be ignored in our register. We assume that undereporting of resources used was balanced between both groups, and this did not significatively affect to our results.

In spite of the study limitations and the lack of generalization of the results to the HIV infected patients visited in other clinical units, it was an asset to manage the intern available resources in the unit where the study was performed. The conclusions of this work are similar to what Goldie et al.[65] reported, where they mention that in spite of improving the patients' health related quality of life "*the cost of the programme represented a key variable*".

The decision trees are very useful to describe situations where a simple choice and the set of possible outcomes are not very extense. The simplicity of this technique has the limitation of not reflecting the evolution of the health outcomes over time, in this method the value at the end of follow-up is used as an indicator of success or failure.

Conclusion

The study performed can guide the selection of the therapeutic strategies applied to the clinical practice. The program to promote the HIV treatment adherence resulted in a few immunological or health related quality of life improvement, it seems cost-effective in terms of virological suppression if the decision-makers on health resources allocation consider worthy increasing the treatment cost. In our setting the increase estimated is of €14.53PPM to obtain a 1% of additional health outcome.

Summary Chapter 3.

COST-EFFECTIVENESS STUDY FOR COMPARISON OF BAZEDOXIFENE WITH RALOXIFENE IN OSTEOPOROSIS PREVENTION. MARKOV MODEL

The simulation of a Spanish cohort of postmenopausal women and their possible osteoporotic fractures was done to assess the performance of two treatments for the prevention of vertebral and non-vertebral fractures in terms of cost-effectiveness. Simulation by means of a Markov model required that:

i) the disease evolution and the related events were simplified using a finite number of health states and

ii) the probabilities of moving from one state to another as the time goes on were defined.

Probability sensitivity analysis (PSA) was also performed to assess the uncertainty of the results. It was observed that the use of bazedoxifene slightly increases the patients QALYs and the cost of the treatment (0.02 QALYs, 445€). In the PSA, the deterministic results were confirmed in 52% of the realizations; with a willingness to pay for an additional QALY gained ranging from 0 to a maximum of €50,000 In this context, the decision between treatments should be reinforced with other clinical features not included in the model.

3. COST-EFFECTIVENESS STUDY FOR COMPARISON OF BAZEDOXIFENE WITH RALOXIFENE IN OSTEOPOROSIS PREVENTION. MARKOV MODEL

Markov models are used to simulate a cohort of patients at a population level and their path towards different health states. As a result, the cost and health parameters obtained allow performing a comparison between treatments to prevent osteoporosis in menopausal women.

3.1. Markov model

Markov models are a commonly used tool in medical decision analysis. They are especially appropriate when the disease of interest is characterised by the recurrence of specific events and when these events are based on continuous risk over time[81].

The simulated cohort of patients is divided into a finite number of states based on, for example, the current health status of the patient. The states are supposed to be mutually exclusive and collectively exhaustive and they can be defined as transient or absorbing states. It is said that a state is absorbing when the individuals in the model cannot leave this state and transient otherwise. Suppose we are observing random variables X_0, X_1, X_2… which are the successive states of a system with some sort of random functioning. And suppose also that the states can be numbered 1, 2, …. We call this system a Markov chain if the probabilities passing into the next state are completely determined by the present state of the system. More precisely, in a discrete setting, the sequence X_0, X_1, X_2 … will be called a Markov chain if for any sequence of states x_0, x_1, …, x_{n+1}

$$P(X_{n+1}= x_{n+1} | X_n= x_n,\cdots, X_0= x_0)= P(X_{n+1}= x_{n+1} | X_n= x_n).$$

In other words, the probability of moving from the n^{th} state x_n to the $(n+1)^{st}$ state x_{n+1} does not depend on how we got the n^{th} state; that is, does not depend on $x_1,\cdots,x_{n-1}$. This property is called Markovian property and refers to the memoryless property of a stochastic process[82]. The conditional probabilities

$$P(X_{n+1}=j \mid X_n=i)$$

of moving to state j at time n+1 given that we were in state i at time n are called the transition probabilities for the process and are denoted by

$$p_n(j \mid i).$$

The possible values of X_i form a countable set S called the state space of the chain.

Example:

A simple example of a three-state Markov model to simulate a cohort of patients at a population level and their path towards different health states is provided in figure 3.1. Time is handled as discrete periods of the same length (cycles). The state space of the chain is S={Well, Sick, Dead}, with 2 transient states -Well and Sick- and 1 absorbing state -Dead-.

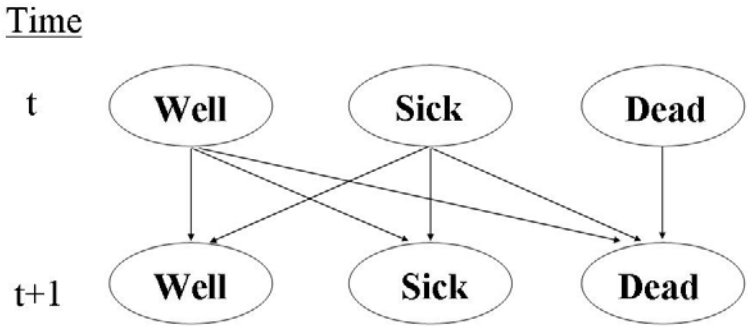


Figure 3.1. *Representation of a simple Markov model. The arrows represent possible transitions between health states (ovals) in a cycle. Transitions between health states with probability 0 are not connected by arrows.*

The Markov models can be represented by a decision tree with many branches while every cycle the patient has the chance to remain in the same health state or switch to any of the others which probability of transition is different from 0 (see Figure 3.2).

Example:

The previous Markov model with 3 health states (Well, Sick and Dead) can be represented using a tree structure.

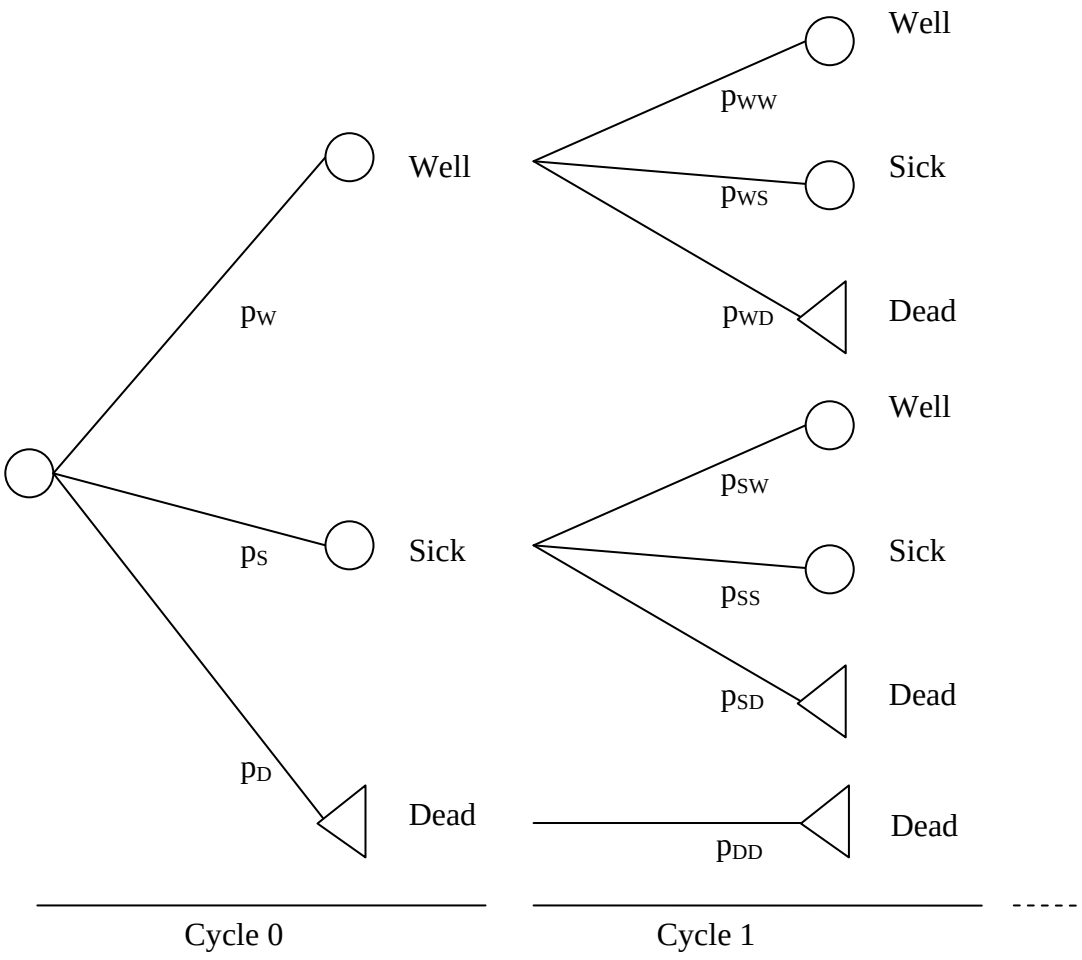


Figure 3.2. *Decision tree structure for the Markov Model in Figure 3.1. The circles represent the probability of the event and the triangles indicate a final state. Well, and Sick are transient states, and Dead is an absorbing state.*

The health states can be transient or absorbing. This can be stated formally as $p_n(i|i)=1$ and $p_n(j|i)=0$ for $i \neq j$.

The elements of the matrix of transition probabilities (p_{ij}) indicate the probability to travel from the current health (i) state to the next (j) in one cycle, i.e., from time t to time t+1 –named $p_{ij}(t)$. It is required that the sum of probabilities in a row equals 1. The structure of a transition probabilities matrix, A, using the examplecase is shown in Figure 3.3[83].

Example:

The transition probabilities for the Markov model with 3 health states (Well, Sick and Dead) are represented using a matrix structure. The matrix cells contain the probabilities of being in the state i move to state j in one clyce, i.e., p_{ij}.

	To		
From	Well	Sick	Dead
Well	$p_{WW}=1-(p_{WS}+p_{WD})^*$	p_{WS}	p_{WD}
Sick	p_{SW}	$p_{SS=}=1-(p_{SW}+p_{SD})^*$	p_{SD}
Dead	0	0	$p_{DD}=1$

Figure 3.3. *Structure of a transition probabilities matrix for a three-state Markov model. The probabilities are different from 0 when a transition between health states is possible. Transitions between health states with probability 0 are not feasible, such as the ones starting in the health state Dead.*

**Example of probabilities estimated by difference.*

From a given state, for instance Well, after 1 cycle, and once the probabilities of going to Sick state and Dead state have been calculated (p_{WS} and p_{WD}), the probability of staying Well

is the "residual probability" computed as the difference from 1 of $p_{WS}+p_{WD}$ (see figure 3.3). This method allows obtaining information that is not usually reported in published health studies (research papers, epidemiological tables, etc.).

The model is initially filled by distributing the simulated individuals across a number of starting health states according to parameters defining the probability of being in each of these states. These parameters can be extrapolated from the sickness prevalence in the population of interest. This is done by specifying the dimension of the set of states, which is 1×s, where s is the total number of health states in the Markov model and the starting vector P_0, which contains the probability of the patients of starting in each health state.

The proportion of the initial cohort in each of the three states after one cycle (P_1) can be calculated by multiplying P_1 by the matrix of transition probabilities, A. More generally the proportion of the initial cohort in each state after k cycles becomes $P_k = P_{k-1}$*A, where P_k –with dimension 1×s– display the proportion of the cohort contained in the defined states at cycle k.

The structure for a Markov model will depend on the clinical application, the available data and how many simplifying assumptions are made. However, there are a number of essential steps to follow when constructing a Markov model:

i) Specify the Markov states to reflect the relevant states of health and resources expenditure associated with the disease and treatment over time

ii) Choose the cycle length to be used in the simulation, which must be a constant increment of time. The selected elapse of time should be short enough to consider the changes of clinical effects and resource use in

patients between the cycles. The time horizon for the analysis also should be chosen

iii) A cost and utility should be assigned to each health state. In order to calculate discounted utility or cost, they should be divided by $(1+r)^k$, where r is the discount rate corresponding to the cycle length and k is the cycle index[84]

iv) A set of transition probabilities must be specified. They indicate the chance of the individuals in the model to move from one health state to another. They can be defined as a function of time. For that purpose, a different matrix A_k for each cycle k should be defined to provide a transition probability linked to be health states and incorporate the time elapsed after an event. Introducing a statistical distribution (e.g., the exponential) or temporary and tunnel states can accomplish this purpose. The temporary states are used when a health situation has a short duration but has an important effect in costs or outcomes; the patients can only stay at the state for, at most, one cycle; their use enables the model users to assign state specific transition probabilities and adjust utilities and costs. The tunnel state, in which patients can only transit in a fixed sequence, is analogous (given the nature of life-threatening disease) to passing through a tunnel, and would be used when a temporary state would last more than one cycle[85].

The cohort simulation at the population level procedure consists on a hypothetical cohort of people who begin the process with some determined distribution among the states (P_0). In the next cycle, the cohort is divided between the states according to the probability of transition, thus yielding a new distribution of the cohort between the states. This will continue in the subsequent cycles until the process has reached a cycle limit. The movement of the cohort through the health states during the simulated time produces estimations for the cumulative

utilities and costs. Table 3.1 illustrates the Markov trace for the first 2 cycles for the 3-state model used as an example (a numerical example can be followed in Annex VI). The simulation is run until the entire initial cohort resides in an absorbing state or until the upper limit of time that was considered clinically reasonable for the assessed health problem is reached.

Example:

Markov model trace for the two first cycles is displayed below:

Table 3.1. *Two-cycle Markov trace for a 3-state Markov model with health states: Well, Sick and Dead. Utility scores for the health states are u_W, u_S, u_D, respectively. Costs are defined analogously using the c as notation. P_0=(1,0,0), i.e., P_0=(p_{0W}, p_{0S}, p_{0D}). Column 1 show the cycle number (k), columns 2 to 5 show the proportion of the cohort in each of the 3 health states at each cycle k (P_k), the last 2 columns show the utility and the cost contribution in each cycle*

Cycle (k)	Well	Sick	Dead	Cycle utility	Cycle cost[¤]
0	1	0	0	1* or 0.5* (p_{kW}*u_W+ p_{kS}*u_S+ p_{kS}*u_D)[#]	1* or 0.5* (p_{kW}*c_W+ p_{kS}*c_S+ p_{kS}*c_D)[#]
1	p_{0W} * p_{WW}+ p_{0S} * p_{SW}	p_{0S} * p_{SS}+ p_{0W} * p_{WS}	p_{0D} * p_{DD}+ p_{0W} * p_{WD}+ p_{0S} * p_{SD}	(p_{kW}*u_W+ p_{kS}*u_S+ p_{kS}*u_D)	(p_{kW}*c_W+ p_{kS}*c_S+ p_{kS}*c_D)
2	p_{k-1W} * p_{WW}+ p_{k-1S} * p_{SW}	p_{k-1S} * p_{SS}+ p_{k-1W} * p_{WS}	p_{k-1D} * p_{DD}+ p_{k-1W} * p_{WD}+ p_{k-1S} * p_{SD}	(p_{kW}*u_w+ p_{kS}*u_s+ p_{kS}*u_D)	(p_{kW}*c_w+ p_{kS}*c_s+ p_{kS}*c_D)

[#] *At cycle 0, the utility and the cost can be multiplied by 0.5 to take into account that some individuals transit in the middle of the cycle, which is known as the half-cycle correction.*

[¤] *To obtain discounted expected utility (or cost) values the cycle utility (or cost) would be divided by its discount factor $(1+r)^k$.*

To draw a cohort simulation at the individual level we perform a first-order Monte Carlo simulation. The individual track is simulated, one at a time, through the tree of possible states. The first individual would start in the "Well" health state, based on P_0, the next cycle visited will be determined using a random number drawn from a Uniform[0,1] and using the ordered cumulative probabilities for the cycle 1, i.e.:

$P_1=(p_{1W}, p_{1S}, p_{1D})$

Assuming that $p_{1W}>p_{1S}>p_{1D}$, in case of equality the order can be decided at random.

Then, the value in the [0, 1] obtained from a uniform distribution to allocate the individual in a health state for the cycle 1 is used as follows:

If the uniform drawn value is in the $[0, p_{1D}]$ range the individual is going fall in the Dead health state (D). If it is in the $[p_{1D}, p_{1D}+p_{1S}]$ the health state is going to be Sick (S). Otherwhise (in the $[p_{1D}+p_{1S}, 1]$) the individual will reside, at least for the cycle 1, in the Well state. The simulation will be repeated for an individual until the dead state or the end of simulation time is reached; individual tracks would be performed up to the sample size wished for the cohort. The quality-adjusted life years (or cost) are calculated by taking the average of all the quality-adjusted life (or cost) spans in the cohort.

The individual simulation has the advantage that conditional factors can be set up (e.g., conditional adherence) because the simulation is performed for individuals rather than for a full cohort. This approach offers plenty of flexibilities but often requires a very large number of simulations for accuracy of estimates. The standard error of the sample

mean can be estimated from a preliminary sample of, say n=1000. Since the standard error is quasi-proportional to the square root of n, the standard error with sample size N would be estimated to be roughly $S_n*(n/N)^{1/2}$. The required sample size, N, depends on the magnitudes of the transition probabilities, the differences in utilities between states, and the effect sizes of interest. The HIV model by Freedberg et al. uses N=1,000,000 in order to obtain reliable estimates of cost-effectiveness ratios[86].

To seize parameter uncertainty for a cohort at population or individual level a probabilistic sensitivity analysis or a second-order Monte Carlo can be used. Both procedures require the input values to be extracted from a probability distribution. The results of the sensitivity analysis account for the variability in the input parameters. Even other distribution can fit the input parameters; cost can be drawn from a Gamma distribution, probabilities can be draw from a Beta or a Uniform distribution and utilities can be distributed as a Lognormal, Beta, or Uniform law. Several simulations are run using different input parameters. The analysis of the outputs obtained from these simulations provide a broad view of how much the variation in the inputs might affect the results and acts as a tool to check whether the assumptions made in the model definition are reasonable and do not influence the result. Both the cost-effectiveness acceptability curves (CEACs) and the scattered plot in the incremental cost-effectiveness plane are a good summary for the outputs of the sensitivity analysis and show the uncertainty of the model results.

The CEACs depict the probability that each scenario is the most cost-effective at any particular willingness to pay (or ceiling ratio) per unit of health gained. They are constructed by plotting the proportion of cohort simulations were each of the treatments assessed were cost-effective

for many ceiling ratios. It is noteworthy that the sum of the plotted proportions for every ceiling ratio value is 1.

The other figure is obtained by displaying the pairs of cost and effectiveness values for every simulation over an incremental cost-effectiveness plane. As it was described in Subsection 1.3.2.

Usually, the scatter plot covers all four quadrants, indicating uncertainty about whether or not the intervention is cost-effective, and at what value it is cost-effective. The purpose of the CEAC is to summarise this uncertainty[87].

3.2. Introduction to osteoporosis disease

Thirty percent of the postmenopausal women suffer osteoporosis in Spain[175]. This diseases is characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures, especially of the hip, spine and forearm, with vertebral fractures, although any bone can be affected[88-90]. Of all patients that developed a vertebral fracture, it is estimated that 20% will suffer a new vertebral fracture within a year[91]. Of all osteoporotic fractures, hip fractures are the most dangerous with an elevated mortality risk as well as a high hospital burden in Spain[92]. Osteoporosis has a negative impact on the health related quality of life (HRQoL) of the affected individual[93]. The increasing number of fractures due to osteoporosis in the past 20 years combined with the development of novel agents for the prevention or treatment of osteoporosis results in a health resources allocation problem[94].

Various treatments are approved for the prevention of osteoporotic fractures. Although they have been considered effective for the treatment of postmenopausal osteoporosis, some of them are not

appropriate for all women because of safety and/or tolerability issues[95, 96]. The selective estrogen receptor modulator (SERM) therapies, both raloxifene and bazedoxifene, had shown to reduce the risk of vertebral fractures in postmenopausal women[97]. Bazedoxifene has also associated with a favourable endometrial, ovarian, and breast safety profile in a 2-year, phase 3 study of postmenopausal women at risk for osteoporosis[98-100].

In Spain, approximately 2 million women[101] were estimated to have osteoporosis in 2010. Treating this population is associated with a high socioeconomic burden and both clinical and economic implications should be taken into consideration to build a model to compare the treatment options to achieve higher long-term benefits of fractures risk reduction.

Many models have been developed to study the socioeconomic impact of osteoporosis treatments for the Spanish National Health Service, as well as for patients[102-105]. Different tools are being used to estimate fracture risk which, at the same time, can vary significantly between countries[105], these items can influence the results of any cost-effectiveness analysis. A recently published cost-effectiveness analysis comparing bazedoxifene with placebo used the FRAX® algorithm that provides fracture probabilities for specific populations[105]. Although FRAX® can be used to predict the probability of hip or other major osteoporotic fractures, the criteria should not be generalized to other countries having different fracture incidence rates and health care[106]. Therefore, when comparing the cost-effectiveness of bazedoxifene with raloxifene for Spanish osteoporotic women, it is important to take into account that the incidence of fractures is different for Southern European countries than countries in the Scandinavian region[107, 108].

The objective is to build a model to evaluate the cost-effectiveness of bazedoxifene and raloxifene for the prevention of vertebral and non-vertebral fractures among women diagnosed with osteoporosis,

accommodating the special characteristics of the disease in the Spanish setting.

3.3. Model to estimate the cost-effectiveness of bazedoxifene versus raloxifene

Cost-Effectiveness analysis

Our work sought to assess the cost-effectiveness of the available SERM treatments in terms of cost per QALY. The clinical evolution of the disease was based on the Osteoporosis Study[109] and applied to the Spanish setting. The simulation model is implemented in Microsoft® Excel to calculate cost-effectiveness using an updated Markov model that has been used previously to estimate the cost-effectiveness of bazedoxifene incorporating the FRAX® algorithm using a European perspective[105].

The assessment was performed from the perspective of Spanish National Health Service and the time-horizon considered was 27 years, from 55 years old to 82 years old. The starting age was based on women recruited for bazedoxifene's 3-year treatment clinical trial[109] and 82 years old correspond to the life expectancy of a Spanish women[110].

QALYs gained was included as an effectiveness measure to allow us to compare the value of the interventions across different disease states. The incremental cost-effectiveness ratio (ICER), which is a measure of the added cost per QALY gained, is given as an output of this model.

Decision analytic model

The model evaluated the cost-efficacy of receiving bazedoxifene or raloxifene during this 27 year time. It was assumed that no patient discontinued treatment because of adverse effects.

Model specification

The model simulated the transition of postmenopausal osteoporotic women through six defined health states (represented by ovals in figure 3.4) based on yearly transition probabilities. All patients began in the well-health state or no event state. In each cycle, a patient had a probability of sustaining a fracture, remaining healthy, or dying. After one year in any fracture state, the patient had a risk of sustaining a new fracture or dying. When a woman passes away, she would continue into the dead-health state for the rest of the simulation. After one year, the patient moved to the corresponding post-fracture state if no additional fracture occurred. The patient would automatically remain in the post-fracture state (shown as a circular arrow) if she did not die or sustain a new fracture. Fractures could be vertebral or non-vertebral, consisting half of hip fractures and half of wrist fractures. After a non-vertebral fracture, it was possible to suffer a vertebral fracture or another non-vertebral fracture (Figure 3.4).

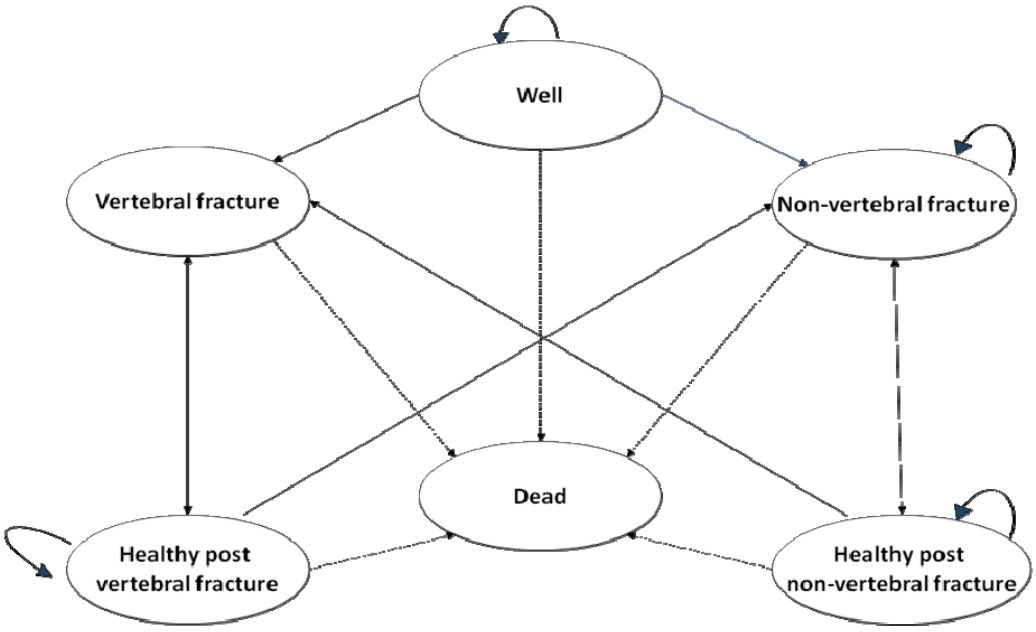


Figure 3.4. Graphic representation of the simulation model. Ovals represent the health states and the arrows the possible transitions among them.

The travelling between health states are made following the probabilities reported in the probability transition matrices for the patients treated with bazedoxifene or raloxifene, respectively. The efficacy and mortality data were obtained from published clinical trials and population demographics.

In Annex VII, the input parameters and their sources are detailed. The cohort simulation was run to obtain 2 cohorts of 100,000 women treated with bazedoxifene or raloxifene. For the cohort path in the disease evolution, cost and utility values were assigned according to the time of permanence in every health state. The values for cost and utilities were calculated accounting for the adverse events (also detailed in Annex VII).

3.4. Results

Results from the Markov model simulation using the input parameters in a deterministic way and a simulation of 1,000 trials using input parameters drawn from a theoretical probability distribution with 2 cohorts of 100,000 women are reported. The model validation is done by means of probabilistic simulation (see the model worksheets in Annex VIII).

Costs are reported in 2010€ and both costs and benefits are discounted at a 3% rate.

Deterministic analysis results

Deterministic results using a 27-year horizon and a 2 cohort of 100,000 women revealed that the expected cost per patient was 445€ higher in the raloxifene cohort compared with the bazedoxifene cohort (€13,436

vs. €13,881). The estimated QALYs gain was slightly higher in the bazedoxifene treatment branch than in the raloxifene one (14.56 vs. 14.54 QALYs). Their Incremental Cost-effectiveness Ratio (ICER) was estimated to be -22,250 €/QALY. In absolute terms, it can be said that bazedoxifene was the dominant treatment strategy, being less costly and more effective than treatment with raloxifene (Table 3.2 and Figure 3.5).

Table 3.2. Total Cost, Incremental Costs, QALY, QALYs Gained, and ICER

Treatment	Cost	Incremental costs	QALY	QALYs gained
Bazedoxifene	13,436 €	-445 €	14.56	+ 0.02
Raloxifene	13,881 €		14.54	

QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

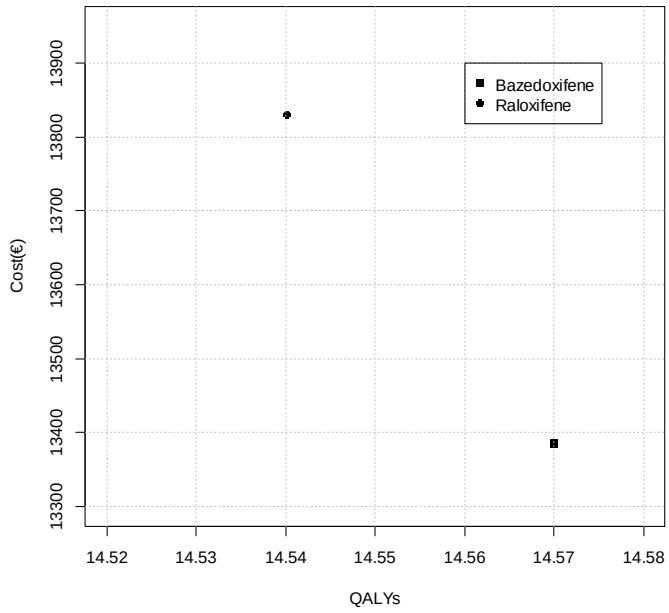


Figure 3.5. Cost efficacy plot for the two evaluated treatments. The values for cost and quality-adjusted life years (QALYs) are displayed.

Probabilistic analysis results

Beta and gamma distributions were used for probabilities and utilities, and costs to generate the values employed in the simulation. The model was run 1,000 times with all these three parameters varying

simultaneously. The results were presented as cost-effectiveness acceptability curves (CEACs) and as a scattered plot in the incremental cost-effectiveness plane.

The cost-effectiveness acceptability curves (CEACs) depict the probability that Bazedoxifene or Raloxifene are cost-effective, given the observed data, for a range of maximum monetary values that a decision-maker might be willing to pay for one QALY gain. It can be seen that bazedoxifene had a slightly higher probability of being cost-effective than raloxifene for a willingness to pay value ranging from 0 to €50,000 per an additional QALY gained (Figure 3.6). This range includes the commonly accepted willingness-to-pay threshold of €30,000 for a QALY in the health care sector in Spain[111], showing that bazedoxifene can be a cost-effective option for the Spanish National Health Service.

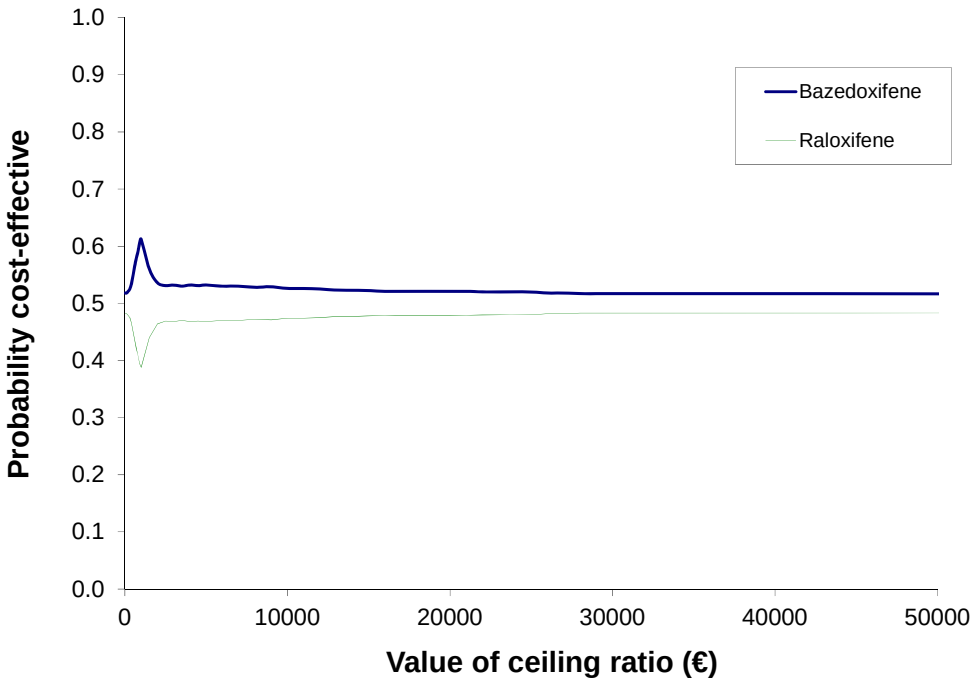


Figure 3.6. Cost-effectiveness acceptability curves: bazedoxifene versus raloxifene.

The mean incremental QALY and cost gain were estimated to be 0.16 and €-428, respectively, which showed that bazedoxifene was the dominant treatment strategy (Figure 3.7). It can be observed a large variability in the results: the dots that conform the ellipse fall within all of the quadrants, being the majority contained within the north-east (NE) and south-west (SW) quadrant. Realizations falling in the NE quadrant correspond to simulations that resulted in treatment more costly and more effective; the ones falling in the SW with the majority contained within the SW quadrant shown to be less costly and less effective. A 52% of observations were allocated in the south quadrants (below the X-axis) indicating that, in these cases, bazedoxifene was cheaper than raloxifene. The observations located on the east quadrants (right of the Y-axis) indicated that the 51% of the realizations showed that a greater QALY for bazedoxifene than for raloxifene.

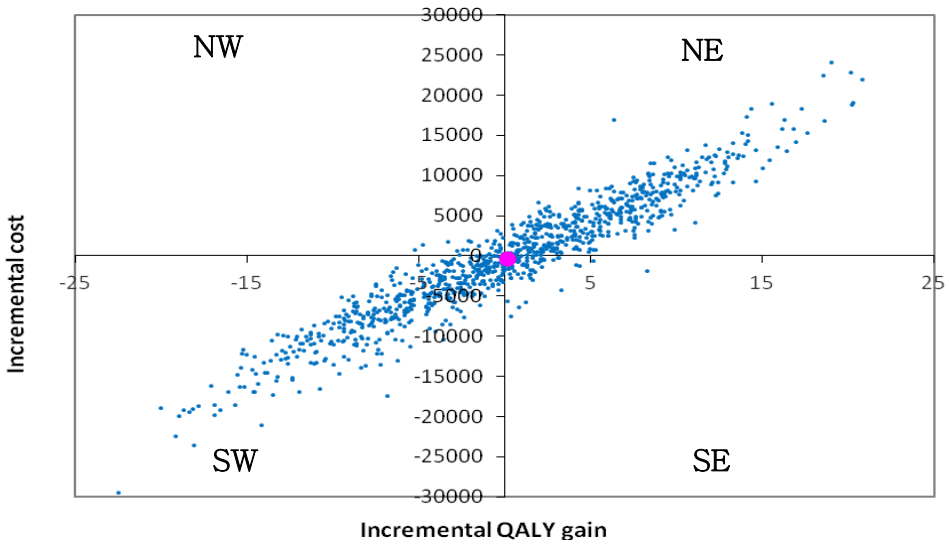


Figure 3.7. Cost-effectiveness of bazedoxifene versus raloxifene in postmenopausal osteoporotic women. Quality-adjusted life years (QALY). The large dot indicates the mean incremental cost and incremental QALY gain.

Model validation

The probability analysis was used also as a sensitivity analysis, as it was said, it accommodates the variation of the input parameters. It was observed that bazedoxifene generated slightly greater health benefit in terms of QALYs gained, but for some input parameters combination raloxifene could be preferable. As the difference between treatment cost and utilities is small a few variation among these input parameters can change the result in terms of labelling the dominant treatment, even the relative difference in cost and health outcome remain small.

3.5. Discussion and conclusion

Discussion

The accuracy of the results of the model depends on the quality of the input parameters, as always happen for these models. All of the parameters used where extracted from published studies. We selected the ones that reflect more closely the Spanish patient's characteristics and the clinical practice. One of considerable strengths of this study is that data on event incidences, post-event mortality, and costs were country-specific. The lack of specific data can be addressed assuming conservative scenarios and by including a probabilistic sensitivity analysis to assess possible deviations from the base-case analysis.

The disease evolution simplification can produce results separated from what could happen in reality and can be considered study limitations:

i) No treatment effect was assumed on non-vertebral fractures as the fracture incidence did not differ significantly from bazedoxifene treatment and placebo[97, 109], and raloxifene with placebo

ii) The adverse event considered relevant were extracted from the published paper. To increase or reduce this list with other possible adverse events could modify the results obtained

iii) The presence of adverse events did not result in treatment discontinuation

iv) The adverse events were assumed to decrease a 10% of the HRQoL for the first year and subsequent years based on assumption as appropriate estimates found on the utility loss was lacking in the literature. The assumption of 10% of utility loss due to leg cramps and breast cyst or fibrocystic breast disease could differ from the reality. These assumptions matter because once the utilities were corrected for HRQoL loss, QALY gain was slightly higher for the bazedoxifene cohort leading to a better cost-effectiveness. The change in the estimates of HRQoL loss could influence cost-effectiveness ratios. This can be controversial and arguable, although these parameters were varied into the probability analysis

v) The situation of multiple fractures simultaneously was not considered in the model and costs and HRQoL was not evaluated in this case. Furthermore, no data on patients sustained multiple fractures simultaneously was found in the literature

vi) The probability of suffering fractures is constant in time. This is one feature of the Markov models, even it can be solved, it is not straightforward to implement different transition probabilities depending on patients' age or another characteristic. In addition, most of the times the description of the change of the probabilities cannot be found or derived from the information in the literature

vii) The cost of bazedoxifene and raloxifene in the Spanish market was assumed to be the same. A time after the assessment performance –in November 2012- raloxifene was offered as generic which reduced its price[112]. The cost parameters in the model were established to the

nowadays drugs cost (€286.52 and €171.86 per bazedoxifene and raloxifene treatment per patient year) and the results obtained show that the expected cost per patient was 1,292€ higher in the bazedoxifene cohort compared with the raloxifene cohort. The estimated QALYs gain was slightly higher in the bazedoxifene treatment branch than in the raloxifene one (0.02 QALYs). The PSA shows that bazedoxifene and raloxifene are almost equal in their probability of cost-effectiveness.

The model was implemented using Microsoft® Excel Office 2007. It was built allowing the user to restore the original default parameters easily and to evaluate different possible scenarios, all input parameters were presented on one input worksheet and outputs displayed in several worksheets in a logical manner that summarizes the findings for the user, displaying tables and plots. The introductory worksheets describe the structure and the assumptions. These properties make this tool available and easy to use for the health care managers that should choose the best health care options.

Other software options are available for implementing the Markov models for simmulation, such as R or Matlab. More specific programs designed with the aim of using decision trees and Markov models for decisions in an applied environment are also in the market –for instance, TreeAge©– but they are not simple enough to allow a basic user to change the input parameters to calculate the results for different scenarios.

Conclusion

This study investigated the cost-effectiveness of bazedoxifene compared with raloxifene in Spanish postmenopausal osteoporotic women and indicated that bazedoxifene was the dominant treatment strategy compared with raloxifene for the prevention of vertebral and non-vertebral fractures in postmenopausal osteoporotic women aged 55 to 82

years. The probabilistic sensitivity analysis that accounted for parameter uncertainty confirmed the deterministic results in a 52% of the realizations and did not create an evidence to select between treatments. The use of bazedoxifene supposes a small gain in terms of cost and QALYs and the decision between treatments should be reinforced with other clinical features not included in the model, such can be safety and tolerability[113].

Raloxifene was available later (November 2012), as a generic, for a lower cost than bazedoxifene. The cost-effectiveness analysis with the current prices showed that it can be a cost-effectiveness option when compared with bazedoxifene (Data not shown).

Summary Chapter 4.

HIV TROPISM TESTING FOR MARAVIROC ALLOCATION. MARKOV MODEL IN N-STAGES

Markov models were adapted to reflect that the risk of suffering an event can change over time. This analytical model was applied to elucidate which of 3 available co-receptors tests is cost-effective to determine patient's suitability to benefit from the use of an antiretroviral treatment that includes maraviroc. All HIV strains require binding to CD4 plus at least one of the 2 co-receptors CCR5 or CXCR4 to enter human cells. Some HIV patients can use both co-receptors, and some individuals have a mixture of strains. Only patients with exclusively CCR5-tropic HIV are eligible to use the CCR5 antagonist maraviroc.

The co-receptor assessment with 454 test or PS is nearly equal in effectiveness to Trofile-ES test but less expensive. Their Incremental Cost-effectiveness Ratios (ICER) were estimated to be 68,185 €/utility and 77,482 €/utility. There is not a dominating strategy; the expensive strategies also have a higher health outcome. The results of the PSA showed that the differences between tests are very small and we cannot claim the superiority of any of them. The choice will depend on the maximum that the health service is prepared to pay per additional unit of utility gained.

4. HIV TROPISM TESTING FOR MARAVIROC ALLOCATION. MARKOV MODEL IN N-STAGES

The HIV/AIDS is a major health problem but antiretroviral (ART) regimens proved to be effective in decreasing HIV plasma viral load, improving CD4 cell counts, and have substantially altered the natural history of HIV infection. The introduction of new antiretroviral agents has broadened the number of active agents available for treatment of patients with infection due to HIV virus with certain particularities such as, its co-receptor type and/or the presence of drug resistance mutations. The new drugs in combination with new tools for the diagnosis have improved the success rate of therapy. In the case of the maraviroc, only patients with exclusively CCR5 HIV co-receptor (not CXCR4 either mixed-tropic virus) are considered eligible to use the CCR5 antagonist maraviroc.

The objective of our work is to compare the cost-effectiveness of three different tests to determine HIV co-receptor usage (CCR5 and/or CXCR4) in order to select candidates for maraviroc. Markov models are used to simulate a cohort of patients at a population level and its path through different health states to calculate cost and health parameters. The resulting cohort will be used to assess the performance of diagnostic tests in HIV antiretroviral treatment allocation. This is an adaptation of the available methodology implemented to add flexibility to the Markov models.

4.1. HIV antiretroviral treatment and HIV co-receptor usage tests

The HIV/AIDS is considered a pandemic, a disease outbreak that is not only present over a large area but is actively spreading[114]. Standard ART

therapy consists of the combination of at least three ART drugs to maximally suppress the HIV virus and stop the progression of HIV disease. Raltegravir, darunavir, maraviroc, and etravirine are new drugs frequently considered for use, particularly in ART experienced patients. Limited information exists regarding optimal combinations of these agents for the treatment. Selection of treatments combinations is often based on resistance testing results, prior treatment history, and any intolerance.

Maraviroc was shown to be cost-effective, particularly in individuals with limited options for active antiretroviral therapy[115]. However, the role of maraviroc in this setting has been limited because of the high frequency of dual/mixed-tropic or CXCR4-tropic virus in patients with long-standing HIV infection and the necessity for expensive tropism assay testing[116]. Various strains of HIV use one of two co-receptors -CCR5 or CXCR4- along with the CD4 receptor to enter human cells. Some HIV can use both co-receptors, and some individuals have a mix of strains (known as mixed-tropic virus). Only patients with exclusively CCR5-tropic HIV are considered eligible to use the CCR5 antagonist maraviroc, which blocks the virus from using this co-receptor.

Patients susceptible to be treated by the drug are screened using a phenotypic viral tropism assay, the standard of care is the called Enhanced sensitivity Trofile test. As the MERIT-ES study demonstrated, accurate identification of patients with CCR5-tropic virus is an important predictor of treatment response[117, 118]. Recently, researchers have shown that a genotypic tropism test -the 454 sequencing-, or Population Sequencing test -PS- may perform well in predicting which patients will respond to maraviroc and other drugs in its class. Genotypic tests (which look at viral genetic sequences) are easier to perform than phenotypic tests (which look at how the virus behaves in a test tube), and therefore are usually less expensive (see characteristics in figure 4.1).

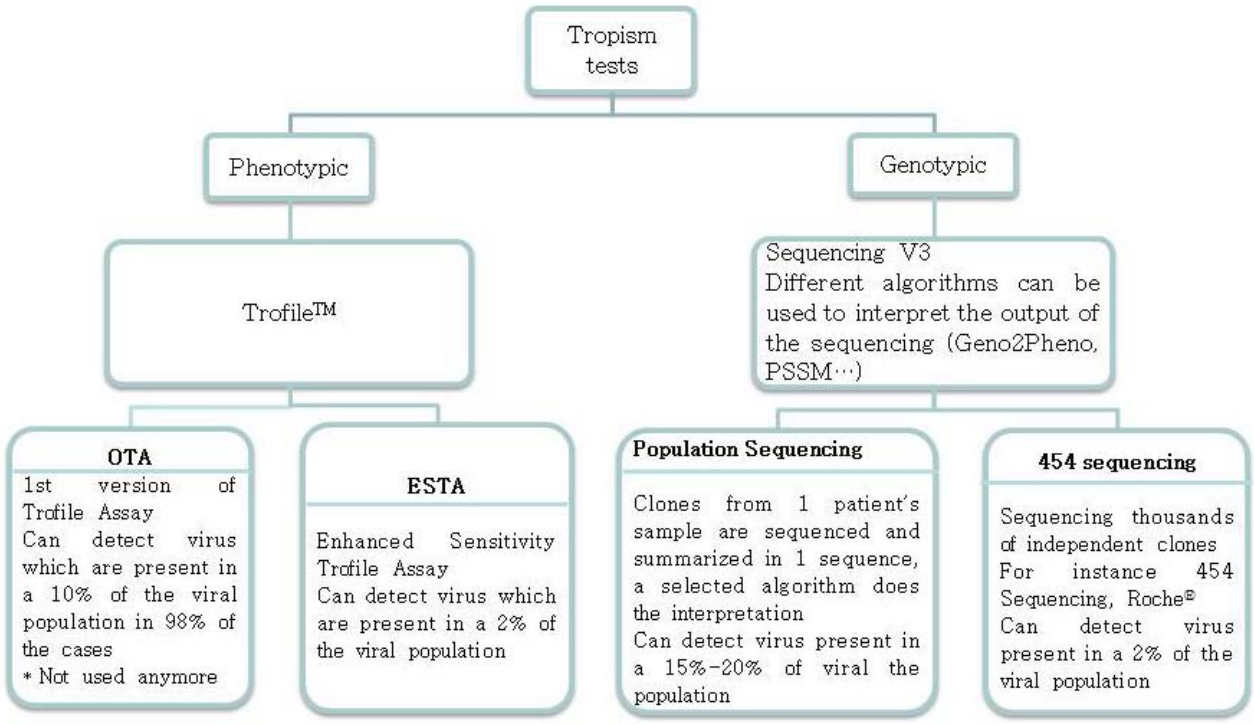


Figure 4.1. Description of the available tropism tests grouped by phenotypic and genotypic procedure. Their characteristics and their accuracy in virus detection are reported.

Investigators retrospectively analyzed stored samples from a subset of 572 participants in the MOTIVATE-1 trial, **which evaluated maraviroc versus placebo, combined with an optimized background regimen**, in treatment-experienced patients[119]. They compared treatment response rates between patients identified as having CCR5 virus according to the genotypic test and the Trofile assay. Note that this study used the original Trofile test, not the enhanced sensitivity assay used in the MERIT-ES re-analysis.

The genotypic test looked at the V3 loop of the HIV-1 gp120 protein, which plays a role in interactions between the viral envelope and host cell co-receptors.

V3 genotype and standard Trofile were comparable in predicting antiviral responses to maraviroc in treatment experienced patients[120]. Despite

apparently poor sensitivity of standard genotyping for predicting non-CCR5 HIV relative to standard Trofile, these findings suggest the potential of genotyping as an accessible assay to select candidates for maraviroc.

HIV V3 genotyping shows promise as a significantly faster and more cost-effective way to correctly identify patients who would benefit from CCR5 antagonists. Furthermore, the genotypic test is based on methods that are already widely used through the same labs that provide HIV drug resistance testing; this approach could become broadly available and be conducted at the same time as resistance testing to determine susceptibility to all drugs, including maraviroc.

The model should be realistic and reflect all the variability that the test selection implies in the daily clinical practice, furthermore than the accuracy, the cost of the tests and the possibility to extend their use for all patients should be considered. We adapt the simulation based on Markov models allowing different phases of the evolution of the disease process characterized by different transitions probabilities matrices. The full program for cost-effectiveness and sensitivity analysis was implemented in R (see Annex IX).

4.2. Markov models in n-stages

Markov models are a simulation tool frequently used in medical decision analysis. These models are especially appropriate when the disease of interest is characterized by the recurrence of particular events and when these are associated with a continuous risk over time[81]. The basic feature of the Markov model is that future events only depend on the current state that the patient is in, and not on prior events. A disease is characterized by using a finite number of health states and time is

handled as discrete periods of the same length. The implementation of the models is done assuming that the probability of travelling between health states is the same over time; flexibility can be added by introducing tunnel states and tolls, which make the model more complex.

For some of the biological parameters assessed in cost-effectiveness studies, it is relevant to consider various phases on the evolution, which can be characterized for different probabilities of transition among the health stages defined in the structure of the Markov model. A 2-phase evolution process can be observed in several biological parameters such as the control of the HIV viral load, the recovery of CD4, CD8 or lymphocyte cells under active ART therapy or the serologic course of Hepatitis A-E virus infection under treatment[121-125]. The model adaptation performed in this thesis allows considering different matrices of transition probabilities to describe different phases of evolution for the disease course.

The cohort simulation at a population level considers a hypothetical cohort of people were all members begin the process with some determined distribution among the states, usually designated according to the characteristics of our population of interest and/or the information found on the literature. In the next cycle, the cohort is divided among the states according to transition probabilities, which yields a new distribution of the cohort among the states. This continues in subsequent cycles until the process has reached the horizon time or the entire cohort reaches an absorbing state.

For the model building several elements must be defined:

i) A finite number of informative and realistic health states that can result from the evaluated therapies. The states should be mutually exclusive and collectively exhaustive

ii) The cycle length and the study horizon time. The time horizon should be equal to the sum of the lengths of the different phases considered

iii) Costs and utilities assigned to every health state

iv) The transition probabilities matrices must be specified. The number of transiton matrices is function of the number of therapeutic strategies assessed and they correspond to the number of Markov process to run. The performance of one Markov process was described in Section 3.1. When several phases of outcome evolution are considered, the probability of travelling between health states depend on the phase; this is reflected in the model by using different transition probability matrices.

Example:

A simulation by a Markov model in 2-phases is illustrated below, the 3 health states model introduced previously is used. Figure 4.2 represents the procedure of simulation to be run for every assessed therapeutic strategy.

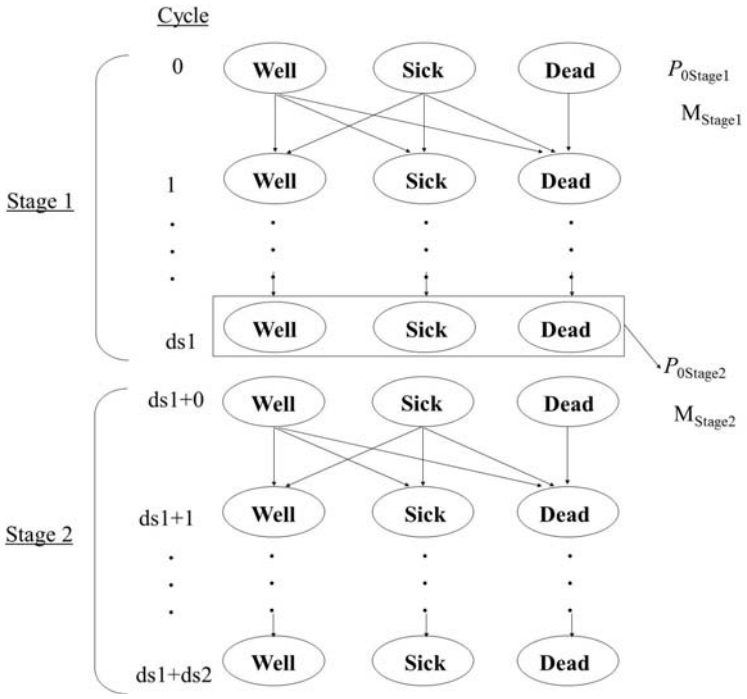


Figure 4.2. *Representation of a 2-stage Markov model. The arrows represent possible transitions between health states (ovals) in a cycle. Arrows do not connect health states with transition probability equal to 0. ds1 and ds2 are the cycles duration of stage 1 and stage 2, respectively.* $P_{0Stage1}$ *and* $P_{0Stage2}$ *are the proportions of the cohort in each state at time 0 and at the starting time of the Stage 2.* M_{Stage1} *and* M_{Stage2} *are the transition probabilities matrices associated to each evolution stage.*

The proportion of patients allocated in each health state at cycle 0 is defined initially and the distribution for next stages start is taken from the model, i.e., P at the end of stage 1 (time=ds1) is going to be used as starting proportion for the stage 2, considering a cohort with n individuals: P_{ds1}*=(number patients in Well state at ds1/n, number patients in Sick state at ds1/n, number patients in Dead state at ds1/n, number patients in Sick state at ds1/n). The simulation is run up to the horizon time or all the cohort is death.*

The model validation by means of sensitivity analyses and probabilistic study can be performed using the corresponding transition probabilities matrices and proportions of cohort at the starting time for the different stages. This adaptation of the procedure also works for the simulations performed at individual level, where the patients, one by one, travel in the different health states.

4.3. Model definition for the HIV co-receptors testing

The cohort simulation model was build to reflect the 2-phases of evolution of the outcome studied: the proportion of patients that achieve the control of the HIV viral load (HIV RNA VL≤50 copies/mL). The issues that have to be addressed are:

i) Definition and selection of the parameters needed in the simulation (transition probabilities matrices, utilities and cost for a patient being in a health status for a cycle, horizon time)
ii) definition of the structure of the Markov model
iii) selection of the summaries for reporting cost-effectiveness score of the evaluated strategies
iv) sensitivity analyses performance to explore the impact of taking alternative assumptions for the input values on the results.

Cost-Effectiveness analysis

Our study uses data about the target population, sensitivity and specificity of the evaluated tests and effectiveness of the intervention measured by means of utilities.

The interest of this work is restricted to the patients that have shown a Non X4 co-receptor and the use of maraviroc. The cost of tropism

testing for the patients whose test shows a X4 tropism is not considered as they are not in the studied therapeutic strategy: tropism testing plus treatment which includes maraviroc.

We simulate a cohort as described in section 4.2 of HIV infected whose characteristics are similar to those in MOTIVATE[119] or MERIT trial[117]. The simulation was performed up to 3 years of lifetime horizon[126]. The analysis was conducted from the perspective of the health care payer in Spain.

Cost-effectiveness was analyzed by estimating incremental cost and effectiveness.

Decision analytic model

In the situation of an HIV infected patient, maraviroc can be a therapeutic option. To assess whether the patient is susceptible to benefit from the treatment and if it can save resources, it is required to test the HIV co-receptor. The interest of this work is restricted to the patients that have shown a Non X4 co-receptor and the use of maraviroc (See Figure 4.3). The proportion of patients within each group can be calculated taking into consideration the prevalence of each co-receptor and the sensibility and specificity of the test to detect the co-receptor.

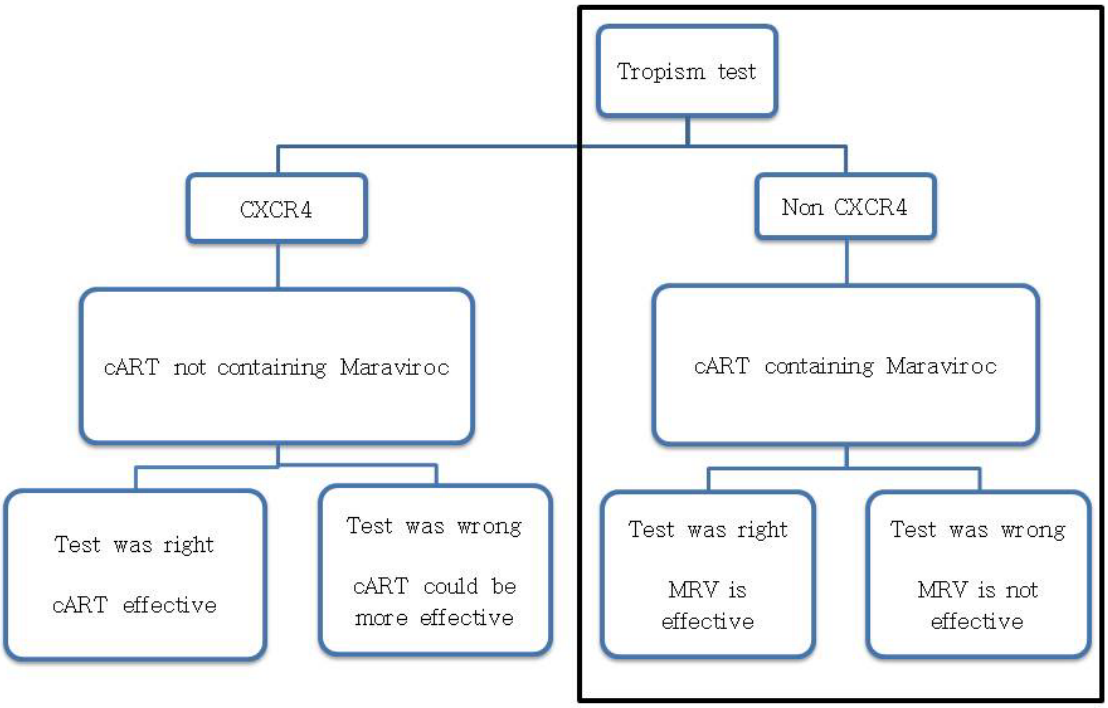


Figure 4.3. Flow chart for the tropism test result and treatment allocation. The assessment is focused on the patients receiving maraviroc, framed by a rectangle.

The evaluated tests to determine the HIV co-receptor were the Enhanced Sensitivity Trofile (Trofile-ES), the 454 test and population sequencing test (PS). The sensitivity and specificity of these tests are given in Table 4.1.

Table 4.1. Sensitivity, specificity of the assessed co-receptor tests are displayed.

	Trofile-ES	454 sequencing	PS
Sensitivity	100	73	60
Specificity	100	95	100

The prevalence of HIV infected patients with X4 co-receptor drive to the proportion of patients that receive MRV properly or improperly. For the study, null efficacy on virological control was assumed when prescribing maraviroc to patients with X4 co-receptor.

Model specification

The actual model contains the following health states: HIV RNA viral load (VL) under control (undetectable VL, i.e.: VL≤50 copies/mL), HIV RNA viral load detectable (VL>50 copies/mL) and death. The graphic representation of the health states and outcomes is shown in figure 4.4.

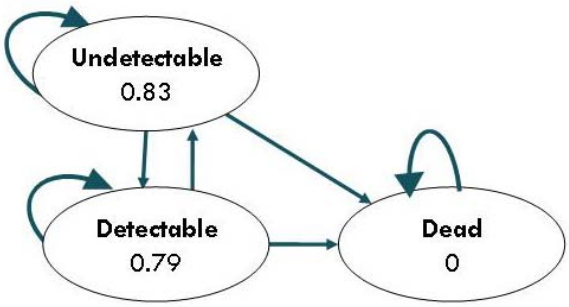


Figure 4.4. Graphic representation of the different health states included in the Markov model. Ovals represent the health states and the arrows the possible transitions among them. The utility scores are indicated into the oval in a scale from 0 (death) to 1 (perfect health).

A hypothetical group of patients starts in one of the Markov health states (ovals) and has a specified rate of transition (arrows) to other Markov states.

Two phases of achieving undetectability where considered[121]. The probability of travelling between health states is different for the period from week 0 to 24 weeks and over 24 weeks (Figure 4.5); this is reflected in by using different transition probability matrix.

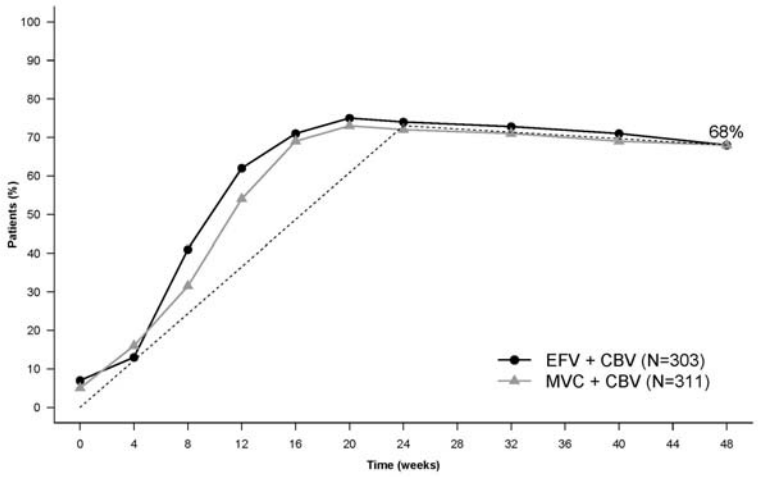


Figure 4.5. Graphic representation of the percentage of individuals achieving indetectability over time, results from the MERIT-ES study. Two phases were distinguished: from week 0 to 24 and from 24 to 48 weeks-depicted using the dashed line[118].

There were 6 Markov processes:

- patients allocated to Trofile-ES test,
- those allocated to the 454 and
- the population sequencing

all separated by the time (from week 0 to 24 and over 24 weeks). Table X.1 in Annex X shows the probability of travelling through the health-states in 1 cycle (3 months) by co receptor test; notated as MT1, MT2, MG1, MG2, MPS1 and MPS2, respectively[118].

Three hypothetical cohorts of 10,000 patients were assumed to be tested by Trofile-ES, 454 and PS tests. In order to assess the potential clinical and economic impact of the treatment alternatives, 3-month treatment cycles were estimated for each strategy. The cycles finished with 3 years of follow-up or death, which is an absorbing state.

All patients are assumed to begin in the Markov state "VL>50" equivalent to detectable HIV viral load.

Efficacy data and health-state utilities were obtained from published studies (See details in Annex X).

Costs were reported from the third party health care payer perspective, acknowledging that Spain has universal health care coverage that includes tests and prescript antiretroviral ART drugs for this patient's group (see disclosure in Table X.2). Considering the proportion of patients with adverse events (MERIT-ES study) the mean cost per patient/cycle were €3,161.13 for patients allocated to the Trofile-ES test, €3,067.38 for the patients allocated to the 454 test and €3,051.13 for the PS test group.

The utilities related to the states of Undetectable, Detectable and Death were 0.83, 0.79 and 0, respectively.
Cost and effectiveness annual discount rates were both set at 3%.

4.4. Results

Analytical results

The results were based on deterministic model calculations. The model estimated the average costs and utilities per patient of the lifetime horizon for the three groups of testing.
The utility for patients screened with Trofile-ES test was similar to patients screened with 454 or PS test (10.67, 10.66, and 10.65 respectively; equivalently 3.557, 3.553 and 3.550 utilities per year). The utilities gained were less than 0.1 utilities. This indicates that all co-receptor tests have a very similar performance in guiding the therapeutic strategy.
The expected cost per patient per 3 years of treatment was higher in patients tested with Trofile-ES test (€41,037; €13,679 per year) in comparison with patients in 454 test cohort (€39,821; €13,274 per year)

and the PS test (€39,609; €13,203 per year) with a difference of €1,216 and €1,428 (equivalent to €405 and €476 per year). This indicates that testing patients with the Trofile-ES test leads to more expensive treatment under the assumed conditions (Figure 4.6).

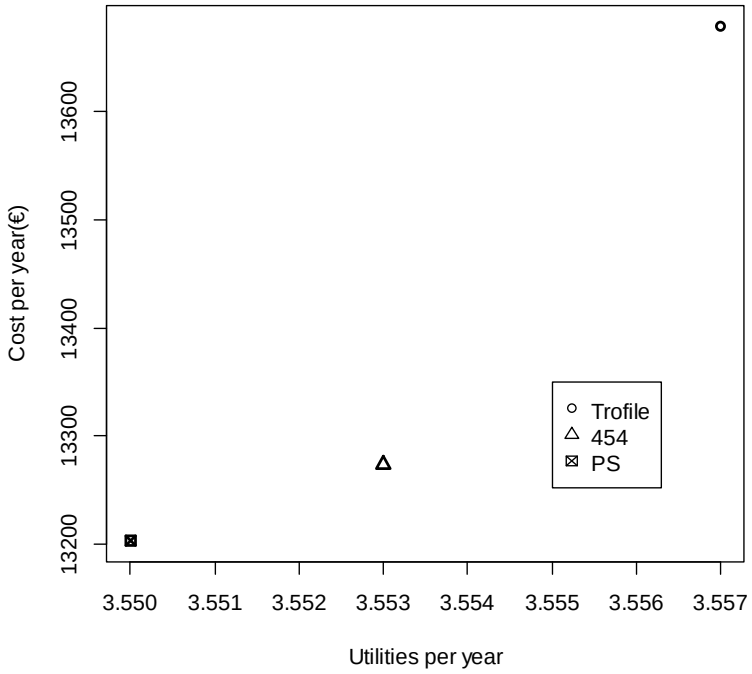


Figure 4.6. Cost efficacy plot for the three therapeutic strategies evaluated. The values for cost and utility for a year of simulation are displayed.

Therefore, the testing with 454 test or PS is nearly equal in effectiveness as Trofile-ES test but less expensive. Their Incremental Cost-effectiveness Ratios (ICER) were estimated to be 68,185 €/utility and 77,482 €/utility. There is not a dominating strategy; the expensive strategies also have a higher economical cost.

Model validation

The results produced by a model are as reliable as the quality of the data used to generate the results. In the Markov cohort model, the estimated average effects (Utilities) and costs are the direct outcome measures,

but they are ultimately dependent on the accuracy of the HIV-tropism test. The model's ability to translate test accuracy into patients with undetectable VLs is instrumental in the calculation of the ICER, which is the primary outcome measure that incorporates both costs and utilities. A penalization for the fact that a patient has to wait to know the HIV-tropism was introduced in the model by decreasing the utility in a 5% for every week of turn-around test result (Scenario 8 in the Table 4.2).

To assess the consequences of using concrete input parameters, the base case output was compared to the model output under a range of input parameters. A series of deterministic one and two-way sensitivity analyses were conducted to explore the impact on the ICERs of alternative assumptions for the values of key input parameters. The parameters and values tested generate a list of possible scenarios, which are described in the Table 4.2.

Table 4.2. Fifteen scenarios were created changing the input parameters to perform a sensitivity analysis. The Scenarios 1 to 8 are one-way analysis, and the following ones are two-way analysis

	Test Sensitivity	Costs	Utilities	Comments
Scenario 1		454, from 250€ to 150€		
Scenario 2		454, from 250€ to 100€		
Scenario 3	454, from 73% to 63%			
Scenario 4	454, from 73% to 83%			
Scenario 5	PS, from 60% to 50%			
Scenario 6	PS, from 60% to 70%			
Scenario 7			VL>50 from 0.79 to 0.69	
Scenario 8			Trofile-ES, VL≤50: 0.622;VL>50: 0.592 454, VL≤50: 0.705;VL>50: 0.671 PS, VL≤50: 0.746;VL>50: 0.710	The utilities are reduced to penalize for the turn-around test. A week of waiting time reduces 5% the utility. Trofile-ES: 5 weeks; 454: 3 weeks; PS: 2 weeks.
Scenario 9		454, from 250€ to 150€	Trofile-ES, VL≤50: 0.622;VL>50: 0.592 454, VL≤50: 0.705;VL>50: 0.671 PS, VL≤50: 0.746;VL>50: 0.710	Two-way sensitivity analysis: Scenario 1+ Scenario 8
Scenario 10		454, from 250€ to 100€	Trofile-ES, VL≤50: 0.622;VL>50: 0.592 454, VL≤50: 0.705;VL>50: 0.671 PS, VL≤50: 0.746;VL>50: 0.710	Two-way sensitivity analysis: Scenario 2+ Scenario 8
Scenario 11	454, from 73% to 63%		Trofile-ES, VL≤50: 0.622;VL>50: 0.592 454, VL≤50: 0.705;VL>50: 0.671 PS, VL≤50: 0.746;VL>50: 0.710	Two-way sensitivity analysis: Scenario 3+ Scenario 8
Scenario 12	454, from 73% to 83%		Trofile-ES VL≤50: 0.622;VL>50: 0.592 454, VL≤50: 0.705;VL>50: 0.671 PS, VL≤50: 0.746;VL>50: 0.710	Two-way sensitivity analysis: Scenario 4+ Scenario 8
Scenario 13	PS, from 60% to 50%		Trofile-ES, VL≤50: 0.622;VL>50: 0.592 454, VL≤50: 0.705;VL>50: 0.671 PS, VL≤50: 0.746;VL>50: 0.710	Two-way sensitivity analysis: Scenario 5+ Scenario 8
Scenario 14	PS, from 60% to 70%		Trofile-ES, VL≤50: 0.622;VL>50: 0.592 454, VL≤50: 0.705;VL>50: 0.671 PS, VL≤50: 0.746;VL>50: 0.710	Two-way sensitivity analysis: Scenario 6+ Scenario 8
Scenario 15			Trofile-ES, VL≤50: 0.622;VL>50: 0.517 454, VL≤50: 0.705;VL>50: 0.586 PS, VL≤50: 0.746;VL>50: 0.620	Two-way sensitivity analysis: Scenario 7+ Scenario 8

The results of the series of sensitivity analysis performed to explore the impact of taking alternative assumptions for the input values on the results are displayed in the Table 4.3.

Table 4.3. Results of the cost-effectiveness study, in terms of cost-effectiveness ratios (ICERs), according to the various possible scenarios (units given in 2010 Euros)

Analysis	Trofile test		Genotypic 454 test		PS		ICER		
	Total Cost	Total Utilities	Total Cost	Total Utilities	Total Cost	Total Utilities	Trofile vs 454	Trofile vs PS	454 vs PS
Base-case	41037	10.67	39821	10.66	39609	10.65	68185	77482	353767
Scenario 1	41037	10.67	**39659**	10.66	39609	10.65	77287	77482	83300
Scenario 2	41037	10.67	**39578**	10.66	39609	10.65	81837	77482	-51933
Scenario 3	41037	10.67	39821	**10.66**	39609	10.65	67504	77482	505381
Scenario 4	41037	10.67	39821	**10.66**	39609	10.65	68377	77482	326554
Scenario 5	41037	10.67	39821	10.66	39609	**10.65**	68185	75998	221104
Scenario 6	41037	10.67	39821	10.66	39609	**10.65**	68185	78418	558564
Scenario 7	41037	**10.42**	39821	**10.36**	39609	**10.35**	19209	22129	171177
Scenario 8	41037	**8.42**	39821	**9.05**	39609	**9.58**	-1916	-1231	-404
Scenario 9	41037	**8.42**	**39659**	**9.05**	39609	**9.58**	-2186	-1235	-95
Scenario 10	41037	**8.42**	**39578**	**9.05**	39609	**9.58**	-2314	-1235	59
Scenario 11	41037	**8.42**	39821	**9.05**	39609	**9.58**	-1916	-1231	-404
Scenario 12	41037	**8.42**	39821	**9.05**	39609	**9.58**	-1916	-1231	-404
Scenario 13	41037	**8.42**	39821	**9.05**	39609	**9.58**	-1916	-1231	-404
Scenario 14	41037	**8.42**	39821	**9.05**	39609	**9.58**	-1916	-1230	-404
Scenario 15	41037	**7.81**	39821	**8.80**	39609	**9.31**	-1230	-953	-416

Note: Values in black represent the changes with respect to the base-case analysis.
A negative ICER means that the 2nd therapeutic strategy improves the utility and reduces the cost.

A great variability can be observed from the results obtained for the different scenarios. As a summary, it can be said that, for a 46.7% (7/15) of the cases, the Trofile test showed to be more costly and more effective than the 454 test (ICER>0). In a 46.7% (7/15), the Trofile-ES was more costly and more effective than the PS test and for a 46.7% (7/15) the 454 test was more costly and more effective than the PS test.

In addition to the deterministic sensitivity analyses, a probabilistic sensitivity analysis was conducted.

Probabilistic sensitivity analysis (PSA)

The probabilistic simulation was performed by drawing each model parameter value from a specific probability distribution reflecting either patient's individual characteristics or parameter uncertainty.

The Beta distribution was used to generate the transition probabilities, and the utility values, the Gamma distribution was used for the costs. The distributions'parameters was computed by using the base-case value and its standard deviation assigned to be the 10% of the value, since these data were not available[127].

The utilities and cost of the 1,000 simulated trials per each of the three therapeutic strategies were computed. The cost-effectiveness ratios were plotted on the cost-effectiveness plane, and the cost-effectiveness acceptability curves were derived.

It is required to define the ceiling Ratio and compute the net monetary benefit for each therapeutic strategy in order to plot the acceptability curve. The ceiling ratio indicates the amount of Euros that is worth to pay for the gain of one unit of health, 1 unit of utility in our case. The net monetary benefit for each therapeutic strategy was computed per every trial as the utility multiplied by the ceiling ratio minus the cost, and this value was used to assign a 1 to the therapeutic strategy that has the larger benefit, and a 0 to the other 2.

A range of values of the ceiling ratio was used in order to plot the probability of each therapeutic strategy to show a larger benefit than the others.

The PSA showed results in which all treatments can be cost-effective since the density of the point estimates were spread in all quadrants of the cost-effectiveness plane (Figure 4.7). Regarding the mean of the incremental cost and utilities for the comparisons two by two it can be said that, in mean, the Trofile-ES test was dominated compared to the 454 test (Incremental cost=987.57, Incremental utility=-0.07); and also when it was compared with the PS test (Incremental cost=1,304.71, Incremental utility=-0.02). When comparing the 454 test and the PS, the first had a larger cost and a larger gain in health (Incremental cost=317.14, Incremental utility=0.04).

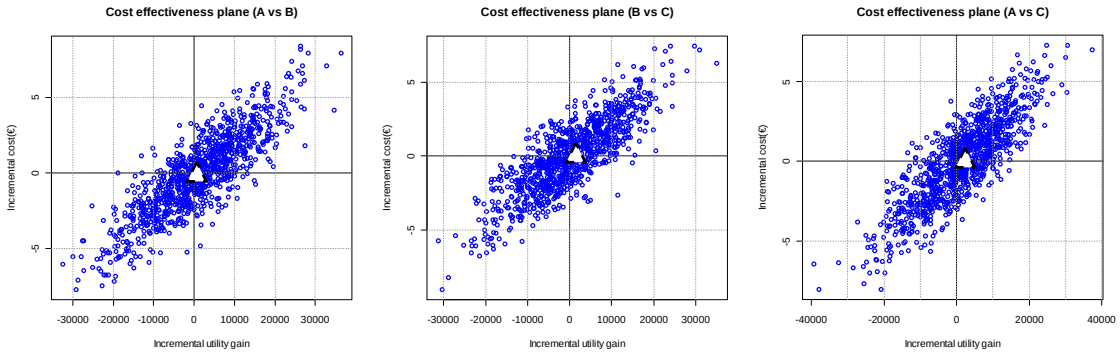


Figure 4.7. Cost-effectiveness plane for the comparison between therapeutic strategies. A=Trofile-ES, B=454 test and C=PS.

The figure 4.8 shows the probability that a treatment is the most effective of the three therapeutic strategies at a different threshold values for cost-effectiveness (ceiling ratio). For small willingness to pay quantities (under €10,000) the differences are small and the cheapest test seems preferable. For ceiling ratios from 10,000 onwards the difference between tests are very small and we cannot claim the superiority of any of them.

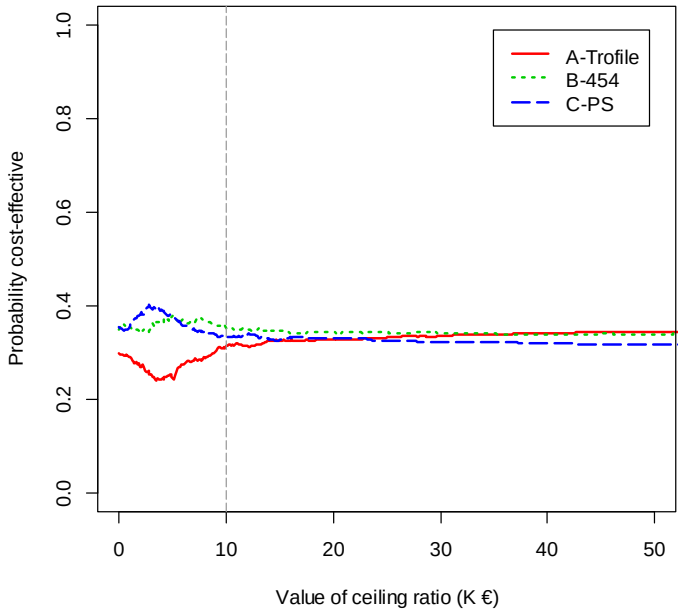


Figure 4.8. Cost-effectiveness acceptability curve for the three therapeutic strategies by different values of the ceiling ratio.

4.5. Discussion and conclusion

The limitations and the strengths of the model are detailed, the contextualization of these issues allow us to understand better the relevance and applicability of the conclusions.

Study limitations

There are several gaps in empirical data that need to be filled. Information is lacking, for instance, on the relation between test accuracy and treatment allocation. The hypothesis that a wrong treatment allocation drives to treatment failure is not right in 100% of the cases, since the ART treatment is composed by 3 or 4 antiretroviral drugs, even MRV is not active the other drugs can control the virus replication leading to an HIV-RNA undetectable viral load. This assumption avoided

adding the probability of failure as a parameter in the model. Treatment efficacy reduction due to poor compliance and aspects such as treatment switching were not included in the model.

The sensitivity analysis tried to account for the variability generated by the previously described terms and other unknow ones, while extra-assumptions about them were not added in the base-case analysis.

A higher-order Markov model can include historical information on several patients' health states in the probabilities of moving next into a health state or another [128]. In addition, microsimulation models, which during the last 20 years have been increasingly applied in qualitative and quantitative analysis of public policies, can solve this issue. Their technique would let each patient start the simulation at a different risk of becoming undetectable and this risk changes over time[129]. The microsimulation requires a larger set of input parameters than the cohort simulation and, it usually, gives similar results.

The efficacy data used in this analysis were taken from a North-American population. Compliance with treatment recommendations and consistency of refilling are also likely to differ between health-care systems and cultural settings. It was shown that insurance coverage for prescription drugs increases the probability of use[130]. Thus, the availability of country-specific data when evaluating the cost-effectiveness is of relevance.

Strengths of the model

The implemented model could accommodate 2-phases of evolution of the outcome studied, emulating what happens in "real" life. It was a useful tool to learn about the cost-effectiveness of the three assessed tests to determine the HIV co-receptor without the need of doing a prospective clinical study.

Discussion

The use of HAART had reduced the viral replication and reconstituted immunity, leading to longer periods of symptom-free disease and survival after AIDS diagnosis, and to changes in the natural history of HIV-associated illnesses. This encompasses an increase in the number of individuals that require treatment, taking into account the limited resources that can be spent on health services, the economic assessment for new antiretroviral medications are of interest for the health decision-makers to optimize the use of health care resources.

Cost-effectiveness analysis aim to provide information on the value of a new co-receptor test compared to the standard intervention. Cost-effectiveness does not necessarily mean cost-saving; the total cost of a therapeutic strategy can be higher, but still considered good value for money if it enhances significantly the health outcome relative to the current standard.

The model performed is an attempt to simulate a real world process using input data describing physical characteristics of the system, a set of algorithms to transform input data to output parameters of interest and simplifying assumptions to limit the scope of the model. The accuracy of the output measures depends on the quality of the input parameters and the structure of the model.

The input parameters are estimations that have an implicit variability, which was not considered in the modelling process, but sensitivity analysis measured how this uncertainty can affect the results.

The time horizon was settled to 3 years, longer simulation times can be unrealistic for the following reasons:

- the patient's characteristics change over the time,
- therapeutic strategies and SOC can evolve,
- and new variables of decision to allocate test and treatment can be identified as relevant.

The current economic evaluation applies to the Spanish situation. The inputs for the model have been obtained from published literature review. The scope of the analysis was to compare the performance of three HIV co-receptor tests. The study was performed from the payer's perspective, in which only direct medical costs were included.

Conclusion

The deterministic incremental analysis showed that the 454 test could be considered cost effective when compared to the gold standard test. The cost of the therapeutic strategy that includes the 454 test is cheaper than the one including the Trofile-ES test, and the obtained utilities are very similar. The Population Sequencing test showed a smaller health benefit, but it is cheaper than the other two options. The probability sensitivity analyses have shown that all tests can be considered cost-effective when the ceiling ratio of 10,000 is surpassed. The relevant point is to fix the maximum that the health service is prepared to pay per additional unit of utility gained.

Summary Chapter 5.

COST OF A NEW TREATMENT FOR THE PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH). BUDGET IMPACT ANALYSIS

Chapter 5 provides an example of cost study for a rare disease, the paroxysmal nocturnal haemoglobinuria (PNH). A budget impact analyses was performed to assess the economic effects of introducing eculizumab for treating the PNH. Direct and indirect costs of this disease treatment were estimated and reported from the perspective of the health care system and from the societal perspective. The use of eculizumab for treating the PNH would imply an incremental yearly cost of €300,650 per patient compared to standard of care, but would provide larger societal benefits and an improvement in health related quality of life of the PNH affected patients leading to overall savings.

5. COST OF A NEW TREATMENT FOR THE PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH). BUDGET IMPACT ANALYSIS

Interest in cost analyses has accompanied concerns about rising health care costs, pressures on health care policymakers to allocate resources, and the need for health product makers, and other technology advocates, to demonstrate the economic benefits of their technologies[131]. Accordingly, assessing such costs with accuracy and building a predictive model for future medical costs are of interest. The budget impact analysis (BIA), also called financial model, is a methodology for the estimation of the economical cost and consequences of adopting a new health-care intervention within a specific health-care setting or system.

Studies of costs and related economic implications comprise a major group of methods used in health technology assessment. These studies can involve attributes of primary data collection and/or integrative methods, i.e., cost data can be collected as part of RCTs and other clinical studies, and also through administrative databases used in health care payment[131]. Cost data from one or more such sources often are combined with data from primary clinical studies, epidemiological studies, and other sources to conduct cost-effectiveness analyses and other cost studies that involve evaluating health and economic impacts of health technology.

The objectives in this chapter are to estimate the direct, and indirect, costs of extending a new therapy (eculizumab) for a rare disease such as paroxysmal nocturnal hemoglobinuria (PNH), compared to the standard care and to provide a prediction of the cost impact for the next 5 years. Moreover, this evaluation was conducted from the perspectives of the health care system and the societal care system.

Section 5.1 explains the methodological approach used to perform a BIA. In section 5.2, the clinical background of the PNH is described, next the model details to perform this analysis for the PNH treatment are given (Section 5.3). The results, and the final discussion and conclusions are displayed in sections 5.4 and 5.5.

5.1. Budget impact analysis (BIA)

The BIA has two goals: the estimation of the average cost of different therapy strategies used to treat a health condition and the prediction of how a change in treatment will influence the trajectory of spending on that health issue. This analysis can be used for budget planning, forecasting and for calculating the impact of health technology changes on health-care guidelines; it could be a good complement to the cost-effectiveness analysis (CEA), which accounts for the cost per unit of health improvement[132]. National regulatory agencies of several regions in the world including Australia, North America (Canada, United States), Europe (England and Wales, Ireland, Belgium, France, Hungary, Italy, Poland) and the Middle East (Israel), have included a request for BIA alongside the CEA, when submitting evidence to support national or local formulary approval or reimbursement of the new health-care interventions. Other countries have typically performed their own BIA (The Netherlands) rather than requesting it from the manufacturer, although voluntary submission is permitted. Country-specific guidelines for constructing BIAs are also available [133-143]. These guidelines are variable in terms of defining what constitutes a BIA and most of them provide only limited details on the important factors. An exception are the Polish guidelines[142], which provide precise recommendations on perspective, time horizon, reliability of data sources, reporting of results,

rates of adoption of new therapies and sensitivity analysis. The Spanish national regulatory agency does not have any guidelines or recommendations.

A literature review published in 2005 by Mauskofp et al.[144] indicate that the number of studies in peer-reviewed journals is limited and varied greatly in the methods they used. Estimations of the financial impact for different timeframes and/or target patients were described:

i) for a timeframe of 1 to 3 years

ii) for lifetime costs for a specific cohort

iii) for a set of representative individuals being started on competing treatments.

A more limited number of published studies attempt to explicitly estimate the financial and health-care service impact of a new therapeutic strategy for a well-defined national or health plan population.

Instead of publication, budget impact analyses are more frequently presented directly to decision makers as interactive computer programs designed to calculate the financial impact for specific health plans. There is also the ongoing debate about whether a BIAs should be totally or partially publicly available for review.

BIA methods

Whereas an economic analysis addresses the additional health benefit gained from the resources invested in health, the BIA addresses the affordability of a new therapeutic strategy. Several factors, which are not generally needed for cost-effectiveness analysis, should be part of a comprehensive budget impact analysis including the size of the treated population, second-order costs, market diffusion rates for the new drug, and off-label use[137]. See in Figure 5.1 how the information of BIA and the

incremental cost-effectiveness ratio (ICER) as a summary of a cost-effectiveness analysis (CEA) can be obtained.

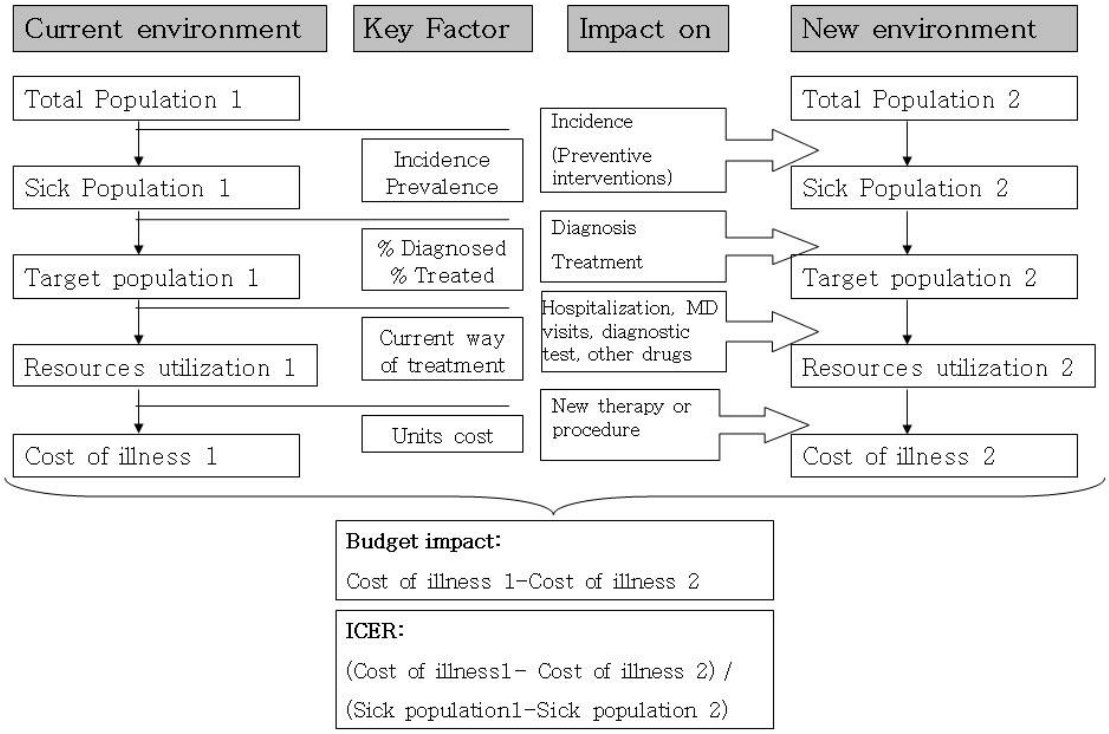


Figure 5.1. Schematic representations of the budget impact and ICER computation. Both approaches compare the current environment with a new one –which can include a new therapeutic strategy–. BIA reflects resources use and the ICER considers both costs and health outcome. Adapted from Brosa et al.[145]. MD stands for medical doctor.

The quantification of the affected population out of the total and the definition of the target population that can be benefited from the use of the health care intervention assessed is relevant, these numbers are going to frame the cost analysis. For instance, if the interest is to assess the congenital toxoplasmosis, the population of interest should be reduced to pregnant women. The epidemiologic information, the demographic data, and some risk factors should be taken into account to form the right frame for the study.

The resources used to treat a particular health condition should be listed as detailed as possible, but the cost assessment will be quantified for some selected items (or all) according to the cost component (or components) and the perspective of interest.

Costs in health care can be subdivided into three components: Direct costs, indirect costs, and intangible costs. The items included in each component are described as follows:

- The direct costs reflect the amount of money spent on medical products and/or services as a direct result of an illness
- The indirect costs are the lost potential productivity resulting from illness-related absences or impaired performance at the workplace and at patient's normal life activities
- The intangible costs include humanistic measures of changes in health status such as health related quality of life, joy, and satisfaction or the cost of worries, pain, and suffering. These items are often included in the health outcome quantification by means of a health related quality of life or utility score.

Further definitions about cost are given in Annex XI.

The direct costs are relatively easy to measure. The indirect costs are considered costs from the perspective of society as a whole. Many of these are difficult to measure, and there is some controversy over which ones to include in the list and how to measure them. For instance, the UK National Institute for Clinical Excellence, NICE, adopts a limited societal perspective in its evaluations and considers the direct costs falling on the UK National Health Services, and those indirect costs funded by the state such as unemployment and sickness benefits[146].

Two perspectives can defined in terms of the view point of the analysis: If the health care payer point of view is selected, the study only accounts for the direct costs of health care for this specific payer and if the study

is conducted from the perspective of the society as a whole, direct, and indirect cost are both important. In general, the **societal perspective** is considered the most appropriate, but a health care manager with a limited budget might be tempted to ignore the societal view and consider only the costs that affect his own budget. An example of this situation is a study of migraine performed under the health service perspective only suggested that sumatriptan in migraine (an expensive drug in comparison with a cheaper treatment as the standard of care) was highly undesirable, but a study taking a societal perspective came to the opposite conclusion[147]. This example drives us to note that the comparison between 2 or more treatment scenarios is possible by repeating the cost calculations under the current environment and under the environment where the new treatment strategy is used, which is displayed in the last column of the figure 5.1, labelled as "New environment".

Two important concepts are the opportunity cost and the marginal cost. The **opportunity cost** is defined as the benefit foregone when selecting one alternative intervention (treatment A) over the next best alternative (treatment B). The opportunity cost of investing in a healthcare intervention (treatment A) is best measured by the health benefits that could have been achieved if the same amount of money had been spent on the next best alternative intervention (treatment B). The **marginal cost** is the resource cost associated with the use of treatment A in spite of treatment B, being an indicator of the amount of additional resources that must be expended or can saved (see detailed explanations in Annex XI).

The perspective and items included in the analysis should be defined clearly and the data collection needs to be reflecting values as updated and accurate as possible. The validity of the results depends on the quality of this data.

The first models on value of health were developed in the insurance industry to assess and to characterize both the risk of suffering a disease, and the population health-care cost. The data used in the modelling was the recorded by the health insurance claims. During the last years, the study and prediction of the cost became an important subject of research to guide the health resources allocation; some of the authors have applied different statistical techniques to do the estimations and prediction[148]. Some published examples of budget impact analyses are described in the review by Mauskopf et al[144]. As time goes by, more data derived from administrative databases and/or expert opinion is available.

In order to predict the financial impact the most common approaches are

- to estimate the direct costs of the treatment of a health condition by assuming a linear behaviour in the cost for the near-term years and updating the proportion on the target population.
- Alternatively to impose a tax of increase of target population into a Markov model incorporating clinical and epidemiological data to simulate the target population throughout the timeframe analysis. This method is suitable for diseases with rapid evolution.
- Regression models are also used to characterize the cost as dependent variable in function of a set of independent variables selected by their clinical and economical relevance. The use of the coefficient estimated by the model can be used to predict the mean cost for next years.
- Data mining tools were the newest and accurate approach that Bertsimas et al. applied to provide predictions of future health-care costs. With the use of decision trees and clustering algorithms along with claims data from over 1,000,000 insured individuals over three years discovered that the pattern of past cost data is a strong predictor of future costs and medical

information provides an accurate prediction of medical costs particularly on high-risk members[148].

5.2. The paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, genetically acquired blood disorder characterised by chronic intravascular hemolysis (destruction of red blood cells). PNH is clinically defined by the lack of the complement inhibitory protein CD59 on the surface of red blood cells. CD59 normally blocks the formation of the terminal complement complex on the surface of the red blood cell, which prevents hemolysis. The list of signs and symptoms of PNH include hemoglobinuria (presence of blood in the urine), anaemia, fatigue, difficulty swallowing, abdominal pain, erectile dysfunction in men and thrombosis[149-151]. PNH is most common among men in their 20s, but it occurs in both genders and at any age, causing high morbidity and mortality.

It is estimated that rare diseases -those whose frequency is under 5 cases / 10,000 people- affect about 6% of the European population. The PNH is considered a rare disease which affects an annual rate of 1-2 cases per million[152]. Hill et al.[157] estimated that the annual incidence is 1.3 cases per million, and the prevalence is of 15.9 cases per million of inhabitants. Men and women are affected equally and PNH may occur at any age but it frequently is found among young adults with a median age at the time of diagnosis of around 42 years (range, 16-75 years). This disease process is insidious and has a chronic course, with a median survival of about 10.3 years after the diagnoses[153].

PNH is the only hemolytic anaemia caused by an acquired intrinsic defect in the cell membrane. In the field of anaemia, 1% of couples are at risk of having a newborn with a severe syndrome of haemoglobin such are

sickle-cell disease or thalassemia. More than 330,000 children are born worldwide each year affected by one of these disorders. In Spain, the average risk of having a newborn with a rare or unusual anaemia has increased due to African immigration[154].

Treatment of PNH consists on supportive care measures including corticosteroids, androgen hormones, iron and folate supplementation, sometimes transfusions (generally reserved for crises) and allogenic stem cell transplantation which have been successful in a small number of cases until the development of a new drug known as eculizumab. This is a recombinant humanized monoclonal antibody that works by binding to complement protein C5, inhibiting its enzymatic cleavage, blocking the formation of the terminal complement complex, and thus preventing red cell lysis*. In 2007, the drug (eculizumab, Soliris™; Alexion Pharmaceuticals, Inc., Cheshire, CT), received approval as an orphan drug by the U.S. Food and Drug Administration (FDA) and by the European Medicines Agency (EMEA) for the treatment of patients with PNH to reduce hemolysis[155]. The FDA approval was based mainly on a randomized, double-blind, placebo-controlled, clinical trial in 87 RBC transfusion-dependent adult PNH patients, with supportive evidence from two observational studies:

- A phase II pilot study involving 11 PNH transfusion-dependent patients, and
- a 52-week, open-label, non-placebo-controlled, single-arm study in 96 PNH patients[156].

Two clinical trials to study the efficacy of eculizumab were published; Sheperd[165] and Triumph[162], both has shown that eculizumab reduces intravascular hemolysis after the first week of treatment. The control of the hemolysis reports anaemia diminution and consequently the required

* Lysis is defined as destruction or decomposition, as of a cell or other substance, under influence of a specific agent.

blood transfusions were reduced by 51%. Fatigue was also reduced after a few weeks of treatment, and the release was maintained up to the end of the study. Also, 3 phase II* studies concluded that eculizumab treatment leads to less blood transfusions need and a reduction on risk of thrombosis events[157, 158].

The aim of this study was to assess the budgetary impact in Spain of using eculizumab as a newly approved pharmacotherapy for PNH compared to the standard of care. Two perspectives were used: the health care system and the societal care system considering the cost of the comorbidities and the patient's inability to work and perform a "normal life".

5.3. Model for assessing the PNH treatment

Model

A budgetary impact model using Microsoft Excel Office 2007 following the international recommendations has been elaborated to estimate healthcare costs of the extended use of eculizumab as a treatment for PNH. The model was implemented allowing the user to restore the original default parameters easily and to evaluate different possible combinations. All input parameters were presented on one input worksheet and outputs were displayed in several worksheets that summarize the findings for the user, displaying tables and plots. The introductory worksheets describe the structure, assumptions, and use of

* There are 5 phases for describing the clinical trial of a drug based on the study's characteristics. Phase 2 studies gather preliminary data on effectiveness (whether the drug works in people who have a certain disease or condition). For example, participants receiving the drug may be compared with similar participants receiving a different treatment, usually an inactive substance (called a placebo) or a different drug. Safety continues to be evaluated, and short-term adverse events are studied. [Reference: http://www.clinicaltrials.gov/ct2/info/glossary#P]

the model furthermore than all sources and assumptions associated with the input (see Annex XII and Annex XIII).

Published clinical guidelines, clinical literature and expert opinion were employed to describe the required treatment and progress-over-time of patients affected by PNH. The analytical model was built as a flexible tool to predict the potential financial impact when changing some input parameters.

Population

The eligible population was obtained from estimates of the number of Spanish citizens affected by PNH.

Treatment options

Two therapeutic strategies are applied in the Spanish region: the standard of care consisting in blood transfusion, anticoagulant treatments, hematopoietic stem cell transplantation and/or bone marrow transplantation and the new treatment with eculizumab, which was the only treatment approved for the PNH[159, 160]. The standard of care has a limited and variable efficacy a non ignorable amount of adverse events that require continuous concomitant treatments complicate tackling the disease[159, 161]. Two scenarios were compared in the analysis: patients treated with blood transfusion versus the eculizumab treatment. These are the two common therapeutic strategies used in practice.

An expected 15%, 35%, 55%, 70%, 85% and 100% of patients receiving eculizumab treatment were considered in the model in the first, second third, fourth and fifth year, respectively. It was assumed that patients with PNH are going to switch progressively from the standard of care treatment to eculizumab.

Time horizon, perspective, and discounting

The analysis was performed with a 5-year time projection from the public payer and societal perspective. The costs were in Euros (EUR, 2010) and were reported with and without discounting by a 5% annual rate[135, 136]. The undiscounted values are given because in the good practices of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) reports is stated that budget impact analyses present financial streams over time and it is not necessary to discount the costs. However, some national guidelines published for BIA performances advise to apply a discount 6% annual rate, instead of 5% as we did.

Resources and costs

The model has been developed considering the costs associated to the standard of care and eculizumab treatments using the evolution of the disease and treatment efficacy and adverse event described in the Hillmen et al.[162-164], Brodsky et al.[165] and Kelly et al.[166] research papers.

The base-case analysis was defined as the eculizumab treatment and the alternative scenario was defined as the standard of care, mainly based in blood transfusions.

The following resources and treatment components were identified and quantified as direct costs: drug costs, dispensing and administrating costs, the cost of treating the adverse and PNH related events. In the indirect cost setting, patients' traveling expenses to attend to the health center and the loss of production due to PNH were included.

Eculizumab should be administrated in doses of 600mg per week during the first 4 weeks of treatment, 900mg in the 5th week and after the 6th week 1 dose of 900mg every 2 weeks[166]. The cost of eculizumab for the first year is 342,650€ and for the 2nd and consecutive ones is of 320,400€ per patient year (PPY). The mean cost PPY is 315,479€.

Costs of treatment administration and visits to the clinic where also quantified. For both treatments, associated costs of medical supervision, screening and transfusions cost were considered. For the standard treatment the same cost where considered. For the eculizumab treatment the cost of drug doses administration by nursing staff were also added.
Input parameters are displayed in the Annex XII: data for adverse events, direct and indirect costs related to PNH.

Sensitivity analysis

One-way sensitivity analyses were performed to test the robustness of the model. Direct and indirect costs in addition to the survival time used as input parameters in the base case analysis were modified one at a time to see the differences in the results obtained when changing the data.

5.4. Results

Base-case analysis

In the base-case analysis (eculizumab), the estimated drug cost was €318,842, a 88.05% higher than in the case of the alternative scenario (Standard of care). The administration costs were of €559, a 34.54% higher than in the standard of care. The cost of the adverse events were estimated to be €72, a 7.17% lower than in the standard of care.
It is remarkable the difference between the prevalence of thrombotic episodes in both treatment groups: a 3% for patients treated with eculizumab and a 27% for the standard of care. In addition, a higher number of chronic kidney disease in stages 1-3 is observed in the standard of care (59% versus 34%). The higher cost to deal with an

adverse event is the treatment for the chronic kidney disease in stages 4-5, with a cost of €62.4, in the base-case assuming the need of 5 dialysis per year[167].

The direct total costs for 1 year of eculizumab treatment were estimated to be €319,473, being superior to the costs of the standard of care. The difference is due to the drug and administration cost, the other costs are favorable to eculizumab.

The indirect costs rise to €104 plus €130 for the travelling to the medical visits and for the drug administration. The total cost per loss of production is non-existent, the losses were due to the time required for drug administration €4,693, being €5,197 the total indirect cost associated to eculizumab treatment versus €384,662 for the standard of care. This large difference is due to the larger survival (mean survival time for patients treated with eculizumab is 25 years larger than the survival receiving the standard of care) and, consequently non-productivity loss for patients treated with eculizumab (see Table 5.1 below, and tables XII. 2 and XII.3 in Annex XII).

Table 5.1. Summary of direct, indirect and total costs per patient year by treatment group (2010 Euros)

	Eculizumab	Standard of care	Difference
Direct Costs			
Drug costs	318,842	18,468	300,374
Administration costs	559	272	287
AE and events related to PNH cost	72	83	-11
Total Direct Costs	319,473	18,823	300,650
Indirect Costs	5,197	384,662	-379,465
Total Costs	**324,670**	**403,485**	**-78,815**

Alternative scenario

The direct drug cost for the standard of care treatment amounted to €18,468, while administration cost were €272, the cost of treating the adverse-events were €83, and the cost per chronic kidney disease in stage 4-5 was €60.72. The total amount of direct costs per patient year was €18,823. A large difference in drug costs favorable to the standard of care is observable.

The indirect costs for travelling expenses were €520 (€208 for medical visits plus €312 for drug administration), the cost of the administration time amounted to €22,846 and the loss of productivity was estimated in €361,296. The loss of productivity due to drug administration is higher for the standard of care in comparison to eculizumab.

Even the direct costs for the eculizumab treatment are higher than the costs in the standard therapy; the indirect costs show the inverse situation. In the indirect costs items, the loss of productivity, the loss of working time, and the travelling costs are higher for the standard of care. The computation of the different items of costs can be summarized in two values: the societal total cost for eculizumab treatment was €324,383 per patient year, and the cost for the standard of care was €403,484. The treatment with eculizumab represent a saving of €79,102 relative to the standard of care (See Figure 5.2).

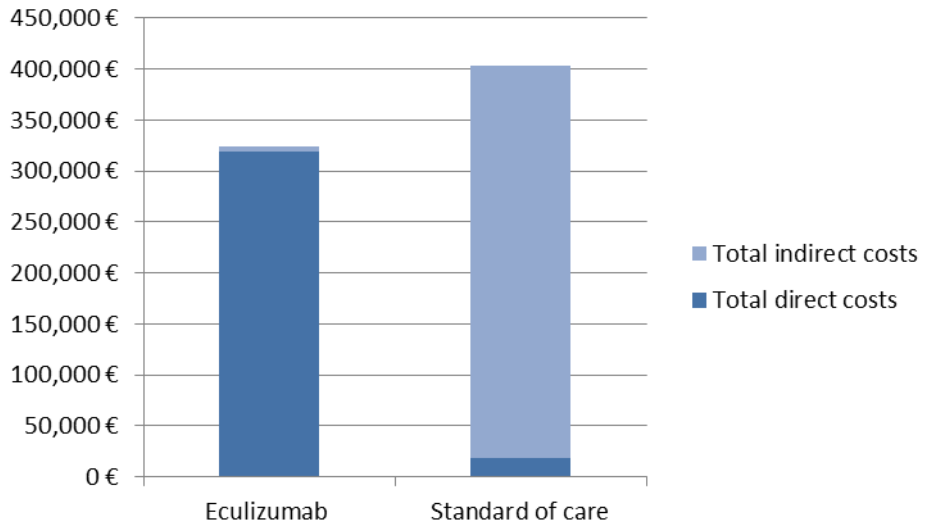


Figure 5.2. Direct and indirect total costs for the Eculizumab treatment and the standard of care.

Sensitivity analysis

One-way sensitivity analyses were performed to test the robustness of the model. Base-case values were modified for the following parameters:

- Direct costs. Differences of adding and subtracting a 10% in cost were tested. These were labelled as Scenario A1 and A2
- Indirect costs. Differences of ± 10% in cost were tested (Scenarios B1 and B2)
- Survival time after diagnoses: Influence of adding and subtracting a 10% of mean survival to the PNH patients were evaluated (Scenarios C1 and C2).

The sensitivity analysis had shown that the results for the assessed scenarios agree with those obtained in the base-case analysis. It was seen that the higher cost could reach a total of €356,265 in the eculizumab treatment and a total of €445,172 in the Standard of care. The largest difference between treatment arms was seen when the scenario C2, where the incremental cost for using eculizumab amount to €120,790 more than in the standard of care. Detailed results are shown in Table 5.2 and in Figure 5.3.

Table 5.2. Direct and indirect costs are displayed by the different scenarios and by treatment group (2010 Euros)

Scenario and treatment	Direct Costs	Indirect Costs	Total costs
A1-Eculizumab	351357	4910	356267
A1-Standard of care	20669	384662	405331
A2-Eculizumab	287588	4910	292498
A2-Standard of care	16976	384662	401637
B1-Eculizumab	319473	5401	324874
B1-Standard of care	18823	423128	441950
B2-Eculizumab	319473	4419	323892
B2-Standard of care	18823	346195	365018
C1-Eculizumab	319473	4910	324383
C1-Standard of care	18823	342974	361796
C2-Eculizumab	319473	4910	324383
C2-Standard of care	18823	426350	445172

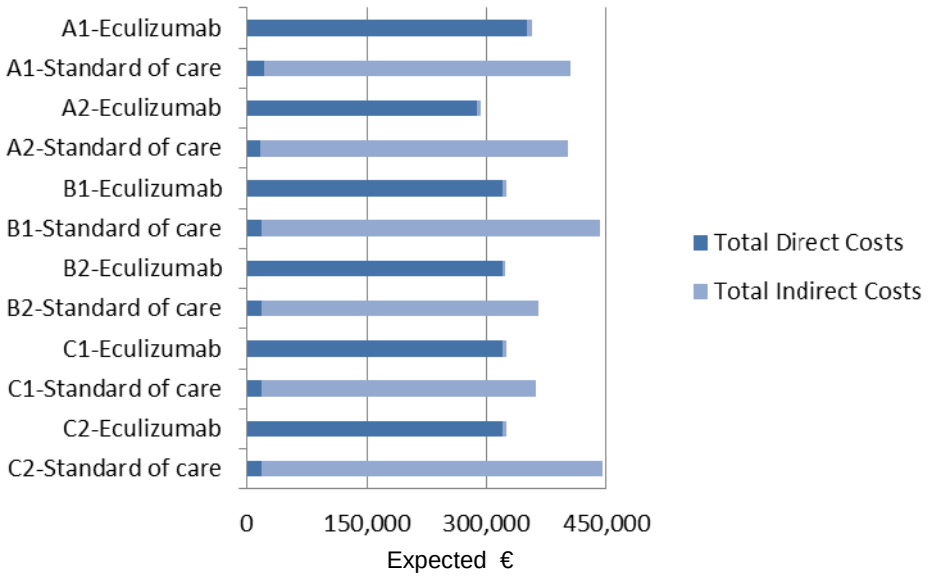


Figure 5.3. Diagram indicating the direct and indirect costs for the different scenarios of the sensitivity analysis.

Budget impact analysis

The budget impact analysis provides and estimation of the cost of the substitution of the standard of care by the eculizumab treatment. The percentages of patients treated with eculizumab are 15%, 35%, 55%,

70%, 85% and 100% at five years. The calculations are done taking into account the total direct costs per patient.

Total budgetary impact for a hypothetical population of 100 patients with an annual growing tax of 1% for 5 years of time horizon has shown an increase on PNH treatment expenditure when the number of patients treated with eculizumab is larger. The expenditure is calculated in 2010€ with a 5% of discount tax, see Table 5.3 and Figure 5.4.

Table 5.3. Budget impact analysis of the use of eculizumab versus the standard of care for 5 years

% Patients Treated	Now	1st year	2nd year	3rd year	4th year	5th year
Eculizumab	15%	35%	55%	70%	85%	100%
Standard of care	85%	65%	45%	30%	15%	0%

Total annual direct and indirect costs	Now	1st year	2nd year	3rd year	4th year	5th year
Eculizumab	€ 4,865,739	€ 11,466,926	€ 18,199,649	€ 23,394,822	€ 28,692,078	€ 34,092,940
Standard of care	€ 34,296,158	€ 26,488,739	€ 18,521,741	€ 12,471,306	€ 6,298,009	€ 0

Discounted total annual costs	Now	1st year	2nd year	3rd year	4th year	5th year
Eculizumab	€ 4,865,739	€ 10,893,579	€ 16,425,183	€ 20,058,135	€ 23,369,877	€ 26,380,467
Standard of care	€ 34,296,158	€ 25,164,302	€ 16,715,871	€ 10,692,586	€ 5,129,768	€ 0

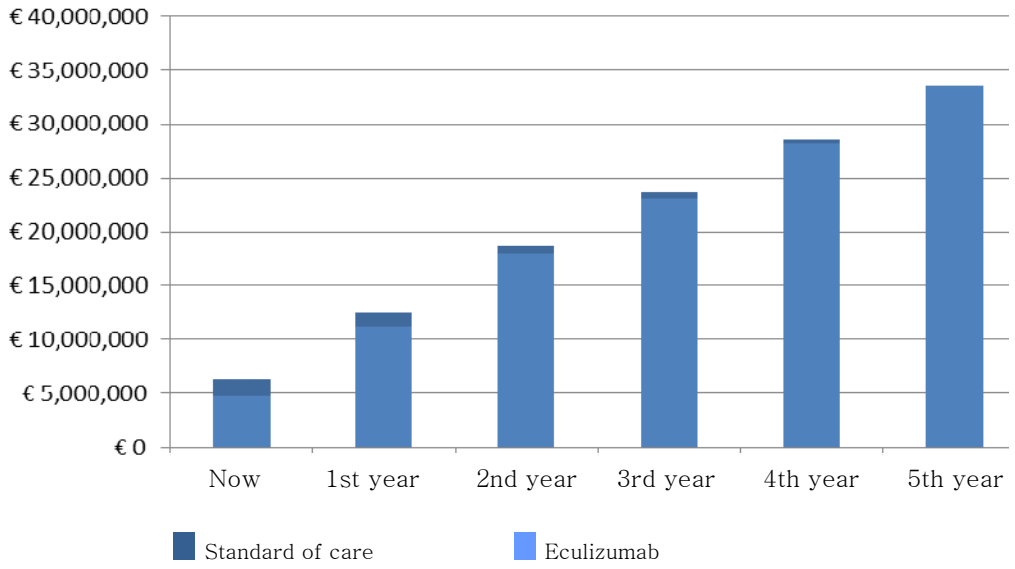


Figure 5.4. Budget impact of the use of eculizumab versus the standard of care for 5 years while the percentage of patients treated with eculizumab increases over time.

Treating patients suffering from PNH with eculizumab instead of the Standard of care resulted in a reduction in total societal costs of €79,102 per patient year, even the direct costs are larger when treating patients with eculizumab.

5.5. Discussion and conclusion

Discussion

The present work is an update of the current situation in terms of a number of patients and costs of the PNH. The goal is to provide details of the resource consumption and more accurate estimates of the budgetary impact, based on data following the complete clinical situation, including adverse events and events related to the studied disease.

There are several limitations to be considered in this model, including the very limited number of published reports regarding resource consumption in PNH treatment. Prospective studies conducted under standard clinical practice, designed to collect resources and costs data associated to PNH would be desirable and could provide reliable information to be used in further economic evaluations[168]. Potential improvements in health related quality of life and benefits resulting from better health at a social level were included in the present model, but future works could be even more useful if a health score would be added, such can be the utility or a burden of disease score.

An increase in the number of patients under PNH seems to be realistic; this was reflected in the budget impact analysis for 5 years using the 1% of patients growing tax.

Conclusion

The introduction of new (and expensive) pharmaceutical products is one of the major challenges for health systems[169]. The use of eculizumab for treating the PNH would imply an incremental yearly cost of €300,650 per patient compared to standard of care, but would provide larger societal benefits and an improvement in health related quality of life of the PNH affected patients leading to overall savings. These results would help the Regional, and National Authorities to perform a better allocation of

available resources, decisions in incorporating the new treatments to the guidelines and into the new standard of care can be taken with objective information.

Summary Chapter 6.

DALYS IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS. HEALTH BENEFITS QUANTIFICATION

Most of the published clinical studies are focused on measuring health in terms of efficacy and/or safety. Sometimes health and well-being quantification is not a direct measurement. The calculation of the burden of disease for osteoporotic women who may suffer from fractures done at an individual level was presented in terms of disability adjusted life years (DALYs). It was quantified that Mean (SD) overall undiscounted DALYs lost per woman were 6.1 (4.3), with a significantly higher loss in women with severe osteoporosis with prior bone fracture (BF); 7.8 (4.9) compared with osteoporotic women (5.8 (4.2)) or postmenopausal women with a BMD >-2.5 T-score after receiving a drug-based therapy (6.2 (4.3)). Factors explaining the variation in the levels of health were the alcohol consumption, having rheumatoid arthritis, previous osteoporotic bone fracture, family history of osteoporosis, using corticosteroids and a lower BD revealed to be linked to a larger DALYs lost. Few studies of burden of diseases are available, and even less for Spanish population and performed using individual characteristics. The identification of risk factors can improve the clinical practice by guiding the concerns that should be considered in the osteoporosis prevention.

6. DALYS IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS. HEALTH BENEFITS QUANTIFICATION *

Different approaches are available for measuring the health benefit of any therapeutic strategy or any intervention performed. Historically, mortality rates have been used to describe health status across communities. These measures do not fully account for the burden of premature mortality, an important indicator of a population health. In fact, since most deaths occur among persons in older age groups, mortality rates are dominated by the underlying disease processes of the elderly[170]. Premature mortality entails estimating the average time a person would have lived if he or she had not died prematurely. This estimation inherently incorporates age and death, rather than merely the occurrence of death itself[171]. Over the last decades the need of measure the health outcome has increased. The introduction of an objective summary to quantify the health status is needed to better explain health across populations and to compare different treatments and/or individual groups (see further definitions in Annex II).

When morbidity is taken into account, the two dominating summary measures are the Quality Adjusted Life Years (QALYs), and the Disability Adjusted Life Years (DALYs). QALYs and DALYs represent an implicit trade-off between quantity for quality of well-being. In QALYs, premature death is combined with morbidity by attaching a weight to each health state such that value 0 represents death, while value 1 represents full health. The number of QALYs for a health profile is found by multiplying the health related quality of life weight (HRQoL) of the health state, with the duration of the health state. Like the QALY, the DALY measure facilitates comparisons of all types of health outcomes by

* The DALY calculations and some of the statistical analysis presented in this chapter have been performed along with Lisette Kaskens

attaching disease weights were value 0 represents full health and value 1 represents death. Note that these disease weights are the opposite of the HRQoL weights in the QALY. A DALY can therefore be seen as an inverse QALY[172].

The goal of this chapter is to assess the burden of disease of the osteoporosis in postmenopausal women. DALYs are computed using individual information. Section 6.1 describes how the DALYs can be calculated. Section 6.2 contains the details of the calculation of the DALYs for the postmenopausal women with osteoporosis, the details of the available data and the statistical analysis. The description of the health quantification by means of DALYs and the factors associated to a higher burden of disease are given in section 6.3. The discussion and conclusions are displayed in the last section.

6.1. DALYs calculation

The description of the characteristics of the disability-adjusted life year (DALY) for individual data is presented in the followoing. DALYs can be calculated according to Fox-Rushby et al.[173].

Previous to the DALYs computation we must state some definitions:

K is the standard age-weighting modulation factor;

C is a constant;

r is the discount rate, usually r=0 or 0.03;

a is the age of death or the age of onset of disability, for the calculation of Years of life lost (YLLs) and Years of life lived with disability (YLDs), repectively;

β is the parameter from the age weighting function

L is the standard expectation of life at age a or the duration of the disability for the calculation of YLLs and YLDs, repectively;

D is the disability weight.

Calculations done using the individual data of the subjects in the sample:

1) Utility (U) and disutility (D) values:

$$D = 1 - U$$

The disutility value can be used in the following formulas as the disability weight.

2) Years of life lost (YLLs):

The term YLLs is calculated using the following formula:

$$YLLs[r, K, \beta] = \frac{KCe^{ra}}{(r+\beta)^2}\left\{e^{-(r+\beta)(L+a)}[-(r+\beta)(L+a)-1] - e^{-(r+\beta)a}[-(r+\beta)a-1]\right\} + \frac{1-K}{r}\left(1-e^{-rL}\right)$$

3) Years of life lived with disability (YLD) is equivalent to the YLLs (adapting the definition of a and L) multiplied by the disability weight, in the formula noted as D:

$$YLDs[r, K, \beta] = D * YLL[r, K, \beta]$$

4) Life expectancy (LE) at a particular age is

$$LE[a] = LE - a$$

5) And years of life lived with disability at age a is the product of disability weight and duration of disability at age a, i.e.

$$YLD[a] = Life\ lived\ with\ disability[a] * D\,.$$

6) DALY equals to the sum of YLLs and YLDs.

$$DALYs = YLLs + YLDs\,.$$

For the calculations at steps 2 and 3: The values introduced for r, K, and β were the ones recommended by Murray et al.[196]: r=0.03, K=1 and β=0.04. C is a constant with value 0.1658. These values constitute the base case analysis. The YLLs and YLDs can be computed without a discount rate (r=0) and without age weighting (K=0).

The life expectancy, LE, was extracted from the Spanish national statistics database[174]. The information of the individuals recorded in the data set was used in the YLLs and YLDs calculations. The onset of the disease, life expectancy at a particular age and the disability weight were included in the formulas in order to obtain a particular value for each individual.

It is noteworthy that 4 values for the DALY can be computed for every individual in the data set, depending on the discounting and age weighting combinations: Discounted, weighted by age; Discounted, non-weighted by age; Non discounted, weighted by age and Non discounted, non-weighted by age.

The DALYs calculation using individual information is illustrated in the case of a sample of postmenopausal women. The reported DALYs are with and without a discount rate and without age weighting. Once calculated, the DALY values are analyzed as a dependent variable with the goals to estimate and describe the burden of the disease.

6.2. DALYs calculation for postmenopausal women with osteoporosis using individual information

The osteoporosis disease and its clinical importance was described in section 3.2.

The burden of osteoporosis in Spanish postmenopausal women has not been established. Osteoporosis is a very common disease; about three million people have this health problem in Spain, most of which are women. Approximately 30 out of every 100 women suffer of osteoporosis after menopause. Every year osteoporosis causes more than 1.3 million fractures of vertebrae, hips, and wrists in the world. Most of the fractures require a delicate and expensive surgical operation that does not ensure perfect patient recovery. It was found that fractures caused by osteoporosis cause a substantial hospital burden in Spain[175].

6.2.1. Data

The data used for the DALYs calculations belong to a cross-sectional, epidemiological one-visit study that enrolled 4,157 postmenopausal women (at least 12-month after last menstrual period) with osteoporosis, who were attending outpatient clinics of Gynecology in Spain. The patients' clinical characteristics, bone densitometry and health related quality of life (HRQoL) data were recorded. The DALYs could be computed in 2,782 (67% out of 4,157) Spanish postmenopausal women with a diagnosis of osteoporosis (spinal bone mineral density -BMD- T-score < -2,5 according to WHO criteria and identified by DXA) within the last two years with information on BMD, date of diagnosis and HRQoL at the time of data collection.

The groups of interest were defined by using the T-score value and the fact of having suffered an osteoporotic bone fracture: Osteoporotic women with bone fracture (BF), Osteoporotic women without BF and T-score > -2.5[176].

Demographics and clinical details of women (2,782) who were included in the DALY analyses are summarized in Table 6.1. The total sample has 9.8% of the women in the osteoporotic with bone fracture group, 70.4%

in the osteoporotic without bone fracture and 19.8% in the osteopenic group. The respective mean ages are 63, 61 and 60 years old, and 28.3%, 41.3% and 45.1% of each of them are working. The body mass index (BMI) mean of the studied women are 25.6 kg/m^2 for the osteoporotic with BF, 25.8 kg/m^2 for the women in the osteoporotic without BF group and 25.7 kg/m^2 for those with osteopenia. The clinical characteristics show significative differences between groups on age, the presence of comorbidities such as diabetes mellitus, hypertension, rheumatoid arthritis, and malabsorption syndrome and osteoporosis disease data. Also the employment situation and educational level is related to the prevalence of osteoporosis[177-179].

Relative to background therapies used among the studied groups, calcium supplement and vitamin D are the most used therapies (approximately 80% of the women use it), followed by the Biphosphonates (approx. 50%). The Selective Estrogen Receptor Modulators (SERM) is used in more than 40% of the women belonging to osteoporotic women and women with osteoporosis without BF, and a 26.5% of the women with osteoporosis with BF.

Table 6.1. Socio-demographics, clinical characteristics and participant background for all included women and by study group

Variable	All (n=2782)	Study group by BMD			
		Severe osteoporosis with prior BF (n=272)	Osteoporosis (n=1958)	T-score >-2.5 (n=552)	F or Chi-^{2} (p value)[£]
Socio-demographic data					
Age (years)	61.0±7.3	63.3±7.3	60.9±7.4	59.9±6.6	20.3 (p<0.001)
Age group (%)					
≤44	0.4	0.0	0.5	0.2	38.4 (p<0.001)
45-49	3.6	1.5	3.7	4.2	
50-54	13.8	9.6	13.6	16.8	
55-59	28.3	21.7	28.4	31.0	
60-64	25.3	28.7	24.9	25.0	
≥65	28.6	38.6	28.9	22.8	
Employment situation (%)					
Working	40.7	28.3	41.3	45.1	37.4 (p<0.001)
Transitory sick leave	2.3	4.0	2.2	1.6	
Permanent disability	0.8	1.5	0.7	0.5	
Unemployment	3.2	3.3	3.6	2.0	
Retired	20.3	29.0	20.1	16.7	
Housewife	32.6	33.8	32.1	34.1	
Education level (%)					
None	6.8	12.2	6.5	5.3	23.7 (p=0.003)
Primary	35.3	39.6	34.4	36.6	
Secondary	28.8	25.2	29.3	28.8	
Undergraduate	15.9	13.3	16.7	14.5	
Degree	13.2	9.6	13.2	14.9	
Environment (%)					
Rural	10.9	16.6	9.9	11.6	0.1 (p=0.702)
Semi-urban	22.1	21.8	22.7	20.1	
Urban	39.6	34.3	38.8	45.0	
Metropolitan	27.4	27.3	28.6	23.2	
Clinical characteristics					
BMI (kg/m^2)	25.6±4.3	25.8±4.1	25.6±4.3	25.7±4.4	0.4 (p=0.675)
Cigarettes/day	1.7±0.7	1.6±0.7	1.6±0.7	1.8±0.7	2.2 (p=0.113)
Smoking (%)					
Non-smoker	67.4	67.3	67.7	66.7	1.1 (p=0.889)
Former smoker	17.7	16.2	17.8	18.2	
Smoker	14.9	16.5	14.6	15.1	
Alcohol consumption, any (%)	18.2	22.2	17.5	18.7	3.7 (p=0.156)
Alcohol consumption > 30gr/day (%)	1	1.9	0.8	1.5	4.2 (p=0.125)
Background of co-morbidities(%)					
Diabetes mellitus					
No	92.3	81.0	93.2	94.5	51.9 (p<0.001)
Type I	1.7	3.7	1.2	2.6	
Type II	6	15.3	5.6	2.9	
Hypertension (%)	23.6	37.8	21.9	22.7	33.2 (p<0.001)
Rheumatoid arthritis	4.5	7.6	4.3	3.7	6.9 (p=0.031)
Anorexia nervosa	0.3	0.4	0.3	0.4	0.1 (p=0.968)
Hyperparathyroidism	0.4	0.8	0.3	0.4	1.0 (p=0.602)
Hyperthyroidism	2.4	3.8	2.5	1.3	5.1 (p=0.078)
Chronic liver diseases	0.6	0.8	0.7	0.4	0.8 (p=0.664)
Malabsorption syndrome	0.4	1.9	0.2	0.6	10.0 (p=0.007)
Osteoporosis data					
Age at diagnosis (years)	58.8±6.8	59.9±6.8	58.9±6.9	58±6.4	8.7 (p<0.001)
BMD (DXA)	-2.5±1.2	-2.9±0.4	-2.8±0.5	-0.9±1.9	990.3 (p<0.001)
# of risk factors for osteoporotic BF	0.7±0.8	1.9±0.8	0.5±0.7	0.5±0.7	495.7 (p<0.001)
# of risk factors for osteoporosis	5.1±1.8	6.9±0.3	5.0±1.8	4.9±1.8	172.9 (p<0.001)
Time from diagnosis (years)	2.25±2.9	3.4±3.8	2.1±2.8	2.1±2.8	24.0 (p<0.001)

Note: Values are mean (standard deviation) or percentage relative to total in the group. [£]Chi^2 may be lineal for trend or likelihood ratio. Environment; rural (≤10,000 inhabitants), semi-urban (>10,000 to ≤30,000 inhabitants), urban (>30,000 to ≤200,000 inhabitants) and metropolitan (>200,000 inhabitants). BMD=Bone Mineral Density; BF=Bone fracture.

6.2.2. Missing data study

Missingness can contain information. In order to be sure that missing data could not be allocated to a special group of participants, characteristics of the participants with a value for DALYs were compared univariatedly with participants without a DALY value by means of chi-square or t-test.

No significant differences between groups were observed in age, smoking and the BMI categorized by 20 kg/m^2. Henceforth, the mechanism for the missing data was assumed to be missing at random. In this case the available information of the outcome and covariates combined is representative of the information that is not observed or registered. Under this assumption the results obtained are valid even they are underpowered due to the reduction in the sample size because the used models are likelihood based. This seems to be a plausible assumption as long as the features of the women used in the DALYs calculation do not differ from the total sample included in the study.

6.2.3. Utility and disutility weight

The HRQoL was assessed using the generic Medical Outcomes Study (MOS)-Short Form (SF) with 12 items questionnaire (SF-12v2)[180], which was used to derive disutility values (see Annex XIV).

Numbers derived from SF) surveys or other health profiles generally cannot be used directly for cost-effectiveness analyses. Preference-based approaches, such as the EuroQol EQ-5D[181]. The EQ-5D is a standardised, non-disease-specific instrument for describing and valuing health. It yield interval level scores anchored at 0 (death) and 1 (perfect health) that represent preferences for particular health states, characteristics essential for use in cost-effectiveness analyses[182].

Thus, although SF and other instruments for valuing health have distinct uses, researchers seeking to reduce respondent burden in primary data collection and those relying on existing data for secondary analyses may benefit from the ability to translate between profile measure scores and preference scores.

The work published by Franks et al.[183] presented the coefficients of a second-degree polynomial model that allows the EQ-5D calculation by using the SF-12 scores.

The SF-12 survey is combined to generate physical component summary (PCS) and mental component summary (MCS) scales. The PCS is derived from questions on physical functioning, the physical part of role functioning, pain, and general health; the MCS is derived from questions of vitality, social functioning, the emotional part of role functioning and mental health.

The PCS and MCS values for each individual were centered by subtracting the mean of each variable for the total sample (in the studied dataset, 43.09 and 47.57 units respectively).

The EQ-5D was calculated using the formula that includes PCS, MCS main effects and interaction, also second degree variables:

$$EQ-5D = 0.847 + X_1 \times 0.013 + X_2 \times 0.008 - X_1^2 \times 0.00009 - X_2^2 \times 0.00015 - X_1 \times X_2 \times 0.00015,$$

where X_1 are the PCS centered, i.e., the PCS is observed value minus the PCS sample mean. And X_2 is the analogous for the MCS.

Then,

$$Utility = Index\ \ EQ-5D$$

and

$$D = 1 - Index\ \ EQ-5D\ .$$

6.2.4. YLLs and YLDs

For the calculation of years of life lost (YLLs) the value of 84.6 years of life expectancy for Spanish women with a low mortality rate and

mortality data associated with osteoporosis was used to determine the value of L, being L= 84.6-a.

In the calculation of years of life lived with disability (YLDs) L took the value of the difference between the life expectancy and the age of diagnosis of osteoporosis.

6.2.5. Data analysis

The DALYs were compared by group (Osteoporotic women with bone fracture (BF), Osteoporotic women without BF and T-score > -2.5) by means of analyses of variance and covariance (ANOVA and ANCOVA). The null hypothesis is that the mean DALYs are all equal for all the assessed groups:

$$H_0 : \mu_{OBF} = \mu_{OWBF} = \mu_{Ot}$$

vs.

$$H_A : \textit{At least one of the means is different .}$$

A MANCOVA or multivariate linear regression models were adjusted to assess the effect of the following factors on the mean DALYs:
Bone Density, BMI above 20 kg/m^2, previous osteoporotic fracture, active smoking, alcohol consumption above or equal to 30g/day, rheumatoid arthritis, presence of family antecedents of osteoporosis and the use of corticosteroids therapy was done.

Subsequently, paired-comparison analyses were completed for factors showing significant group differences in univariate ANOVA, in order to further evaluate specific group contrasts Games-Howell correction[184] was made to give an overall significance level of alpha = 0.05.

The SPSS code for the data analysis and DALYs calculation is provided in Annex XV.

6.3. Results

The overall DALYs both undiscounted and discounted by the study groups are shown in Figure 6. 1. The mean (SD) undiscounted and discounted years loss are 6.1(4.3) and 4.2(2.9) for the entire sample.

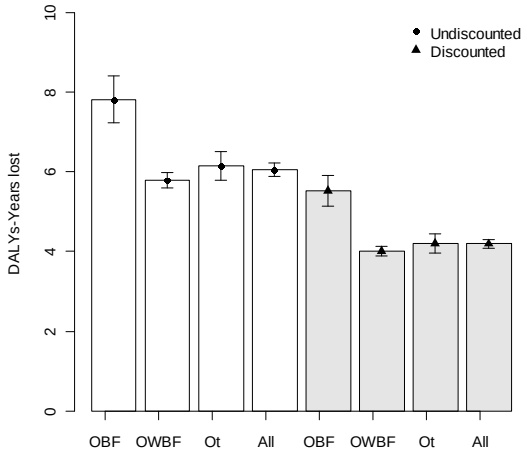


Figure 6.1. Mean (95% confidence interval) DALYs loss, undiscounted (white bars) and discounted (grey bars) per group and for the total population; OBF=Osteoporosis with BF, OWBF=Osteoporosis without BF, Ot=Osteopenic with a BD >-2.5.

There are significative differences in the DALYs between groups (ANOVA, p-value<0.001), when the comparison is made by pairs the differences are placed in the mean DALYs for osteoporotic women with BF and without BF (7.8 (4.9) and 5.8 (4.2) respectively) and on the osteoporotic women with BF and the osteopenic ones (6.2 (4.3)).

The same differences (and p-values<0.001) were observed for the discounted DALYs, being the mean values of 5.5 (3.3), 4.0 (2.8) and 4.2 (2.8).

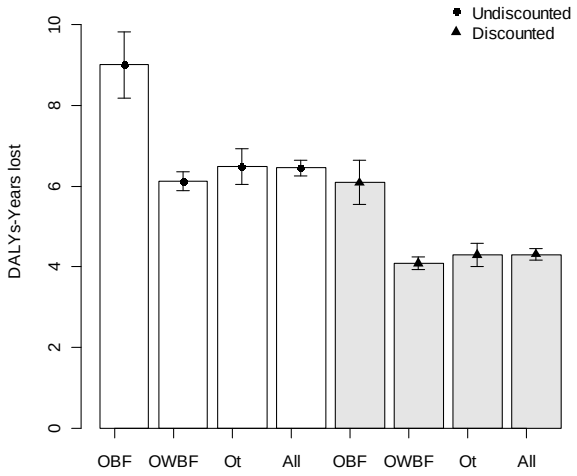
The same evaluation was done separating by the women's age, grouped in younger than 65 years and with 65 years old and older. According to

the criteria for treatment recommendations in primary prevention in Spain[185].

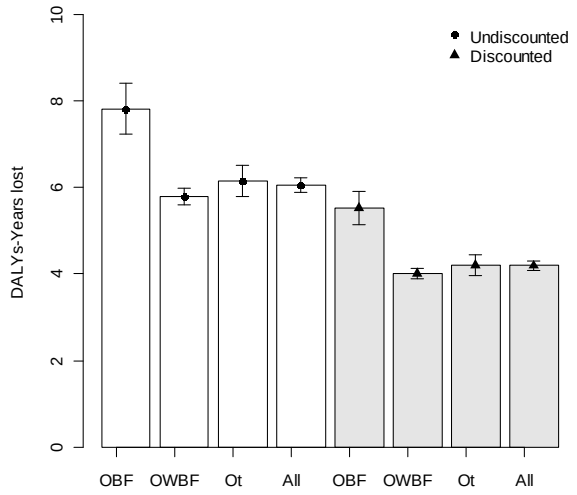
The DALYs values were significatively higher for the younger, with a mean of 6.4 (4.7) versus the 5.1 (3.1) of the elderly group, also in the discounted values 4.3 (3.1) versus 3.9 (2.3), (p-value for undiscounted DALY comparison <0.001 and 0.03 for the discounted values).

In the group younger than 65 years old there were significant differences between osteoporotic with BF and without BF (p-value<0.001) and between osteoporotic with BF and osteopenic women (p-value<0.001), both for the undiscounted and discounted DALYs lost (Figure 6.2. A).

In the group with 65 years old and older the differences that achieve signification were between osteoporotic with BF and without BF with p-values of 0.010 and 0.006 for undiscounted and discounted DALYs. The differences between osteoporotic with BF and osteopenic women were significant when the discounted DALYs were compared (p-value=0.034) but it lost the significance in the undiscounted values (p-value=0.062) (Figure 6.2 B).



A) Postmenopausal women <65 years of age



B) Postmenopausal women ≥ 65 years of age.

Figure 6.2. Mean (95% confidence interval) DALYs loss, undiscounted (white bars) and discounted (grey bars) per group (OBF=Osteoporosis with BF, OWBF=Osteoporosis without BF, Ot=Osteopenic with a BD >-2.5.) and for the total population < 65 years of age and ≥ 65 years.

When the relationship between the mean value of DALYs loss and the number of risk factors that a patient account for (0, 1 or 2 or more with mean values of 5.5 (4.0), 6.1 (4.2) and 6.4 (4.9)) was assessed

significative differences were observed between the group with 0 and 1 risk factors (p-value=0.014) and nearly significative differences between the group with 0 and 2 or more risk factors (p-value=0.056). Significance was lost when the discounted DALYs were evaluated (none versus 1 p-value=0.071 and none versus 2 or more p-value=0.220).

The mean DALY loss and its 95% confidence interval (CI) are larger for those who consume alcohol, have rheumatoid arthritis, family antecedents of osteoporosis and use of corticosteroids (Table 6.2).

Table 6.2. Mean (95% confidence interval) DALYs loss, undiscounted and discounted by the presence of a risk factor.

		Undiscounted			*Discounted*		
			95% CI			95% CI	
		Mean	Lower	Upper	Mean	Lower	Upper
BMI	≥ 20 kg/m2	6.05	5.89	6.22	4.20	4.09	4.31
	< 20 kg/m2	6.06	5.25	6.88	4.06	3.54	4.59
Smoking	Non-smoker	6.02	5.85	6.20	4.20	4.09	4.32
	Smoker	6.26	5.81	6.71	4.17	3.87	4.47
Alcohol consumption	<30g/day	6.03	5.87	6.20	4.19	4.08	4.30
	≥30g/day	8.64	6.59	10.69	5.76	4.48	7.05
Rheumatoid arthritis	Absence	5.92	5.76	6.08	4.10	3.99	4.21
	Presence	8.92	8.02	9.82	6.36	5.76	6.96
Family antecedents of osteoporosis	Absence	5.76	5.55	5.97	4.00	3.86	4.15
	Presence	6.49	6.24	6.75	4.48	4.31	4.65
Corticosteroids	Non-use	6.04	5.88	6.20	4.19	4.08	4.29
	Use	9.84	6.63	13.04	6.68	4.62	8.74

The same risk factors showed statistical signification in the model when adjusting by BD and previous osteoporosis fracture, both for undiscounted and discounted DALY loss. When the multivariate model was build, the factors that remain significant were rheumatoid arthritis, family antecedents of osteoporosis and use of corticosteroids, which absence reduce the mean undiscounted DALY loss (14.6 years) by 2.8, 0.4 and 3.6 years respectively. A similar model was found for the mean discounted DALYs which included the rheumatoid arthritis and use of

corticosteroids, with a overall mean of 10.0 and a 2.1 and 2.2 of mean reduction for the non-rheumatic women and non-corticosteroids consumers (Table 6.3).

Table 6.3. Variables associated with DALY loss, undiscounted and discounted; adjusted by BD and previous osteoporosis BF

Undiscounted DALYs			95% CI				95% CI	
Parameter (category considered)	Estimate	p-value	Lower	Upper[$]	Estimate	p-value	Lower	Upper[£]
BD	0.12	0.066	-0.01	0.25	0.20	0.004	0.06	0.33
Prior osteoporosis BF (No)	-1.96	<0.001	-2.50	-1.42	-1.78	<0.001	-2.34	-1.22
BMI<20 kg/m^2 (No)	0.05	0.898	-0.68	0.78				
Smoking status (Non-smoker)	-0.22	0.336	-0.68	0.23				
Alcohol consumption ≥30g/day (No)	-2.44	0.003	-4.04	-0.84				
Rheumatoid arthritis (No)	-2.87	<0.001	-3.64	-2.09	-2.76	<0.001	-3.55	-1.98
Family antecedents of osteoporosis (No)	-0.39	0.033	-0.75	-0.03	-0.44	0.016	-0.80	-0.08
Use of corticosteroids (No)	-3.61	0.002	-5.87	-1.36	-3.56	0.003	-5.89	-1.23
Discounted DALYs								
BD	0.07	0.102	-0.01	0.16	0.13	0.004	0.04	0.22
Prior osteoporosis BF (No)	-1.48	<0.001	-1.84	-1.12	-1.44	<0.001	-1.81	-1.08
BMI<20 kg/m^2 (No)	0.18	0.462	-0.31	0.67				
Smoking status (Non-smoker)	0.04	0.793	-0.26	0.34				
Alcohol consumption ≥30g/day (No)	-1.45	0.008	-2.52	-0.39				
Rheumatoid arthritis (No)	-2.15	<0.001	-2.67	-1.63	-2.09	<0.001	-2.61	-1.57
Family antecedents of osteoporosis (No)	-0.18	0.132	-0.42	0.06				
Use of corticosteroids (No)	-2.35	0.002	-3.86	-0.84	-2.15	0.007	-3.71	-0.60

[$]Model build for each factor adjusted by BD and prior osteoporotic BF.
[£]Model calculated with all the factors at the same time.
The global mean (95%CI) for the undiscounted DALYs multivariate model was 14.61 (12.16; 17.07) and 9.95 (8.32; 11.58) for the discounted DALYs.

6.4. Discussion and conclusion

The use of the DALYs as a measure of health is controversial; this health outcome has two main components: the quality of life reduced to a disability and the lifetime lost due to premature mortality. The methods used to assign disability weightings to life years are critical such it requires diagnostic group's definition and, in function of the relative severity of their disease, a disability weight should be assigned. In this case, the matter was solved by using individual data collected through a validated survey.

The DALYs can be reevaluated by applying a discount and weighting by age. The first option gives higher value of the present years than to the future ones, and the second option modifies the DALYs giving less value to the children and old people life years. The calculations were performed for undiscounted and discounted DALYs and it is remarkable that both drive to the same conclusions. The age weighting was not applied since the population of interest is elderly women.

A limiting factor of this study concerns the methodology used to determine the EQ-5D used as disability weight since it is made by using a formula that explains the 63% of the variability. However, it ensures a utility weight calculation already validated and published. Another limitation is the fact that the enrolled individuals are women attending outpatient gynecology clinics, which have fewer comorbidities and a different life style than inpatients, this may have introduce some selection bias.

These results represent the first DALYs loss quantification for osteoporosis disease in Spain, which was reported in general terms and for different groups of interest. It was found that alcohol consumption, having rheumatoid arthritis, previous osteoporotic bone fracture, family antecedents of osteoporosis, using corticosteroids and a lower BD revealed to be linked to a larger DALYs lost. The identification of risk factors can improve the clinical practice by guiding the concerns that should be considered in the osteoporosis prevention.

7. CONCLUSIONS

Based on the work developed on this thesis, the following conclusions and goals were achieved:

1. Data recorded in the framework of a prospective clinical trial fail to reflect the patients' diversity and have a limited time horizon. To improve the accuracy, data collection should continue after the patient's study treatment discontinuation.
2. A cohort simulation avoid to experiment directly with patients, it is a cheaper and a faster method than prospective studies to gain knowledge about the available therapeutic strategies. A sensitivity analysis varying he input parameters and using probabilistic techniques should be performed to inform about the variability and the uncertainty of the results.
3. Markov models were adapted to reflect the fact that the risk of suffering an event can change over time. The deterministic incremental analysis and the probabilistic sensitivity method were implemented in R software.
4. A budget impact analysis requires being clear on the items considered as resources used under the study perspective applied and need to be filled with realistic and precise clinical practice procedures and resource prices.
5. Epidemiological estimations of incidence, prevalence, and mortality rates due to a specific disease do not capture the burden of disease that cause in the population. The target of interest is the measure of the population health and well-being. The known indicators, such as DALYs and QALYs are based on utilities for a year of life in a health status. Usually, the utilities are derived from a patient's health related quality of life survey and the desirable is to use specific population

and country data when available. Although choosing same parameters' value is discussable and makes these measurements controversial.

6. The adherence promoting program in HIV infected patients has a positive impact on the health outcome, even its implantation would depend on the willingness to pay per additional unit of health gained.
7. A Markov model with 2-phases was used to study the suitability of diagnostic test to guide the use of maraviroc. The analysis showed that the 454 test to assess the HIV coreceptor could be cost effective when compared to the Trofile test; the Population Sequencing test showed a smaller health benefit. However, it is cheaper than the other two tests. The choice will depend on the maximum that the health service is prepared to pay per additional unit of utility gained.
8. A Markov model was built to assess the cost-effectiveness of two treatments to prevent osteoporosis fractures in postmenopausal women. The new treatment was shown to be equal in probability of cost-effectiveness than the SOC.
9. The calculation of the burden of disease for osteoporotic women who may suffer from fractures done at an individual level was performed. Few studies of burden of disease are available and even less for Spanish population and/or performed using individual characteristics.
10. The use of eculizumab for treating the PNH would imply an incremental yearly cost of €300,650 per patient compared to standard of care but would provide larger societal benefits.

8. FUTURE RESEARCH

Based on the work developed on this thesis, the following research issues are suggested:

1. The challenge remains in adapting the methods to reflect complex systems and implement them. Other models of simulation besides those described in this thesis are available. For instance, the dynamic population modelling could be a good approach to model highly infectious and/or communicable diseases impact in an entire population; including both the diseased and healthy citizens could be useful to do a cost-effectiveness analysis. Another approach to perform a simulation is the based on discrete-events. This method seems appropriate to model diseases were the change between health states can be assigned to discrete points in time, HIV disease evolution is susceptible to be modelled using these mechanism.
2. We are working to estimate the differences in the results for a cost-effectiveness evaluation analysis using a simulated cohort or using real data.
3. The calculation of confidence intervals for the ICER can be complex, and the possibility that the numerator and/or denominator tend to 0 complicate the calculations even further. Because of these challenges, a number of alternative methods for calculating confidence intervals have been proposed. These methods include the use of Fieller's theorem and non-parametric bootstrapping[186, 187]. We would like to explore the methods that can help to quantify the ICER variability and uncertainty and we plan to continue our research along this aspect.
4. Other possible summaries for the performance of therapeutic strategies are the incremental net health benefit (INHB) and the incremental net monetary benefit (INMB) were the cost and health outcome are assessed in terms of health and money, respectively.

Both measures depend on the willingness to pay per unit of outcome gained. A future work would be to study these options.

5. The consideration of directional statistics to deal with the limitations of the ICER. This technique uses unit vectors (possibly with unknown sign) as observations in the plane or in 3-dimensional space, being the sample space a circle or a sphere. The research on special directional methods for the analysis of unit vectors would be a next step.
6. The simulation models implemented in this thesis were done using the cohort approach, which differs from the individual simulation for the fact that subgroups of patients travel together through the health states. In the individual simulation, every patient travels alone through the health states, this is computationally more costly, but it can reflect some variability that can be closer to reality. Even some studies already mentioned that differences between cohort and individual simulation are small; it is of our interest to go deep in the quantification of the advantages and disadvantages associated to the individual simulation. The next step would be to work on the implementation of models for individual simulation in R software. The acquired knowledge will help in the technique selection for future studies.
7. We are eager to use the model with n-stages of simulation in other health areas, which has the good feature of allowing a simulating process using different transition probabilities matrix for the n stages defined in the disease evolution.

ANNEXES

Annex I: Discrete-event simulation. Another technique for model building

In the following, we introduce the discrete-event simulation approach that can be used in decision analysis to represent and simulate the natural history of the disease under study.

Discrete-event simulation has been extensively used to address various industrial problems. Interest in the application of this technique is increasing, even though Markov models are the most popular approach in the evaluation of health care technology and products[188].

Modelling based on discrete-event simulation is characterized by the fact that the state variables only change at discrete points in time at which events occur, for example, in a transition between health states. Events occur as a consequence of activity times and delays. Entities, i.e., patients in our clinical framework, move through the states of the system and may join queues while waiting for the next state to occur. Activity and delay times may "hold" entities for periods of time. A discrete-event simulation model is conducted over time by a mechanism that moves simulated time forward. The system state is updated at each event along with capturing and occupancy of states that may occur at that time[189]. The figure I.1 shows the time flow in a discrete-event simulation for N patients that move through 3 possible heath states: Well, Sick, or Dead. It is noteworthy that the simulation skips inactivity periods. Each node represents an occurring event, and the system is refreshed when an event occurs, i.e., at times t+ u, t+ v, and t+ w.

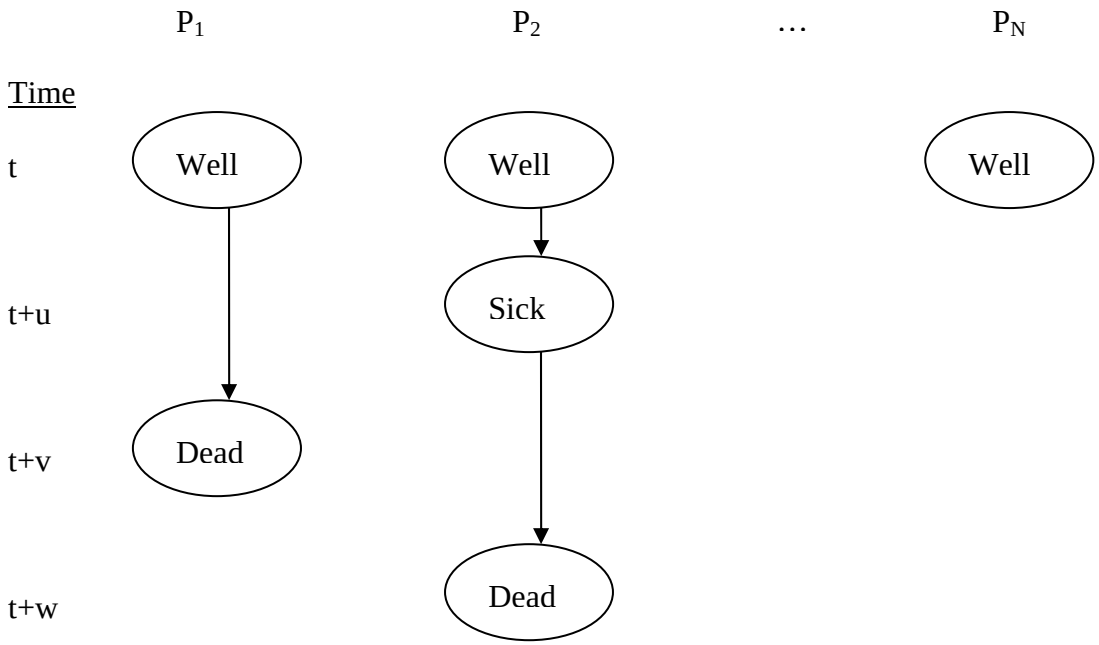


Figure I.1. Representation of a simple discrete-event simulation process for N patients in three health states: Well, Sick, and Dead. Based on the work by Overeinder et al.[190].

Discrete-event simulation is not commonly used in clinical research, although it could prove to be a promising technique in cohort simulations. The main challenge with this approach lies in the specification of system attributes and constraints in the transition between states, i.e., specification of the different health states and the rules for assessing disease outcome.

Annex II: Health outcome measures

The score of health or burden of disease can be produced considering two different approaches depending on the interest in measure the health of a community or in quantify the individual health. In the application developed here the individual health score is calculated using disaggregated person's information, for this reason, a larger description is given for these techniques.

The summary **measures of population health** combine information on mortality and non-fatal health outcomes to describe the health of a particular community as a single number[191]. The simplest and most widely used method for producing population health statistics is to aggregate data on individuals in order to generate summaries like the proportion of the population (or of a particular age-sex group) suffering from a particular health problem or in a particular health state. When the concern is to **measure the individual health,** non-aggregated information should be considered; this evaluation can be done using the direct health outcomes or combining some of them into new scores.

In the context of individual health measures, the assessment can be performed in randomized clinical trials (RCTs), cohort of patients or in some health services administrative data sets. The outcome can be measured by using natural units of health (e.g. mortality, number of individuals with viremia under control, units of cholesterol reduced), effects can be expressed in monetary units or by means of people's preferences on the trade-off between length of life and subjective levels of well-being associated with health states.

In order to construct scores that allow the comparison of: health conditions between various health problems, populations or time points, a common metric is the key to provide objective information for the economic evaluation of interventions and to set priorities for health resources[192,193].

Summary measures can be classified according to **health expectancies** or **health gaps**. Both types use time (lived in health states or lost through premature death) as an appropriate common metric for measuring the impact of mortality and non-fatal health outcomes. These two classes of measures are complementary (see Figure II.2).

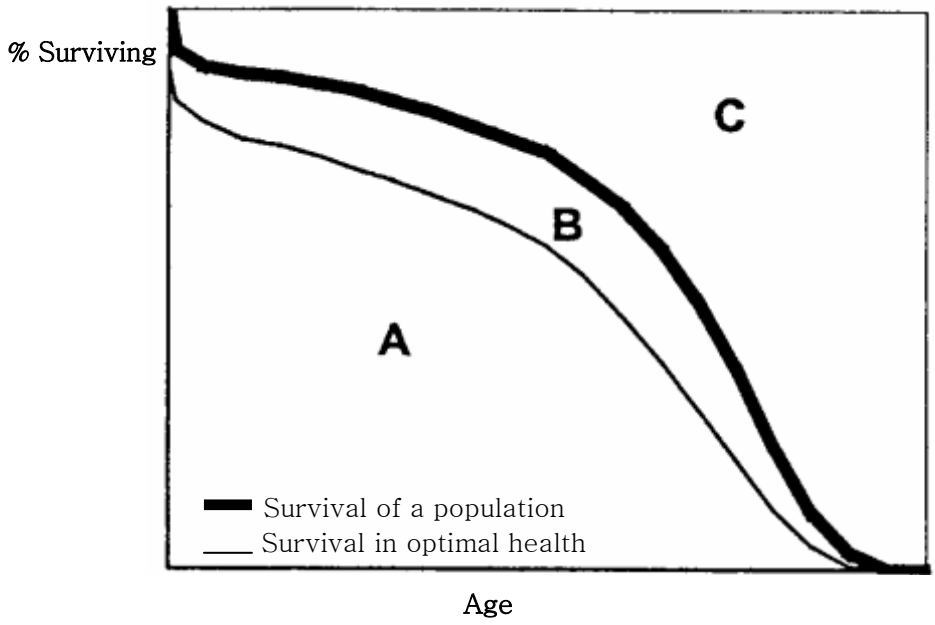


Figure II.2. Survivor curves for a population and the time lived in optimal health and the areas defined by these curves that allow illustrating different summaries for measures of population health. Area under the curve A represents time lived in optimal health, area B time lived in suboptimal health, and area C represents time lost due to mortality.

The total life **expectancy** (LE) at birth is given by the area under the bold curve (Area A plus Area B):

$$LE = A + B$$

Health expectancies (HE) are population indicators that account for the average time that a person could expect to live in a defined state of health. Examples include disability-free life expectancy (DFLE), active life expectancy and disability-adjusted life expectancy. These extend the concept of life expectancy to refer to expectations of different states of health. In terms of Figure II.2, health expectancy is given by:

$$HE = A + f(B),$$

where f( ) is some function that assigns weights to years lived in suboptimal health, usually, optimal health has a weight of 1 and the worst health state has weight 0. As summary measures of the burden of disability from all causes in a community, healthy life expectancy and health-adjusted life expectancy (HALE) has the advantage of being meaningful by themselves and being understandable concepts to a non-technical audience.

Assesment of potential years of life lost due to premature mortality are used to measure the mortality burden of different causes of death. These all measure the **gap** in years between age at death and some arbitrary standard, i.e., the difference between actual population health and some specified norm or goal.

$$\text{Health gap} = C + g(B)$$

where g( ) is some function that assigns weights to health states lived during period B, assigning weight 1 to time lived in a health state equivalent to death.

Following the pioneering work of Dempsey (1947)[194], several measures of years of life lost due to premature mortality have been proposed (Area labeled C in Figure II.2). Health gaps extend the notion of mortality gaps to include time lived in states of suboptimal health (Area labeled B in Figure II.2).

The central feature defining a health gap measure is the population norm (age) chosen to define the period before which death or disability is considered premature. For some types of health gap measures, the implied target age may vary as the mortality level change, which is a highly undesirable property for comparisons.
Methods for defining health states and for obtaining health state evaluations affect the calculation and interpretation of health gaps and health expectancies. The incorporation of social values and their weight in the calculation also affect the result, and it can be controversial.

The best known utility measure is the quality-adjusted life year (QALY), which, in turn, is tightly linked to the term "utility"[195]. The utility score ranges from 0 to 1, being the larger values related to a higher degree of functionality and independence. The utility values can be converted into QALYs by multiplying the years spent in a particular health state by the utility of the concrete health state. The DALY measurement for a health outcome appeared in the 1990s, in the Quality Adjusted Life Years (QALY) framework[196]. The DALY is primarily a measure of disease burden (disability weights measure loss of functioning) and its used in economic evaluations is relatively general. The DALY incorporates an age-weighting function assigning different weights to life years lived at different ages, and the origins of disability and health related quality of life weights differ significatively[197].

The previously defined health measures can be computed for a population or for individual data, with the corresponding adjustments.

The fundamental goals in constructing summary measures are to describe the relative magnitude of many health problems and to identify risk factors for losing life and/or health expectancy.

Annex III: Ethical considerations in the use of the pharmacoeconomic studies

The methodological development and its correct application should be our goal. Although good tools for pharmacoeconomics evaluations are available other problems can limit the application of the results obtained in the cost-effectiveness studies to the daily clinical practice[198]:

- Sometimes the results are under suspicion because the study can be funded by pharmaceutical companies and it can be used as a marketing tool.
- Doctors may tend to think that is not ethical to base clinical decisions in cost-effectiveness results. If the reasoning is done thinking in the waste of resources when a most cost-effective option is not prescribed, this can reduce the ability to give care to a larger number of patients, which can be labelled as unethical.
- Sometimes the cost-effective option requires a present large investment to obtain long term savings, and this spending is not affordable. For instance, the purchase of a screening machine to detect a disease in early stages, it is a big investment that will save money and increase the long term population's health.
- The budgets are decided in isolation, and it is not easy to move money from one to another. For instance, the prescription of a drug that can avoid a considerable number of hospital admissions. Usually pharmacy and hospital services have a different budget and one is not going to promote an expenditure that does not revert in their own efficacy numbers.

Despite these problems, economic evaluations of therapeutic strategies are increasingly important in decision making for health care resources allocation to promote efficiency and effectiveness of choices.

Annex IV: Input parameters for ProAdh study in HIV infected patients

Costs

The direct costs linked to the treatment options were measured as the total cost of drug treatment, blood analysis and human resources for health. The total cost of combined antiretroviral therapy (cART), the blood tests and the human resources were obtained from the medical supplies of the hospital where the study was performed; the concomitant treatment was priced using the PVL reported in the web site. The costs, in Euros 2010, are reported in Table IV.1. The trial neither intervened in the cART prescribed nor in the concomitant treatment, i.e., the listed drug treatments were the ones decided by the medical doctors for the care of each patient who participated in the trial.

Table IV.1. Cost per item (Euros 2010)

Item	Units	Cost(EUR)2010
Antiretroviral treatment		
NORVIR/100-24,PREZISTA400/800-24	Patient/day	15.58
VIRAMUNE/200-12,KIVEXA/1-24	Patient/day	19.13
TRUVADA/1-24,VIRAMUNE/200-12	Patient/day	21.42
KIVEXA/1-24,SUSTIVA 600/600-24	Patient/day	21.52
ATRIPLA/1-24	Patient/day	23.62
SUSTIVA 600/600-24,TRUVADA/1-24	Patient/day	23.81
VIRAMUNE/400-24,KIVEXA/1-24	Patient/day	25.93
NORVIR/100-24,TRUVADA/1-24,PREZISTA600/600-24	Patient/day	26.51
NORVIR/100-24,KIVEXA/1-24,PREZISTA400/800-24	Patient/day	27.91
TRUVADA/1-24,VIRAMUNE/400-24	Patient/day	28.22
NORVIR/100-24, TRUVADA/1-24, PREZISTA400/800-24	Patient/day	30.20
ETRAVIRINA/1-24,TRUVADA/1-24	Patient/day	30.22
KIVEXA/1-24,ISENTRESS/99-12	Patient/day	36.25
TRUVADA/1-24,ISENTRESS/99-12	Patient/day	38.54
TRUVADA/1-24,ISENTRESS/400-12	Patient/day	38.54
PREZISTA400/800-24,NORVIR/100-24,TRUVADA/1-24,ISENTRESS/400-12	Patient/day	54.12
CELSENTRI 300 MG COMP/300-12,TRUVADA/1-24,ISENTRESS/400-12	Patient/day	66.28
Concomitant treatment		
Enalaprim and pravastatin	Patient/day	0.14
Captopril and hidrosaluteril	25mg/day	0.19
Atorvastatin	20mg/day	0.33
Insulin (supposed the need of 1 vial per month)	Patient/day	0.33
Metformin	Patient/day	0.70
Risperdal	Patient/day	3.16
Human resources		
Nurse visit	1	50
Visit to specialist physician, dietician or psychologist	1	100
Psychoeducational intervention visit	1	150
Blood tests		
Baseline analyses	1	421.22
Monitoring analyses	1	131.14

Health outcome assessment

The clinical performance was evaluated using two outcomes: the percentage of individuals in each group that achieved undetectable RNA HIV viral load and the increment of 100 CD4 cells/mm^3 at the end of 1 year of follow-up.

The health related quality of life was measured using the Medical Outcomes Study (MOS), which is a brief questionnaire to assess the health status. The MOS-HIV (MOS validated for HIV infected patients) questionnaire is one of the most widely used to evaluate the health related quality of life in HIV clinical trials[199].

The health related quality of life areas assessed were the physical health, mental and psychological health, relationships and social activities, and finally the global health. These aspects were scored by the patient giving punctuation in a scale from 1 to 6, being 6 the maximum well-being and 1 the worse. The measurements of health outcome for these areas were the change in the score reported in baseline respect to the score reported at the end of follow-up.

Annex V: Data analysis code for ProAdh study in HIV infected patients

```
* SPSS syntax for the data management and statistical analysis*.
*** Sample description*.
COMPUTE edat= DATEDIFF(Fechadeentrevista,FechadeNacimiento,"year") .
EXECUTE.

FREQUENCIES
  VARIABLES= ViadeInfección
  /ORDER=  ANALYSIS.

FREQUENCIES
  VARIABLES=num_tarvs_durante_studio edat
 /FORMAT=NOTABLE
  /PERCENTILES= 25 75
  /STATISTICS=STDDEV MINIMUM MAXIMUM MEAN MEDIAN
  /ORDER=  ANALYSIS.

***Description by group*.
SORT CASES BY Grupo.
SPLIT FILE
  SEPARATED BY Grupo.

FREQUENCIES
  VARIABLES= ViadeInfección
  /ORDER=  ANALYSIS.

FREQUENCIES
  VARIABLES=num_tarvs_durante_studio edat
 /FORMAT=NOTABLE
  /PERCENTILES= 25 75
  /STATISTICS=STDDEV MINIMUM MAXIMUM MEAN MEDIAN
  /ORDER=  ANALYSIS.

SPLIT FILE
  OFF.

*** Cost calculation*.
*The expenditure on human resources and blood tests per visit and patient were recorded.
File: “fecha entrevista+visitas seleccionadas.sav”*.
```

```
COMPUTE                                                    Temps_entrevista_visita_mesos=
DATEDIFF(DataProgramada,Fechadeentrevista,"month") .
EXECUTE.

AGGREGATE
  /OUTFILE='E:\IOMEGA\Copia de seguridad_8-7-09\FLS_8-7'+
 '-09\ProADH\ProADH_abril2012\suma coste visitas y analiticas'+
 ' seleccionadas.sav'
  /BREAK=NHC
  /Nom_first = FIRST(Nom) /Cognom1_first = FIRST(Cognom1) /Cognom2_first =
  FIRST(Cognom2) /Grupo_mean = MEAN(Grupo) /CodigoPaciente_first =
  FIRST(CodigoPaciente) /cost_analiticas_sum = SUM(cost_analiticas)
 /coste_visita_prof_sum = SUM(coste_visita_prof) /coste_visita_infer_sum =
  SUM(coste_visita_infer) /coste_psico_visita_estudio_sum =
  SUM(coste_psico_visita_estudio) /Temps_entrevista_visita_mesos_max =
  MAX(Temps_entrevista_visita_mesos).
```

File: suma coste visitas y analíticas seleccionadas.sav.

Add the variable "coste_analiticas_corregido". The minimum expenditure due to blood test screening during the study is supposed to be €945.78 for the patients that have 12 months of follow-up. The baseline blood test costs was estimated at €421.22 and at €131.14 the blood tests performed at 3, 6, 9 and 12 months.

*In the data set used, the cART treatment cost was done taking into consideration the cost for every drug and the period of time of consumption. For each patient the cART and his/her date of starting and date of ending were recorded.

The time under study that each patient takes a specific treatment combination should be calculated*.

Data file:demo+seguimiento+tarv15dec2012.sav.

```
COMPUTE Temps_tarv1_dias= DATEDIFF(periodo_vigencia_arv1,DataInicial,"day").
EXECUTE.
COMPUTE Temps_tarv2_dias= DATEDIFF(periodo_vigencia_arv2,DataInicial_arv2,"day").
EXECUTE.
COMPUTE Temps_tarv3_dias= DATEDIFF(periodo_vigencia_arv3,DataInicial_arv3,"day").
EXECUTE.
COMPUTE Temps_tarv4_dias= DATEDIFF(periodo_vigencia_arv4,DataInicial_arv4,"day").
EXECUTE.
COMPUTE Temps_tarv5_dias= DATEDIFF(periodo_vigencia_arv5,DataInicial_arv5,"day").
EXECUTE.
```

*To be able to perform the following calculations, missing values were substituted by 0 *.
COMPUTE Temps_total=
Temps_tarv1_dias+Temps_tarv2_dias+Temps_tarv3_dias+Temps_tarv4_dias+Temps_tarv5_dias.
EXECUTE.

*cART cost by patient during the study period of time**.
*To be able to perform the following calculations, missing values in the variable "precio_tarv_dia" were substituted by 0 *.

COMPUTE cost_TARV_temps_estudi=Temps_tarv1_dias*precio_tarv_dia+
Temps_tarv2_dias*precio_tarv_dia_arv2+Temps_tarv3_dias*precio_tarv_dia_arv3+Temps_tarv4_dias*precio_tarv_dia_arv4+Temps_tarv5_dias*precio_tarv_dia_arv5.
EXECUTE.

Concomitant treatment cost calculation.
COMPUTE cost_TConcom_temps_estudi=Temps_total*cost_dia_tto_concomitant.
EXECUTE.
*****.

Add the cost for human resources use.
COMPUTE
cost_recursoshumanos_temps_estudi=coste_visita_prof_sum+coste_visita_infer_sum+coste_psico_visita_estudio_sum.
EXECUTE.

COMPUTE
cost_total_temps_estudi=cost_TARV_temps_estudi+cost_TConcom_temps_estudi+coste_analiticas_corregido+cost_recursoshumanos_temps_estudi.
EXECUTE.

COMPUTE cost_total_per_mes=cost_total_temps_estudi/12.
EXECUTE.

***** Cost description*.**
SORT CASES BY Grupo.
SPLIT FILE
  SEPARATED BY Grupo.

```
FREQUENCIES
  VARIABLES=cost_TARV_temps_estudi cost_TConcom_temps_estudi
  coste_analiticas_corregido cost_recursoshumanos_temps_estudi cost_total_per_mes
 /FORMAT=NOTABLE
  /PERCENTILES= 25 75
  /STATISTICS=STDDEV MINIMUM MAXIMUM MEAN MEDIAN
  /ORDER=  ANALYSIS.

SPLIT FILE
  OFF.
```

***** Health outcomes calculation*.**

```
RECODE
  DiffCD4_w0_48
  (SYSMIS=SYSMIS)  (Lowest thru 99.99=0)  (99.9999 thru Highest=1)  INTO
DiffCD4_w0_48_cat .
EXECUTE.
VALUE LABEL   DiffCD4_w0_48_cat  0'Aument inferior a 100 cels' 1'Aument superior o igual a
100 cels'. EXECUTE.
COMPUTE MOSHIVP1_w0_48= MOSHIVP1_48-MOSHIVP1_0.
EXECUTE.

COMPUTE MOSHIVP2_w0_48= MOSHIVP2_48-MOSHIVP2_0.
EXECUTE.
COMPUTE MOSHIVP3_w0_48= MOSHIVP3_48-MOSHIVP3_0.
EXECUTE.
COMPUTE MOSHIVP4_w0_48= MOSHIVP4_48-MOSHIVP4_0.
EXECUTE.

RECODE
  MOSHIVP1_w0_48
  (SYSMIS=SYSMIS)  (Lowest thru -0.01=0)  (0 thru Highest=1)  INTO  MOSHIVP1_w0_48_cat.
EXECUTE.
VALUE LABEL   MOSHIVP1_w0_48_cat  0'No mejora' 1' Igual o mejora'. EXECUTE.

RECODE
  MOSHIVP2_w0_48
  (SYSMIS=SYSMIS)  (Lowest thru -0.01=0)  (0 thru Highest=1)  INTO  MOSHIVP2_w0_48_cat.
EXECUTE.
VALUE LABEL   MOSHIVP2_w0_48_cat  0'No mejora' 1' Igual o mejora'. EXECUTE.
```

```
RECODE
  MOSHIVP3_w0_48
  (SYSMIS=SYSMIS)  (Lowest thru -0.01=0)  (0 thru Highest=1)  INTO  MOSHIVP3_w0_48_cat.
EXECUTE.
VALUE LABEL   MOSHIVP3_w0_48_cat  0'No mejora' 1' Igual o mejora'. EXECUTE.

RECODE
  MOSHIVP4_w0_48
  (SYSMIS=SYSMIS)  (Lowest thru -0.01=0)  (0 thru Highest=1)  INTO  MOSHIVP4_w0_48_cat.
EXECUTE.
VALUE LABEL   MOSHIVP4_w0_48_cat  0'No mejora' 1' Igual o mejora'. EXECUTE.

*** Health outcomes description*.
SORT CASES BY Grupo.
SPLIT FILE
  SEPARATED BY Grupo.

FREQUENCIES
  VARIABLES= CV_indect_w48_50indetect
  /ORDER=  ANALYSIS.

FREQUENCIES
  VARIABLES= DiffCD4_w0_48_cat
  /ORDER=  ANALYSIS.

FREQUENCIES
  VARIABLES=MOSHIVP1_w0_48_cat
MOSHIVP2_w0_48_cat
MOSHIVP3_w0_48_cat
MOSHIVP4_w0_48_cat
  /ORDER=  ANALYSIS.

SPLIT FILE
  OFF.

*** Health outcomes comparison by group*.
CROSSTABS
  /TABLES= CV_indect_w48_50indetect
DiffCD4_w0_48_cat
```

```
MOSHIVP1_w0_48_cat
MOSHIVP2_w0_48_cat
MOSHIVP3_w0_48_cat
MOSHIVP4_w0_48_cat  BY Grupo
  /FORMAT= AVALUE TABLES
  /STATISTIC=CHISQ
  /CELLS= COUNT ROW COLUMN
  /COUNT ROUND CELL.
```

Annex VI: Numerical example for a cohort simulation using a Markov model

Parameters that fulfill the transition probability matrix, A:

p_{ww} 0.7

p_{ws} 0.29

p_{wd} 0.01

p_{sw} 0.5

p_{ss} 0.4

p_{sd} 0.1

p_{dw} 0

p_{ds} 0

p_{dd} 1

Utility contribution of each health state per cycle

u_w 1

u_s 0.5

u_d 0

Cost contribution of each health state per cycle

c_w 20

c_s 200

c_d 0

Table VI.1. Two-cycle Markov trace for a 3-state Markov model with health states: Well, Sick and Dead. P_0=(1,0,0). Column 1 show the cycle number (k), columns 2 to 4 show the proportion of the cohort in each of the 3 health states at each cycle k (P_k), the last 4 columns show utility (and cost) contribution in each cycle and cumulative utilities in the simulation time

Cycle (k, in years)	Well	Sick	Dead	Cycle utility	Cumulative utility	Cycle cost	Cumulative cost
0	1	0	0	0.5	0.5	10	10
1	0.7	0.29	0.01	0.845	1.345	72	82
2	0.635	0.319	0.046	0.7945	2.1395	76.5	158.5

[#]At cycle 0, the utility and the cost were multiplied by 0.5 to take into account that some individuals transit in the middle of the cycle, which is known as the half-cycle correction.

[¤] To obtain discounted expected utility (or cost) values the cycle utility (or cost) would be divided by its discount factor $(1+r)^k$. Not applied to the table calculations, i.e., undiscounted values for utility and cost are shown.

When k is displayed in years, it can be said that, on average, the cohort contributes 0.845 quality-adjusted during the first cycle. Note that at cycle 0 the maximum utility value is 0.5 because the half-cycle correction is used.

If the simulation were run until all cohort fall in the dead health state the cumulative "utility" in the last cycle would represent the quality-adjusted life expectancy of the cohort. Similarly, the cumulative costs n the last cycle represent the average lifetime costs of the cohort.

Summing the health state probabilities for a particular state for all cycles results in the average length of time that the cohort spent in that health state.

Annex VII: Input parameters for the bazedoxifene versus raloxifene´s model

Treatment, incidence and risk fracture, and mortality

Treatments efficacy

The Osteoporosis Study[109] was a 3-year, randomized, double-blind, placebo- and active-controlled trial, including 7,492 healthy postmenopausal osteoporotic women aged between 55 to 85 years. All women were at least 2 years postmenopausal and had osteoporosis. Women were assigned to treatment randomly, stratifying by prevalent vertebral fracture status to ensure similar distribution of subjects with and without prevalent vertebral fracture across treatment groups. The treatment groups where 20 mg bazedoxifene daily (N=1,886), 40 mg bazedoxifene daily (N=1,872), 60 mg raloxifene daily (N=1,849), or placebo (N=1,885) for 36 months. From the total number of eligible patients the percentage of patients that completed the study was 66% of patients receiving bazedoxifene 20 mg or 40 mg daily, 68% of patients receiving bazedoxifene 60 mg daily and 67% of patients receiving placebo. The clinical trial included participants among whom approximately 56% in each treatment group had at least one vertebral fracture at baseline, and the majority of these had one mild vertebral fracture. In this study patients were compared who either received 20 mg bazedoxifene daily or 60 mg raloxifene daily.

For osteoporosis patients without fractures, a relative risk (RR) reduction for vertebral fractures of 35% (95% confidence interval [CI], 0.32-1.30) was seen in patients treated with bazedoxifene versus 41% (95% CI, 0.29-1.21) for patients treated with raloxifene (Table VII.1). RR reductions were 45% (95% CI, 0.32-0.94) for bazedoxifene versus 43% (95% CI, 0.34-0.97) for raloxifene in patients with prior vertebral

fractures (Table VII.2). No differences in the incidence of non-vertebral fractures were observed between both treatments in women without prior fractures, although the reduced RR in patients with previous fractures was 46% with bazedoxifene and 8% with raloxifene.

Incidence and fracture risk

Country and age-specific normal populations' incidences were used when possible. A vertebral fracture can be classified as a clinical fracture (i.e., symptomatic fractures that come to clinical attention) or as morphometric, which includes all fractures both symptomatic and asymptomatic. For this study, the morphometric definition of a fracture was used as it provided more specific incidence data with an age standardized incidence ratio of 10.2 (95% CI 4.7-15.7) per 1,000 inhabitants for the Southern European female population because clinical fracture data were lacking[108].

Incidence rates of non-vertebral fractures (ratio 24.2 non-vertebral fractures per 1,000 female inhabitants) were obtained from Marín et al (2006)[200] and consisted mostly of wrist fractures (36.7%) and hip fractures (14.9%). Population fracture incidence rates were adjusted to reflect the risk in both treatment groups.

The probability of having a first fracture, a second fracture, or remaining healthy is determined by the RR of vertebral or non-vertebral fractures affected by treatment with bazedoxifene or raloxifene based on the Osteoporosis Study[109] (Tables VII.1 and VII.2).

Mortality

Age-specific normal population mortality rates were obtained from the Spanish national statistics agency[110]. These were adjusted in the model to take into account mortality associated with fractures[105, 201-204]. In this analysis, we derived estimates of the excess mortality after vertebral

fractures from a study based on Spanish patients who showed an increase in mortality between 20% and 34% in 5 years after its fracture[205]. The RR in the year after a vertebral fracture was estimated at 5.4 and was similar in subsequent years. The RR of mortality in the year after a non-vertebral fracture was 20[206]. RRs of excess mortality in subsequent years after a non-vertebral fracture were estimated at 30 due mostly to hip fractures, though there are studies which claim there is little or no relation between co-morbid conditions and post-fracture mortality[102]. Based on this study, a RR of 10 was assumed for patients that sustained a non-vertebral fracture in subsequent years, as these not only involved hip fractures but also wrist fractures.

Table VII.1. Transition Probabilities for Bazedoxifene 20 mg/day

	Well	Vertebral fracture	Non-vertebral fracture	Healthy vertebral fracture	Healthy non-vertebral fracture	Dead
Well	0.94479[a]	0.00901[b,c]	0.024 [b,d]	0	0	0.022 [e]
Vertebral fracture	0	0	0	0.9768120[a]	0	0.023188 [e]
Non-vertebral fracture	0	0	0.1384667 [b,f]	0	0.8351333[a]	0.0264 [g]
Healthy vertebral fracture	0	0.0275706 [b,h]	0.1986292 [b,i]	0.7506122[a]	0	0.023188 [j]
Healthy non-vertebral fracture	0	0.0103615 [b]	0.0528313 [h]	0	0.9126072[a]	0.0242 [k]
Dead	0	0	0	0	0	1

[a]Residual probability; [b] Silverman et al.[109]; [c] Felsenberg et al.[108]; [d] Marin et al.[200]; [e] MSPI[110]; [f] Christodoulou et al. [207]; [g] SNAMFAP[206]; [h] SEIOMM[93]; [i] Naves et al.[208]; [j] AIAQS[205]; [k] Borgstrom et al.[105]. All probabilities without notes are based on assumption.

Table VII.2. Transition Probabilities for Raloxifene 60 mg/day

	Well	Vertebral fracture	Non-vertebral fracture	Healthy vertebral fracture	Healthy non-vertebral fracture	Dead
Well	0.944994[a]	0.008806 [b,c ,23]	0.024 [b,d]	0	0	0.022 [e]
Vertebral fracture	0	0	0	0.9768120 [a]	0	0.023188 [e]
Non-vertebral fracture	0	0	0.1897467 [b,f]	0	0.7838533[a]	0.0264 [g]
Healthy vertebral fracture	0	0.0271577 [b,h]	0.2287228 [b,i]	0.7209315 [a]	0	0.023188 [j]
Healthy non-vertebral fracture	0	0.0100682[b]	0.0608356 [h]	0	0.90489624[a]	0.0242 [k]
Dead	0	0	0	0	0	1

[a]Residual probability; [b] Silverman et al.[109]; [c] Felsenberg et al.[108]; [d] Marin et al.[200]; [e] MSPI [110]; [f] Christodoulou et al.[207]; [g] SNAMFAP[206]; [h] SEIOMM [93]; [i] Naves et al[208]; [j] AIAQS [205]; [k] Borgstrom et al.[105] . All probabilities without notes are based on assumption.

Cost and effectiveness input data

Costs for osteoporosis treatment consisted of drug costs, diagnostic and follow-up tests, as well as physician visits. Costs were represented in 2010 Euros (EUR) and discounted according to health economic guidelines, resulting in a 3% discount for costs and benefits[209]. Drug prices were derived from a Spanish drug-cost database[210]. Drug costs for bazedoxifene were assumed to be similar as for raloxifene. The monitoring of osteoporosis treatment was estimated to include one yearly physician visit and one year BMD measurement based on other studies and expert opinion[211, 212].

Event-related fracture resource utilization was obtained by expert consultation. Vertebral fractures were assumed to be associated with two days of hospitalization. Outpatient treatment comprised of two imaging procedures, three specialist visits, and concomitant medication

as analgesics during 90 days. Vertebral fracture costs resulted in approximately €3,878 per event.

Non-vertebral fracture costs were assumed to consist of 50% hip fractures and 50% wrist fractures. Hip fractures were associated with 15 hospitalization days and similar outpatient treatment to vertebral fractures, including additional rehabilitation costs during a 40-day period. Wrist fractures included four hospitalization days, surgery costs and outpatient treatment similar to that for hip fractures, with one less image procedure. Non-vertebral fracture costs were estimated at €7,478 per event (Table VII.3).

Table VII.3. Osteoporosis Treatment and Fractures: Resource Utilization in Units and Costs

	Units	Cost (EUR) 2010
Osteoporosis treatment		
Drug costs		287[a]
Conventional blood test	1	21[b]
Bone density scan (DXA)	1	165[c]
Visit to rheumatologist	1.5	69[d]
Annual treatment costs		**576**
Vertebral fracture		
Hospitalization vertebral fracture (average 2 days)		3,513.90[e]
Radiography	1	32.80[f]
Bone scan	1	232.34[g]
Visit to orthopedist	2	44.10[d]
Analgesics (2 tablets/day, 90 days)		0.06[a]
Annual treatment costs		**3,878**
Non-vertebral fracture		
Hip fracture		
Hospitalization hip fracture (average of 15 days)		7,956.70[e]
Visits to orthopaedist	3	44.10[d]
Radiography	2	32.80[f]
Rehabilitation (40 days)		52.87[b]
Analgesics (2 tablets/day, during 90 days)		0.06[a]
Wrist fracture		
Surgery	1	96.97[h]
Hospitalization wrist fracture (average of 4 days)	4	555.71[d]
Visits to orthopedist	3	44.10[d]
Radiography	3	32.[8f0]
Rehabilitation (40 days)		52.87[b]
Analgesics (2 tablets/day, during 90 days)		0.06[a]
Annual treatment costs (50% hip and 50% wrist)		**7,478**

[a]Vademecum[210]; [b]Hospital Lluís Alcanyis[213]; [c]Hospital de la Esperanza[214]; [d]INSALUD[215]; [e]Finnern et al.[216]; [f]Cernuda[217]; [g]DOGC[218] ; [h]DOGC[220].

Adverse Events incidence

Bazedoxifene and raloxifene have a number of associated adverse events (AEs), including leg cramps, venous thrombolytic events (VTEs) such as deep vein thrombosis (DVT), and breast cysts/fibrocystic breast disease[109, 219]. To account for these AEs costs and utilities for each health state were corrected based on their incidences (Table VII.4).

Table VII.4. Adverse Events and Incidence Rates (%) per 1,000 Postmenopausal Women With Osteoporosis

Adverse events	Incidence rates in %	
	Bazedoxifene	Raloxifene
Leg cramps[a]	10.9	11.7
Deep vein thrombosis[b]	0.4	0.4
Breast cysts/fibrocystic breast disease[a]	0.7	1.7

[a] *P-value for the comparison between treatments was* <0.01.
[b] *P-value for the comparison between treatments was* <0.05.

Resource utilization associated with the treatment of AEs such as leg cramps, deep vein thrombosis, and breast cysts or fibrocystic breast disease, was added to all health states based on the treatment-related incidence and expert validation (Table VII.5). Treatment of leg cramps and breast cysts or fibrocystic breast disease required one diagnostic test and one specialist physician visit per year. Deep vein thrombosis treatment included several diagnostic tests, a specialist physician visit, and the use of concomitant medication.

Table VII.5. Adverse Events: Resource Utilization in Units and Costs

Adverse events	Units	Cost (EUR) 2010
Leg cramps		
Basic analyses: blood, biochemistry, ions	1	39[a] [59]
Visit to specialist physician	1	46[b] [60]
Annual treatment costs		85
Deep vein thrombosis		
Basic analyses: blood, biochemistry, ions	1	39[a] [59]
Doppler echocardiogram	1	70[b] [60]
Plethysmography of legs	1	111[b] [60]
Venography	1	79[b] [60]
Visit to specialist physician	1	46[b] [60]
Sodic Heparin (injections 5,000 UI/mL, during 5 days)		1.83[c] [37]
Warfarin (5 mg/day, 40 days)		2.30[c] [37]
Annual treatment costs		349
Breast cysts/fibrocystic breast disease		
Mammography	1	128[b] [60]
Visit to specialist physician	1	46[b] [60]
Annual treatment costs		174

[a] DOGC (2009)[220]; [b] BOR (2009)[221]; [c] Vademecum (2011)[210]

The total of healthcare costs for osteoporosis treatment and fractures per postmenopausal woman were very similar for both treatment groups and once corrected for the incidence of AEs, resulted in 1€ higher cost for raloxifene than for bazedoxifene (Table VII.6). Bazedoxifene was being evaluated to be introduced in the Spanish market, and its price was assumed the same as raloxifene, the difference in the adverse events incidence rate produced the cost difference between treatments.

Table VII.6. Annual Cost per Health State; general prices and adding cost for AES by treatment group

Health state	Cost (EUR) 2010	Corrected costs for AEs	
		Bazedoxifene	Raloxifene
Well	576 €	580 €	581 €
Vertebral fracture	3,878 €	4,458 €	4,459 €
Non-vertebral fracture	7,478 €	8,058 €	8,059 €
Healthy post vertebral fracture	576 €	580 €	581 €
Healthy post non-vertebral fracture	576 €	580 €	581€

EUR, Euros; AE, adverse event.

Health related quality of life

Utility weights were derived from a global longitudinal study among 57,141 postmenopausal osteoporotic women aged 55 years and older that examined HRQoL in women who sustained fractures and the effect of fracture location on their HRQoL[222]. Utility values were evaluated using the EQ-5D and SF-36 subscales mapped to a country-specific preference based value. The reduction in HRQoL after a vertebral fracture was 38% lower than that observed in a healthy individual, and for non-vertebral fracture was 39% (based on reductions for hip and wrist fractures). The reduction in HRQoL in subsequent years after a vertebral fracture was 9% lower compared with that of a healthy individual and a reduction of 6% for hip and wrist fractures after a non-vertebral fracture.

VTEs, primarily DVT, were assumed to be associated with a 10% utility loss per year based on assumptions in previous publications [223, 224]. No appropriate estimate was found for utility loss due to leg cramps and breast cyst or fibrocystic breast disease and a 10% HRQoL loss was assumed for them as it was documented for DVT. Based on the incidence rate of AEs for both treatments, utilities were corrected for HRQoL loss associated with AEs (Table VII.7).

Table VII.7. Utilities for postmenopausal population and utilities corrected by the AEs presence by treatment

Health condition	Utility[a]	Corrected utility for AEs	
		Bazedoxifene[b]	Raloxifene[b]
Well	1	0.996	0.9954
Vertebral fracture	0.620	0.61752	0.617148
Non-vertebral fracture	0.651	0.647898	0.6475077
Healthy post vertebral fracture	0.910	0.90636	0.905814
Healthy post non-vertebral fracture	0.940	0.9358416	0.93527784
HRQoL loss due to each AE of 10%[c,d *]	-0.1	-	-

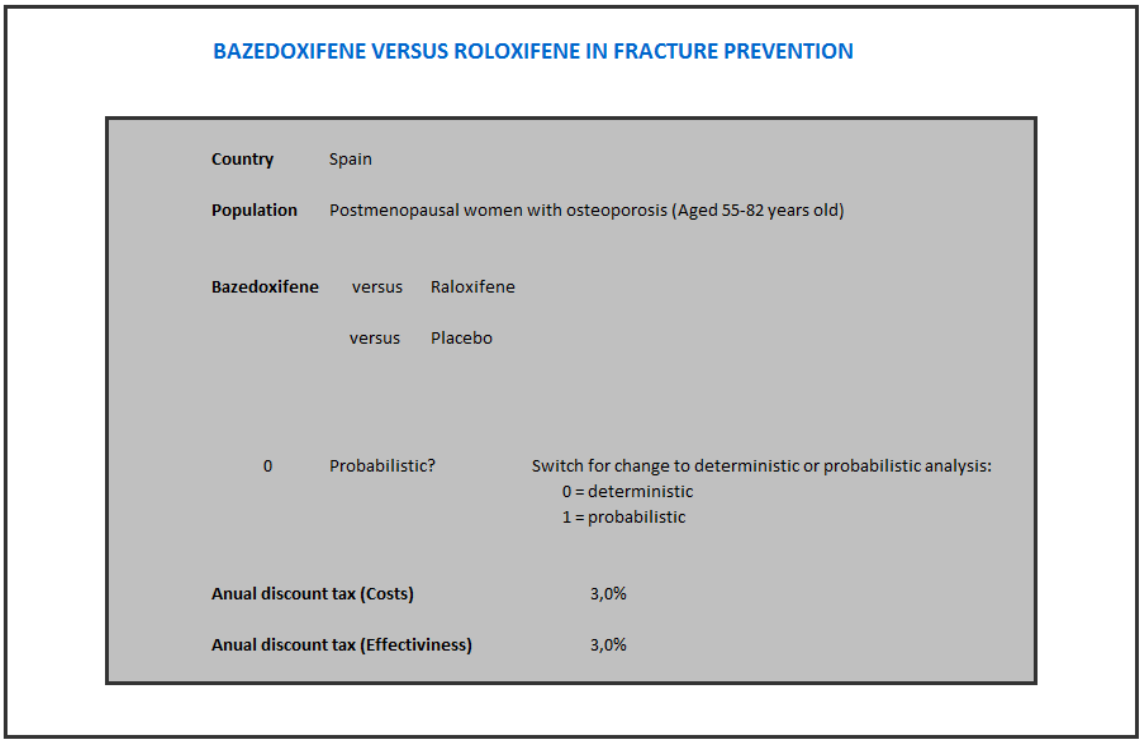
HRQoL, health related quality of life; AE, adverse event.
*Includes assumption ;[a] Adachi et al.[222]; [b] Silverman et al.[109];[c] Sobocki et al.[223] ;[d] Zethraeus et al.[224].

Annex VIII: Analysis worksheets for the bazedoxifene versus raloxifene model

The simulation model to assess the cost-effectiveness of the two assessed treatments was implemented in Microsoft® Excel.

The model input and output parameters are organized into 12 (the placebo scenario is not shown) Excel sheets: Frontpage, Results, Model and Probabilities, Bazedoxifene, Raloxifene, Costs and Utilities, Drug costs, Parameters, Simulation, CEA Curve, CEP, and CEAC.

VIII.1 Frontpage



VIII.2 Results

Cost-effectiveness and fracture prevention

Results (deterministic)

Treatment	Cost	QALY
Bazedoxifene	13.436 €	14,56
Raloxifene	13.881 €	14,54
Diff Bzd vs Ral	-445 €	0,02

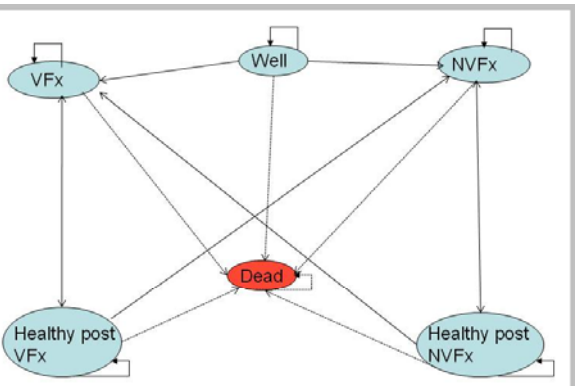
ICER:
Bzd vs Ral: dominated by QALY

Results (probabilistic) Run macros

Treatment	Cost	QALY
Bazedoxifeno	15.246 €	16,63
Raloxifene	15.675 €	16,47
Dif Bzd vs Ral	-428 €	0,16

ICER:
Bzd vs Ral: dominated by QALY

VIII.3 Model and Probabilities



One year annual cycles

BAZEDOXIFENE (20mg)	Well	VFx	NVFx	Healthy pVFx	Healthy pNVFx	Dead
Well	0,94479	0,00901	0,024	0	0	0,022
VFx	0	0	0	0,9768120	0	0,023188
NVFx	0	0	0,1384667	0	0,8351333	0,0264
Healthy pVFx	0	0,0275706	0,1986292	0,7506122	0	0,023188
Healthy pNVFx	0	0,0076585	0,0528313	0	0,9153102	0,0242
Dead	0	0	0	0	0	1

RALOXIFENE (60mg)	Well	VFx	NVFx	Healthy pVFx	Healthy pNVFx	Dead
Well	0,944994	0,008806	0,024	0	0	0,022
VFx	0	0	0	0,9768120	0,0000000	0,023188
NVFx	0	0	0,1897467	0,0000000	0,7838533	0,0264
Healthy pVFx	0	0,0271577	0,2287228	0,7209315	0,0000000	0,023188
Healthy pNVFx	0	0,0075438	0,0608356	0	0,9074206	0,0242
Dead	0	0	0	0	0	1

PLACEBO	Well	VFx	NVFx	Healthy pVFx	Healthy pNVFx	Dead
Well	0,9436	0,0102	0,0242	0	0	0,022
VFx	0	0	0	0,976812	0	0,023188
NVFx	0	0	0,2	0	0,7736	0,0264
Healthy pVFx	0	0,03672	0,23474	0,705352	0	0,023188
Healthy pNVFx	0	0,0102	0,062436	0	0,903164	0,0242
Dead	0	0	0	0	0	1

VIII.4 Bazedoxifene cohort

Bazedoxifene Cohort

Years old	Cycle	Well	VFx	NVFx	Healthy post VFx	Healthy post NVFx	Dead	Total	QALYs without discount tax	QALYs with discount tax	LYs without discount tax	LYs with discount tax	Cost without discount tax	Cost with discount tax
55	0	100000						100000	99600	99600	100000	100000	57.997.114 €	57.997.114 €
56	1	94479	901	2420	0	0	2200	100000	96225	93423	97800	94951	78.312.427 €	76.031.482 €
57	2	89263	851	2621	880	2021	4363	100000	93819	88433	95637	90147	78.371.562 €	73.872.713 €
58	3	84335	844	2805	1492	4039	6485	100000	91468	83706	93515	85579	78.483.112 €	71.823.165 €
59	4	79679	832	2939	1944	6039	8567	100000	89192	79246	91433	81237	78.233.493 €	69.509.445 €
60	5	75279	818	3040	2272	7982	10608	100000	86983	75032	89392	77111	77.753.375 €	67.070.744 €
61	6	71123	802	3116	2504	9846	12609	100000	84837	71049	87391	73189	77.095.113 €	64.565.943 €
62	7	67197	785	3170	2663	11614	14571	100000	82749	67283	85429	69462	76.298.999 €	62.038.069 €
63	8	63487	768	3208	2766	13278	16494	100000	80718	63720	83506	65920	75.396.350 €	59.518.575 €
64	9	59982	750	3231	2826	14832	18379	100000	78741	60348	81621	62556	74.411.749 €	57.030.410 €
65	10	56670	732	3244	2854	16275	20225	100000	76814	57157	79775	59360	73.364.558 €	54.590.121 €
66	11	53541	714	3247	2857	17606	22035	100000	74938	54136	77965	56324	72.270.074 €	52.209.439 €
67	12	50585	696	3243	2842	18827	23807	100000	73108	51277	76193	53440	71.140.422 €	49.896.460 €
68	13	47792	678	3232	2813	19940	25543	100000	71325	48569	74457	50701	69.985.250 €	47.656.550 €
69	14	45154	661	3216	2774	20951	27244	100000	69587	46005	72756	48101	68.812.268 €	45.493.016 €
70	15	42661	644	3196	2728	21863	28909	100000	67891	43577	71091	45631	67.627.663 €	43.407.623 €
71	16	40306	627	3172	2676	22680	30539	100000	66238	41277	69461	43286	66.436.423 €	41.400.982 €
72	17	38080	611	3144	2621	23409	32135	100000	64625	39099	67865	41060	65.242.592 €	39.472.841 €
73	18	35978	595	3114	2564	24052	33697	100000	63052	37036	66303	38946	64.049.464 €	37.622.310 €
74	19	33992	579	3082	2506	24616	35226	100000	61518	35083	64774	36940	62.859.739 €	35.848.031 €
75	20	32115	564	3048	2446	25105	36722	100000	60021	33232	63278	35035	61.675.638 €	34.148.305 €
76	21	30342	549	3011	2387	25524	38187	100000	58561	31479	61813	33228	60.498.999 €	32.521.193 €
77	22	28667	535	2974	2328	25877	39619	100000	57136	29819	60381	31512	59.331.352 €	30.964.588 €
78	23	27084	521	2935	2270	26169	41021	100000	55746	28246	58979	29884	58.173.972 €	29.476.272 €
79	24	25589	507	2895	2212	26404	42393	100000	54390	26757	57607	28339	57.027.929 €	28.053.962 €
80	25	24176	494	2855	2156	26586	43734	100000	53068	25345	56266	26873	55.894.121 €	26.695.344 €
81	26	22841	481	2813	2101	26718	45046	100000	51777	24009	54954	25482	54.773.304 €	25.398.092 €
82	27	21580	468	2771	2046	26805	46329	100000	50518	22743	53671	24162	53.666.113 €	24.159.897 €

					Bazedoxifene qalys				Bazedoxifene cost	
					20,146	14,567	20,933	15,085	18.952 €	13.385 €

VIII.5 Raloxifene cohort

Raloxifene Cohort

Years old	Cycle	Well	VFx	NVFx	Healthy post VFx	Healthy post NVFx	Dead	Total	QALYs without discount tax	QALYs with discount tax	LYs without discount tax	LYs with discount tax	Cost without discount tax	Cost with discount tax
	0	100000						100000	99540	99540	100000	100000	58.077.861 €	58.077.861 €
	1	94499	881	2420	0	0	2200	100000	96175	93374	97800	94951	78.312.285 €	76.031.345 €
	2	89301	832	2746	860	1897	4363	100000	93736	88355	95637	90147	79.306.464 €	74.753.949 €
	3	84389	824	2994	1433	3874	6486	100000	91370	83616	93514	85579	79.898.712 €	73.118.640 €
	4	79747	811	3174	1838	5862	8567	100000	89084	79150	91433	81237	79.982.513 €	71.063.426 €
	5	75361	796	3309	2118	7807	10609	100000	86868	74933	89391	77110	79.751.228 €	68.794.110 €
	6	71215	780	3411	2305	9678	12611	100000	84717	70949	87389	73187	79.286.341 €	66.401.062 €
	7	67298	763	3487	2423	11456	14573	100000	82627	67183	85427	69460	78.644.714 €	63.945.349 €
	8	63596	745	3541	2492	13128	16497	100000	80593	63621	83503	65918	77.868.498 €	61.470.111 €
	9	60098	727	3580	2524	14689	18382	100000	78613	60250	81618	62553	76.989.587 €	59.006.108 €
	10	56792	709	3605	2530	16135	20230	100000	76685	57061	79770	59357	76.032.293 €	56.575.167 €
	11	53669	691	3619	2516	17467	22040	100000	74806	54041	77960	56320	75.015.259 €	54.192.619 €
	12	50716	673	3623	2488	18686	23813	100000	72975	51183	76187	53436	73.952.871 €	51.869.056 €
	13	47927	655	3621	2451	19796	25550	100000	71190	48477	74450	50697	72.856.311 €	49.611.602 €
	14	45290	638	3612	2407	20802	27251	100000	69450	45915	72749	48096	71.734.338 €	47.424.848 €
	15	42799	621	3597	2358	21707	28917	100000	67753	43488	71083	45626	70.593.878 €	45.311.524 €
	16	40445	605	3578	2307	22517	30548	100000	66099	41190	69452	43280	69.440.461 €	43.272.999 €
	17	38220	589	3555	2254	23237	32145	100000	64485	39014	67855	41054	68.278.543 €	41.309.641 €
	18	36118	573	3529	2200	23873	33708	100000	62911	36953	66292	38940	67.111.759 €	39.421.085 €
	19	34131	558	3499	2146	24429	35237	100000	61376	35002	64763	36933	65.943.104 €	37.606.431 €
	20	32254	543	3467	2092	24910	36734	100000	59878	33153	63266	35029	64.775.070 €	35.864.386 €
	21	30480	529	3432	2039	25321	38199	100000	58417	31402	61801	33221	63.609.756 €	34.193.378 €
	22	28803	515	3396	1986	25667	39633	100000	56992	29744	60367	31505	62.448.942 €	32.591.635 €
	23	27219	501	3357	1935	25953	41035	100000	55602	28173	58965	29877	61.294.154 €	31.057.242 €
	24	25722	488	3317	1884	26182	42407	100000	54246	26686	57593	28332	60.146.705 €	29.588.193 €
	25	24307	475	3276	1835	26358	43749	100000	52923	25277	56251	26866	59.007.739 €	28.182.425 €
	26	22970	463	3233	1787	26485	45062	100000	51633	23942	54938	25474	57.878.250 €	26.837.839 €
	27	21706	451	3189	1740	26567	46346	100000	50374	22678	53654	24155	56.759.110 €	25.552.330 €

					Raloxifene qalys				Raloxifene cost	
					20,111	14,544	20,931	15,083	19.650 €	13.831 €

VIII.6 Costs and Utilities

Table 1.Cost for tests and visits

Diagnostic tests	Units	Cost (€)
Conventional blood test	1	21 €
Bone density scan (DXA)	1	165 €
Cost per unit year		**186 €**
Visits	**Visits**	**Cost (€)**
Visits to rheumatologist	1,5	69 €
Cost per unit year		**103 €**

Table 2. Cost for 1 osteoprotic fracture

Hip Fracture	Units	Cost (€)
Hospital costs		7.956,70 €
Visits to traumatologist	3	44,10 €
X-ray	2	32,80 €
Rehabilitation (40 days)	40	52,87 €
Analgesics (2 units by 90 days)	180	0,06 €
Anual mean cost for hip fracture		**10.280,20 €**
Vertebral Fracture	**Units**	**Cost (€)**
Hospital costs		3.513,90 €
Visits to traumatologist	2	44,10 €
X-ray	1	32,80 €
Bone gammagrafy	1	232,34 €
Analgesics (2 units by 90 days)	180	0,06 €
Anual mean cost for vertebral fracture		**3.878,04 €**
Wrist Fracture	**Units**	**Cost (€)**
Surgery		96,97 €
Hospital costs (Trauma unit)	4	555,71 €
Visits to traumatologist	3	44,10 €
X-ray	3	32,80 €
Rehabilitation (40 days)[3]	40	52,87 €
Analgesics (2 units by 90 days)[4]	180	0,06 €
Anual mean cost for wrist fracture		**4.676,11 €**

Table 3. Costs associated to adverse events(AE)

Diagnostic tests	Units	Cost (€)	Associated AE	Reference
General blood test	1	21 €		
Blood test+bioquimics and iones test	1	39 €	LegC;DVT	DRG_Catalunya-2009
Mammografy	1	128 €	Breast D	DRG-Rioja-2009
Doppler ecography	1	70 €	DVT	DRG-Rioja-2009
Legs pletismography	1	111 €	DVT	DRG-Rioja-2009
Venoegraphy	1	79 €	DVT	DRG-Rioja-2009-estudios con contraste
Cost per unit year				
Health workers	**Visits**	**Cost (€)**	**Associated AE**	
Visits to gynecologist	1	46 €	Breast D	
Visits to doctor	1	46 €	LegC;DVT	
Cost per unit year		**103 €**		
Drugs	**Units**	**Cost (€)**	**Associated AE**	
Sodic Heparin (5.000UI/ml)		1,83 €	DVT	PVL-Vademecum.es
Warfarin (Aldocumar 1 compr.		2,30 €	DVT	PVL-Vademecum.es

Summary

EA	Cost
Breast disease	174 €
Deep Vein Tromb	349 €
Leg Cramps	85 €

Table 4. Utilities and costs

Summary	Applied Direct Costs (€ 2009)	Utility SELECTED	10% of utility value	Pooled costs_Baz	Pooled costs_Ral	Pooled costs_Pla	Pooled Utility_Baz	Pooled Utility_Ral	Pooled Utility_Pla
Well	Pool Table 3 and AE	1,000	0,100	579,97114	580,7786067	292,02801	0,996	0,9954	0,9969
Healthy post Vertebral Fracture (VFx)	equal to Well costs	0,910	0,091	579,97114	580,7786067	292,02801	0,90636	0,905814	0,907179
Healthy post Non-Vertebral Fracture (VFx)	equal to Well costs	0,940	0,094	579,97114	580,7786067	292,02801	0,9358416	0,93527784	0,93668724
VFx	Well+VFx	0,620	0,062	4.458,01 €	4458,818607	4.170,07 €	0,61752	0,617148	0,618078
NVFx (Estimated as (fract. Hip+ Wrist)/2	Well+NVFx	0,651	0,065	8.058,13 €	8.058,93 €	7770,18301	0,647898	0,6475077	0,64848345
AE QoL 10% loss (expressed over 1)	table below	-0,1							
Dead	0	0,000	0,000				0	0	0

*QoL loss associated with thromboembolic events (VTE) were assumed to be associated with a 10% utility loss the fist year after the event

**It was assumed be the same QoL for leg cramps and breast cyst/fibrocystic breast disease

Table 5. Adverse events incidence and cost

AE(incidence,%) ->divided by100 over 1	Bazedoxifene	Raloxifene	Placebo	DIRECT COST
Breast cyst/fibrocystic breast disease	0,7	1,7	1	174 €
Deep vein thrombosis	0,4	0,4	0,1	349 €
Leg cramps	10,9	11,7	8,2	85 €

Tabla 6. Cost per unit/year of the treatment with Bazedoxifene, Raloxifene and placebo

Concept	Bazedoxifene	Raloxifene	Placebo
Drugs	287 €	287 €	0 €
Diagnostic and control tests	186 €	186 €	186 €
Health workers	103 €	103 €	103 €
Treatment costs in €	**576 €**	**576 €**	**289 €**

Tabla 7. Summary mean cost/year per fracture (Fx)

Mean cost for VFx	3.878 €	
Mean cost for NVFx	7.478 €	Assuming 50% Hip Fx and 50% Wrist Fx

VIII.7 Drug costs

	Annual treatment cost in €	Posology	Manufacturer selling price MSP in €	Source
Raloxifene (Evista)	287 €	Oral QD	22,04 €	Vademecum
Bazedoxifene (Conbriza)	287 €			FRAX_Conbriza_CEA_Europe.pdf; pag 4

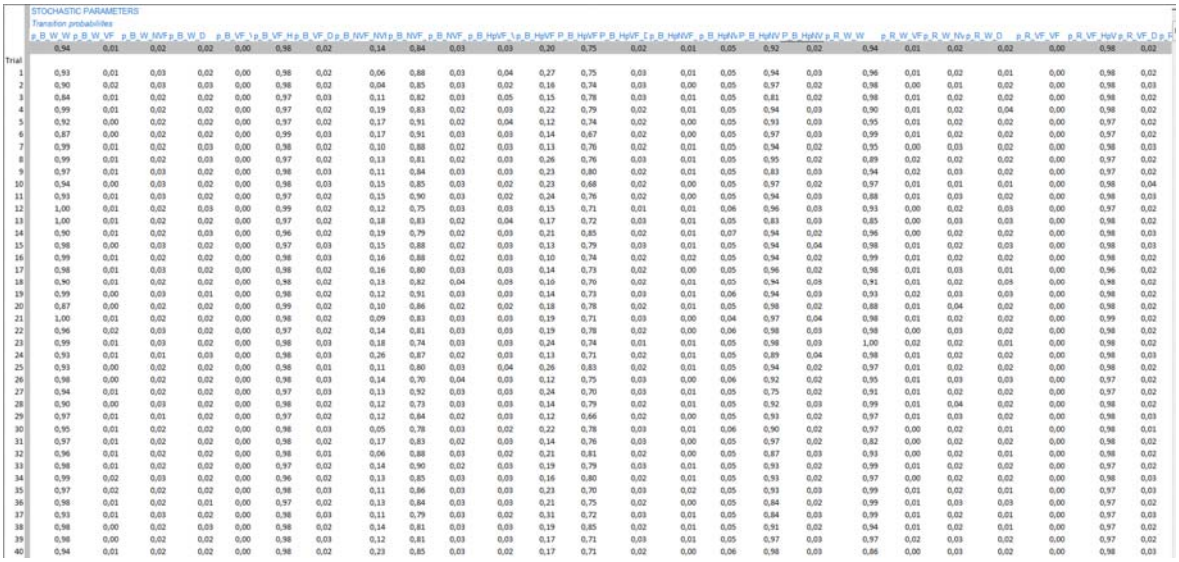
VIII.8 Parameters

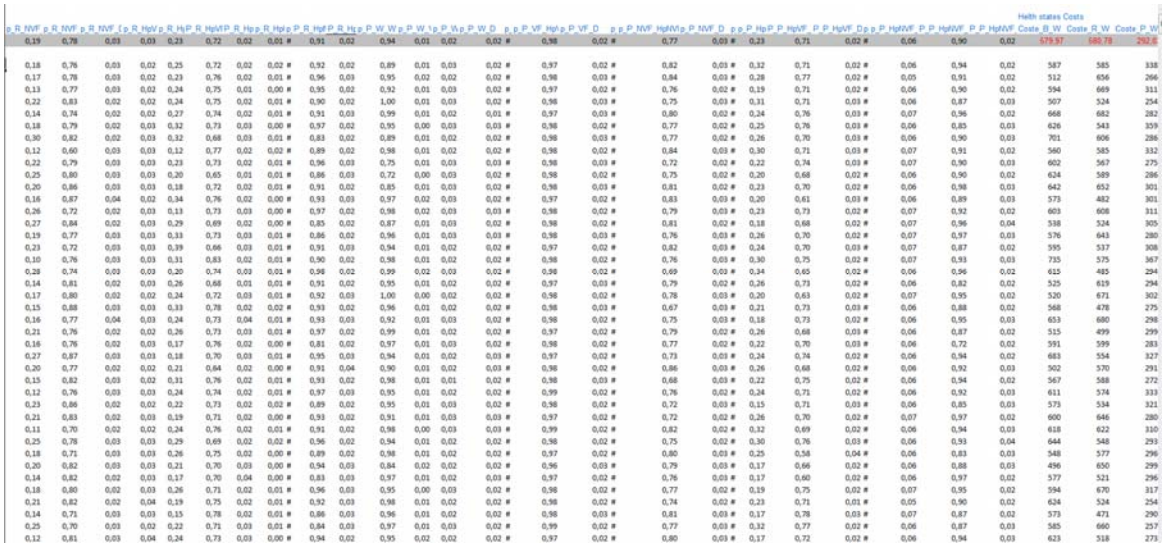
Parameters

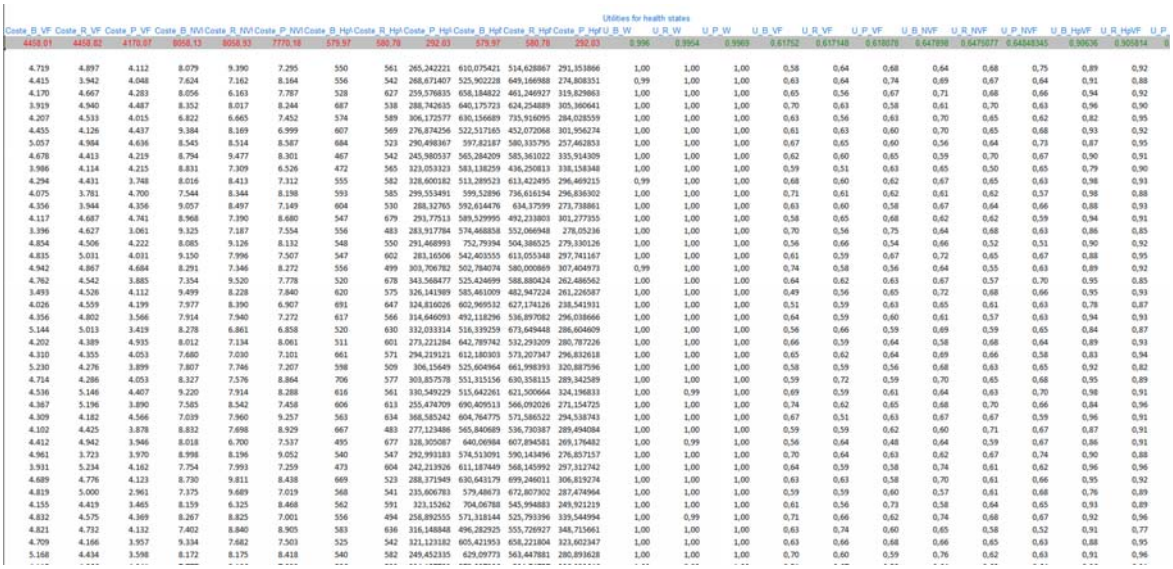
	Name	Life Value	probabilistic	deterministic	tandard erro	distribution	alpha	beta
Bazedoxifene	p_B_W_W	0,94	0,98	0,945	0,050	Beta	18,77	1,10
	p_B_W_VF	0,01	0,01	0,009	0,005	Beta	3,21	352,94
	p_B_W_NVF	0,02	0,03	0,024	0,005	Beta	22,83	920,74
	p_B_W_D	0,02	0,02	0,022	0,005	Beta	18,91	840,73
	p_B_VF_VF	0,00	0,00	0,000	0,000	Beta	-	-
	p_B_VF_HpVF	0,98	0,97	0,977	0,005	Beta	884,03	20,99
	p_B_VF_D	0,02	0,02	0,023	0,005	Beta	20,99	884,03
	p_B_NVF_NVF	0,14	0,10	0,138	0,050	Beta	6,47	40,25
	p_B_NVF_HpNVF	0,84	0,87	0,835	0,050	Beta	45,16	8,92
	p_B_NVF_D	0,03	0,03	0,026	0,005	Beta	27,12	1000,01
	p_B_HpVF_VF	0,03	0,04	0,028	0,005	Beta	29,54	1041,88
	p_B_HpVF_NVF	0,20	0,11	0,199	0,050	Beta	12,45	50,22
	P_B_HpVF_HpVF	0,75	0,70	0,751	0,050	Beta	55,45	18,42
	P_B_HpVF_D	0,02	0,02	0,023	0,005	Beta	20,99	884,03
	p_B_HpNVF_VF	0,01	0,00	0,008	0,005	Beta	2,32	300,67
	p_B_HpNVF_NVF	0,05	0,06	0,053	0,005	Beta	105,69	1894,91
	P_B_HpNVF_HpNVF	0,92	0,90	0,915	0,050	Beta	27,47	2,54
	P_B_HpNVF_D	0,02	0,03	0,024	0,005	Beta	22,83	920,74
Raloxifene	p_R_W_W	0,94	0,91	0,945	0,050	Beta	18,70	1,09
	p_R_W_VF	0,01	0,01	0,009	0,005	Beta	3,07	345,07
	p_R_W_NVF	0,02	0,02	0,024	0,005	Beta	22,83	920,74
	p_R_W_D	0,02	0,01	0,022	0,005	Beta	18,91	840,73
	p_R_VF_VF	0,00	0,00	0,000	0,000	Beta	-	-
	p_R_VF_HpVF	0,98	0,98	0,977	0,005	Beta	884,03	20,99
	p_R_VF_D	0,02	0,03	0,023	0,005	Beta	20,99	884,03
	p_R_NVF_NVF	0,19	0,19	0,190	0,050	Beta	11,48	49,02
	p_R_NVF_HpNVF	0,78	0,69	0,784	0,050	Beta	52,34	14,43
	p_R_NVF_D	0,03	0,02	0,026	0,005	Beta	27,12	1000,01
	p_R_HpVF_VF	0,03	0,03	0,027	0,005	Beta	28,67	1027,13
	p_R_HpVF_NVF	0,23	0,21	0,229	0,050	Beta	15,91	53,65
	P_R_HpVF_HpVF	0,72	0,76	0,721	0,050	Beta	57,30	22,18
	P_R_HpVF_D	0,02	0,02	0,023	0,005	Beta	20,99	884,03
	p_R_HpNVF_VF	0,01	0,02	0,008	0,005	Beta	2,25	296,22
	p_R_HpNVF_NVF	0,06	0,06	0,061	0,005	Beta	138,97	2145,41
	P_R_HpNVF_HpNVF	0,91	0,96	0,907	0,050	Beta	29,58	3,02
	P_R_HpNVF_D	0,02	0,03	0,024	0,005	Beta	22,83	920,74
Placebo	p_P_W_W	0,94	0,99	0,944	0,050	Beta	19,14	1,14
	p_P_W_VF	0,01	0,01	0,010	0,005	Beta	4,11	398,73
	p_P_W_NVF	0,02	0,03	0,024	0,005	Beta	22,83	920,74
	p_P_W_D	0,02	0,03	0,022	0,005	Beta	18,91	840,73
	p_P_VF_VF	0,00	0,00	0,000	0,000	Beta	-	-
	p_P_VF_HpVF	0,98	0,98	0,977	0,005	Beta	884,03	20,99
	p_P_VF_D	0,02	0,03	0,023	0,005	Beta	20,99	884,03
	p_P_NVF_NVF	0,20	0,18	0,200	0,050	Beta	12,60	50,40
	p_P_NVF_HpNVF	0,77	0,82	0,774	0,050	Beta	53,42	15,63
	p_P_NVF_D	0,03	0,02	0,026	0,005	Beta	27,12	1000,01
	p_P_HpVF_VF	0,04	0,04	0,037	0,005	Beta	51,92	1361,95
	p_P_HpVF_NVF	0,23	0,20	0,235	0,050	Beta	16,63	54,22
	P_P_HpVF_HpVF	0,71	0,69	0,705	0,050	Beta	57,93	24,20
	P_P_HpVF_D	0,02	0,02	0,023	0,005	Beta	20,99	884,03
	p_P_HpNVF_VF	0,01	0,01	0,010	0,005	Beta	4,11	398,73
	p_P_HpNVF_NVF	0,06	0,06	0,062	0,005	Beta	146,13	2194,38
	P_P_HpNVF_HpNVF	0,90	0,96	0,903	0,050	Beta	30,69	3,29
	P_P_HpNVF_D	0,02	0,03	0,024	0,005	Beta	22,83	920,74
	Costs							
	Coste_B_W	580 €	568 €	580 €	58 €	Gamma	99,99	5,80
	Coste_R_W	581 €	483 €	581 €	58 €	Gamma	100,27	5,79
	Coste_P_W	292 €	289 €	292 €	29 €	Gamma	101,40	2,88
	Coste_B_VF	4.458 €	3.836 €	4.458 €	446 €	Gamma	99,91	44,62
	Coste_R_VF	4.459 €	4.317 €	4.459 €	446 €	Gamma	99,95	44,61
	Coste_P_VF	4.170 €	3.978 €	4.170 €	417 €	Gamma	100,00	41,70
	Coste_B_NVF	8.058 €	8.293 €	8.058 €	806 €	Gamma	99,95	80,62
	Coste_R_NVF	8.059 €	8.450 €	8.059 €	806 €	Gamma	99,97	80,61
	Coste_P_NVF	7.770 €	6.753 €	7.770 €	777 €	Gamma	100,00	77,70
	Coste_B_HpVF	580 €	727 €	580 €	58 €	Gamma	99,99	5,80
	Coste_R_HpVF	581 €	600 €	581 €	58 €	Gamma	100,27	5,79
	Coste_P_HpVF	292 €	255 €	292 €	29 €	Gamma	101,40	2,88
	Coste_B_HpNVF	580 €	553 €	580 €	58 €	Gamma	99,99	5,80
	Coste_R_HpNVF	581 €	668 €	581 €	58 €	Gamma	100,27	5,79
	Coste_P_HpNVF	292 €	358 €	292 €	29 €	Gamma	101,40	2,88
	Utilities							
	U_B_W	1,00	1,00	0,9960	0,00	Beta	3967,07	15,93
	U_R_W	1,00	1,00	0,9954	0,00	Beta	4556,78	21,06
	U_P_W	1,00	1,00	0,9969	0,00	Beta	3079,81	9,58
	U_B_VF	0,62	0,59	0,6175	0,05	Beta	57,72	35,75
	U_R_VF	0,62	0,63	0,6171	0,05	Beta	57,71	35,80
	U_P_VF	0,62	0,63	0,6181	0,05	Beta	57,74	35,68
	U_B_NVF	0,65	0,54	0,6479	0,05	Beta	58,47	31,78
	U_R_NVF	0,65	0,66	0,6475	0,05	Beta	58,47	31,83
	U_P_NVF	0,65	0,63	0,6485	0,05	Beta	58,48	31,70
	U_B_HpVF	0,91	0,95	0,9064	0,05	Beta	29,86	3,09
	U_R_HpVF	0,91	0,86	0,9058	0,05	Beta	30,01	3,12
	U_P_HpVF	0,91	0,84	0,9072	0,05	Beta	29,65	3,03
	U_B_HpNVF	0,94	0,93	0,9358	0,05	Beta	21,54	1,48
	U_R_HpNVF	0,94	0,90	0,9353	0,05	Beta	21,71	1,50
	U_P_HpNVF	0,94	0,99	0,9367	0,05	Beta	21,28	1,44

VIII.9 Simulation

Calculations replicated up to 1000 trials.

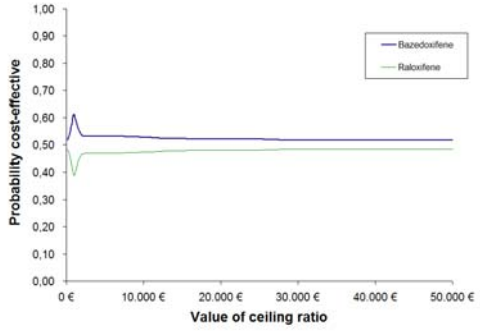




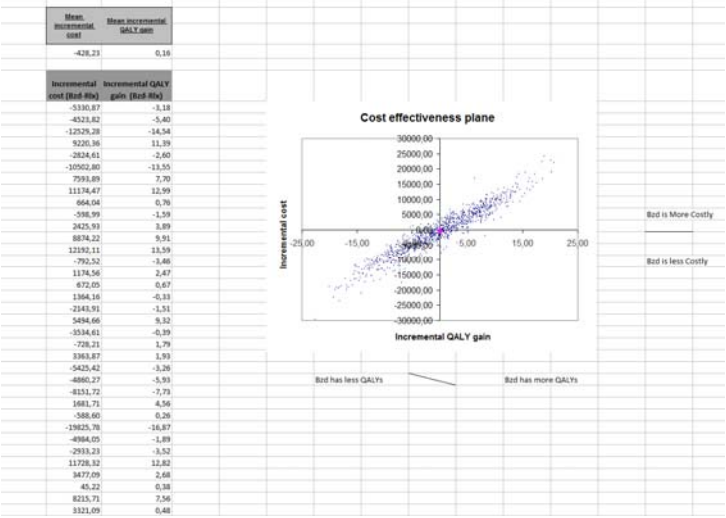


_HgVF	U_B_HgNVF	U_R_HgNVF	U_P_HgNVF	Cost-effectiveness results						cRatio	100000	Cost-effective?		Acceptability curves		
				Bazedoxifene			Raloxifene			Net monetary benefits						
				QALYs	LYG	Cost	QALYs	LYG	Cost	Bazedoxifen	Raloxifene	Bazedoxifen	Raloxifene	cRatio	Bazedoxifen	Raloxifene
907179	0,9358416	0,93527764	0,93668724	14,57	15,08	13.385	14,54	15,08	13.831			0,516	0,484			
0,97	0,92	0,81	0,90	14,01	14,66	13506,36	17,18	18,41	18.837,23	1387051	1699386	0	1	0	0,518	0,482
0,83	0,96	0,82	0,98	12,40	12,87	10980,20	17,80	18,55	15.504,02	1229414	1764815	0	1	100	0,518	0,482
0,96	0,95	0,95	0,92	6,50	6,64	5629,53	21,04	21,65	18.158,81	644658	2086302	0	1	200	0,521	0,479
0,84	0,97	0,97	0,97	21,60	22,15	18425,91	10,21	10,51	9.205,54	2141932	1011984	1	0	300	0,525	0,475
0,94	0,98	0,93	0,94	11,89	12,15	10822,79	14,49	14,94	13.647,39	1177684	1435018	0	1	400	0,534	0,466
0,98	0,91	0,97	0,97	9,27	9,67	8809,62	22,81	23,39	19.312,42	917717	2262004	0	1	500	0,549	0,451
0,89	0,97	0,90	0,93	21,57	22,23	21471,66	13,87	14,40	13.877,77	2135298	1373127	1	0	600	0,565	0,435
0,86	0,98	0,86	0,94	22,21	22,85	20442,84	9,22	9,64	9.268,36	2200419	912284	1	0	700	0,579	0,421
0,83	0,94	0,86	0,93	16,93	17,56	16607,69	16,17	17,60	15.943,65	1676632	1601178	1	0	800	0,59	0,41
0,94	0,99	0,89	0,93	15,44	15,77	14247,01	17,03	17,56	14.846,00	1529780	1688459	0	1	900	0,605	0,395
0,96	0,99	0,99	0,96	13,85	14,18	13089,36	9,96	10,25	10.663,43	1371617	985333	1	0	1000	0,612	0,388
0,84	0,98	0,99	0,94	23,63	24,12	20545,49	13,71	14,01	11.671,27	2341959	1359786	1	0	1500	0,56	0,44
0,95	0,95	0,99	0,97	22,23	22,83	20121,54	8,64	8,85	7.929,43	2203232	856433	1	0	2000	0,536	0,464
0,90	0,94	0,94	0,93	11,55	12,02	11450,14	15,01	15,44	12.242,67	1143359	1488489	0	1	2500	0,531	0,469
0,79	0,93	0,92	0,98	20,58	21,34	19327,32	18,12	18,78	18.152,76	2038726	1793389	1	0	3000	0,532	0,468
0,95	0,96	0,85	0,99	21,53	22,05	19288,31	20,85	21,77	18.616,26	2133282	2066479	1	0	3500	0,53	0,47
0,92	0,91	0,86	0,97	21,39	22,45	22827,99	21,72	23,06	21.463,83	2116106	2150504	0	1	4000	0,532	0,468
0,70	0,90	0,97	0,93	10,28	10,68	8952,23	11,79	12,20	11.190,20	1018043	1107338	0	1	4500	0,591	0,409
0,89	0,96	0,91	0,98	23,81	24,36	20852,74	14,49	15,25	15.358,08	2360183	1433304	1	0	5000	0,532	0,468
0,87	0,97	0,83	0,91	9,36	9,65	7945,61	9,74	10,54	11.480,22	927685	962747	0	1	6000	0,53	0,47
0,95	0,95	1,00	1,00	23,85	24,45	18841,40	22,05	22,75	19.569,61	2365984	2185837	1	0	7000	0,53	0,47
0,89	0,98	0,93	0,97	21,68	22,46	22586,76	19,75	20,49	19.222,89	2145487	1955647	1	0	8000	0,528	0,472
0,96	0,98	0,76	0,90	25,06	25,87	23319,28	28,32	31,37	28.764,70	2482551	2802743	0	1	9000	0,529	0,471
0,97	0,97	0,94	0,89	12,50	12,81	10699,60	18,43	18,89	15.559,88	1238899	1827308	0	1	10000	0,526	0,474
0,95	0,98	0,92	0,93	12,05	12,28	10890,33	19,78	20,79	19.042,05	1194391	1959200	0	1	11000	0,526	0,474
0,96	0,95	0,98	0,92	19,46	19,87	15149,77	14,89	15,26	13.468,07	1930752	1475944	1	0	12000	0,525	0,475
0,93	0,94	0,91	0,87	12,18	12,49	11183,14	11,92	12,53	11.771,73	1207267	1180510	1	0	13000	0,523	0,477
0,91	0,96	0,95	0,99	9,80	10,07	8979,16	26,68	27,75	28.804,94	971428	2639071	0	1	14000	0,523	0,477
0,90	0,98	0,92	0,94	16,80	17,06	12479,99	18,69	19,46	17.464,04	1667846	1851413	0	1	15000	0,522	0,478
0,87	0,95	0,95	0,99	13,78	14,20	12534,41	17,30	17,75	15.467,64	1365746	1714734	0	1	16000	0,521	0,479
0,92	0,96	0,95	0,94	18,66	19,20	16728,18	5,83	6,01	4.999,86	1848830	578365	1	0	17000	0,521	0,479
0,96	0,99	0,92	0,97	15,85	16,24	15779,28	13,16	13,70	12.302,20	1568780	1303856	1	0	18000	0,521	0,479
0,96	0,93	0,96	0,91	21,55	22,27	19186,65	21,17	21,75	19.141,43	2135910	2097483	1	0	19000	0,521	0,479
0,97	0,80	0,92	0,96	25,40	27,29	25766,80	17,84	18,43	17.551,09	2513979	1766175	1	0	20000	0,521	0,479
0,95	0,85	0,91	0,99	19,74	21,19	19100,24	19,25	19,79	15.779,15	1954461	1909607	1	0	21000	0,521	0,479
0,89	0,93	0,99	0,98	18,60	19,22	17482,45	24,77	25,39	22.910,61	1842613	2454305	0	1	22000	0,52	0,48
0,89	0,98	0,96	0,96	11,97	12,22	11821,54	23,08	23,74	20.485,10	1185269	2287741	0	1	23000	0,52	0,48
0,86	0,93	0,95	0,85	19,73	20,34	16430,58	12,54	12,91	10.169,90	1954566	1243573	1	0	24000	0,52	0,48
0,87	0,87	0,91	0,98	21,10	22,08	19712,85	18,04	18,76	19.375,51	2090687	1784438	1	0	25000	0,52	0,48
0,91	0,96	0,78	0,92	16,12	16,57	15989,40	8,10	8,76	7.431,26	1595808	802179	1	0	26000	0,518	0,482

VIII.10 CEA Curve



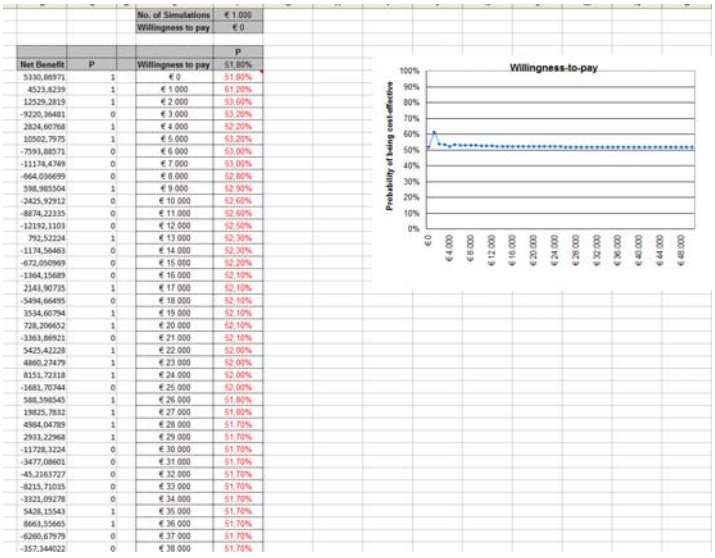
VIII.11 CEP



Mean incremental cost	Mean incremental QALY gain
-428,23	0,16

Incremental cost (Bzd-Rlx)	Incremental QALY gain (Bzd-Rlx)
-5330,87	-3,18
-4523,82	-5,40
-12529,28	-14,54
9220,36	11,39
-2824,61	-2,60
-10502,80	-13,55
7593,89	7,70
11174,47	12,99
664,04	0,76
-598,99	-1,59
2425,93	3,89
8874,22	9,91
12192,11	13,59
-792,52	-3,46
1174,56	2,47
672,05	0,67
1364,16	-0,33
-2143,91	-1,51
5494,66	9,32
-3534,61	-0,39
-728,21	1,79
3363,87	1,93
-5425,42	-3,26
-4860,27	-5,93
-8151,72	-7,73
1681,71	4,56
-588,60	0,26
-19825,78	-16,87
-4984,05	-1,89
-2933,23	3,52
11728,32	12,82
3477,09	2,68
45,22	0,38
8215,71	7,56
3321,09	0,48

VIII.12 CEAC



		No. of Simulations	€ 1.000
		Willingness to pay	€ 0
Net Benefit	P	Willingness to pay	P 51,80%
5330,86971	1	€ 0	51,80%
4523,8239	1	€ 1.000	51,20%
12529,2819	1	€ 2.000	53,60%
-9220,36481	0	€ 3.000	53,20%
2824,60768	1	€ 4.000	52,20%
10502,7975	1	€ 5.000	53,20%
-7593,88571	0	€ 6.000	53,00%
-11174,4749	0	€ 7.000	53,00%
-664,036699	0	€ 8.000	52,60%
598,985504	1	€ 9.000	52,90%
-2425,92912	0	€ 10.000	52,60%
-8874,22335	0	€ 11.000	52,60%
-12192,1103	0	€ 12.000	52,50%
792,52224	1	€ 13.000	52,30%
-1174,56463	0	€ 14.000	52,30%
-672,050969	0	€ 15.000	52,20%
-1364,15689	0	€ 16.000	52,10%
2143,90735	1	€ 17.000	52,10%
-5494,66495	0	€ 18.000	52,10%
3534,60794	1	€ 19.000	52,10%
728,206652	1	€ 20.000	52,10%
-3363,86921	0	€ 21.000	52,10%
5425,42228	1	€ 22.000	52,00%
4860,27479	1	€ 23.000	52,00%
8151,72318	1	€ 24.000	52,00%
-1681,70744	0	€ 25.000	52,00%
588,598545	1	€ 26.000	51,80%
19825,7832	1	€ 27.000	51,80%
4984,04789	1	€ 28.000	51,70%
2933,22968	1	€ 29.000	51,70%
-11728,3224	0	€ 30.000	51,70%
-3477,08601	0	€ 31.000	51,70%
-45,2163727	0	€ 32.000	51,70%
-8215,71035	0	€ 33.000	51,70%
-3321,09278	0	€ 34.000	51,70%
5428,15543	1	€ 35.000	51,70%
8663,55665	1	€ 36.000	51,70%
-6260,67979	0	€ 37.000	51,70%
-357,344022	0	€ 38.000	51,70%

VIII.13 Macros for Microsoft Project using Visual Basic for Applications (VBA)

```
'
'The most of the calculations were implemented using formulae in the calculus sheets. The plots
'were done using the chart menu.
'

Sub Analisis()
'
' Analisis Macro
' Macro recorded 02/12/2010
'
'
Application.ScreenUpdating = False

Simulacion
CEAcurva

Sheets("Results").Select
Range("A1").Select

End Sub

*****************.

Sub CEAcurva()
'
' CEAcurva Macro
' Macro recorded 01/12/2010
'

'
Application.DisplayStatusBar = True
Sheets("Simulation").Select
Index = 0
Trials = 58

Do

   Range("CW6").Select
```

```
    ActiveCell.Offset(Index, 0).Range("A1").Select
    Selection.Copy
    Range("CR1").Select
    ActiveSheet.Paste
    Range("CT4:CU4").Select
    Application.CutCopyMode = False
    Selection.Copy
    Range("CX6").Select
    ActiveCell.Offset(Index, 0).Range("A1").Select
    Selection.PasteSpecial Paste:=xlValues, Operation:=xlNone, SkipBlanks:= _
        False, Transpose:=False
        Index = Index + 1
    Application.StatusBar = "Calculation " & Index & " of " & Trials

Loop While Index < Trials

Application.DisplayStatusBar = False
Sheets("Simulation").Select
Range("CM1").Select

End Sub
**********************************.


Sub Simulacion()
'
' Simulacion Macro
'
'

'

Sheets("Main").Select
Range("E19").Select
ActiveCell.FormulaR1C1 = "1"
Application.DisplayStatusBar = True
Sheets("Simulation").Select
Index = 0
Trials = 1000
```

```
Do

    Range("C4:CO4").Select
    Selection.Copy
    Range("C6:CO6").Select
    ActiveCell.Offset(Index, 0).Range("A1").Select
    Selection.PasteSpecial Paste:=xlValues, Operation:=xlNone, SkipBlanks:= _
        False, Transpose:=False
    Index = Index + 1
    Application.StatusBar = "Simulation " & Index & " of 1000 trials"

Loop While Index < Trials

Application.DisplayStatusBar = False
Sheets("Main").Select
Range("E19").Select
ActiveCell.FormulaR1C1 = "0"
Sheets("Simulation").Select
Range("A1").Select

End Sub
```

**********.

Annex IX: Cohort simulation and cost-effectiveness analysis code with R

Once the health states, the probabilities for fulfilling the transition probabilities matrices, the costs, and utilities for each health state and the simulation stages are determined the cohort simulation can be performed.

The code is displayed below. The same code is used for the sensitivity analysis, to generate different scenarios by changing the input values.

```
###### Generalization Cohort Simulation for 2-stages ##########

##### Functions
# Function to perform the Markov model run
cohortsim = function()
        {
        #matrix that is going to contain the number of patients in each health state over the
        #simulation cycles. The number of columns is nhs and the number of rows are steps
        ncycle<-matrix(nrow = steps, ncol=nhs, byrow=TRUE, dimnames = list(c(1:steps),
        c("C.1", "C.2", "C.3")))

        # 1st cycle of the simulation
        ncycle[1,]<-Nstartv%*%mtrans1

        #1st phase simulation
        b<-steps1-1
                for (i in 1:b)

                {
                        ncycle[i+1,]<-ncycle[i,]%*%mtrans1
                }

        #2nd phase simulation
        Nstartv<-ncycle[steps1,]
        ncycle[steps1+1,]<-Nstartv%*%mtrans2

        b<-steps2-1

                for (i in 1:b)
```

```
        {
                ncycle[i+1+steps1,]<-ncycle[i+steps1,]%*%mtrans2
        }

    cat("Patients at each health state per cycle\n")
    print(ncycle)

    }



# Allocate cost and utilities
  costuts = function()
   {
    cost<- matrix(c(cost1,cost2,cost3), nrow = 1, ncol=nhs, byrow=TRUE, dimnames =
    list(c("row1"),c("C.1", "C.2", "C.3")))
    ut<- matrix(c(ut1,ut2,ut3), nrow = 1, ncol=nhs, byrow=TRUE, dimnames =
    list(c("row1"),c("C.1", "C.2", "C.3")))

    #imputation of the cost (and utilities) for the patients in each health status. [lenght it is
    #time horizon, here not used. 3 months cycles. Simulation lasts X
    #months=steps*3months]
    #       steps<-length(ncycle)/3

    costcycle<-matrix(nrow = steps, ncol=nhs, byrow=TRUE, dimnames = list(c(1:steps),
    c("C.1", "C.2", "C.3")))
    utcycle<-matrix(nrow = steps, ncol=nhs, byrow=TRUE, dimnames = list(c(1:steps),
    c("C.1", "C.2", "C.3")))

    for (i in 1:steps)
        {
        for(j in 1:nhs)

            {
            costcycle[i,j]<-cost[j]%*%ncycle[i,j]
            utcycle[i,j]<-ut[j]%*%ncycle[i,j]
            }
        }
```

```
        cat("Total cost for all patients at each health status\n")
        print(costcycle)
        cat("Total utilities for all patients at each health status\n")
        print(utcycle)
        aux<-cbind(costcycle,utcycle)

    }
```

Define input parametres

```
#Treatment A: MRV-454 Tropile test
#Total health state number
nhs<-3

#Total number of clinical phases that are going to be simulated
nphases<-2

#Total number of individuals in the simulated cohort
N<-100000

#The state where the (a concret number of) individuals are starting in the simulated cohort. The
#sum of the individuals in each health state should equal N. Nstartv has nrow=1 and ncol=nhs

Nstartv<- matrix(c(N,0,0), nrow = 1, ncol=nhs, byrow=TRUE,dimnames = list(c("row1"),c("C.1",
"C.2", "C.3")))


#Each phase should have a transition probabilities matrix (mtrans), then the same number of
#mtrans than nphases are required


mtrans1<-matrix(c(0.9298,0.07,0.0002,0.36,0.6398,0.0002, 0,0,1), nrow = nhs, ncol=nhs,
byrow=TRUE, dimnames = list(c("row1", "row2", "row3"),c("C.1", "C.2", "C.3")))
mtrans2<-matrix(c(0.9773,0.0225,0.0002,0.01,0.9898,0.0002,0,0,1), nrow = nhs, ncol=nhs,
byrow=TRUE, dimnames = list(c("row1", "row2", "row3"),c("C.1", "C.2", "C.3")))


#Simulate steps through the Markov Chain (Attention! Zero time point should be inclused, this is
#reflected by adding an extra step)
steps<-13
```

```
steps1<-3
steps2<-steps-steps1

# Allocate cost and utilities
# The cost for 1 patient in each health state are 1, 2, 3
cost1<-3161.13
cost2<-3161.13
cost3<-0
# The Utilities for 1 patient in each health state are 1, 2, 3
ut1<-0.83
ut2<-0.79
ut3<-0

#Treatment B: MRV-454 tropism test
mtrans1<-matrix(c(0.9048,0.095,0.0002,0.2628,0.737,0.0002,0,0,1), nrow = nhs, ncol=nhs, byrow=TRUE, dimnames = list(c("row1", "row2", "row3"),c("C.1", "C.2", "C.3")))
mtrans2<-matrix(c(0.98338,0.01643,0.00020,0.00730,0.99250,0.0002,0,0,1), nrow = nhs, ncol=nhs, byrow=TRUE, dimnames = list(c("row1", "row2", "row3"),c("C.1", "C.2", "C.3")))

# The cost for 1 patient in each health state are 1, 2, 3
cost1<-3067.38
cost2<-3067.38
cost3<-0
# The Utilities for 1 patient in each health state are 1, 2, 3
ut1<-0.83
ut2<-0.79
ut3<-0

#Treatment C: MRV-PS (geno2pheno) test
mtrans1<-matrix(c(0.9048,0.095,0.0002,0.216,0.7838,0.0002,0,0,1), nrow = nhs, ncol=nhs, byrow=TRUE, dimnames = list(c("row1", "row2", "row3"),c("C.1", "C.2", "C.3")))
mtrans2<-matrix(c(0.98630,0.01350,0.00020,0.00600,0.99380,0.00020,0,0,1), nrow = nhs, ncol=nhs, byrow=TRUE, dimnames = list(c("row1", "row2", "row3"),c("C.1", "C.2", "C.3")))

# The cost for 1 patient in each health state are 1, 2, 3
cost1<-3051.13
cost2<-3051.13
cost3<-0
# The Utilities for 1 patient in each health state are 1, 2, 3
ut1<-0.83
```

```
ut2<-0.79
ut3<-0


##### Call functions and see output at the screen.
#Read the parameters for one of the therapeutic strategies and call the functions

#Read parameters for treatment A
ncycle<- cohortsim();
cost_utcycle<- costuts();
treatA<-cbind(ncycle, cost_utcycle)
treatA<-data.frame(treatA)
names(treatA) <-
c("nstat1A","nstat2A","nstat3A","cstat1A","cstat2A","cstat3A","ustat1A","ustat2A","ustat3A")

#Read parameters for treatment B
ncycle<- cohortsim();
cost_utcycle<- costuts();
treatB<-cbind(ncycle, cost_utcycle)
treatB<-data.frame(treatB)
names(treatB) <-
c("nstat1B","nstat2B","nstat3B","cstat1B","cstat2B","cstat3B","ustat1B","ustat2B","ustat3B")

#Read parameters for treatment B
ncycle<- cohortsim();
cost_utcycle<- costuts();
treatC<-cbind(ncycle, cost_utcycle)
treatC<-data.frame(treatC)
names(treatC) <-
c("nstat1C","nstat2C","nstat3C","cstat1C","cstat2C","cstat3C","ustat1C","ustat2C","ustat3C")


##### Data management
#Simulated time, in years. It has to be coherent with the discount tax units
#Simulation of 12 cycles of 3 months

time_sim<-seq(0,by=0.25, length.out=steps)
out<-cbind(treatA,treatB,treatC,time_sim)
summary(out)
```

```
write.table(out,"C:\\Documents and Settings\\nperez\\Escritorio\\Maraviroc_redo\\output.txt", dec = ".", row.names = TRUE,col.names = TRUE)

data<-read.table("C:\\Documents and Settings\\nperez\\Escritorio\\Maraviroc_redo\\output.txt", header=T, dec=".")
summary(data)
```

Cost-effectiveness analysis

```
#Summaryze cost-effectiviness information
#The code for treatment A is shown, the sema has to be done for treatment B and C by
#changing the A by B or C in the value names.

#CEA: Calculations for treatment A

#Cost  (Non discounted)
 data$cA<-( data$cstat1A+ data$cstat2A+ data$cstat3A)
resumcA<-sum( data$cA)/N

#Cost  (Discounted ->discount tax 3%, introduced as 0.03)
 data$cAdisc<-( data$cstat1A+ data$cstat2A+ data$cstat3A)/((1+0.03)^time_sim)
resumcAdisc<-sum( data$cAdisc)/N

#Utility  (Non discounted)
 data$uA<-( data$ustat1A+ data$ustat2A+ data$ustat3A)
resumuA<-sum( data$uA)/N

#Utility  (Discounted ->discount tax 3%, introduced as 0.03)
 data$uAdisc<-( data$ustat1A+ data$ustat2A+ data$ustat3A)/((1+0.03)^time_sim)
resumuAdisc<-sum( data$uAdisc)/N

#Life years (Non discounted)
 data$lyA<-(data$nstat1A+data$nstat2A)
resumlyA<-sum( data$lyA)/N

#Life years  (Discounted ->discount tax 3%, introduced as 0.03)
 data$lyAdisc<-(data$nstat1A+data$nstat2A)/((1+0.03)^time_sim)
resumlyAdisc<-sum( data$lyAdisc)/N

resumcA
```

```
resumcAdisc
resumuA
resumuAdisc
resumlyA
resumlyAdisc

# Difference between treatments A and B
difcdiscAB<-resumcAdisc-resumcBdisc
difcdiscAB
difudiscAB<-resumuAdisc-resumuBdisc
difudiscAB

# Difference between treatments A and C
difcdiscAC<-resumcAdisc-resumcCdisc
difcdiscAC
difudiscAC<-resumuAdisc-resumuCdisc
difudiscAC

# Difference between treatments B and C
difcdiscBC<-resumcBdisc-resumcCdisc
difcdiscBC
difudiscBC<-resumuBdisc-resumuCdisc
difudiscBC

#Labelling output of the difference between costs and utilities (can be done analogously for
#AvsC and BvsC
AvsB <- if ((resumcAdisc>resumcBdisc)&(resumuAdisc<resumuBdisc)) 'Dominant' else if
((resumcAdisc<resumcBdisc)&(resumuA>resumuBdisc)) 'Dominated' else 'Non conclusive'
 AvsB

Results<-matrix(c(resumcA, resumcB,resumcAdisc,resumcBdisc, resumuA,resumuB,
resumuAdisc, resumuBdisc,resumlyA,resumlyB,resumlyAdisc,resumlyBdisc), nrow = 6, ncol=2,
byrow=TRUE, dimnames = list(c("resum cost","Discounted cost","Resum utility","Discounted
utility","resum ly ","Discounted ly disc"),c("Treatment A", "Treatment B")))

Results_diffs<-matrix(c(resumcA, resumcB,resumcAdisc,resumcBdisc, resumuA,resumuB,
resumuAdisc, resumuBdisc,resumlyA,resumlyB,resumlyAdisc,resumlyBdisc, resumcA-
resumcB,resumcAdisc-resumcBdisc, resumuA-resumuB, resumuAdisc-resumuBdisc,resumlyA-
resumlyB,resumlyAdisc-resumlyBdisc), nrow = 6, ncol=3, byrow=TRUE, dimnames =
```

```
list(c("resum cost","Discounted cost","Resum utility","Discounted utility","resum ly ","Discounted ly disc"),c("Treatment A", "Treatment B", "Difference")))

#Cost efficacy plot for the treatments assessed
x<-c(resumuA,resumuB)
y<-c(resumcA,resumcB)
plot(x,y, xlab="Utilities", ylab="Cost(€)", main="Cost Efficacy pot",pch=15, col="blue")
y1<-c(3715,3722)
x1<-c(0.98562,0.98572)
points(x1, y1, pch=16, col="green")
```

The following code is used to generate the input parameters for the probabilistic sensitivity analysis. The use of the code is the following: first, the functions should be read, after reading the input parameters for the therapeutic strategies assessed the funcions can be executed, and, finally, the output information can be saved.

```
##### Functions
### Execute the functions needed for distribution assignation

#Assign theoretical distributions to the parameters
#Probabilities and utilities follow a Beta distribution
#Costs follow a Gamma distribution

#Assign SD to the values
### 2.1.1 SD to the probabilities
#nhs is the total health states (HS)
#mat is the matrix or vector containing the transition probabilities between HS.
SDmat<-function(nhs,mat){
                        mat<-as.vector(t(mat))
                        SDmat<-array(NA,length(mat))
                          for (i in 1:length(mat)) {if((mat[i]<0.1)){SDmat[i]<-0.005}
                                                    if(mat[i]<0.001){SDmat[i]<-mat[i]}
                                                    if(mat[i]>0.1){SDmat[i]<-0.05}
                                                    }
```

```
                print(SDmat)

                }

#2.2 Funtions for parameters on the distributions

#parameters for the Beta- Function
alpha_b<-function(value,sd) {a<-value*(value*(1-value)/(sd*sd)-1)
                #print(a)
                }

beta_b<-function(value,sd) {b<-value*(1-value)/(sd*sd)-1-(value*(value*(1-value)/(sd*sd)-1))
                #print(b)
                }

### Function that gives the probabilities of transiton and the utilities (both follow a beta
#distribution)
# In the beta_trials functions the parameters for the beta distribution are generated, the columns
have the name o btrials (parameters for the trials that follow a beta distribution)

beta_trials<-function(ntrials,mat,s){
                        mat<-as.vector(t(mat))
                        btrials<-array(NA,ntrials)
                        aux<-seq(1, ntrials, by = 1)
                        for(i in 1:length(mat)) { if(mat[i]==0){btrials<-array(0,ntrials)}
                                        if(mat[i]==1){btrials<-array(1,ntrials)}
                                        if((mat[i]>0)&(mat[i]<1)){btrials<-
rbeta(ntrials, alpha_b(mat[i],s[i]), beta_b(mat[i],s[i]), ncp = 0)}
                                        aux<-cbind(aux,btrials)
                                }
                #print(aux)
                beta_trials<-aux
                }


#parameters for the Gamma- Function
alpha_g<-function(value,sd) {a<-((value/sd)^2)
                #print(a)
                }
```

```
beta_g<-function(value,sd) {b<-(sd*sd)/value
                            #print(b)
                           }


### Function that gives the costs (follow a Gamma distribution)
#in the gamma_trials functions the parameters for the beta distribution are generated, the columns have the name o gtrials (parameters for the trials that follow a Gamma distribution)

gamma_trials<-function(ntrials,mat,s){
                                      gtrials<-array(NA,ntrials)
                                      aux<-seq(1, ntrials, by = 1)
                                      for(i in 1:length(mat)) { if(mat[i]==0){gtrials<-array(0,ntrials)}
                                                                if(mat[i]>0){gtrials<-
rgamma(ntrials,alpha_g(mat[i],s[i]), 1/beta_g(mat[i],s[i]))}
                                                               aux<-cbind(aux,gtrials)
                                                              }
                                    #print(aux)
                                    gamma_trials<-aux
                                    }


##### Read input parameters
nhs<-3
mtrans1<-matrix(c(0.9298,0.07,0.0002,0.36,0.6398,0.0002, 0,0,1), nrow = nhs, ncol=nhs, byrow=TRUE, dimnames = list(c("row1", "row2", "row3"),c("C.1", "C.2", "C.3")))
mtrans2<-matrix(c(0.9773,0.0225,0.0002,0.01,0.9898,0.0002,0,0,1), nrow = nhs, ncol=nhs, byrow=TRUE, dimnames = list(c("row1", "row2", "row3"),c("C.1", "C.2", "C.3")))


##we need to read the components of the matrix as an array
mat1<-as.vector(t(mtrans1))
mat2<-as.vector(t(mtrans2))

# The cost for 1 patient in each health state are 1, 2, 3
cost1<-3161.13
cost2<-3161.13
cost3<-0

# The Utilities for 1 patient in each health state are 1, 2, 3
```

```
ut1<-0.83
ut2<-0.79
ut3<-0

ntrials<-1000

###  SD to the costs
#Gamma distribution for the cost
#As long as the number of nhs
#SD of cost is going to be taken to the 10% of the value.
SDcost1<-cost1*0.1
SDcost2<-cost2*0.1
SDcost3<-cost3*0.1

### SD to the utilities
#Beta distribution
#As many SDut1, SDut2... as the number of nhs
SDut1<-ifelse(ut1>0.1, 0.05, 0.005)
SDut2<-ifelse(ut2>0.1, 0.05, 0.005)
SDut3<-ifelse(ut3>0.1, 0.05, 0.005)
```

Call functions and safe the output

```
###For the phases of simulation considered. In our case we have 2.
probs_trials1<-beta_trials(ntrials,mtrans1,SDmat(nhs,mtrans1))
probs_trials2<-beta_trials(ntrials,mtrans2,SDmat(nhs,mtrans2))

#Costs and SD are introduced in an array for the use of the function gamma_trials
costs<-array(c(cost1,cost2,cost3))
SDcosts<-array(c(SDcost1,SDcost2,SDcost3))
costs_trials<-gamma_trials(ntrials,costs,SDcosts)

### Function that gives the utilities
uts<-array(c(ut1,ut2,ut3))
SDuts<-array(c(SDut1,SDut2,SDut3))
uts_trials<-beta_trials(ntrials,uts,SDuts)

###Bind all the information of the parameters in a data frame
#Probability Simulation Parameters
probsimpar<-cbind(probs_trials1,probs_trials2[,-1], costs_trials[,-1],uts_trials[,-1])
```

```
#Attention! Names depend on the treatment branch and on the total nhs.
probsimparA<-data.frame(probsimpar)
names(probsimparA) <-
c("trial","prob11A1","prob12A1","prob13A1","prob21A1","prob22A1","prob23A1","prob31A1","pro
b32A1","prob33A1","prob11A2","prob12A2","prob13A2","prob21A2","prob22A2","prob23A2","pr
ob31A2","prob32A2","prob33A2","cost1A","cost2A","cost3A","ut1A","ut2A","ut3A")
write.table(probsimparA,"C:\\Documents and
Settings\\nperez\\Escritorio\\Maraviroc_redo\\probsimparA.txt", dec = ".", row.names =
TRUE,col.names = TRUE)

# The code is the same for treatment B and C. Input parameters and value labels should be
#changed
```

CEA_output of n trials

The cohort simulation is going to be performed n times (to generate n trials) using the input parameters generated by means of the parametrical distributions. The funcitons “cohortsim” and “costuts” as implemented before are going to be used.

```
##### Input parameters
#Parameters (For cohortsim and some of them for costuts)
#Total health state number
nhs<-3
#Total number of clinical phases that are going to be simulated
nphases<-2
#Total number of individuals in the simulated cohort
N<-100000

#The state where the (a concret number of) individuals are starting in  the simulated cohort. The
sum of the individuals in each health state should equal N. Nstartv has nrow=1 and ncol=nhs
Nstartv<- matrix(c(N,0,0), nrow = 1, ncol=nhs, byrow=TRUE,dimnames = list(c("row1"),c("C.1",
"C.2", "C.3")))

#Required parameters for CEA for ntrials
```

```
# Parameters for the ntrials are stored at "probsimpar*.txt"
# For treatment A at data1, treatment B at data 2 and treatment C at data 3
data1<-read.table("C:\\Documents and Settings\\nperez\\Escritorio\\Maraviroc_redo\\probsimparA.txt", header=T, dec=".")
data2<-read.table("C:\\Documents and Settings\\nperez\\Escritorio\\Maraviroc_redo\\probsimparB.txt", header=T, dec=".")
data3<-read.table("C:\\Documents and Settings\\nperez\\Escritorio\\Maraviroc_redo\\probsimparC.txt", header=T, dec=".")

data<-cbind(data1,data2,data3)
summary(data)

#Number of trials should be the same as in the generation of parameters
ntrials<-1000

#Simulate steps through the Markov Chain (Initial time point should be included, remember to
#add an extra step)
steps<-13
steps1<-3
steps2<-steps-steps1


##### Cohort simulation for n trials
attach(data)

all_summaries<- data.frame(uA=numeric(0), lyA=numeric(0), cA=numeric(0), uB=numeric(0), lyB=numeric(0), cB=numeric(0),uC=numeric(0), lyC=numeric(0), cC=numeric(0))

t=1

#for t in 1:ntrials
for (t in 1:ntrials) {
        #Treatment A
        mtrans1<-matrix(c(prob11A1[t], prob12A1[t], prob13A1[t], prob21A1[t], prob22A1[t], prob23A1[t], prob31A1[t], prob32A1[t], prob33A1[t]), nrow = nhs, ncol=nhs, byrow=TRUE, dimnames = list(c("row1", "row2", "row3"),c("C.1", "C.2", "C.3")))
        mtrans2<-matrix(c(prob11A2[t], prob12A2[t], prob13A2[t], prob21A2[t], prob22A2[t], prob23A2[t], prob31A2[t], prob32A2[t], prob33A2[t]), nrow = nhs, ncol=nhs, byrow=TRUE, dimnames = list(c("row1", "row2", "row3"),c("C.1", "C.2", "C.3")))
        cost1<-cost1A[t]
```

```
cost2<-cost2A[t]
cost3<-cost3A[t]
ut1<-ut1A[t]
ut2<-ut2A[t]
ut3<-ut3A[t]

ncycle<- cohortsim();
cost_utcycle<- costuts();

treatA<-cbind(ncycle, cost_utcycle)
treatA<-data.frame(treatA)
names(treatA) <-
c("nstat1A","nstat2A","nstat3A","cstat1A","cstat2A","cstat3A","ustat1A","ustat2A","ustat3
A")


#Treatment B
mtrans1<-matrix(c(prob11B1[t], prob12B1[t], prob13B1[t], prob21B1[t], prob22B1[t],
prob23B1[t], prob31B1[t], prob32B1[t], prob33B1[t]), nrow = nhs, ncol=nhs,
byrow=TRUE, dimnames = list(c("row1", "row2", "row3"),c("C.1", "C.2", "C.3")))
mtrans2<-matrix(c(prob11B2[t], prob12B2[t], prob13B2[t], prob21B2[t], prob22B2[t],
prob23B2[t], prob31B2[t], prob32B2[t], prob33B2[t]), nrow = nhs, ncol=nhs,
byrow=TRUE, dimnames = list(c("row1", "row2", "row3"),c("C.1", "C.2", "C.3")))
cost1<-cost1B[t]
cost2<-cost2B[t]
cost3<-cost3B[t]
ut1<-ut1B[t]
ut2<-ut2B[t]
ut3<-ut3B[t]

ncycle<- cohortsim();
cost_utcycle<- costuts();

treatB<-cbind(ncycle, cost_utcycle)
treatB<-data.frame(treatB)
names(treatB) <-
c("nstat1B","nstat2B","nstat3B","cstat1B","cstat2B","cstat3B","ustat1B","ustat2B","ustat3
B")

#Treatment C
```

```
mtrans1<-matrix(c(prob11C1[t], prob12C1[t], prob13C1[t], prob21C1[t], prob22C1[t], prob23C1[t], prob31C1[t], prob32C1[t], prob33C1[t]), nrow = nhs, ncol=nhs, byrow=TRUE, dimnames = list(c("row1", "row2", "row3"),c("C.1", "C.2", "C.3")))
mtrans2<-matrix(c(prob11C2[t], prob12C2[t], prob13C2[t], prob21C2[t], prob22C2[t], prob23C2[t], prob31C2[t], prob32C2[t], prob33C2[t]), nrow = nhs, ncol=nhs, byrow=TRUE, dimnames = list(c("row1", "row2", "row3"),c("C.1", "C.2", "C.3")))
cost1<-cost1C[t]
cost2<-cost2C[t]
cost3<-cost3C[t]
ut1<-ut1C[t]
ut2<-ut2C[t]
ut3<-ut3C[t]

ncycle<- cohortsim();
cost_utcycle<- costuts();

treatC<-cbind(ncycle, cost_utcycle)
treatC<-data.frame(treatC)
names(treatC) <-
c("nstat1C","nstat2C","nstat3C","cstat1C","cstat2C","cstat3C","ustat1C","ustat2C","ustat3C")

#Simulated time, in years. It has to be coherent with the discount tax units
#Simulation of 12 cycles of 3 months.

time_sim<-seq(0,by=0.25, length.out=steps)
out<-cbind(treatA,treatB,treatC,time_sim)

### CEA: Calculations.
# Treatment A
#Utility  (Non discounted)
 out$uA<-( out$ustat1A+ out$ustat2A+ out$ustat3A)
resumuA<-sum( out$uA)/N

#Life years (Non discounted)
out$lyA<-(out$nstat1A+out$nstat2A)
resumlyA<-sum( out$lyA)/N

#Cost  (Non discounted)
 out$cA<-( out$cstat1A+ out$cstat2A+ out$cstat3A)
```

```
resumcA<-sum( out$cA)/N

#Treatment B
#Utility  (Non discounted)
out$uB<-( out$ustat1B+ out$ustat2B+ out$ustat3B)
resumuB<-sum( out$uB)/N

#Life years (Non discounted)
out$lyB<-(out$nstat1B+out$nstat2B)
resumlyB<-sum( out$lyB)/N

#Cost  (Non discounted)
 out$cB<-( out$cstat1B+ out$cstat2B+ out$cstat3B)
resumcB<-sum( out$cB)/N

#Treatment C
#Utility  (Non discounted)
out$uC<-( out$ustat1C+ out$ustat2C+ out$ustat3C)
resumuC<-sum( out$uC)/N

#Life years (Non discounted)
out$lyC<-(out$nstat1C+out$nstat2C)
resumlyC<-sum( out$lyC)/N

#Cost  (Non discounted)
out$cC<-( out$cstat1C+ out$cstat2C+ out$cstat3C)
resumcC<-sum( out$cC)/N

### Save the summary of a CEA calculation per every trial
all_summaries[t,]<-c(resumuA, resumlyA, resumcA, resumuB, resumlyB, resumcB,
resumuC, resumlyC, resumcC)
t=t+1
        } #closes the repetition for the number of trials selected

#Save the output of the simulation for the n trials
write.table(all_summaries,"C:\\Documents                                    and
Settings\\nperez\\Escritorio\\Maraviroc_redo\\all_summaries.txt", dec = ".", row.names =
TRUE,col.names = TRUE)
```

Plots for PSA

The following code can be used or plotting the Cost-effectiveness analysis (CEA) and the Cost-effectiveness acceptability curves (CEAC) resulting of the probability sensitivity analysis performance.

```
CEA_PSA<-read.table("C:\\Documents and Settings\\nperez\\Escritorio\\Maraviroc_redo\\all_summaries.txt", dec = ".", header = TRUE)
names(CEA_PSA)
summary(CEA_PSA)
dim(CEA_PSA)
attach(CEA_PSA)


##### Cost-effectiveness plane
#Trofile vs 454
CEA_PSA$Incr_costAB<-CEA_PSA$cA-CEA_PSA$cB
CEA_PSA$Incr_utAB<-CEA_PSA$uA-CEA_PSA$uB

#454 vs PS
CEA_PSA$Incr_costBC<-CEA_PSA$cB-CEA_PSA$cC
CEA_PSA$Incr_utBC<-CEA_PSA$uB-CEA_PSA$uC

#Trofile vs PS
CEA_PSA$Incr_costAC<-CEA_PSA$cA-CEA_PSA$cC
CEA_PSA$Incr_utAC<-CEA_PSA$uA-CEA_PSA$uC

plot(CEA_PSA$Incr_costAB,CEA_PSA$Incr_utAB,xlab="Incremental utility gain", ylab="Incremental cost(€)", main="Cost effectiveness plane (A vs B)",type="p",lty=3,lwd=2.5,col="blue")
abline(h=0, v=0)
abline(h =c(-5,0,5), v = c(-30000,-20000,-10000,0,10000,20000,30000,40000), col ="gray60", lty=3)
points(mean(CEA_PSA$Incr_costAB), mean(CEA_PSA$Incr_utAB), pch = 23, bg = "red")
mean(CEA_PSA$Incr_costAB)
mean(CEA_PSA$Incr_utAB)

plot(CEA_PSA$Incr_costBC,CEA_PSA$Incr_utBC,xlab="Incremental utility gain", ylab="Incremental cost(€)", main="Cost effectiveness plane (B vs C)",type="p",lty=3,lwd=2.5,col="blue")
```

```
abline(h=0, v=0)
abline(h =c(-5,0,5), v = c(-30000,-20000,-10000,0,10000,20000,30000,40000), col ="gray60", lty=3)
points(mean(CEA_PSA$Incr_costBC), mean(CEA_PSA$Incr_utBC), pch = 23, bg = "red")
mean(CEA_PSA$Incr_costBC)
mean(CEA_PSA$Incr_utBC)


plot(CEA_PSA$Incr_costAC,CEA_PSA$Incr_utAC,xlab="Incremental utility gain", ylab="Incremental cost(€)", main="Cost effectiveness plane (A vs C)",type="p",lty=3,lwd=2.5,col="blue")
abline(h=0, v=0)
abline(h =c(-5,0,5), v = c(-30000,-20000,-10000,0,10000,20000,30000,40000), col ="gray60", lty=3)
points(mean(CEA_PSA$Incr_costAC), mean(CEA_PSA$Incr_utAC), pch = 23, bg = "red")
mean(CEA_PSA$Incr_costAC)
mean(CEA_PSA$Incr_utAC)


##### Cost effectiveness acceptability curve
#Define Ceiling ratio
#CEA_PSA$cratio<-100000
vary_cratio<-seq(from = 0, to = 100000, by = 100)
cratioplot<-array(NA,(100000/100))

plotingCEAC<- data.frame(cratioplot=numeric(0),prob_A=integer(0), prob_B=integer(0), prob_C=integer(0))
i=1
for (i in 1:(100000/100))
                {
                cratioplot<-array(vary_cratio[i],(100000/100))

                #Create a indicator variable for the treatment which is more cost effective
                #Multiplied by 100 because the values are very similiar (utilities differs in the 3rd
                #position after 0) *100 enlarge differences
                CEA_PSA$NMB_Aaux<-((CEA_PSA$uA*cratioplot)-CEA_PSA$cA)*100
                CEA_PSA$NMB_Baux<-((CEA_PSA$uB*cratioplot)-CEA_PSA$cB)*100
                CEA_PSA$NMB_Caux<-((CEA_PSA$uC*cratioplot)-CEA_PSA$cC)*100

                for (j in 1:length(CEA_PSA$NMB_Aaux)){
```

```
                    CEA_PSA$max[j]<-
                    max(CEA_PSA$NMB_Aaux[j],CEA_PSA$NMB_Baux[j],CEA_P
                    SA$NMB_Caux[j])
                                        }
CEA_PSA$probCEA_A<-ifelse(CEA_PSA$max==CEA_PSA$NMB_Aaux,1,0)
CEA_PSA$probCEA_B<-ifelse(CEA_PSA$max==CEA_PSA$NMB_Baux,1,0)
CEA_PSA$probCEA_C<-ifelse(CEA_PSA$max==CEA_PSA$NMB_Caux,1,0)


plotingCEAC[i,]<-                          c(cratioplot[1],
mean(CEA_PSA$probCEA_A),                   mean(CEA_PSA$probCEA_B),
mean(CEA_PSA$probCEA_C))
i=i+1

}
```

```
write.table(plotingCEAC,"C:\\Documents and Settings\\nperez\\Escritorio\\Maraviroc_redo\\plotingCEAC.txt", dec = ".", row.names = TRUE,col.names = TRUE)

plot(plotingCEAC$cratioplot/1000, plotingCEAC$prob_A,xlab="Value of ceiling ratio (K €)",ylab="Probability cost-effective",xlim=c(0,100),ylim=c(0.00,1.00),type='l',lty=1,col=2,lwd=2)
lines(plotingCEAC$cratioplot/1000, plotingCEAC$prob_B,lty=3,col=3,lwd=2)
lines(plotingCEAC$cratioplot/1000, plotingCEAC$prob_C,lty=5,col=4,lwd=2)
legend(70,0.99, c("A-Trofile","B-454","C-PS"),lty=c(1,3,5),col=c(2,3,4),lwd=2)
```

Annex X: Input parameters for the model of HIV tropism testing

Table X.1. Transition probabilities matrices by co-receptor test and phase of HIV viremia control

Trofile-ES test and treated with MRV						
	Week 0 to 24 week (MT1)			>24 weeks (MT2)		
	VL≤50	VL>50	Dead	VL≤50	VL>50	Dead
VL≤50	0.9298	0.0700	0.0002	0.9773	0.0225	0.0002
VL>50	0.3600	0.6398	0.0002	0.0100	0.9898	0.0002
Dead	0	0	1	0	0	1
Roche 454 test and treated with MRV						
	Week 0 to 24 week (MG1)			>24 weeks (MG2)		
	VL≤50	VL>50	Dead	VL≤50	VL>50	Dead
VL≤50	0.9048	0.0950	0.0002	0.9834	0.0164	0.0002
VL>50	0.2628	0.7370	0.0002	0.0073	0.9925	0.0002
Dead	0	0	1	0	0	1
PS test and treated with MRV						
	Week 0 to 24 week (MPS1)			>24 weeks (MPS2)		
	VL≤50	VL>50	Dead	VL≤50	VL>50	Dead
VL≤50	0.9048	0.0950	0.0002	0.9863	0.0135	0.0002
VL>50	0.2160	0.7838	0.0002	0.0060	0.9938	0.0002
Dead	0	0	1	0	0	1

MT1: Probabilities used for the simulation of the cohort of patients allocated in the Trofile-ES test in the time from zero to 24 weeks.

MT2: Idem than MT1 for the time from 24 weeks to 144 weeks.

MG1: Probabilities used for the simulation of the cohort of patients allocated to the 454 Roche test in the time from zero to 24 weeks.

MG2: Idem than MG1 for the time from 24 weeks to 144 weeks.

MPS1: Probabilities used for the simulation of the cohort of patients allocated to the population sequencing test in the time from 0 to 24 weeks.

MPS2: Idem than MPS1 for the time from 24 weeks to 144 weeks.

The simulation was run using the MT1, MG1 and MPS1 for the first 2 cycles (equivalent to 24 weeks) and the next cycles the patients in each health status travel according to the transition probabilities in matrices MT2, MG2 and MPS2 up to 3 years of follow-up (12 cycles) or death.

It is relevant to take into account that the prevalence of HIV infected patients with X4 coreceptor corresponds to the population of patients who had an "improperly" received MRV.

Cost and utility input data

The direct cost of the hospital medical supplies where used. The reported proportion of adverse events also was used to increment the treatment cost.

Table X.2. The imputed costs per patient and a period of 3 months

Concept	Cost (€)
ARV (3months)	3033
Trofile-ES test (3 months)[+]	125
Roche 454 (3 months)[+]	31,25
PS (3 months)[+]	15
Cost increase for adverse event (mean per patient per 3 months)[*]	71

[*] 1 extra medical visit: €59 Euros+ concomitant treatment €12

[+] The cost of the test was divided into the number of cycles simulated. Trofile-ES cost was €1000, Roche 454 test cost was €250 and PS test cost was €120.

Utility weights range between 0 and 1, being 1 the higher utility. The applied utilities for each state were derived from the published article of Sanders et al.[225]. The utilities were calculated taking into consideration the adverse events frequency reported form the MERIT study: 4.2% of patients reported the presence of adverse events for the MRV group. The utility score was decreased in 0.02 units for the presence of adverse events.

Annex XI: Costs: Definitions and concepts

There are three types of cost: direct, indirect, intangible. Their definitions are given below.

- The direct costs are those associated with the medical recovery of the patient. They can be quantified as the value of resources (products and/or services) used directly when providing the treatment. It includes pharmaceutical products, hospital care, physician care, nursing services, etc. They also include the costs of resources consumed directly to produce a certain health outcome, for instance physician's, nurse's, or pharmacist's time, equipment, etc. Other direct, non-medical, costs include the products and/or services that are needed to obtain care, although they do not directly contribute to health care. For instance, transportation to the hospital or hiring a baby sitter so a parent can visit the doctor.
- The indirect costs list include those resulting from a patient being unable to perform normal activities due to illness, change in health status and mortality such as loss of earnings, loss of productivity or family time devoted to the patient's care.
- To facilitate quantifying the benefit of certain medical treatments and measures, studies in the field of health care economics also consider intangible costs that cannot be directly measured in monetary form; it would be even unethical to try it. Intangible effects, such as pain, joy, or physical limitations are assessed using the patient's biopsychosocial health related quality of life after the accident; health related quality of life in this context includes physical health as well as social contacts and emotional health[226].

Two important concepts associated with the costs assessment:

- The concept of **opportunity cost** is fundamental to the economist's view of costs. Since resources are scarce relative to needs, the expenditure on a given health care intervention prevents to spend the same money on something else. When dealing with the opportunity cost we have to figure out if the whole set of benefits gained with the new therapy (treatment B) could buy a larger health benefit in the cheaper therapy (treatment A) or in some other part of the health care system. The comparative nature of health economics reflects that the interest is in the incremental analysis of costs and benefits. Either cost-effectiveness or cost-utility studies permit to compare the opportunity costs of the interventions assessed.
- The **marginal cost** refer to the cost change when comparing between therapeutic strategies, the fixed costs should not be included in the marginal cost calculation. For instance, if treatment B enables patients to be discharged from hospital a day earlier than treatment A, the additional costs for the treatment A will only include the costs of the patient's meals, treatment and perhaps nursing time of the extra day. These are the marginal costs, where the resource use actually changes substantially, but all the fixed capital charges for a hospital bed, which go into the **average cost**, e.g. costs of laboratories, kitchens, and building maintenance, will be largely unchanged when the patient is not admitted in the hospital. Incremental analysis is concerned with the marginal and not the average costs. Marginal costs are often very difficult to measure, and the use of average costs can be justified. In this particular example, if enough bed days are saved by the widespread adoption of treatment B to reduce bed numbers and to close wards.

Annex XII: Input parameters for the PNH model

Advers events profile, direct and indirect costs related to PNH

The profile of adverse events and events related to PNH where obtained from Hillmen et al.[162] study and their direct costs of them are listed in the Table XII.1.

Table XII.1. Drug costs to handle with adverse events and events related to PNH

Adverse Event	Drug Cost
Headache	1.86 €
Nasopharingitis	1.92 €
Respiratory tract infection	2.41 €
Back pain	2 €
Nausea	1.52 €
Cough	4.04 €
Diarrhea	1.21 €
Arthralgia	12.63 €
Abdominal pain	0 €
Dizziness	4.31 €
Vomiting	1.52 €
Fatigue	3.36 €
Viral infection	10 €
Events related to PNH	
Trombosis	41.98 €
Chronic Kidney Disease-stage 1-3	4.54 €
Chronic Kidney Disease stage 4-5	1,171.80 €

The percentages of individuals suffering the adverse events in both groups of treatment were used in the estimation of the mean direct costs that suppose to treat them. The direct costs per patient year are reported in Table XII.2.

Table XII.2. Summary of direct costs (€) per patient year

Costs	Eculizumab	Standard of care	Difference
Drug costs	318,842	18,468	300,374
Administration costs	559	272	287
AE and events related to HPN cost	72	83	-11
Total	**319,473**	**18,823**	**300,650**

The indirect costs derived of the patient's resources expenses to receive the PNH care (drugs administering, waiting time, time and cost of travelling to the ambulatory care clinic and productivity loss) were evaluated. The disaggregated items and their costs are listed in Table XII.3.

Table XII.3. Indirect costs by treatment group

	Eculizumab	Standard of care
Diagnoses Age	37	37
Mean survival time after the diagnoses (years)	40	15
Cost of the drug administering time		
Travelling time per ambulatory visit	1	1
Waiting	0.50	0.50
Administration time	1	8
Required visits	27	8
Total time use	1,890	1,140
Time value (€/hour)	13.36 €	13.36 €
Total time cost	25,250.40 €	15,230.40 €
Travel costs for administration		
Cost per km	0.52 €	0.52 €
Round trip (km)	50	50
Cost per round trip	26 €	26 €
Number of travels	27	8
Total travel cost	702 €	208 €
Productivity loss*		
Loss in productive time (annual)	0 €	13
Time economic value (annual wages)	27,792 €	27,792 €
Human resources lost	0 €	361,296 €
Travel cost for medical visits		
Cost per km	0.52 €	0.52 €
Round trip (km)	50	50
Cost per round trip	26 €	26 €
Number of travels	4	8
Total travel cost	104 €	208 €

*The productivity loss is computed as years lost in human resources due to death, and using 65 years-old as the age of retirement.

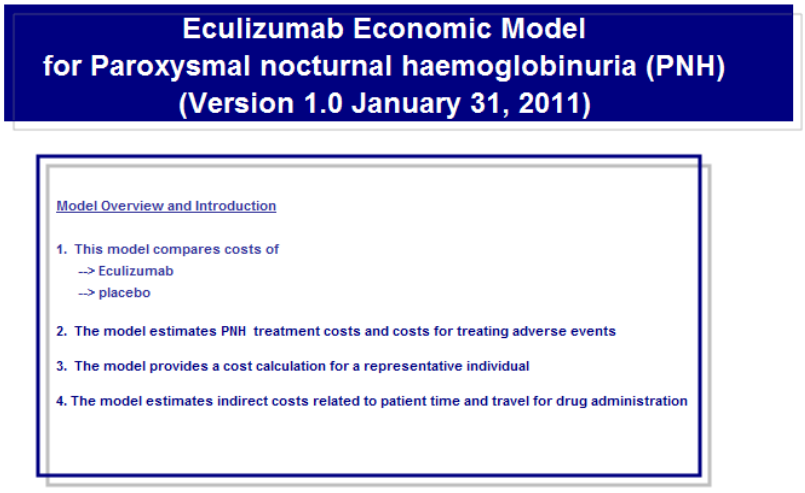
All costs are expressed in Euros (€, 2010). Resource unitary costs were collected from literature and Spanish public costs database updated to 2010 value with Consumer Price Index[227].

Annex XIII: Analysis worksheets for the PNH model

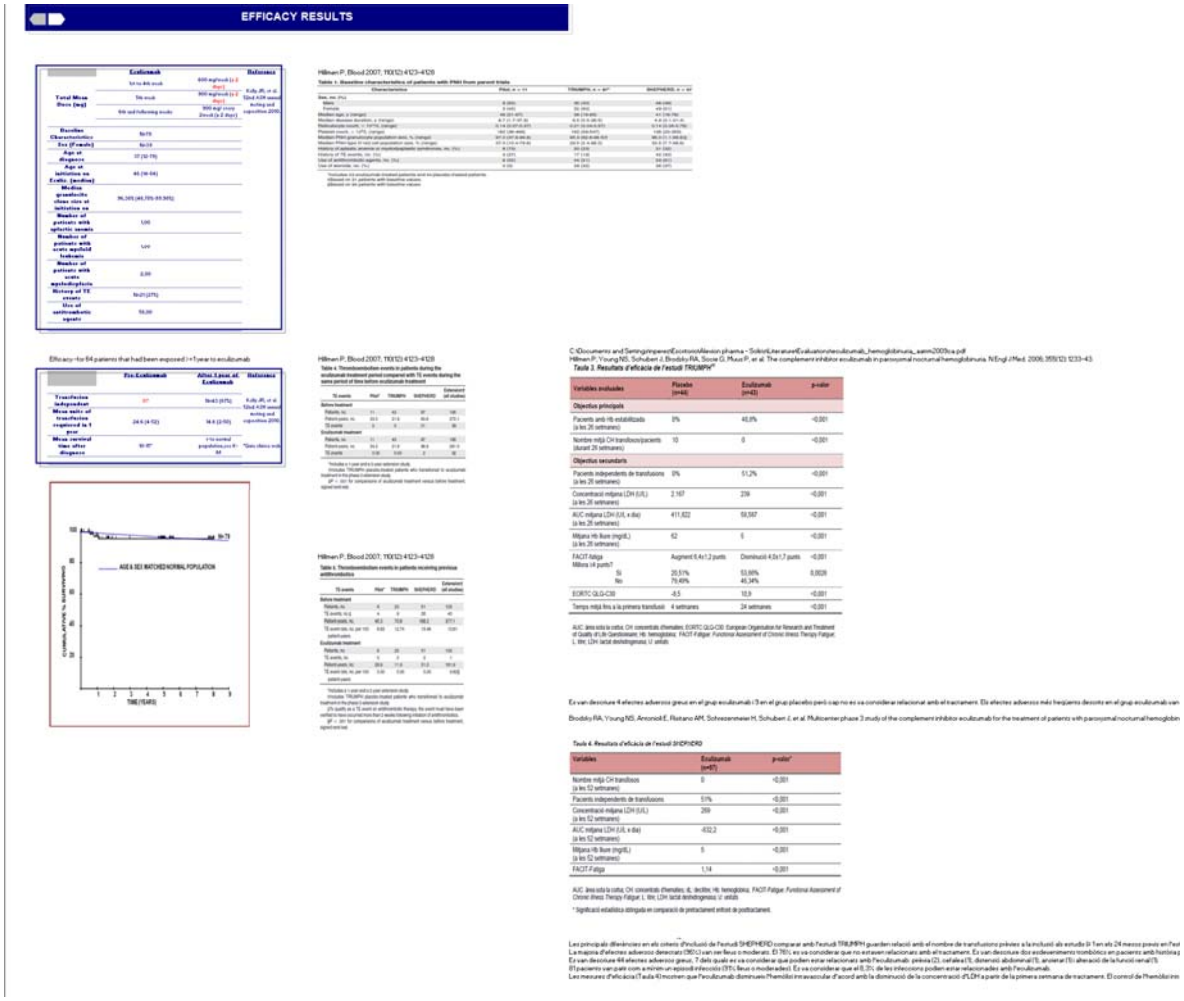
Model implemented in Microsoft® Excel to estimate the costs of PNH.

Excel sheets: Introduction, Efficacy, Adverse Events, Key Trial Data, Treatment Inputs, Treatment cost, Cost of Adverse Events, Results, Inputs I, Results DI, Simple BI, Simple BI total cost.

XIII.1. Introduction



XIII.2. Efficacy



XIII.3. Adverse Events

Hillmen P, N Engl Med 2006; 355:1233-43

Table 4. Adverse Events.*

Adverse Event	Placebo Group (N=44)	Eculizumab Group (N=43)
	no. (%)	
Total no. of serious adverse events	9 (20)	4 (9)
Exacerbation of PNH	3 (7)	1 (2)
Renal colic	0	1 (2)
Lumbar or sacral disk prolapse	0	1 (2)
α-Hemolytic streptococcal bacteremia	0	1 (2)
Central-line and urinary tract infections	1 (2)	0
Upper respiratory tract infection	1 (2)	0
Probable viral infection	1 (2)	0
Neutropenia	1 (2)	0
Cellulitis, folliculitis, and neutropenia	1 (2)	0
Anemia and pyrexia	1 (2)	0
Most frequent adverse events†		
Headache‡	12 (27)	19 (44)
Nasopharyngitis	8 (18)	10 (23)
Upper respiratory tract infection	10 (23)	6 (14)
Back pain	4 (9)	8 (19)
Nausea	5 (11)	7 (16)
Cough	4 (9)	5 (12)
Diarrhea	5 (11)	4 (9)
Arthralgia	5 (11)	3 (7)
Abdominal pain	5 (11)	2 (5)
Dizziness	5 (11)	2 (5)
Vomiting	5 (11)	2 (5)
Fatigue	1 (2)	5 (12)
Viral infection	5 (11)	1 (2)

* Adverse events were coded with the use of preferred terms from the MedDRA.
† The event occurred in at least 10% of patients in either group.
‡ After the first 2 weeks of treatment, 10 patients (23%) receiving placebo and 9 patients (21%) receiving eculizumab had headache.

XIII.4. Key Trial Data

KEY TRIAL DATA

	Eculizumab		Placebo		Reference
Total Mean Dose (mg)	1st to 4th week	600 mg/week (± 2 days)			Hillmen P, N Engl Med 2006; 355:1233-43
	5th week	900 mg/week (± 2 days)			
	6th to 26th week	900 mg/ every 2week (± 2 days)			
Baseline Characteristics	N=43		N=44		
Sex (Female)	N=23		N=29		
Age (Median)	41,00		35,00		
Duration PNH (Median yr)	4.3 (0.9-29.8)		9,20		
Use of erythopoietin - no. (%)	3	7	0,00	0	
Use of cyclosporine -no. (%)	1	2	1 (2)	2	
Use of anticoagulant agents (coumarins or heparins) - no (%)	21	49	11 (25)	25	
Use of corticoesteroids or androgenic steroids - no (%)	12	28	12 (27)	27	

XIII.5. Treatment Inputs

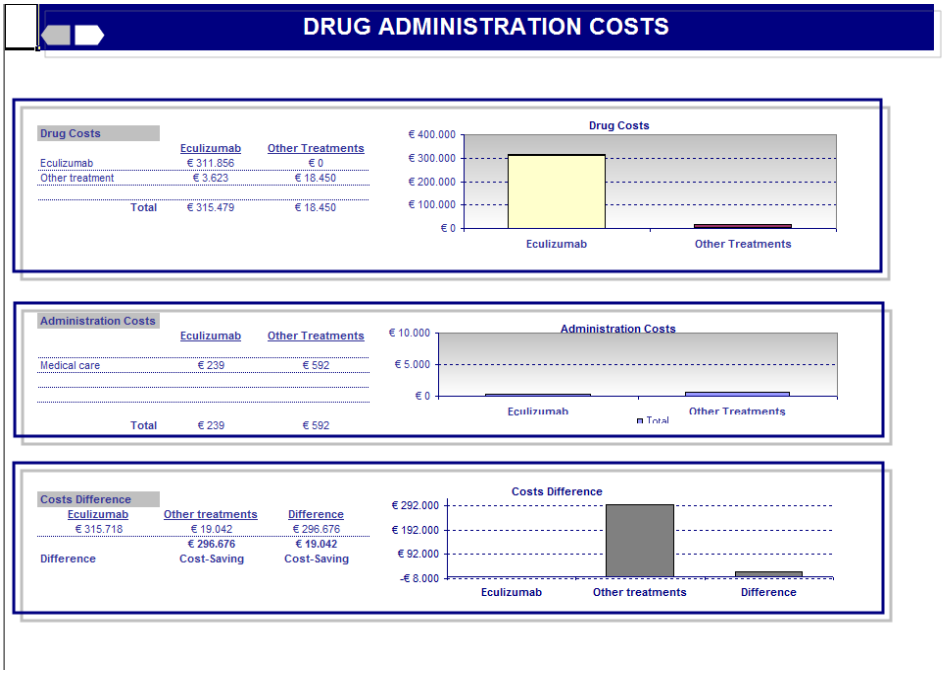
DIRECT MEDICAL COSTS

Treatment	Cost (PVL)	€/mg	
Eculizumab per year	€ 311.856,00		<-Budget impact a 5 años. Coste Eculizumab=(342650+320400*4)/5 y -4% de IVA
Iron	€ 3.007,68		<-EPREX Sol. iny. 10000 UI/1 ml. Env. De 5 amp. 1 ampolla a la semana
Folic acid	€ 73,61		<-1 comp al dia de FOLAXIN Comp. 2,5 mg TODO EL AÑO
Erythropoietin (Use: 7% Eculizumab; 0% placebo)	€ 4.385,33		<-Epoetina alfa. Farmaco: EPREX Sol. iny. 10000 UI/1 ml . (Env. con 6 jeringas de 0,5 ml) 2 veces por semana. TODO EL AÑO
Corticoesteroids			
Anabolic steroids			
Warfarin	€ 41,98		<-Aldocumar 5 mg. 2 comprimidos al dia
Anticoagulant	€ 68,99		<-Heparina sódica. FOLAXIN Comp. 2,5 mg. 2 Grageas al dia
Transfusion (1 bolsa de concentrado de hematies)	€ 750,00		
Neiserria meningitidis vaccination (PVP)	€ 9,99		<-AEMPS, precio de la vacuna

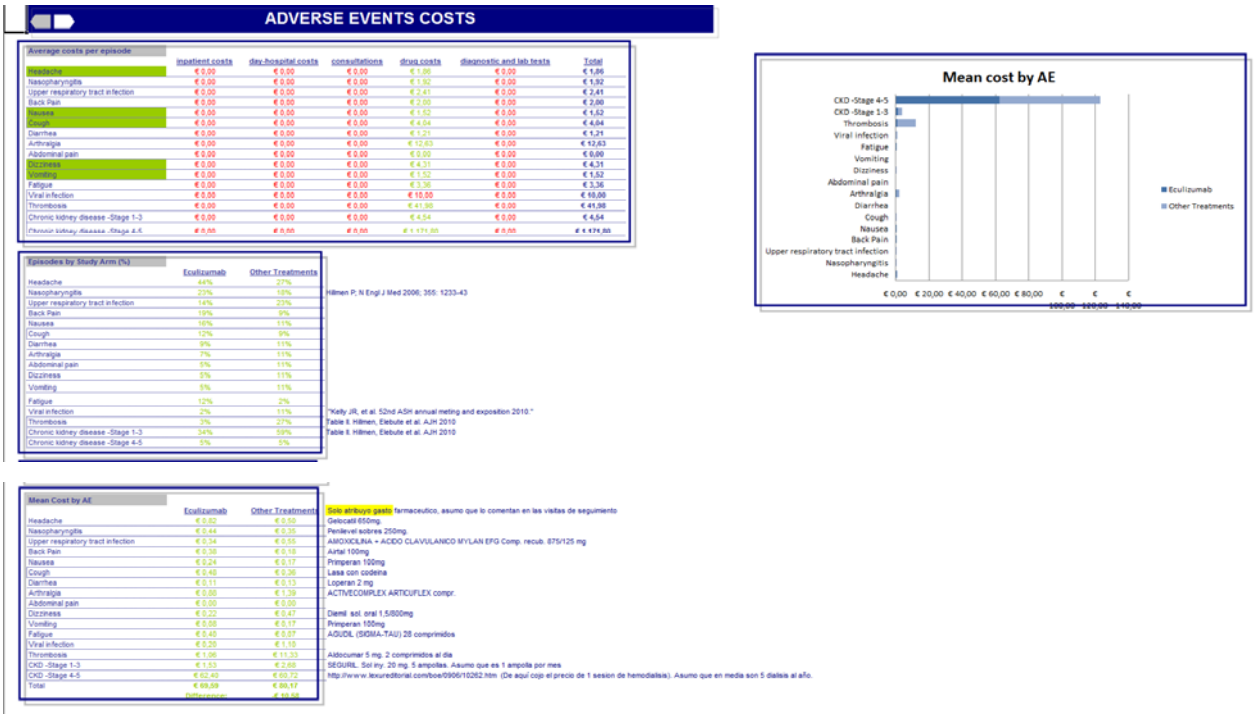
Administration cost of ECULIZUMAB	unit costs	Total units	% of patients	annual costs	Comments
Clinic visits	€ 46,00	4,00	100%	€ 184,00	Tranfusion units from "Kelly JR, et al. 52nd ASH annual meting and exposition 2010."
Serum level monitoring	€ 20,00	2,00	100%	€ 40,00	<-No se cuantas "unidades se necesitan" ni su coste
Vaccination (Nurse)	€ 15,00	1,00	100%	€ 15,00	
Transfusions	€ 750,00	14,60	33%	€ 3.613,50	<-Considerado como Drug cost

Administration cost of OTHER TREATMENTS	unit costs	Total units	% of patients	annual costs	Comments
Clinic visits	€ 46,00	12,00	100%	€ 552,00	Tranfusion units from "Kelly JR, et al. 52nd ASH annual meting and exposition 2010."
Serum level monitoring	€ 20,00	2,00	100%	€ 40,00	<-No se cuantas "unidades se necesitan" ni su coste
Transfusions	€ 750,00	24,60	100%	€ 18.450,00	<-Considerado como Drug cost

XIII.6. Treatment cost



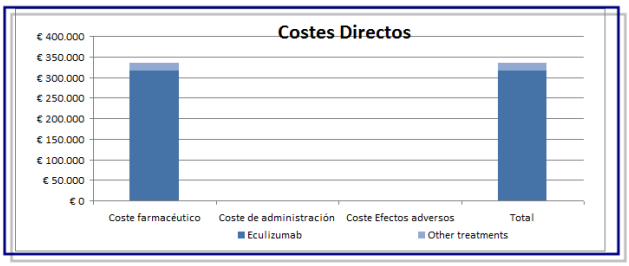
XIII.7. Cost of Adverse Events



XIII.8. Results

DIRECT COSTS RESULTS

Mean Cost Per Patient	Eculizumab	Other treatments	Difference
Coste farmacéutico	€ 315.479	€ 18.450	€ 297.029
Coste de administración	€ 239	€ 592	-€ 353
Coste Efectos adversos	€ 70	€ 80	-€ 11
Total	€ 315.788	€ 19.122	€ 296.666



XIII.9. Inputs I

INDIRECT COSTS

Time Costs Because of illness	Eculizumab	Other treatments
Age at diagnostic	37,00	37,00
Mean survival after diagostic (year)	40,00	15,00
Human Capital		
Producivity lost (years)	0,00	13,00
Annual cost		
Total productivity lost		
Time value (salariobruto anual)	€ 27.792,00	€ 27.792,00
Total human capital cost	€ 0,00	€ 361.296,00
	Difference:	-€ 361.296,00

Travel Costs For Medical consultation	Eculizumab	Other treatments
Travel cost assumptions		
Cost per km	€ 0,52	€ 0,52
Round Trip (Km)	50	50
Cost per round Trip	€ 26,00	€ 26,00
Number of travels	4,00	8,00
Total travel cost	€ 104,00	€ 208,00
	Difference:	-€ 104,00

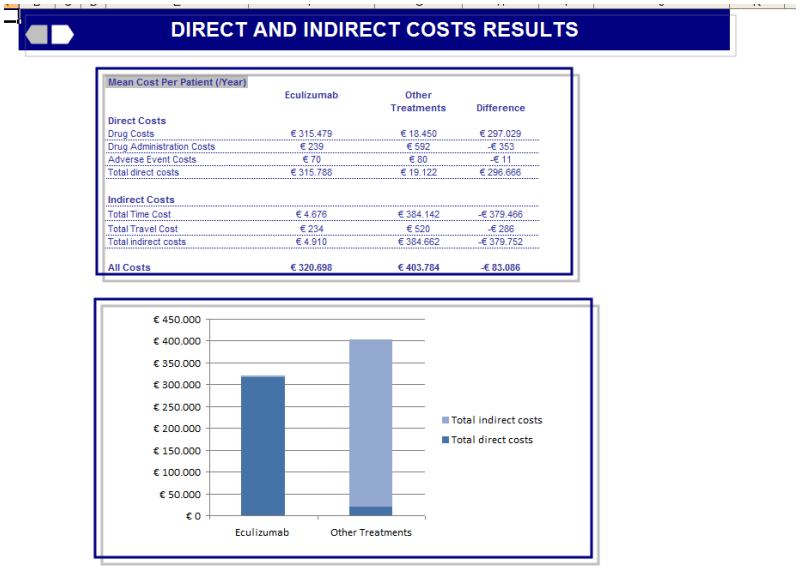
<-8 visitas con otros ttos. Estimado sin datos!!!

Time Costs For Treatment Administration	Eculizumab	Other treatments
Age at diagnostic	37,00	37,00
Mean survival after diagostic (year)	40,00	15,00
Human Capital		
Travel time per visit	1,00	1,00
Waiting	0,50	0,50
Administration time	1,00	8,00
Required visits	5,00	12,00
Total time use	350,00	1710,00
Time value (salario)	€ 13,36	€ 13,36
Total human capital cost	€ 4.676,00	€ 22.845,60
	Difference:	-€ 18.169,60

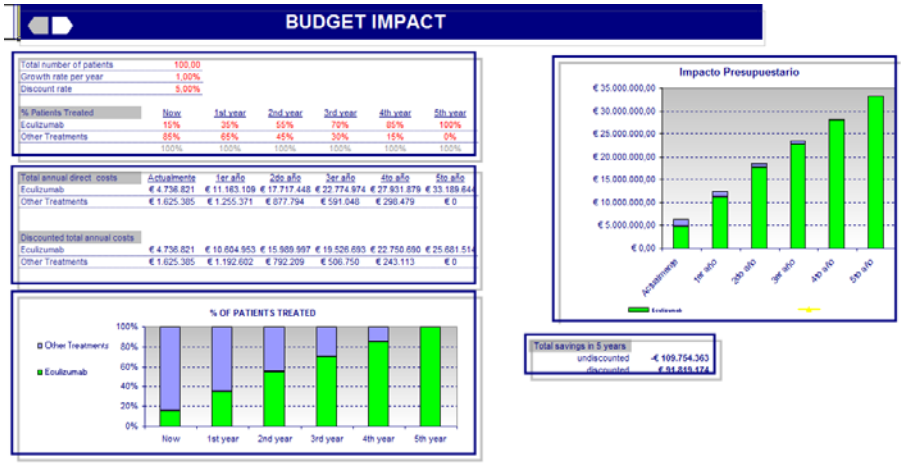
Travel Costs For Treatment Administration	Eculizumab	Other treatments
Travel cost assumptions		
Cost per km	€ 0,52	€ 0,52
Round Trip (Km)	50	50
Cost per round Trip	€ 26,00	€ 26,00
Number of travels	5,00	12,00
Total travel cost	€ 130,00	€ 312,00
	Difference:	-€ 182,00

<-Asumo que los pacientes en "other treatments" hacen una transfusion al mes
<-Asumo que los pacientes en "Eculizumab" hacen una transfusion al mes+ vacunacion + 3 visitas para administración del fármaco

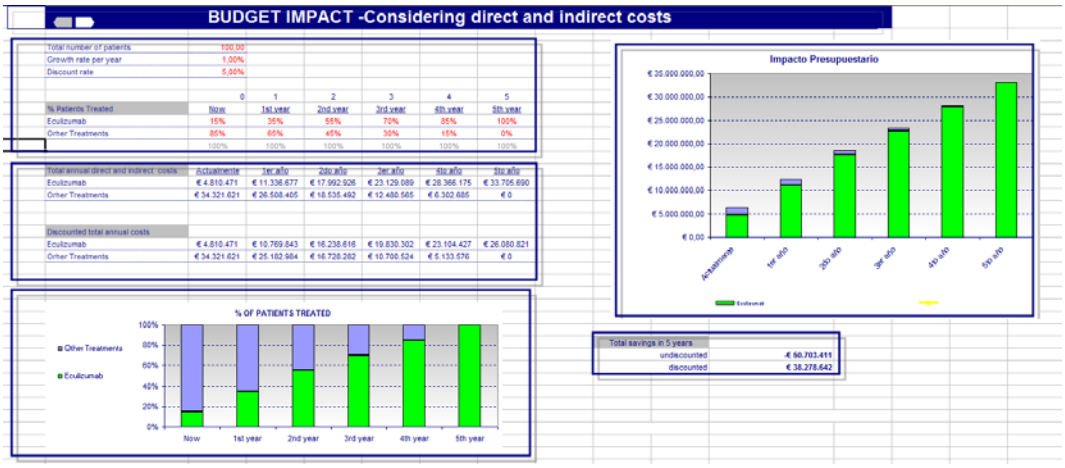
XIII.10. Results DI



XIII.11. Simple BI



XIII.12. Simple BI total cost



Annex XIV: Medical Outcomes Study (MOS)

Medical Outcomes Study (MOS)–Short Form (SF) with 12 items questionnaire (SF-12v2), was used to derive disutility values. One of the most widely used generic quality-of-life instruments is the SF-36. The SF-36 was developed from the RAND Corporation's Health Insurance Experiments in the United States[228]. The SF-36 measures the HRQoL with 36 items, along eight dimensions and one physical component summary score and one mental component summary score. The SF-12 is a 12 items instrument that appears to be a practical alternative to the SF-36 for the purpose of large group comparisons[229, 230].

Annex XV: Data analysis and DALYs calculation code with SPSS

```
*** DALYs Calculation***.
#DALY Calculation code implemented jointly with L. Kaskens.

#### Deaths for patients suffering Osteoporosis with bone fractures.
DATASET ACTIVATE Conjunto_de_datos1.
RECODE edadn (SYSMIS=SYSMIS) (0 thru 69.99=0) (70 thru 74.99=0.000008) (75 thru
79.99=0.000111)  (80 thru 84.99=0.000363) (85 thru 102=0.0001716) INTO deaths_owithf.
EXECUTE.

#### Deaths for patients suffering Osteoporosis without bone fractures.
RECODE edadn (SYSMIS=SYSMIS) (0 thru 59.99=0) (60 thru 69.99=0.000001) (70 thru
74.99=0.000000) (75 thru 79.99=0.000002)  (80 thru 84.99=0.000009) (85 thru 102=0.00004)
INTO deaths_owithoutf.
EXECUTE.

IF(grupo_4cat=0) deaths=deaths_owithf.
EXECUTE.
IF(grupo_4cat=1) deaths=deaths_owithoutf.
EXECUTE.
IF ((grupo_4cat=2) OR (grupo_4cat=3)) deaths=0.
EXECUTE.

#Queda igual que en el fichero del 16-2.
RECODE edadn (SYSMIS=SYSMIS) (0=84.56)
(1=83.81) (2=82.83) (3=81.84) (4=80.85) (5=79.86) (6=78.87) (7=77.87) (8=76.88) (9=75.89)
(10=74.90) (11=73.90) (12=72.91) (13=71.91) (14=70.92) (15=69.92) (16=68.94) (17=67.94)
(18=66.96) (19=65.97) (20=64.98) (21=64.00) (22=63.01) (23=62.02) (24=61.03) (25=60.04)
(26=59.06) (27=58.07) (28=57.08) (29=56.09) (30=55.11) (31=54.12) (32=53.13) (33=52.15)
(34=51.17) (35=50.19) (36=49.21) (37=48.23) (38=47.25) (39=46.28) (40=45.30) (41=44.33)
(42=43.37) (43=42.41) (44=41.45) (45=40.49) (46=39.54) (47=38.59) (48=37.64) (49=36.70)
(50=35.76) (51=34.83) (52=33.90) (53=32.96) (54=32.03) (55=31.11) (56=30.19) (57=29.27)
(58=28.35) (59=27.43) (60=26.52) (61=25.61) (62=24.70) (63=23.80) (64=22.90) (65=22.01)
(66=21.13) (67=20.25) (68=19.36) (69=18.50) (70=17.64) (71=16.77) (72=15.93) (73=15.12)
(74=14.32) (75=13.52) (76=12.75) (77=11.99) (78=11.24) (79=10.52) (80=9.83) (81=9.18)
(82=8.54) (83=7.93) (84=7.36) (85=6.81) (86=6.29) (87=5.83) (88=5.39) (89=4.98) (90=4.61)
(91=4.23) (92=3.92) (93=3.62) (94=3.34) (95=3.10) (96=2.89) (97=2.70) (98=2.47) (99=2.23)
(100=1.94) INTO life_expectancy.
EXECUTE.

RECODE edadn (SYSMIS=SYSMIS) (0=0.1)
(1 thru 4=2.6) (5 thru 9=7.5) (10 thru 14=12.5) (15 thru 19=17.5) (20 thru 24=22.5) (25 thru
29=27.5) (30 thru 34=32.5) (35 thru 39=37.5) (40 thru 44=42.5) (45 thru 49=47.5) (50 thru
54=52.5) (55 thru 59=57.5) (60 thru 64=62.5) (65 thru 69=67.5) (70 thru 74=72.5) (75 thru
79=77.5) (80 thru 84=82.5) (85 thru 105=90) INTO Avg_age_death.
EXECUTE.

COMPUTE Duration_years=life_expectancy.
EXECUTE.

FREQUENCIES VARIABLES=PCS_US
MCS_US
  /FORMAT=NOTABLE
  /NTILES=4
  /STATISTICS=STDDEV VARIANCE MINIMUM MAXIMUM MEAN
  /ORDER=ANALYSIS.

#Our sample values- Reference Franks et al.
COMPUTE restar_PCS=43.091387640576535.
```

```
EXECUTE.
COMPUTE restar_MCS=47.56822530680328.
EXECUTE.

DATASET ACTIVATE Conjunto_de_datos1.
COMPUTE EQ5DS_bis=(0.84690-0.08)+(PCS_US-restar_PCS)*0.01261+(MCS_US-
restar_MCS)*0.00759+(-0.00009*(PCS_US-restar_PCS)**2)+(-0.00015*((MCS_US-
restar_MCS)**2)+(-0.00015*(PCS_US-restar_PCS)*(MCS_US-restar_MCS))).
EXECUTE.

#Utility.
COMPUTE utility=EQ5DS_bis.
EXECUTE.
COMPUTE disability_weight=1-utility.
EXECUTE.

COMPUTE YLL_rate0_agewt0=(deaths*1)*(0*0.1658*((EXP(-0.04*
Avg_age_death))/0.04**2)*((EXP(-0.04* life_expectancy))*(-0.04*( life_expectancy+
Avg_age_death)-1)-(-0.04* Avg_age_death-1))+((1-0)* life_expectancy)).
EXECUTE.
COMPUTE YLL_rate0_agewt1=(deaths*1)*(1*0.1658*((EXP(-0.04*
Avg_age_death))/0.04**2)*((EXP(-0.04* life_expectancy))*(-0.04*( life_expectancy+
Avg_age_death)-1)-(-0.04* Avg_age_death-1))+((1-1)* life_expectancy)).
EXECUTE.
COMPUTE YLL_rate3_agewt0=deaths*1*(0*((0.1658*EXP(0.03*Avg_age_death))/(-
0.07**2))*((EXP(-0.07*( life_expectancy+ Avg_age_death))*(-0.07*( life_expectancy+
Avg_age_death)-1))-(EXP(-0.07* Avg_age_death)*(-0.07* Avg_age_death -1)))+((1-
0)/0.03)*((1-EXP(-0.03* life_expectancy)))).
EXECUTE.
COMPUTE YLL_rate3_agewt1=-1*(deaths*1*(1*((0.1658*EXP(0.03*Avg_age_death))/(-
0.07**2))*((EXP(-0.07*( life_expectancy+ Avg_age_death))*(-0.07*( life_expectancy+
Avg_age_death)-1))-(EXP(-0.07* Avg_age_death)*(-0.07* Avg_age_death -1)))+((1-
1)/0.03)*((1-EXP(-0.03* life_expectancy))))).
EXECUTE.


COMPUTE YLD_rate0_agewt0=(1*disability_weight)*(0*0.1658*((EXP(-
0.04*edad_diag))/0.04**2)*((EXP(-0.04*Duration_years))*(-0.04*(Duration_years+edad_diag)-
1)-(-0.04*edad_diag-1))+((1-0)*Duration_years)).
EXECUTE.
COMPUTE YLD_rate0_agewt1=(1*disability_weight)*(1*0.1658*((EXP(-
0.04*edad_diag))/0.04**2)*((EXP(-0.04*Duration_years))*(-0.04*(Duration_years+edad_diag)-
1)-(-0.04*edad_diag-1))+((1-1)*Duration_years)).
EXECUTE.
COMPUTE YLD_rate3_agewt0=((1*disability_weight)*(0*((0.1658*EXP(0.03*edad_diag))/(-
0.07**2))*((EXP(-0.07*(Duration_years+edad_diag))*(-0.07*(Duration_years+edad_diag)-1))-
(EXP(-0.07*edad_diag)*(-0.07*edad_diag-1)))+((1-0)/0.03)*((1-EXP(-0.03*Duration_years))))).
EXECUTE.
COMPUTE YLD_rate3_agewt1=-1*((1*disability_weight)*(1*((0.1658*EXP(0.03*edad_diag))/(-
0.07**2))*((EXP(-0.07*(Duration_years+edad_diag))*(-0.07*(Duration_years+edad_diag)-1))-
(EXP(-0.07*edad_diag)*(-0.07*edad_diag-1)))+((1-1)/0.03)*((1-EXP(-0.03*Duration_years))))).
EXECUTE.

COMPUTE DALY_rate0_Agewt0=YLL_rate0_agewt0+YLD_rate0_agewt0.
EXECUTE.
COMPUTE DALY_rate0_Agewt1=YLL_rate0_agewt1+YLD_rate0_agewt1.
EXECUTE.
COMPUTE DALY_rate3_Agewt0=YLL_rate3_agewt0+YLD_rate3_agewt0.
EXECUTE.
COMPUTE DALY_rate3_Agewt1=YLL_rate3_agewt1+YLD_rate3_agewt1.
```

```
EXECUTE.

##Remove the  DALYs for the patients with age at diagnose missing. n=632.
## Remove patients with previous fracture that were in the Group of "osteopenia" or "normal".

FREQUENCIES VARIABLES=DALY_rate0_Agewt0 DALY_rate0_Agewt1 DALY_rate3_Agewt0
DALY_rate3_Agewt1
  /FORMAT=NOTABLE
  /NTILES=4
  /STATISTICS=STDDEV MINIMUM MAXIMUM MEAN MEDIAN
  /ORDER=ANALYSIS.

*** Recode into a new group variable*.
IF (grupo_4cat=0) grupo_3cat=0.
EXECUTE.
IF (grupo_4cat=1) grupo_3cat=1.
EXECUTE.
IF ((grupo_4cat=2) OR (grupo_4cat=3)) grupo_3cat=2.
EXECUTE.
value labels grupo_3cat 0'Osteoporosis con fractura' 1'Osteoporosis sin fractura' 2'Normal o
Osteopenia'. EXECUTE.


***Table 6.1***.
*Socio-demographics, clinical characteristics and participant background for all included women
and by study group*.
**[Conjunto_de_datos2] E:\IOMEGA\Copia de seguridad_8-7-09\Freelance\Pfizer - DALYs
osteoporosis_LK_Jul13\Database and sintaxis\DALY results - 4\Marzo 29\Results
1\Database29marzo2012_Corregido_table1.sav
*.
**Description**.
FREQUENCIES
  VARIABLES=grupo_3cat
  /ORDER=  ANALYSIS .

FREQUENCIES
  VARIABLES=edadn imcn cign edad_diag  dxan Nfrfo frmosteo
tiemdiagn/FORMAT=NOTABLE
  /STATISTICS=STDDEV MEAN
  /ORDER=  ANALYSIS .

FREQUENCIES
  VARIABLES=edad_grupo sit_labn niv_estn
habitatn tabacon alcohn frfo3 dmn h_artn
art_reumn anor_nern hiperparan hipertiron hepat_cron sind_malabn
  /ORDER=  ANALYSIS .

*Description and comparision by group*.
SORT CASES BY grupo_3cat .
SPLIT FILE
  LAYERED BY grupo_3cat .

FREQUENCIES
  VARIABLES=edadn imcn cign edad_diag  dxan Nfrfo frmosteo
tiemdiagn/FORMAT=NOTABLE
  /STATISTICS=STDDEV MEAN
  /ORDER=  ANALYSIS .
SPLIT FILE
  OFF.
```

```
ONEWAY
  edadn imcn cign edad_diag  dxan Nfrfo frmosteo tiemdiagn BY grupo_3cat
  /MISSING ANALYSIS .

CROSSTABS
  /TABLES=edad_grupo sit_labn
niv_estn habitatn tabacon alcohn frfo3 dmn h_artn
art_reumn anor_nern hiperparan hipertiron hepat_cron sind_malabn BY grupo_3cat
  /FORMAT= AVALUE TABLES
  /STATISTIC=CHISQ
  /CELLS= COUNT  COLUMN
  /COUNT ROUND CELL .
* Osteoporosis therapy background by study group*.
CROSSTABS
 /TABLES=med_higien calcion calcio_dn ejercn tra_farmn bifosfon sermn otron BY grupo_3cat
  /FORMAT= AVALUE TABLES
  /STATISTIC=CHISQ
  /CELLS= COUNT  COLUMN
  /COUNT ROUND CELL .


***Figure 6.1***.
### Overall DALYs both undiscounted and discounted by the study groups

FREQUENCIES VARIABLES= DALY_rate0_Agewt0 DALY_rate0_Agewt1 DALY_rate3_Agewt0
DALY_rate3_Agewt1
  /FORMAT=NOTABLE
  /NTILES=4
  /STATISTICS=STDDEV VARIANCE MINIMUM MAXIMUM MEAN
  /ORDER=ANALYSIS.

SORT CASES BY grupo_3cat .
SPLIT FILE
  LAYERED BY grupo_3cat .

FREQUENCIES VARIABLES= DALY_rate0_Agewt0 DALY_rate0_Agewt1 DALY_rate3_Agewt0
DALY_rate3_Agewt1
  /FORMAT=NOTABLE
  /NTILES=4
  /STATISTICS=STDDEV VARIANCE MINIMUM MAXIMUM MEAN
  /ORDER=ANALYSIS.

SPLIT FILE
  OFF.


***Figure 6.2**.
#### ANOVAs for the DALY.

#All women <>65 years old
ONEWAY DALY_rate0_Agewt0 BY edadn_cat65
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate0_Agewt1 BY edadn_cat65
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate3_Agewt0 BY edadn_cat65
  /STATISTICS DESCRIPTIVES
```

```
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate3_Agewt1 BY edadn_cat65
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.

#Anova for the variables grupo_3cat.
ONEWAY DALY_rate0_Agewt0 BY grupo_3cat
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate0_Agewt1 BY grupo_3cat
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate3_Agewt0 BY grupo_3cat
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate3_Agewt1 BY grupo_3cat
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.

##by age < 65 and age > 65 and 4 groups of classification: OBF, OWBF, Ot  and Normal.
IF ((grupo_4cat=0) AND (frcv1=0)) grupo_65=00.
EXECUTE.
IF ((grupo_4cat=0) AND (frcv1=1)) grupo_65=01.
EXECUTE.
IF ((grupo_4cat=1) AND (frcv1=0)) grupo_65=10.
EXECUTE.
IF ((grupo_4cat=1) AND (frcv1=1)) grupo_65=11.
EXECUTE.
IF ((grupo_4cat=2) AND (frcv1=0)) grupo_65=20.
EXECUTE.
IF ((grupo_4cat=2) AND (frcv1=1)) grupo_65=21.
EXECUTE.
IF ((grupo_4cat=3) AND (frcv1=0)) grupo_65=30.
EXECUTE.
IF ((grupo_4cat=2) AND (frcv1=1)) grupo_65=31.
EXECUTE.
value labels grupo_65 00'Osteoporosis con fractura<65' 01'Osteoporosis con fractura=>65'
10'Osteoporosis sin fractura<65' 11'Osteoporosis sin fractura=>65' 20'Osteopenia<65'
21'Osteopenia=>65' 30'Normal<65' 31'Normal=>65'. EXECUTE.

ONEWAY DALY_rate0_Agewt0 BY grupo_65
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate0_Agewt1 BY grupo_65
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate3_Agewt0 BY grupo_65
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate3_Agewt1 BY  grupo_65
  /STATISTICS DESCRIPTIVES
```

```
  /PLOT MEANS
  /MISSING ANALYSIS.


***Figure 6.3**.
* DALYs loss, with and without discount by the presence of a risk factor. Mean and 95%
confidence intervals.

USE ALL.
COMPUTE filter_$=(grupo_3cat=0 & grupo_3cat=1).
VARIABLE LABEL filter_$ 'grupo_3cat=0 & grupo_3cat=1 (FILTER)'.
VALUE LABELS filter_$  0 'No seleccionado' 1 'Seleccionado'.
FORMAT filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE .

T-TEST
  GROUPS = frfo1(0 1)
  /MISSING = ANALYSIS
  /VARIABLES = DALY_rate0_Agewt0 DALY_rate3_Agewt0
  /CRITERIA = CI(.95) .
T-TEST
  GROUPS = frfo4(0 1)
  /MISSING = ANALYSIS
  /VARIABLES = DALY_rate0_Agewt0 DALY_rate3_Agewt0
  /CRITERIA = CI(.95) .
T-TEST
  GROUPS = frfo2(0 1)
  /MISSING = ANALYSIS
  /VARIABLES = DALY_rate0_Agewt0 DALY_rate3_Agewt0
  /CRITERIA = CI(.95) .
T-TEST
  GROUPS = frfo3(0 1)
  /MISSING = ANALYSIS
  /VARIABLES = DALY_rate0_Agewt0 DALY_rate3_Agewt0
  /CRITERIA = CI(.95) .
T-TEST
  GROUPS = art_reumn(0 1)
  /MISSING = ANALYSIS
  /VARIABLES = DALY_rate0_Agewt0 DALY_rate3_Agewt0
  /CRITERIA = CI(.95) .
T-TEST
  GROUPS = fam_osteon(0 1)
  /MISSING = ANALYSIS
  /VARIABLES = DALY_rate0_Agewt0 DALY_rate3_Agewt0
  /CRITERIA = CI(.95) .
T-TEST
  GROUPS = frfo8(0 1)
  /MISSING = ANALYSIS
  /VARIABLES = DALY_rate0_Agewt0 DALY_rate3_Agewt0
  /CRITERIA = CI(.95) .
T-TEST
  GROUPS = sermnn(0 1)
  /MISSING = ANALYSIS
  /VARIABLES = DALY_rate0_Agewt0 DALY_rate3_Agewt0
  /CRITERIA = CI(.95) .

FILTER OFF.
USE ALL.
EXECUTE .
```

***Table 6.2**.
* Variables associated with DALY loss, undiscounted and discounted; adjusted by BD and previous osteoporosis BF.

#Undiscounted DALYs

```
ONEWAY DALY_rate0_Agewt0 BY dxan
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate0_Agewt0 BY frfo4
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate0_Agewt0 BY imc_20_cat
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate0_Agewt0 BY frfo2
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate0_Agewt0 BY frfo3
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate0_Agewt0 BY art_reumn
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate0_Agewt0 BY fam_osteon
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate0_Agewt0 BY frfo8
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.

**Final model*.
UNIANOVA DALY_rate0_Agewt0  BY frfo4 art_reumn fam_osteon frfo8 WITH dxan
  /METHOD=SSTYPE(3)
  /INTERCEPT=INCLUDE
  /PRINT=PARAMETER DESCRIPTIVE
  /CRITERIA=ALPHA(.05)
  /DESIGN=frfo4 art_reumn fam_osteon frfo8 dxan .

#Discounted DALYs

ONEWAY DALY_rate3_Agewt0 BY dxan
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate3_Agewt0 BY frfo4
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate3_Agewt0 BY imc_20_cat
```

```
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate3_Agewt0 BY frfo2
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate3_Agewt0 BY frfo3
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate3_Agewt0 BY art_reumn
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate3_Agewt0 BY fam_osteon
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.
ONEWAY DALY_rate3_Agewt0 BY frfo8
  /STATISTICS DESCRIPTIVES
  /PLOT MEANS
  /MISSING ANALYSIS.

**Final model*.
UNIANOVA DALY_rate3_Agewt0  BY frfo4 art_reumn frfo8 WITH dxan
  /METHOD=SSTYPE(3)
  /INTERCEPT=INCLUDE
  /PRINT=PARAMETER DESCRIPTIVE
  /CRITERIA=ALPHA(.05)
  /DESIGN=frfo4 art_reumn frfo8 dxan .

*** Missing data analysis ***.
**4 March de 2013, file: “missing_data_analysis.sps”**.

FREQUENCIES
  VARIABLES=DALYs_available
  /ORDER=  ANALYSIS .

**Comparing the variables at TABLE 6.4.1: ptes with DALY missing vs. DALY available**.
*Socio-demographic data*.

T-TEST
  GROUPS = DALYs_available(0 1)
  /MISSING = ANALYSIS
  /VARIABLES = edadn
  /CRITERIA = CI(.95) .
CROSSTABS
  /TABLES=edad_grupo sit_labn niv_estn habitatn BY DALYs_available
  /FORMAT= AVALUE TABLES
  /STATISTIC=CHISQ
  /CELLS= COUNT ROW COLUMN
  /COUNT ROUND CELL .

*Clinical characteristics*
T-TEST
  GROUPS = DALYs_available(0 1)
  /MISSING = ANALYSIS
  /VARIABLES = imcn cign
  /CRITERIA = CI(.95) .
```

```
CROSSTABS
  /TABLES=tabacon alcohn gramosn  BY DALYs_available
  /FORMAT= AVALUE TABLES
  /STATISTIC=CHISQ
  /CELLS= COUNT ROW COLUMN
  /COUNT ROUND CELL .

**Background*
CROSSTABS
  /TABLES=dmn h_artn art_reumn anor_nern hiperparan hipertiron hepat_cron sind_malabn
BY DALYs_available
  /FORMAT= AVALUE TABLES
  /STATISTIC=CHISQ
  /CELLS= COUNT ROW COLUMN
  /COUNT ROUND CELL .

***Osteoporosis data*.
T-TEST
  GROUPS = DALYs_available(0 1)
  /MISSING = ANALYSIS
  /VARIABLES = edad_diag dxan Nfrfo Frmosteo tiemdiagn
  /CRITERIA = CI(.95) .
CROSSTABS
  /TABLES=imc_20_cat  BY DALYs_available
  /FORMAT= AVALUE TABLES
  /STATISTIC=CHISQ
  /CELLS= COUNT ROW COLUMN
  /COUNT ROUND CELL .


********** Logistic regression***.
**All variables***.
LOGISTIC REGRESSION VARIABLES  DALYs_available
  /METHOD = ENTER edadn sit_labn
niv_estn
habitatn
imcn cign
tabacon
alcohn
gramosn
dmn
h_artn
art_reumn
anor_nern
hiperparan
hipertiron
hepat_cron
sind_malabn
 edad_diag
dxan
Nfrfo
Frmosteo
tiemdiagn
  /CONTRAST (sit_labn)=Indicator(1)
  /CONTRAST (niv_estn)=Indicator(1)
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  /CONTRAST (tabacon)=Indicator(1)
  /CONTRAST (alcohn)=Indicator(1)
  /CONTRAST (gramosn)=Indicator(1)
  /CONTRAST (dmn)=Indicator(1)
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  /CONTRAST (h_artn)=Indicator(1)
  /CONTRAST (art_reumn)=Indicator(1)
  /CONTRAST (anor_nern)=Indicator(1)
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  /CONTRAST (hipertiron)=Indicator(1)
  /CONTRAST (hepat_cron)=Indicator(1)
  /CONTRAST (sind_malabn)=Indicator(1)
  /PRINT = GOODFIT CI(95)
  /CRITERIA = PIN(.05) POUT(.10) ITERATE(20) CUT(.5) .


**Assess and avoid multicolinearity**.
LOGISTIC REGRESSION VARIABLES  DALYs_available
  /METHOD = ENTER edadn sit_labn
niv_estn
habitatn
imcn
tabacon
gramosn
dmn
h_artn
art_reumn
anor_nern
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 edad_diag
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Frmosteo
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  /CONTRAST (sit_labn)=Indicator(1)
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  /CONTRAST (hiperparan)=Indicator(1)
  /CONTRAST (hipertiron)=Indicator(1)
  /CONTRAST (hepat_cron)=Indicator(1)
  /CONTRAST (sind_malabn)=Indicator(1)
  /PRINT = GOODFIT CI(95)
  /CRITERIA = PIN(.05) POUT(.10) ITERATE(20) CUT(.5) .

**Final model include all the significative ones, removing from the multivariate model the non
significative ones (one by one)
**Avoiding multicolinearity and without including Dexa**.
*** Selected model to be reported in the reviewer answer ****.
LOGISTIC REGRESSION VARIABLES  DALYs_available
  /METHOD = ENTER imc_20_cat Nfrfo Frmosteo
  /CONTRAST (imc_20_cat)=Indicator(1)
  /PRINT = GOODFIT CI(95)
  /CRITERIA = PIN(.05) POUT(.10) ITERATE(20) CUT(.5) .
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ADDENDA

Addendum I: Publications related with this thesis as of June 2014

1. Darbà J, Kaskens L, Garreta A, Paredes R, Pérez-Álvarez N. The economic and clinical consequences of pre-treatment human and viral genotyping screening for antiretroviral treatment in HIV infected patients. Pharmacoeconomics. Under revivew.
2. Darbà J, Kaskens L, Pérez-Álvarez N, Palacios S, Neyro JL, Rejas J. Disability-adjusted-life-year loss in postmenopausal women with osteoporosis: a burden of illness study. Menopause. Under review.
3. Darbà J, Pérez-Álvarez N, Kaskens L, Holgado-Pérez S, Racketa J, Rejas J. Cost-effectiveness of bazedoxifene versus raloxifene in the treatment of postmenopausal women in Spain. Clinicoecon Outcomes Res. 2013 Jul 5; 5:327-36.

Addendum II: Conference contributions related with this thesis as of June 2014

Invited presentation

1. 'Markov models used in a 2-stage outcome cohort simulation for an economic evaluation'. 5th International Conference of the ERCIM WG on Computing & Statistics (ERCIM 2012). 1-3 December 2012. Oviedo, Spain.
2. Perez-Alvarez N, Gomez G, Paredes R, Clotet B. Cost-effectiveness of HIV tropism testing to inform antiretroviral treatment with maraviroc. 6th meeting of the Eastern Mediterranean Region International Biometric Society (EMR-IBS). 8-12 May 2011, Crete, Greece.

Contributed presentations

1. Pérez-Álvarez N, Muñoz-Moreno JA, Gomez G. Cost effectiveness evaluation for promoting HIV treatment adherence: cohort simulation using a pilot study data. 7th meeting of the Eastern Mediterranean Region International Biometric Society (EMR-IBS). 22-25 April, 2013. Tel Aviv, Israel.
2. Pérez-Álvarez N, Kaskens L, Darbà J. Cost-effectiveness study of treatments for fracture prevention in postmenopausal women. 2ª Reunión General Biostatnet. January 25-26 2013. Santiago de Compostela, Spain.

Posters

1. Darba J, Kaskens L, Pérez-Álvarez N, Palacios S, Neyro JL, Rejas J. Disability-adjusted life years loss in postmenopausal women receiving major pharmacological interventions for osteoporosis. International Osteoporosis Foundation, European

Congress on Osteoporosis and Osteoarthritis, Orthopaedics Medical Congress. 17 – 20 April 2013. Rome, Italy.

2. Muñoz-Moreno JA, Gillen-Marconi M, Pérez-Álvarez N, Fumaz CR, González-García M, Ferrer MJ, Clotet B.Promotion of HIV Treatment Adherence and its Economical Cost: A Preliminary Cost-Effectiveness Analysis from a Controlled Randomized Prospective Trial. 6th IAS Conference on HIV pathogenesis, treatment and prevention. 17-20 July 2011, Rome, Italy.

Posters with material not included in the dissertation but which constitute an example of application of the methods tackled in the thesis are:

1. Darbà J, Kaskens L, Pérez-Álvarez N. Neuropathic pain: a budget impact analysis to estimate costs due to the introduction of Qutenza® on the spanish market. ISPOR 14th annual European Congress (International Society for Pharmacoeconomics and Outcomes Research). 5-8 November, 2011, Madrid, Spain.
2. Darbà J, Kaskens L, Pérez-Álvarez N. Cost analysis of haemostatic treatment with a fibrin-based sponge versus fibrin sealant in lung surgery and liver resection in a spanish setting. ISPOR 14th annual European Congress (International Society for Pharmacoeconomics and Outcomes Research). 5-8 November, 2011, Madrid, Spain.
3. Darbà J, Pérez-Álvarez N, Kaskens L, Martín P. Dasatinib or imatinib in newly diagnosed chronic myeloid leukaemia patients in the chronic phase: Five-years follow-up simulated cohort. ISPOR 14th annual European Congress (International Society for Pharmacoeconomics and Outcomes Research). 5-8 November, 2011, Madrid, Spain.

Addendum III: Other publications from September 2007 as of June 2014

1. Negredo E, Domingo P, Pérez-Álvarez N, Gutierrez M, Mateo G, Puig J, Escrig R, Echeverría P, Bonjoch A, Clotet B. Improvement in bone mineral density after switching from tenofovir to abacavir in HIV-1-infected patients with low bone mineral density: multicenter randomized pilot study (OsteoTDF Study). CID. Under review.
2. Echeverría P, Bonjoch A, Puig J, Moltó J, Paredes R, Sirera G1, Ornelas A, Pérez-Álvarez N, Clotet B, Negredo E. Randomised Study to Assess the Efficacy and Safety of Once-Daily Etravirine-Based Regimen as a Switching Strategy in HIV-Infected Patients Receiving a Protease Inhibitor-Containing Regimen. Etraswitch Study. PLoS One. 2014 Feb 4;9(2):e84676.
3. Negredo E, Domingo P, Ferrer E, Estrada V, Curran A, Navarro A, Isernia V, Rosales J, Pérez-Álvarez N, Puig J, Bonjoch A, Echeverría P, Podzamczer D, Clotet B. Decreased Peak Bone Mass in Young HIV-Infected Patients Compared With Healthy Controls. J Acquir Immune Defic Syndr. 2014 Feb 1;65(2):207-12.
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5. Muñoz-Moreno JA, Prats A, Pérez-Álvarez N, Fumaz CR, Garolera M, Doval E, Negredo E, Ferrer MJ, Clotet B; NEU Study Group. A brief and feasible paper-based method to screen for neurocognitive impairment in HIV-infected patients: the NEU screen. J Acquir Immune Defic Syndr. 2013 Aug 15;63(5):585-92.

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7. Echeverría P, Bonjoch A, Moltó J, Jou A, Puig J, Ornelas A, Pérez-Álvarez N, Clotet B, Negredo E. Pulse wave velocity as index of arterial stiffness in HIV-infected patients compared with a healthy population.J Acquir Immune Defic Syndr. 2013 Aug 26. [Epub ahead of print].
8. Darbà J, Pérez-Álvarez N, Kaskens L, Martín P, Lees M. Proyección a largo plazo de la supervivencia de los nuevos pacientes con leucemia mieloide crónica que reciben dasatinib o imatinib en primera línea de tratamiento. PharmacoEconomics Spanish Research Articles. July 2013, Volume 10, Issue 2, pp 37-41.
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