ΠΡΟΓΡΑΜΜΑ «ΔΙΟΙΚΗΣΗ ΜΟΝΑΔΩΝ ΥΓΕΙΑΣ»
«Οικονομική και Χρηματοδοτική Διαχείριση Υπηρεσιών Υγείας»

«A quest towards introducing a pharmacoeconomics framework in Cyprus»

ΔΙΔΑΚΤΟΡΙΚΗ ΔΙΑΤΡΙΒΗ

ΠΑΝΑΓΙΩΤΗΣ ΠΕΤΡΟΥ

Διατριβή η οποία υποβλήθηκε προς απόκτηση διδακτορικού τίτλου σπουδών στο Ανοικτό Πανεπιστημίου Κύπρου.

ΛΕΥΚΩΣΙΑ, ΜΑΡΤΙΟΣ 2016

ISBN 978-9963-695-44-7

ΣΕΛΙΔΑ ΕΓΚΥΡΟΤΗΤΑΣ

Υποψήφιος Διδάκτωρ: Παναγιώτης Πέτρου

Τίτλος Διατριβής: A quest towards introducing a pharmacoeconomics framework in Cyprus

Η παρούσα Διδακτορική Διατριβή εκπονήθηκε στο πλαίσιο των σπουδών για απόκτηση Διδακτορικού Διπλώματος στο Πρόγραμμα «Διοίκηση Μονάδων Υγείας» και εγκρίθηκε στις 29 Μαρτίου 2016 από τα μέλη της Εξεταστικής Επιτροπής.

Εξεταστική Επιτροπή:

Αναπλ. Καθηγητής Κρ. Χασάπης, Πανεπιστήμιο Κύπρου – Πρόεδρος Επιτροπής

Επίκουρος Καθηγητής Μ. Τάλιας, Ανοικτό Πανεπιστήμιο Κύπρου (Επιβλέπων) - Μέλος

Καθηγητής Π. Πασιαρδής, Ανοικτό Πανεπιστήμιο Κύπρου – Μέλος

Αναπλ. Καθηγητής Β. Ραφτόπουλος, Τεχνολογικό Πανεπιστήμιο Κύπρου – Μέλος

Καθηγητής Γ. Τσιότρας, Πανεπιστήμιο Μακεδονίας – Μέλος.

……

Μιχάλης Τάλιας – Επιβλέπων
Επίκουρος Καθηγητής στη Σχολή Οικονομικών Επιστημών και Διοίκησης
Ανοικτό Πανεπιστήμιο Κύπρου

ABSTRACT

As the growth of pharmaceutical expenditure exceeds the increase of productive capacity on a global scale, health agencies are under significant pressure by patients, physicians and social stakeholders, to provide timely and unobstructed access to innovative and safe medicines. At the same time, health agencies must safeguard the Research and Development projects of the industry, thus setting fair prices to medicines which will not hinder innovation. A comprehensive decision-making context should encompass all aforementioned needs and attributes of the stakeholders and extenuate their divergent and inconsonant interests, ultimately amalgamating them into a joint strategic framework. It is imperative that the standards of this framework are laid on high grade of evidence data, which, in return, will maximise the utility generated out of health resources. To this end, the economic evaluation of pharmaceuticals has emerged as a pivotal decision-making tool. Accordingly, the current study aims to develop a pharmacoecenomic model to evaluate cost-effectiveness of pharmaceuticals and also to elaborate on an innovative pricing model, which will integrate all attributes of the product, in the theoretical framework of a value based pricing scheme. Prior to this, and due to the lack of data of the Cyprus pharmaceutical market, current thesis will evaluate existing pricing and reimbursement schemes.

The specific study critically assesses Health Technology Assessment in Cyprus and furthermore, the prevailing pricing and reimbursement tool of public health care sector, tendering. The next step of the thesis is the decomposition of public health care sales, spanning a period of seven years, which will identify cost-drivers of the Pharmaceutical Market. Based on these findings, a pharmacoeconomic evaluation was performed on a key cost-driver product. The last part of the thesis explores the potential of price setting based on the clinical and social value of the product. The findings of this study indicate that current pricing and reimbursement tool of public health care sector are potent, nevertheless they are context specific and context sensitive tools with several particularities. Foremost, they are not sensitive to the innovation status of the product. The decomposition study revealed that the oncology segment of the market is the powerhouse of pharmaceutical expenditure and as a result these findings underline that further research in this therapeutic area is incumbent. The pharmacoecenomic evaluation also highlighted, through the expected value of perfect information, the uncertainty that encompass the decision for reimbursement of the given pharmaceutical. The final part of the thesis defined the price, at

which the product can be considered cost-effective, through identification of the health benefits that the product delivers, which exceed the health benefits displaced in the broader health system and society on the grounds of additional cost incurred. Cost–effectiveness analysis can contribute to rational decision making in pharmaceutical and the introduction of uncertainty tackling mechanisms, such as the expected value of perfect information, can reveal areas which could benefit by further research.

Value based pricing, which has been described as the holy-grail of pharmacoeconomics, also delivered significant data. There are also several technical parameters that merit more research such as the introduction of willingness to pay thresholds.

The overall findings of the study epitomise the necessity of implementing a pharmacoecenomic evaluation framework in Cyprus and the value that this can yield to the health policy level. The current study also highlights the complexity of the pharmaceutical market, the need to employ sensitive instruments and the imperative need to incorporate high grade of evidence data. Also, areas that merit additional research have been identified such as expected value of partial perfect information, ethical issues intertwining with willingness-to-pay thresholds and new approximations to quality of life measurement tools.

ΠΕΡΙΛΗΨΗ

Η αύξηση των φαρμακευτικών δαπανών έχει υπερβεί την αύξηση της παραγωγικότητας σε παγκόσμια κλίμακα, κάτι που εντείνει την πίεση των κοινωνικών εταίρων στις Αρχές Δημόσιας Υγείας, με στόχο την έγκαιρη και απρόσκοπτη πρόσβαση των ασθενών σε καινοτόμες και ασφαλείς θεραπείες. Παράλληλα, οι αρμόδιες υπηρεσίες υγείας πρέπει να τιμολογούν δίκαια τα φαρμακευτικά προϊόντα ώστε να διατηρηθεί η βιωσιμότητα της φαρμακευτικής βιομηχανίας. Αυτό είναι εκ των ων ουκ άνευ ώστε να διασφαλιστεί η ικανότητα χρηματοδότησης προγραμμάτων Έρευνας και Ανάπτυξης καθώς υπάρχουν ανεκπλήρωτες ιατρικές ανάγκες σε καινούργια, πιο ασφαλή και πιο αποτελεσματικά, φάρμακα.

Όλα τα προαναφερθέντα χαρακτηριστικά της φαρμακευτικής αγοράς πρέπει να λαμβάνονται υπόψη κατά την λήψη αποφάσεων και να ενσωματωθούν αρμονικά, όπως επίσης και οι συνήθως αποκλίνουσες απόψεις των κοινωνικών εταίρων, στο στρατηγικό πλαίσιο λήψης αποφάσεων. Ένα αποτελεσματικό πλαίσιο λήψης αποφάσεων πρέπει να στηρίζεται σε δεδομένα υψηλού βαθμού τεκμηρίωσης, ώστε να μεγιστοποιηθεί η χρησιμότητα που παράγεται από τους περιορισμένους πόρους υγείας.

Η παρούσα μελέτη έχει ως στόχο την ανάπτυξη ενός φαρμακοοικονομικού μοντέλου για αξιολόγηση του λόγου κόστους/αποτελεσματικότητας φαρμάκων, καθώς και διερεύνηση της δυνατότητας ανάπτυξης και εφαρμογής ενός καινοτόμου μηχανισμού τιμολόγησης φαρμάκων, την τιμολόγηση βάση αξίας. Αυτός ο μηχανισμός τιμολόγησης ορίζει την τιμή του φαρμάκου βασισμένο στο αποδεδειγμένο κλινικό, κοινωνικό και οικονομικό όφελος από την χρήση ενός φαρμάκου, καθώς και τα σχετικά έξοδα. Καθότι, δεν υπάρχουν αρκετές μελέτες για την φαρμακευτική αγορά της Κύπρου, ένας από τους πυλώνες της διατριβής είναι η διερεύνηση του υφιστάμενου περιβάλλοντος και η κριτική αξιολόγηση των υφιστάμενων μεθόδων τιμολόγησης και αποζημίωσης φαρμάκων.

Συγκεκριμένα, η μελέτη αυτή αξιολόγησε την διαδικασία Αξιολόγησης Τεχνολογιών Υγείας και την επικρατέστερη μέθοδο τιμολόγησης και αγοράς φαρμάκων, την προμήθεια μέσω προσφορών. Στο επόμενο στάδιο, η μελέτη αποδόμησε τις πωλήσεις του Δημόσιου τομέα για μια περίοδο εφτά ετών, ώστε να ταυτοποιηθούν οι παράγοντες που επηρεάζουν την αύξηση των φαρμακευτικών εξόδων.

Με βάση αυτά τα ευρήματα, μια φαρμακοοικονομική αξιολόγηση διεξηχθηκε σε ένα βασικό προϊόν οδηγό κόστους. Το τελευταίο μέρος της διατριβής διερεύνησε τη δυνατότητα καθορισμού των τιμών με βάση την κλινική και την κοινωνική αξία του

προϊόντος. Τα ευρήματα της μελέτης αυτής καταδεικνύουν ότι η τρέχουσα μέθοδος τιμολόγησης και αποζημίωσης φαρμάκων είναι αρκετά αποτελεσματική αλλά εμπερικλείει αρκετές ιδιαιτερότητες και η επιτυχία της εξαρτάται από το ευρύτερο πλαίσιο δημόσιας υγείας. Επιπλέον, η μέθοδος των προσφορών δεν είναι ευαίσθητη στο επίπεδο καινοτομίας κάθε προϊόντος. Η μελέτη αποδόμησης αποκάλυψε ότι τα ογκολογικά προϊόντα αποτελούν τον σημαντικότερο οδηγό κόστους, κάτι που υπογραμμίζει ότι η περαιτέρω έρευνα σε αυτόν τον θεραπευτικό τομέα είναι επιβεβλημένη. Η φαρμακοοικονομική αξιολόγηση κατέδειξε, μέσα από την αναμενόμενη τιμή της τέλειας πληροφόρησης, την αβεβαιότητα που περικλείει η απόφαση για την αποζημίωση του συγκεκριμένου φαρμάκου. Το τελευταίο μέρος της διατριβής καθορίζει την τιμή, με την οποία το προϊόν μπορεί να θεωρηθεί πως έχει αποδεκτό λόγο κόστους/αποτελεσματικότητας, μέσω του προσδιορισμού της χρησιμότητας, που το προϊόν αποδίδει, η οποία υπερβαίνει την χρησιμότητα που χάνεται στο ευρύτερο σύστημα υγείας και στην κοινωνία, λόγω του επιπλέον κόστους που συνεπάγεται. Η ανάλυση κόστους/αποτελεσματικότητας μπορεί να συμβάλει στην ορθολογική λήψη αποφάσεων στη φαρμακοβιομηχανία. Παράλληλα η εισαγωγή μηχανισμών αντιμετώπισης της αβεβαιότητας όπως είναι η αναμενόμενη τιμή της τέλειας πληροφόρηση, μπορεί να αποκαλύψει τομείς που θα μπορούσαν να επωφεληθούν από την διενέργεια περαιτέρω στοχευμένης έρευνας.

Η τιμολόγηση βάση αξίας οδήγησε σε σημαντικά συμπεράσματα, όπως και επίσης κατέδειξε σημαντικές τεχνικές παραμέτρους που χρήζουν περαιτέρω έρευνας, όπως ο ορισμός του ποσού προθυμίας πληρωμής.

Συνολικά τα ευρήματα της μελέτης συνοψίζουν την αναγκαιότητα της εφαρμογής ενός πλαισίου φαρμακοοικονομικής αξιολόγησης στην Κύπρο και την αξία που αυτή μπορεί να αποδώσει στο επίπεδο της πολιτικής υγείας. Η τρέχουσα μελέτη τονίζει επίσης την πολυπλοκότητα της φαρμακευτικής αγοράς, την ανάγκη για εισαγωγή ευαίσθητων οργάνων και την επιτακτική ανάγκη για χρήση δεδομένων υψηλού βαθμού τεκμηρίωσης. Επίσης, περιοχές που χρήζουν πρόσθετης μελλοντικής έρευνας έχουν εντοπιστεί, όπως ηθικά διλλήματα σχετικά με τα επίπεδα ποσού προθυμίας πληρωμής, αξίας της μερικής τέλειας πληροφόρησης και νέα εργαλεία αποτύπωσης της ποιότητας ζωής.

Acknowledgements

This thesis has been a long, exemplary and sui-generis quest in the unchartered territories of economic evaluation of pharmaceuticals. As in every journey embarkment, the quote of Odysseus Elytis stands true: "*The distance from nothing to minimal is far greater than the one from minimal to plenty*". Towards this, I am grateful to my parents, Ntinos and Eugenia Petrou, who have set the bearings of this course, much earlier in my life. My tutor, Dr Michael A. Talias proved to be a competent seafarer in this quest and this Thesis is to be perpetuated by greater expeditions. Professor Petros Pashiardis has offered invaluable advices on the final fine-tuning stages of this Thesis, in order to promulgate our findings in a clear and comprehensive way.

Pretty much of the inspiration, resilience and perseverance were derived from Constantinos, Andreas and Myrianthi Petrou, who also comprise the motivational force for this Thesis and helped me withstand the hardships: after all, a smooth sea never made a skilled sailor. Their unconditional support prevented any leeway along the course.

Finally, I am thankful to all of my friends, colleagues, editors and anonymous reviewers, each one in their own capacity, who encouraged me to search for the truth among an ocean of fallacy and sophism, which comes down to the "*you make the truth in the same way you make the lies*".

Contents

List of Figures

List of Tables

ABBREVIATIONS

ATC	Anatomic Therapeutic Chemical classification
BSC	Best supportive care
CEA	Cost effectiveness analysis
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
DDD	Defined daily dose
DALY	Disability Adjusted Life Years
EAC	Equivalent Annual cost
EBM	Evidence based medicine
ERP	External reference pricing
EVPI	Expected value of perfect information
GDP	Gross domestic product
GRADE	Grading of Recommendation, Assessment, Development and Evaluation
HTA	Health technology assessment
ICER	Incremental Cost effectiveness ratio
INB	Incremental net benefit
INN	International Non proprietary Name
LYG	Life years gained
MEA	Managed entry agreements
MoH	Ministry of health
NICE	National Institute for clinical excellence
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PICO	Patient, information, comparison and outcome
QALY	Quality adjusted life years
RCC	Renal cell cancer
RCT	Randomised controlled trials

R&D	Research &Development
TTO	Time-to-trade off
VBP	Value-based pricing
WHO	World Health Organization
WTP	Willingness-To-Pay

A QUEST TOWARDS INTRODUCING A PHARMACOECONOMICS FRAMEWORK IN CYPRUS

1. Introduction–Statement of the research question

There is a wealth of sayings, rituals, spirituals and ceremonies that are influenced by, derived from or recount what really health is. Likewise, peoples' perceptions towards health are quite diverse as well (Brazier, 2007). The most durable definition of Health is delineated in the Constitution of World Health Organization, dating back to 1948: "*Health is a state of complete physical, mental and social well being and not merely the absence of disease and infirmity*" (WHO, 1948). Although it raised several concerns, especially due to not being narrow and specific, it actually encompasses all dimensions of Health. This was based on Sigerist's definition which actually predated. Sigerist, a Director at Johns Hopkins University institute of history of medicine, in 1941 stated that "healthy *individual is a man who is well balanced bodily and mentally, and well adjusted to his physical and social environment. He is in full control of his physical and mental faculties, can adapt to environmental changes, so long as they do not exceed normal limits, and contributes to the welfare of society according to his ability. Health therefore is not simply the absence of disease; it is something positive, a joyful attitude towards life, and a cheerful acceptance of the responsibilities that life puts upon the individual.*

William J. Baumol, in his famous books "*Performing Arts, The Economic Dilemma: a study of problems common to theatre, opera, music and dance*."(Baumol & Bowen, 1966) and "*Why computers get cheaper and health does not*" (Baumol et al., 2012) underlined the financial dimension of creating health, a statement which proved to withstand time. Baumol concluded that the increase rate of health expenditure outpaces the corresponding rates of other economy segments, owing to scarce innovation, medical uncertainty, heavily regulated environment, low productivity increase and the imperfect attributes of the health market. This finding is applicable to the pharmaceutical sector as well-whose sales correspond to 20% of total health expenditure-which demonstrates a consistent increasing trend. This "productivity lag" is augmented by:

1. An aging population, with increased life expectancy and subsequent augmented morbidity on the grounds of rising prevalence of chronic conditions such as Type 2 diabetes mellitus, osteoarthritis and osteoporosis (Maynard and McDaid, 2003).

2. Better and earlier detection of diseases owing to introduction of advanced diagnostic procedures (Dubois et al., 2000).
3. Introduction of expensive medicines (Luz and Comanor, 1998), and
4. Introduction of new agents for conditions that were previously untreated or sub-treated.

In light of the above, Health Agencies worldwide are under significant pressure, in order to harness soaring health expenditure, while concomitantly safeguarding the access of patients to safe and effective medicines. At the same time, health needs increase at a greater pace compared to the allocated funds. This poses a great challenge for the financial sustainability of health systems worldwide. Health is not produced randomly or consistently, consequently, outputs (the benefits of the treatment-figure 1), and relevant costs may greatly vary among comparative therapeutic options. To this direction, the economic evaluation of pharmaceuticals has emerged as a pivotal tool in the classification and prioritization of needs, which constitutes a significant aspect in health. The economic evaluation enhances the elaboration of normative recommendations, which define the optimum allocation of health resources, a process that will ultimately maximise the health utility of the society. A precondition for a robust decision-making process based on economic evaluation, is to ensure access to evidence pertaining to the cost-effectiveness profile of the product under assessment, prior to any decision reached regarding its reimbursement. It is imperative that such decisions are premised on objective, reliable and verifiable criteria in order to abide with the fundamental principles of health, namely solidarity and equity (Dias et al., 2013). The scientific evidence for the reimbursement of pharmaceuticals is delivered by randomised controlled trials (RCT), which are ranked highly in the grading hierarchy of evidence- based medicine (Chatterji et al., 2002; Guyatt et al., 1992). This enables the efficient resource allocation between health sectors, which is a highly competitive and context sensitive process (Weinstein et al., 2003; Drummond et al., 1997; Gold et al., 1996). Nevertheless, the design of a RCT is usually elaborated from a regulatory approval scope, therefore it offers limited input for health care decision-making. Decision makers need data with high internal and external validity and this gap can be breached by the decision-analytic modeling for the economic evaluation of pharmaceuticals. Synthesis of data through economic modeling has been increasingly utilised by health agencies to provide cost-effectiveness data and facilitate informed decision-making. A prerequisite is the inclusion of meta-analysis and randomised

controlled trials (RCT), which carry the strongest grade of level of evidence (Cooper, Sutton & Abrams, 2004, Roberts et al., 2012; Parmigiani, 2002; Spiegelhalter, Abrams & Myles, 2004; Claxton, 1999).

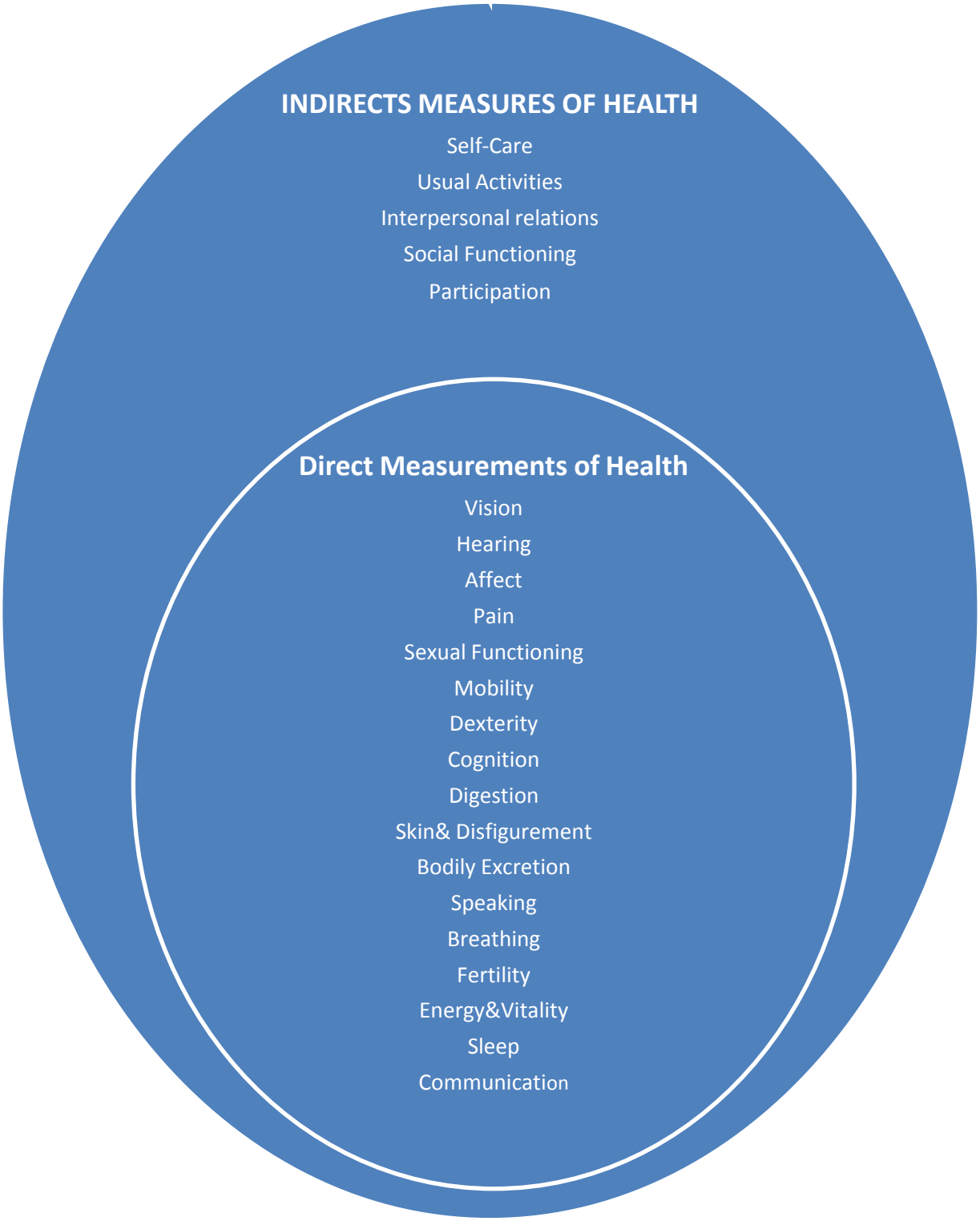
Currently, the fiscal environment is shaped by austerity policies, which are applied all over Europe. Accordingly, these policies adversely lead to curbed health expenditures (Vogler et al., 2011). At the same time, the fiscal crisis has been acknowledged as an independent health risk factor, thus further increasing health needs. This confluence of increasing health needs and reduced funds, amid the complex health operational framework, mandates rational selection of medicines in order to maintain the sustainability of health systems and safeguard the unobstructed access of patients to necessary, effective and safe medicines (Lichtenberg, 2005). Accordingly, it is essential to balance the multiple and diverging policy interests of the major stakeholders of the pharmaceutical sector, that is the Health Agencies, the Industry, physicians and patients. Their strategic goals and pursuits rarely overlap, usually deviate and even conflict, since health agencies strive to contain costs, Industry endeavours to sustain financial prosperity, promote research and development, protect their employment and contribute their positive trade balance, and patients demand timely access to innovative, safe and high-quality medicines.

Health policy for pharmaceuticals (the art of the systematically decision-making procedure in the face of uncertainty) is a quantitative, specific and confining process. It is imperative to be founded on high-grade of evidence data, so as to enhance efficiency and reduce waste. Data must be analyzed with the appropriate economics tools and interpreted in the explicit health context, while the findings and recommendations should be amalgamated in the decision-making context.

In light of the above, the application of decision-analytic economic modeling schemes can provide timely approximations with scientific rigour and policy relevance (Buxton, 1997). These can radically contribute to the decision-making process and enhance the maximization of health utility to the society, a doctrine of necessity in the current fiscal environment.

Figure 1

Measurements of Health



1.1. Purpose of the Study

The purpose of this study is to explore the Health Technology Assessment (HTA) and the cost-effectiveness analysis context in Cyprus; propose a conceptual and technical framework through the introduction of innovative pharmacoeconomic modeling and elaborate pioneering approaches in the pricing of pharmaceuticals through the incorporation of the value of the pharmaceutical product, as defined through Health Technology Assessment, in its final price.

1.2. Research questions

Based on the statement of the research topic and the purpose of the study, this thesis develops the application of cost-effectiveness analysis, through the use of decision-analytic models and evidence synthesis in pharmacoeconomic evaluation. In addition to this, it proposes a pricing model which aligns pharmaceutical value to their prices. Finally, the current thesis critically assesses the applicability of these models in Cyprus public health operational framework. Several intermittent questions have also been raised during the literature review, as following:

1. Is Health Technology Assessment a substantial and reliable tool for introduction of new products in the formulary list of publicly reimbursed pharmaceutical products?
2. How to define cost-effectiveness profile of medicines?
3. What is the value of current pharmaceutical assessment and reimbursement policy?
4. What is the potential of pharmaceutical pricing based on its value, as defined by clinical outcomes (along with exploration of new approaches for integration of value in the price of the product)?
5. Exclusive or adjuvant positioning of economic evaluation in decision-making?
6. What is the cost of acquiring the perfect information? Many researchers point the expected value of perfect information which elucidates the cost of taking a wrong decision. It represents the costs which are justified to spend in order to reach perfect information.
7. How to define willingness to pay thresholds?
8. How to perform sensitivity analysis?
9. How to explore and assess uncertainty of the model?

10. How to define the technical parameters of the model such as time horizon, discounting and distributions of the model?

Prior to the development of the pharmacoeconomic model, this thesis explores the surrogate points that infiltrate-and predominantly predate-economic evaluations. Primarily, we assessed the operational framework of health technology assessment and economic evaluation in Cyprus. Furthermore, an appraisal of the current reimbursement system was performed to define to which extent pharmacoeconomic evaluation is employed in Cyprus. Finally, we used a decomposition study to identify pharmaceutical products with significant budget impact and value increase. Pharmacoeconomic evaluation was performed in these products.

This thesis is performed from a Public payer's perspective in Cyprus, since no data are available for the private sector. As a result, the thesis focuses on the Public health care sector.

1.3. Contribution to theory

The concept of cost-effectiveness evaluations has been emerging in many countries and has been positioned as the core of research in the field of health economics. In spite of its universal and undisputable acceptance, its implementation has been hindered by theoretical and methodological flaws, while statistical inefficiencies have further impeded its dissemination. In fact, many health agencies utilize economic evaluation as adjuvant and not primary tools, since many researchers raised concerns whether an economic evaluation fully captures all costs and utility created by the intervention. In particular, numerous parameters of economic evaluations have not been clearly defined, while their operational framework remains considerably vague. The National Institute of Clinical Excellence (NICE) performs, on a regular basis, cost-effectiveness evaluations, nevertheless some distinct differences, including demographics, disease prevalence and health system types of Cyprus and UK impede and distort the transferability of these data across countries. As a result, the development of a context specific economic evaluation program is preferential, in order to circumvent the aforementioned barriers.

This paper aims to create a theoretical framework by merging two distinct but associated characteristics: the optimal financing approach and data synthesis based on available information. Given these, we elaborate on Decision-making, in the context of

available evidence and the potential for obtaining further evidence to reach more robust decisions.

The ultimate goal is the ability to assess cost-effectiveness of a given product (in the context of a specific and predefined willingness-to-pay threshold). In addition to this, we answered a frequently raised question in the field of economic evaluations: that is, whether it makes sense to search for more data to ultimately minimise uncertainty. Finally, this study explores innovative pricing schemes that embed clinical value of the product. In this approach, the integration of the price minimises inter-and intra-dependencies on other variables. In this sense, this study further defines the operational framework of economic analysis. This study extends beyond mere cost-effectiveness analysis and deals with advanced functions of economic modeling, such as expected value of perfect information and value-based pricing. Currently, only random data have been published in conceptual studies which do not deal with actual data. Value-based pricing constitutes a provocative approach, nevertheless the initial euphoria which has surrounded it, wanes off due to methodological impediments. It is expected that the findings of this study will, in particular, contribute in the contextual framework of value-based pricing. Ultimately, this thesis can elucidate several parameters of value-based pricing, which have not been adequately and convincingly contemplated.

This thesis studies the economic modeling from a payer perspective in Cyprus, a feature which enables the incorporation of all relevant costs and utility data, thus offering a holistic and comprehensive approach to pharmacoeconomic evaluation. It is anticipated that findings will be of utter value to Cyprus' health care sector, which has been devoid of economic evaluation policies, despite it being explicitly promulgated as a prerequisite in the Memorandum of Understanding, which is the agreement between Cyprus and a team of international lenders (MoU, 2013). As such, the disbursement of financial installments is conditional to achievement or not of a bundle of terms, among them the introduction of economic evaluations and Health Technology Assessments. In this context, we are confident that Health Authorities could capitalize on our data, which could serve both as a terms of reference and as a practical guide.

Finally, a significant attribute of this thesis is the utilization of the Bayesian theory in the pharmaceutical modeling. Currently, there are many theoretical papers but literature is void of practical papers of Bayesian modeling. Bayesian theory possesses some attributes such as the incorporation of uncertainty in the model, utilization of prior distribution and the ability to perform unbiased, with respect to the sample size, Markov Model Monte

Carlo simulations. Given this facts, Bayesian modeling constitutes as an exemplary platform for pharmacoeconomic evaluations.

1.4. Contribution to policy and practice

Currently, health agencies worldwide are under significant pressure by governments to restrain health expenditure. In this sense, a blunt reduction of health expenditure will compromise solidarity and equity which are the pillars of health care. Also, restraining access to expensive products is a long-standing practice which does not reduce health expenditure: it shifts costs to a later and costlier stage, "the hidden costs" practice (Zweifel & Manning, 2000; Gold, Siege, Russell & Weinstein, 1996). Thus, the introduction of pharmacoeconomic modeling based on evidence synthesis can significantly contribute to a better resource allocation in the sense of excluding or including pharmaceuticals in the formulary, prioritization of health needs, better forecasting and elaboration of clinical guidelines based on evidence based medicine. This will generate more general benefits for the health care sector in Cyprus by providing the basis for standardized health care, thus avoiding outliers and inefficient practices. The ultimate contribution is the improvement in public health care across country, through enhancement of an efficient allocating procedure of health resources. It is anticipated that the introduction of cost-effectiveness analysis and the proposal of a robust and substantiated methodological framework will accelerate dissemination of evidence-based medicine. This will increase the engagement between industry and payer by capitalizing on meaningful endpoints. Moreover, in the operational framework of health care sector, it is expected that a decision-analytic model can be established as a mainstay for policy-makers in the resource allocating process.

Since pharmaceutical markets are closely interrelated on a European level, it is expected that this thesis will contribute to the European level as well. Although the transferability of pharmacoeconomic data among different health system is occasionally problematic, in general it can be used as a hypothesis-generating approach and as a proxy as well. We must also underline that the economic evaluation of pharmaceuticals is spelled out as a prerequisite in the Memorandum of understanding (MoU), which was contracted between the Cyprus Government, European Commission, European Central Bank and International Monetary Fund. In this context, disbursement of financial installment will depend on the ability of Government to proceed and elaborate a coherent framework for the assessment and the economic evaluation of pharmaceuticals. Finally, the incorporation

of economic evaluation of pharmaceutical in the health policy of Ministry of Health was also raised by the internal audit department of Cyprus Republic (2011).

1.5. Organisation of the Study

Currently the study comprises of five chapters. The first chapter deals with the introduction, the statement of the research questions, the purpose of the research, and its contribution to policy and theory.

The second chapter covers the literature review. More specifically, it goes through the various aspects of Health Technology Assessment, presents and discusses the pillars of pharmacoeconomic evaluation. An extensive literature review was carried out in order to identify all relevant data of economic evaluation through Bayesian methodology.

Third chapter focuses on methodology. In particular, third chapter presents the decomposition study which precedes the Markov Model used for the economic evaluation. Based on the decomposition study, we selected one product, for which the economic evaluation occurred. The product was selected on grounds of budget impact, medical needs and projected sales forecast, for a specific health condition. The methodology part focuses on the analysis, which is a stochastic model employed to model changing systems. More specifically, Markov Model simulates disease progression among possible states of a disease, based on transition probabilities and calculates health gains and costs incurred. In this context, a literature review was performed, in order to define transition probabilities between health stages of selected health condition. The results are presented in the fourth chapter and the discussion in the fifth chapter. The current thesis explores and assesses the several technical parameters of economics evaluation, in the context of Bayesian framework, namely inference, informative distribution and uncertainty. Finally, it assesses innovative pricing schemes, which incorporate the value of the product, in the final procurement price.

1.6. Limitations of the study

This study aspires to explore Health technology assessment and cost-effectiveness analysis context in Cyprus; propose a conceptual and technical framework through the introduction of innovative pharmacoeconomic modeling and elaborate pioneering approaches in pricing of pharmaceuticals through incorporation of value, as defined through health technology

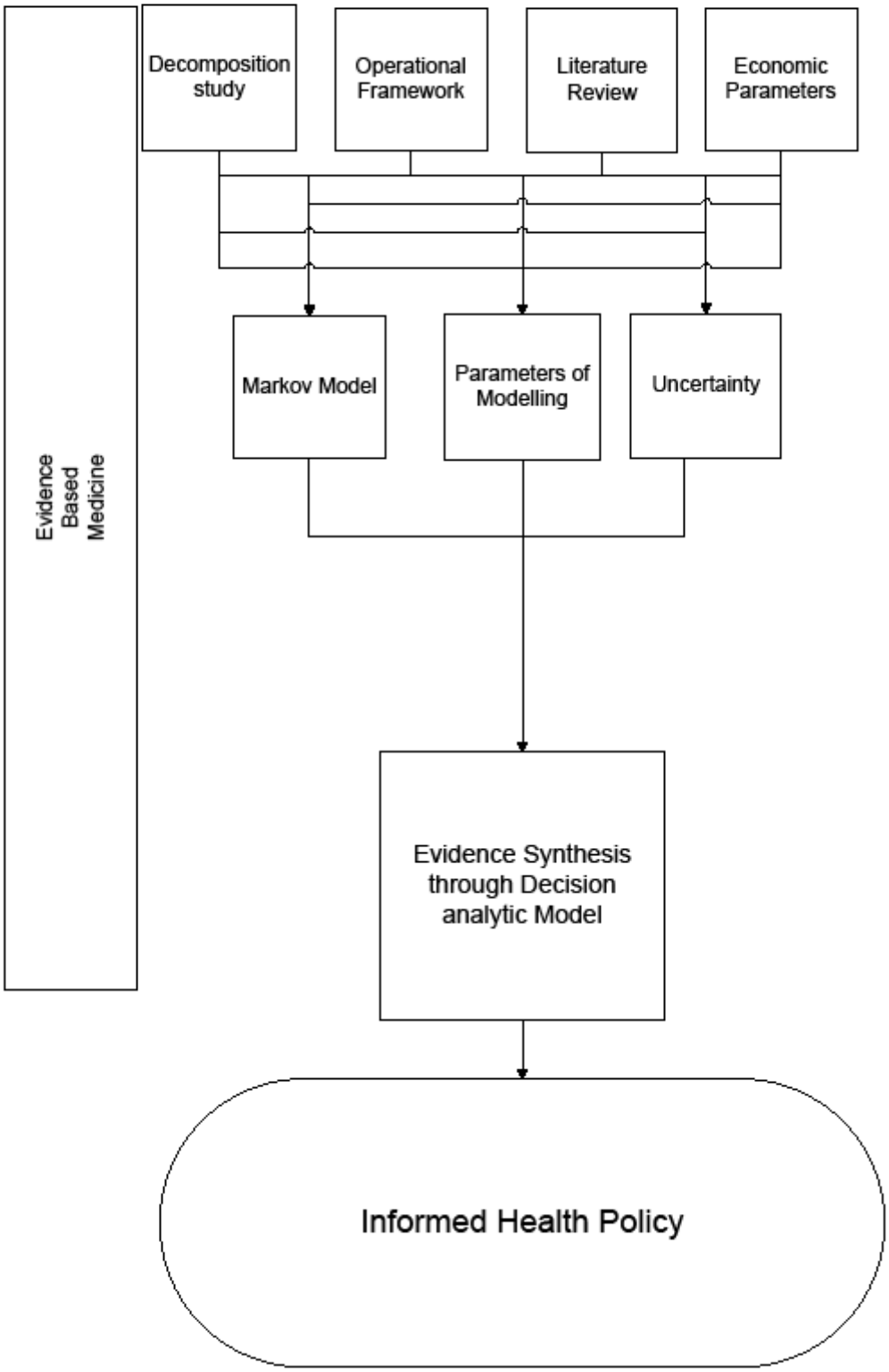
assessment in the price of the product. Modeling constitutes the pillar and the core of this study. As a result, current study is facing some limitations which are as following:

1. Extrapolation of the data beyond the duration of the study. As clinical trials last for a limited and predefined period of time, certain endpoints may as well occur beyond the imposed time limits. As a result, extrapolation of data to capture long term safety and efficacy of a given treatment entails the hazard of obtaining biased data.
2. Validity of the model. Quite often, modeling is described as a "black box", due to limited transparency of its operational framework. Although the same can be said for Randomized controlled trials, this perception is further magnified for modeling. Consequently, it's vital to validate the model, in order to minimize errors, bias, flaws and manipulation of data.
3. Inappropriate use of clinical data. The principal investigator of a specific data has the discretion to pick endpoints, on the grounds of the research questions that were raised, prior to the kick-off of the RCT. Also, incorporation or not of other factor such as drop-out rate, intention-to-treat, may constitute a decisive factor since it may substantially influence final outcomes.

Much effort has been devoted to eliminate or minimise the aforementioned issues.

Table 1

Theoretical Framework



2. REVIEW OF THE LITERATURE

2.1. Pharmaceutical Market

The Pharmaceutical Market is a highly regulated market and in this context, several divergent, overlapping and even conflicting objectives of all involved stakeholders must be integrated in the related pharmaceutical policy (Mossialos, Walley & Mrazek, 2004). Health agencies must ensure that patients will get access to safe and effective pharmaceutical products and, at the same time, the pharmaceutical industry is granted with fair prices. This, in return, will sustain the continuous research and development projects of the industry, aiming to satisfy unmet medical needs, especially in sub-treated, or non-treated at all, therapeutic areas. All the above must be achieved within the boundaries of a constrained pharmaceutical budget.

From an economic standpoint, the pharmaceutical market is a unique and unparalleled market, in the sense that it demonstrates a consistent and impeccable financial growth (Dubois et al., 2000; OECD, 2012). Pharmaceutical expenditures, on a global scale, are rising beyond the increase of productivity and they are stretching health systems beyond their viability. Currently, pharmaceutical expenditure constitute the fastest increasing sector of total health expenditure, being just second to personnel expenses, in term of recurrent costs (Mossialos, Walley & Mrazek, 2004). As an illustration, in 2014, total pharmaceutical expenditure worldwide reached 1.1 trillion USD dollars (IMS Report, 2014) depicting a robust growth, which is becoming more venerable shall we consider the loss of patent exclusivities and some prominent withdrawals of blockbuster products, due to safety reasons (FDA, 2011).

During the successive financial recessions worldwide, the pharmaceutical sector was proved to be a recession-proof one (Laing & Busse, 2012), substantiating the inelasticity of pharmaceuticals as commodity products (Friedman, 1991). The latter was also debated since some authors argue that access to medicines is a right, since this directly intertwines with the integrity of patients (Trebilcock, 1993). The consistent increase of the pharmaceutical expenditure is attributed to the following reasons:

1. An aging population with longer life expectancy which leads to consequential increase of prevalence of conditions related to ageing populations such as type two diabetes mellitus, osteoarthritis and osteoporosis (Maynard & McDaid, 2003).

2. The introduction of advanced diagnostic procedures enhances the earlier and better detection of diseases (Dubois et al., 2000).
3. The rising number of new medicines with high costs (Lu & Comanor, 1998; Abboud et al., 2013) and increased level of uncertainty regarding outcomes and benefit to public health equilibrium (Light, 2010).
4. Genuine innovation is becoming even rarer (Meyer, 2011; Gridchyna et al., 2012; Walker et al., 2009). Indicatively, only 18% of new products as assessed by Haute Authorité de Santé (HAS SANTE-French Health Authorities, 2008) offer medical benefit above moderate level while at the same time, the prices of new medicines are higher even compared to equal older products (Lu & Comanor, 1998).
5. The increase of treatment periods such as in the case of maintenance treatment of depression.
6. The aggressive pharmaceutical marketing (Rhee, 2008).
7. The introduction of new agents which target untreated or sub-treated patients.
8. Inflation which leads to price increase.

The pharmaceutical market is inherently flawed and it displays some distinctive entrenched characteristics, which explicate its failure to meet the criteria for a perfect market (Fuchs, 1998; Roemer, 1961). A competitive market assumes that both sellers and buyers have thorough and technical acquaintance with all essential information and can get access to it. Additionally, both of them are price takers and they are mutually aware of all costs incurred (Rice, 1998). The pharmaceutical market hardly fulfils even one of the above and, consequently, it has to be regulated since the efficient allocation of resources cannot be entrusted to the non-existent market forces (Fuchs, 1998). Pharmaceutical products are best defined as heterogeneous, non-traceable commodities (Fuchs & Zeckhauser, 1987), although several authors object because health is closely interrelated to the integrity of people and as such, the access to pharmaceutical products can be defined as a right (Trebilcock, 1993) and the demand for them is highly unpredictable and irregular. Pharmaceutical products are also social goods, in the sense that the lack of access of an individual to the proper treatment, can negatively affect others, as in the case of an infectious diseases breakout. Medical care is produced and consumed at the same time and is predominantly a personal service, in which physicians are not considered as perfect substitutes (McGuire 2000). Moreover, the pharmaceutical market is an oligopolistic or a monopolistic competitive one (Dranove, 1988), an attribute which further shifts the

bargaining power to the physician's side, as attested by the downward-sloping of their cost curve (Escarce & Pauly, 1998). Its most prevalent and ubiquitous trait is the asymmetry of information, rooted in and derived by the complexity of information, which cannot be easily comprehended by the patient; therefore the patient is considered to be the weak partner (McGuire, 1990). This asymmetry of information emerges when imperfect information on the demand side includes gaps pertinent to the:

1. Current health state/diagnosis.
2. Prognosis.
3. Available interventions.
4. Effectiveness/side-effects of interventions.
5. Cost of interventions.
6. Translation of effectiveness into utility.

The patient's cost of gaining the adequate and clinically meaningful information is substantially high, given that health conditions do not repeat with the same pattern in the same person, or do not follow the same trajectory across individuals. To illustrate this, 75% of all health care users are infrequent ones and in most cases they cannot observe output or input in their condition, a feature which further downgrades their status in the principal-agent relationship (Pauly, 1978). Health is also unpredictable and 75% of medicine users, apart from being infrequent ones-as described earlier-they also use pharmaceuticals inconsistently. Another significant trait of this market is the fact that the patients cannot test a product prior to its usage. In contrast to other markets, wrong decisions in health are usually costlier, predominantly irreversible, and may increase morbidity, and in some cases mortality (Peacock & Richardson, 2007). All aforesaid findings constitute the clinical uncertainty, which is further comprised by the evidence gap and the lack of practical guidelines providing guidance to physicians, a widespread observation that rises up to 85% of all health conditions (DHAC). As a result, patients rely heavily to their physician to span this information gap (McGuire, 1991; Paris et al., 2010). This model perceives the physician as a utility maximising agent on behalf of the patients, who posses imperfect, flawed and fallacious information for their condition. This is imputed to the perceived combination of the physicians' knowledge with the patients' preferences to conclude a choice, that the patients would have reached had they been equally informed. Ultimately, patients' sovereignty diminishes, a development which

disengages supply from demand. These findings establish the physicians' dominance in the health care market since they can exercise power, to an unprecedented level, compared to sellers in other markets, and they are not harnessed by the patient. Accordingly, the abovementioned reasons constitute peremptory reasons for the regulation of pharmaceutical pricing.

Several issues surfaced, which have provoked debates regarding what should the agent maximise in terms of patient's health status, compared to the societal health. The agency relationship is also sustained by the asymmetrical ability and willingness of physician to exercise judgment in the face of uncertainty. All foresaid topics lead to the supplier induced demand: a term which was first introduced by Newshouse in the 70s who claimed that physicians could simply artificially create their market by inducing demand, through utilising their asymmetrical, information-derived, power over patients (Moshialos et al., 2004). The supplier induced demand (SID) can be defined as the connotation of manipulating patients aiming to artificially increase the demand of health services. It is a multidimensional process and primarily it is ascribed to the financial incentives of the physician. Physicians exploited this as a counter-defensive mechanism, by inducement of supply in cases their reimbursement dropped. There is a voluminous literature for supplier induced demand, which is exacerbated in cases where demand of health services by the patients intertwines with the income of physician. For instance, in the USA, an offset increase in some ophthalmologists services was observed, when cataract fees were reduced (Jacobson, 2005).

The financing patterns of the health system influences SID and it was observed that the free selection of doctors and the use of fee-for-service, as a physician's reimbursement method, can induce SID (Bickerdyke et al., 2002). The SID is also attributed to several intrinsic factors, predominantly promotion of well-being of patients, personal reputation of doctors, defensive medicine, environmental influences (such as availability of health infrastructures), lack of understanding of impact of an intervention on patients, and even medical ethics. SID is corollary of the adoption of a disproportionate medical paternalistic approach, pertinent to the patients' welfare. In some cases, it is possible that the SID is caused by the lack of awareness of physicians of costs incurred to the system. In general, the SID drains on resources, without any commensurate improvement in outcomes.

That is to say, the clinical uncertainty on doctors decision-making process also interferes either in the form of the doctor capitalising on his/her superior knowledge, or in the notion of lack of clinical guidance, which culminates to the professional uncertainty

hypothesis (Wennberg et al., 1982). The caveat lies in that the fact that SID waives any incentives for efficiency improvement since any losses can be counterbalanced by a price increase, which distorts the Pareto efficiency outcome. In addition, the demand curves do not reflect the attained social benefits (López-Casasnovas & Puig-Junoy, 2000). The accumulation of significant bargaining power by the physicians, is a major determinant of their transformation from price-takers to price-makers, which unavoidably perpetuates to an allocatively inefficient outcome. Since the aforesaid issues are deep rooted and cannot be readily addressed, the introduction of adjuvant measures such as user charges, were applied in order to ultimately reach the goal of Pareto efficiency in health. In this notion, the co-payment constitutes a price signal which will help percolate needs and curb use of low value services.

The Pharmaceutical market is characterized by low price sensitivity, since in the majority of cases the products are reimbursed, fully or partly, by the payer. In contrast to popular perceptions, the pharmaceutical market is considered to be an oligopoly and monopoly market, even in therapeutic classes with many competitive products, owing to high barriers of entering the market (Dranove, 1988). The pharmaceutical sector demonstrates a unique 3-tier demand and supply structure, consisting of doctor, payer and patient. It is generally accepted that their interests diverge since doctors yearn for efficacy, patients desiderate safety and payer focus on cost approximations (Barber, 1995). The asymmetry of information between the three parts shifts market forces towards doctors. Therefore, the pharmaceutical market exhibits some unique attributes that make it difficult to comprehend and analyse. This impedes the identification of shifting of preference between comparative products for the same indication and affects the adoption rate of new innovative technologies. The competitive forces are frail in the pharmaceutical sector; consequently this constitutes an imperative need for imposing strict regulations.

2.2. The Cyprus Pharmaceutical Market

Cyprus features two fragmented pharmaceutical segments: the private and public sector, whose total value escalated up to 210 million euro in 2011, contributing just 0.1 % to the total EU pharmaceutical market (CB1, 2010; Petrou, 2011). The total pharmaceutical expenditure has been increasing at a steady rate over the recent years, displaying a 63% increase (nominal expenditure) within 8 years. In 2012, the total pharmaceutical expenditure rate declined (vs. previous year) and it was the first time such a sales decline

occurred in Cyprus. This was attributed to a significant reduction in the private sector's sales, indicating potential affordability issues, as an aftermath of the fiscal recession. In contrast, the public pharmaceutical expenditure still increased in 2012, a finding which was also observed in other recession countries, as more patients opted for free public health care (Laing & Buysse, 2010).

The most interesting characteristic of Cyprus is the lack of a universal coverage health system. The current health system lacks a universal coverage, in the sense of redistributing risk by cross-subsiding healthy to the ill and income by cross-subsidizing rich to poor, and is a residual of the British colonial health system. It provides health care to 85% of total population, based on certain socioeconomic eligibility criteria. Nevertheless, the eligibility criteria are rather biased, favouring some cohorts of the population, such as public servants, thus resulting in grossly uneven access to public health care. Hence, people disparage public health care sector (Andreou, Pashardes & Pashourtidou, 2010) (figure 2). The austerity measures, in the form of recruitment freeze which have resulted to excessive waiting times, delays in reimbursement and lack of some products, have furtheraggravated this perception (Petrou, 2011).

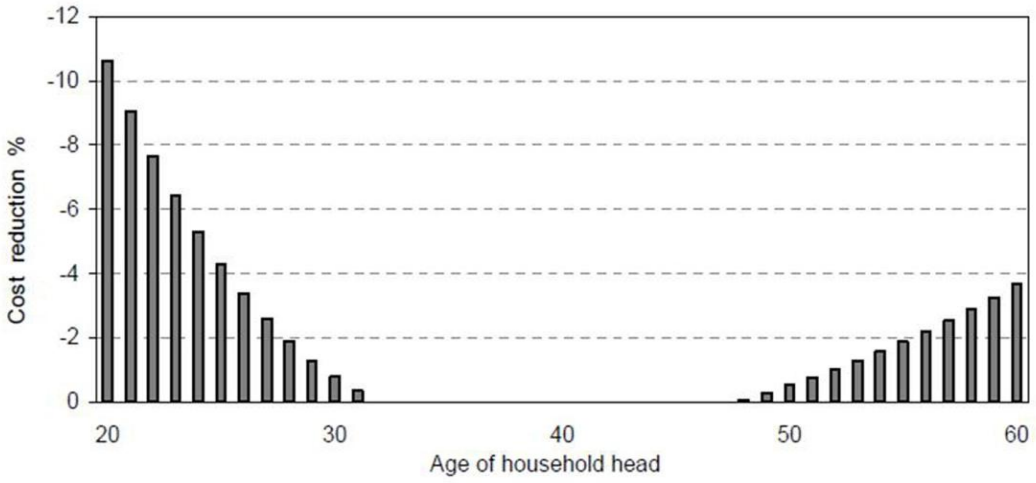
The product-mix composition varies across these two sectors. The public health care sector's cost-drivers segment consists of innovative, high-value and low-volume agents indicated mainly for oncology, rheumatoid arthritis and neurology. It also relies extensively on generics for primary care. The reimbursement of products in the public sector is a multitier and long process. A tender for acquisition of pharmaceuticals is released only after a positive assessment by a drug committee is confirmed. The tendering process, as a heavily regulated legal procedure, can also span more than 4 to 5 months. Having said that, private sector pharmacists are remunerated through a mark-up profit. Since profit is intertwined with the price of the product, generic penetration is low and cost-drivers of the private sector include new products mainly for primary care such as branded statins, proton pump inhibitors, angiotensin receptor blockers, antibiotics and products that address erectile dysfunction. The public pharmaceutical market can be considered as a volume-driven market, while the private sector is a price-driven one. Economic evaluation of pharmaceuticals, apart from some indicative reviews, has not been adopted mainly due to potency of tendering and to the fragmentation and diversity of private and public health care sectors, which hinders dissemination of policies. The lack of any economic evaluations also emanates from marginalization of the private sector, which can be attributed to:

1. The private sector costs incur to patients and not to the public expenditure. As a result, this may waive incentives for the government to actively pursue reforms.
2. The vast majority of private sector's patients are also entitled to free medical public care, to which they usually resort for expensive treatments.
3. As the National Health System, which will unite both sectors, is in implementation phase, any other measures are stagnant.

The marginalization of the private sector can also be confirmed by the lack of price update of catalogue for more than five years, while in other countries this is performed much more often, in often to align prices to the current socioeconomic environment. As a result, prices are significantly higher compared to countries with similar macroeconomic indicators. The efficiency of the pharmaceutical sector is directly correlated to the reduction of waste, in the form of dispense of medicines that do not add to the utility of the population, cost more compared to the alternative agents, or the dispensed quantities are not justified by the treatment pattern. The public health care sector has implemented several cost-containment measures, such as obligatory generic substitution, closed formulary, prescription guidelines and restriction access products, which have led to significant savings.

Figure 2

Estimated savings from free provided public health care services



Estimated Savings from free public health care by age per household member (as percentage of household income)

For beneficiaries to free public health care of the age group 30-50 there is " no perceptible benefit is realized from access to free of charge public medical care". This partly explains the fact that although 85 % of the total population are beneficiaries to fee medical care, Cyprus has one of the highest out of pocket contribution in EU, along with the higher prices of the private sector.

2.2.1. Pricing of Pharmaceuticals

Prior to 2004, Cyprus' maximum retail pharmaceutical prices were based on the ex-factory price of the origin country. This lacked any scientific rationale and clearly created incentives for marketing authorization holders (MAH) to supply products from expensive countries, in order to maximize their profit margins, because of the percentage system implemented. Consequently, Cyprus had considerably high prices, even compared with expensive countries such as Sweden and Denmark (Merkur & Moshialos, 2010). In 2005 a major reform took place and a new external price referencing scheme, which is very popular across the EU, was introduced. The reference price in Cyprus is determined as the average of the available prices in Austria, Sweden, France and Greece, plus three percent to cover importing costs, and a regressive pharmacist mark-up fee. The rationale behind the choice of the reference countries was to include one expensive, one cheap and two medium-price countries, in order to reflect an average EU price. Five alternative countries were also determined for use, when a product is not present in one or more of the reference countries (Denmark, Germany (high price), Italy, Belgium (average price), Spain, Portugal (low price). The private sector is regulated only at the price level (Petrou & Talias, 2013). Patients of private sector are burdened on out-of-pocket payment for the entire cost of their treatment unless they are covered by a voluntary private insurance. In August 2013, massive reforms in eligibility criteria for provision of public health care and amendments in health laws and regulations occurred after the bail-out agreement with Troika was reached. One significant policy is the introduction of co-payment for pharmaceuticals in the form of a fixed and capped amount of 0.5 euro per product dispensed, applicable only within public sector.

2.2.2. Procurement of Pharmaceuticals in Public Sector

The procurement of medicines in the context of tight health budgets, steadily increasing demand and introduction of expensive products has been a great challenge, aggravated by the number of stakeholders involved and the highly regulated environment (WHO, 1999; Kanavos, Seley & Vandoros, 2009)(table 2). An optimum drug procurement system is still an unmet need even among EU countries (Garattini, Cornago & Compadri, 2007; Kanavos et al, 2010) and a diverse spectrum of reimbursement and pricing policies were developed in order to bridge this gap (Leopold, Habl & Vogler, 2008).

In response to the abovementioned concerns, Cyprus Public sector has implemented tendering as its procurement scheme. This applies for all medicines, both for inpatient and outpatient use. Tendering is classified as an aggressive form of pricing and a cost-containment approach (Kannavos, Seeley & Vandoros, 2009). It is considered to be the mainstay for medicine procurement in the hospital sector across Europe. Interestingly, its adoption rate accelerated especially among bail-out countries such as Greece (Vandoros & Stargardt, 2013) which reported unprecedented savings for tendering in-hospital pharmaceuticals. This euphoria was not duplicated in the out-patient sector and only a few countries apply tendering for outpatient sector medicines, albeit confined to a small number of products' categories. Variable context specific tendering approaches have been applied to meet demands and needs of each country, either by granting full market exclusivity to the winner or by elaborating a preferential list, in which the prescribing of the winning product provides some incentives both to prescribers and patients, as in the case of Belgium, where the winner of the simvastatin tender was awarded a 75 % reimbursement rate in contrast to the 50% reimbursement rate of other simvastatins (Arickx et al., 2009). The Netherlands have introduced the preference policy, which provides the reimbursement of the cheapest product and all products that have a price in the range of 5%, with significant savings.

Despite its potent cost reduction ability through promoting competition, further dissemination of tendering in out-patient sector in Europe was hindered by legal issues, competition rights and lack of expertise (Simoens &Coster, 2006). Belgium experienced the reallocation of demand when patient switched from cheap generic simvastatin to branded atorvastatin and rosuvastatin. In addition to this, Belgium faced another hardship interweaved with the failure of the successful bidder to adequately provide the requested quantity, as in the case of amlodipine. This ensued to the termination of tendering. Moreover, despite short-term savings, a long-term decrease in pharmaceutical investments was observed in countries that applied tendering, such as Denmark, with consecutive negative consequences, including less taxes and unemployment increase (PWC, 2007; Dylst, Vulto & Simoens, 2011). Cyprus, being a small market, is not an ideal pharmaceutical one (CBI, 2010) and this could magnify the probability that companies would exist the local market on the grounds of an unsuccessful tender outcome, as observed in Denmark. This has to be closely monitored during current financial recession, especially for branded specialized products, that are not available in the private sector and public sector remains the only market access pathway.

Table 2

Important aspects of successful tendering

Potential Issues	Importance	Measures	Cyprus Approach
Selection of "either-or" (competitive products)	To provide adequate level of pharmaceutical care	Participation of experts in the decision process	Many subcommittees with expertise in certain therapeutic areas were formed
Legal issues	This may lead to an unacceptable delay of the provision of medicines	A thorough and detailed framework will minimize areas of controversy	Firmly Regulated framework in Cyprus
Significant price gap between competitors	No incentive for cheaper product to further lower price	Asking for utilities instead of quantities	Applied pivotally
1st category generic entrance	Doctors may switch to alternative branded products	Guidelines to monitor prescription and limit access to equivalent branded products in selected cases	Prescription guidelines rule these cases
Low efficacy of tender awarded product	This will increase risk for a big proportion of the whole population	Inclusion of the second cheaper product under a certain scheme such as co-payment or preapproval process	A co-payment scheme in cooperation with private pharmacies was introduced
Failure to provide agreed quantity	Public Health will face shortages	Implement guarantee process and sanctions	Law provides specific sanctions

The dominant position of payer may compromise competition and promote oligopoly, with subsequent supply chain irregularities (Carradinha, 2009). This is of particular importance, since generic industry in Cyprus is one of the local economy powerhouses and is the leading exporter force, accounting more than 129 million Euros in 2009 (MOC, 2011).

Lastly, the small size of Cyprus implies that the competitive market forces and the market characteristics cannot enhance competition, which could escalate to price reductions in a regulated market. Indicatively, bigger markets such as Germany and Denmark have reached steep reductions in generic prices through internal price referencing (Stargardt, 2011).

Another drawback of the tendering is the inclusion of only one product in the International Non-proprietary Name **(**INN) sole tender group. This implies that any potential therapeutic failure or impaired tolerance of patients to the reimbursed product, will lead to out-of-pocket payment for an alternative therapeutic option from the private sector, which will be procured in considerably higher prices. Ultimately, this will violate the fundamental principle of universal health care coverage.

It was discussed that legal proceedings hindered implementation of tendering in countries such as Germany and many cases resulted to challenge before the court of law, resulting to a, potentially grave, stagnation in provision of pharmaceuticals. In Cyprus, only a few cases resulted to court litigation. This was attributed to the accurate selection of agents based on Evidence Based Medicine, grant of costlier exemptions (such as branded deferoxamine), multidisciplinary composition of Drugs Committee and a detailed national and EU legal framework, actions that can proactively minimize this risk(EU Directive, 2004).

The legal issues raised were highly heterogenic and included:

1. Currency conversion (Before introduction of euro).
2. Marketing License (Whether a product carried a valid license).
3. Technical details of the tender.
4. Size of order (Competitor vs Government claiming that quantities asked in the tender for a competitive were significantly higher than actual needs and this would lead to induced demand).
5. Therapeutic equivalence between meropenem and imipenem + cilastatin (M.S.Iacovides Ltd vs Republic of Cyprus, 2004).
6. Generic desferoxamine versus branded (Pharmaceutical Trading Co. Ltd vs Republic of Cyprus, 2001). (Although generic product submitted a lower price, the tendering contract was awarded to the branded one due to the dominant scientific evidence that supported procurement of the branded).

The exposure of the majority of Cyprus population to a few or even a single product procured by tender system, urges that the consistent, adequate and sufficient supply of pharmaceuticals to the market has to be safeguarded. For instance, the generic losartan issue hit the headlines after serious, but as finally proved unsubstantiated, allegations regarding safety and efficacy were raised following the introduction of generic losartan as the sole Angiotensin Receptor Blocker (ARB) in the formulary (House of Parliament, 2012). This underlines the need to monitor adverse events especially during the switch period between 2 agents.

Drug shortage, caused by the slow process of tendering, was rare and did not pose a threat to public health. The proper planning and forecasting effectively copes with this concern. Under the anticipated National Health System there will be a unified pharmaceutical market, as opposed to the two parallel that exist today, and any shortages will be really intricate to address in a timely manner. However, it is acknowledged that tendering is a very slow process, can last up to six months and can be further exacerbated by legal actions (table 3).

Table 3

Advantages and disadvantages of tendering

Advantages of Tendering	Disadvantages of Tendering
It enhances competition between suppliers, therefore maximising return on investment (money spent)	Leading suppliers may not tender thus leading to supply of inferior products(Mainly in products massively promoted in private sector)
Equal treatment of all participants	Poor quality products(Partly applicable in pharmaceuticals due to heavily regulated environment)
Significant price reductions	Slow process
	Inability of successful bidder to fulfil the contract will create significant complications
	Massive switch of patients to another product in a short period of time
	Sustainability of Industry may be jeopardised

Table 4

Forms of tendering

Terms of Tendering	INN sole	INN group[1]	INN alternative
Key characteristic	Asking for only one pharmaceutical product. (i.e *bortezomib* for multiple myeloma)	Asking for several products with the same indication (e.g.anti TNF agents for RA) Classified protocol is elaborated based on the tender outcome (Cheapest product gets first line treatment, second cheapest product gets second line treatment) Currently infliximab is first line therapy, *adalimumab* second line and *etanercept* third line for Rheumatoid Arthritis	Asking for one product among several competitive ones. This also provides for therapeutic subcategories such as three categories for statins High Potency: *Atorvastatin or Rosuvastatin* Medium: *Lovastatin or Simvastatin* Low Potency*: Fluvastatin or Pravastatin.* Three categories for ARB Hypertension: *irbesartan* or *candesartan* or *valsartan* or *telmisartan* or *losartan* or *eprosartan* Hypertension and Diabetic Nephropathy as assessed by microalbuminuria: *Irbesartan* or *Losartan* Hypertension and Heart Failure As assessed by ejection fraction <35%, congestive heart failure, and ventricular systolic dysfunction: *Candesartan* or *Valsartan.*
Target group	Orphan, individualized (requiring therapeutic blood monitoring) innovative and highly specialized medicines	High drop-out rate and specialized medicines such as Anti TNF and aromatase inhibitors	Usually high volume primary care products which demonstrate class effect (statins, Proton Pump inhibitors, Angiotensin Receptor Blocker)
Indicatory Savings in 2007	Not assessed	957,600 euros for anti TNF products[2]	1,214,100 euros for statins;1,500,000 euros for ARB

[1] *In the INN groups all products are included in the formulary, in different treatment lines according to bidding price .In the INN alternative only the product with the lowest price is included in the formulary*

Thereof, the establishment of tendering as a long-term approach remains tentative for many countries. As a result, it comes to no surprise that among the European countries only Cyprus, Malta and Iceland apply tender as their primary medicine procurement method and so far, only scarce data exist for tendering in these countries. A tendering procedure begins only after a positive recommendation from a Health Technology Assessment is issued. According to the results of the assessment, a tender is released either by International Non proprietary Name (INN)(sole), INN group (preferential) or INN alternative (table 4) (MOH, 2007).The INN sole tender asks for only one product. The INN group tender asks for several products (usually more than three) and based on the outcome of the tender prices, a protocol is constructed. This implies that the cheapest product is set as the first line therapy, second cheapest as the second, given that the products are equivalent, such as anti-Tumor Necrosis Factors agents in Rheumatoid Arthritis. The INN alternative tender asks for only one product among several competitive, more than three and even up to six, as in the case of ARB for hypertension. Given these facts, one critical and decisive task is to preemptively define the competitive and equivalent products, a topic that can unravel into controversy, especially in cases where there is no established class effect (McAlister et al., 1999; Johnston, 2004). The Ministry of Health (MOH) is legally bound to buy the requested tender quantities at the bidding price and has also enforced a series of binding agreements as a defense line against unreliable bidders such as performance guarantee (10% of the total value). Any free of charge goods are accepted only if they are included in the requested quantity.

The call for tenders is published in the official journal of the Cyprus Government and all participants are informed of the outcome, supporting the magnitude of transparency as a fundamental pillar of the tendering process. The opacity in the tendering process may culminate to the elimination of a proper tender candidate as observed in other countries. In 2007, the Ministry of Health introduced several measures enabling the formation of a therapeutic algorithm based on the tender outcome. Therapeutic equal products compete and instead of eliminating the non-winners, they were designated as 2nd and 3rd line therapy respectively. This occurs in certain therapeutic categories for which there is enough documentation that tolerance to relevant medicines is limited and thereof, there is strong possibility that patients may need to switch treatment. The case of the anti-Tumor Necrosis

[2] *Total Pharmaceutical Expenditure of MOH was 84 million euro. Savings were estimated based on previous tenders that were asking for one product only (INN sole).*

Factor (TNF) was a landmark since the contribution of all stakeholders (MOH, physicians, patients) led to a mutual beneficial outcome and as a result, every year the list for anti-TNF agents has available slots. The major therapeutic categories that got into this scheme include aromatase inhibitors, adjuvant immunosuppressive treatment, such as mycophenolic acid, anti-depressants, antiepileptic agents and erythropoetins. Prior to the assessment, companies are allowed to provide further supporting materials regarding efficacy and estimated cost of their products, which further adds to the transparency of the process. Another concern of the Drug's Committee is the possible off-label use of expensive products, due to overuse of medicines in Cyprus as addressed earlier. This may lead to reduction of health benefit associated with the use of this product, owing to the embedded uncertainty pertinent to the off- label use. For that reason, risk of off-label use is counterbalanced by requirement of preapproval. This was the primary reason for the rejection of ranibizumab, despite the recommendations by NICE (NICE, 2008).

2.3. Health Technology Assessment

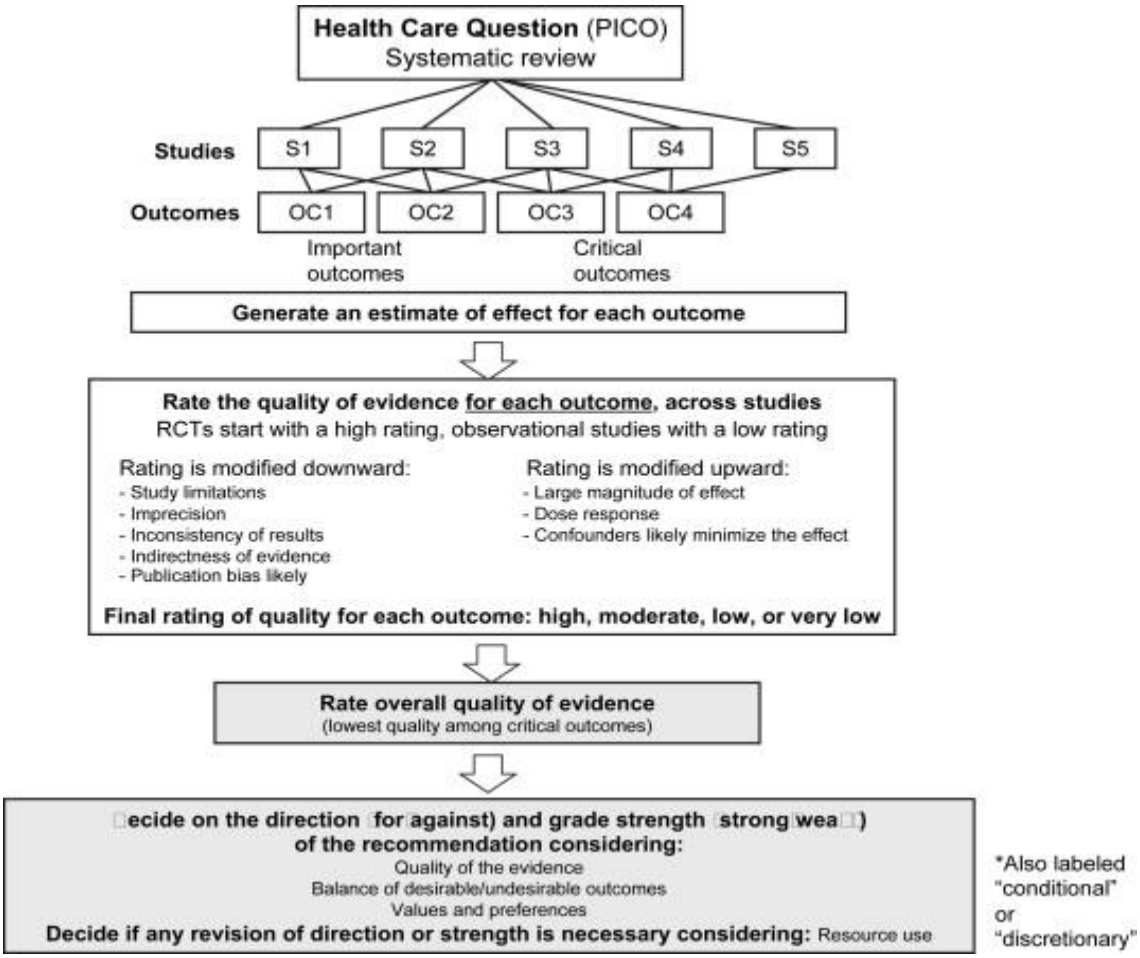
Health Technology Assessment (HTA) is the discipline which aspires to illuminate the medical, social, financial and ethical aspects of an intervention. It was first conceptualized in 1976 (OTA, 1976) and since its inception it has been positioned as the core of research of many authors (Kanavos & Vandegrift, 1997). Specifically, HTA addresses the questions raised by physicians, payers and regulating authorities concerning effectiveness, comparative effectiveness, safety and cost-effectiveness of a given product. These questions include (Battista, 1995; Velasco, 2010; Drummond, Kanavos & Sorenson 2008):

1. What are the indications (disease, health condition) of the health care intervention?
2. Does the health care intervention target a specific subgroup or stage of the disease?
3. Is there a clear and accepted definition (i.e. with a ICD code) of this disease?
4. What is the natural course of the disease and what are the consequences of it?
5. Are there any prognostic factors and/or any response factors as well indicators?
6. What is the prevalence, morbidity and mortality of this disease (expressed in life years lost (LYL), disability adjusted life years (DALY) and/or quality adjusted life years (QALY))?
7. What is the current treatment benchmark?
8. Has a treatment algorithm been elaborated?

All the above can be wrapped up in the PICO framework (figure 3). PICO stands for patient, intervention, comparison and outcome. It entails the most important parameters in the elaboration of a sound HTA.

Figure 3

PICO diagram



2.3.1. HTA in Cyprus

In Cyprus, the HTA was introduced in the term of references of the Drugs Committee, in the early 2000, as a paradigm shift to a rational, evidence-based and efficacy-oriented operation mode, aspiring to yield savings and harness the-largely uncontrolled-pharmaceutical expenditure (MoH, 2007). The Drugs Committee falls under MOH (Pharmaceutical Services). Notably, Cyprus was a late-comer in the field of HTA owing to

the effectiveness of tendering. More specifically, tendering ushered to short-term significantly low prices for the Public sector, thus distorting the need for a sustaining and rational decision-making process. At present, two fragmented systems run in a parallel, overlapping and competitive manner with clear disparities among them: the public and private sector. The MOH is the provider, regulator and payer of public sector beneficiaries. The public health care sector is highly centralized and the policy making process is done at the macro (Ministerial) level. There are two major categories of beneficiaries, pertinent to socioeconomic criteria such as income and employment status. It is essential to underline that 85% of the total population are entitled to free public medical care, without any direct or indirect contribution (as by July, 2013). As a result, moral hazard (Fuchs, 1988; Fuchs & Zeckhauser, 1987; Zweiffel & Manning, 2000) has been prominent in the public sector and in the pharmaceutical sector this it was expressed by overuse and misuse of medicines. In contrast, private sector's patients pay the full amount out-of-pocket, unless the patient is covered by an optional private insurance (Sachs, 2001). Health absorbs 6 % of the Gross Domestic Product (GDP) (Eurostat, 2011) which classifies Cyprus to the European low segment.

The rate of increase of Total Health Expenditure (THE) outpaces almost all other EU countries primarily on the grounds of (Samoutis & Paschalides, 2011; Antoniadou, 2005):

a. An aging population that has an increasing life expectancy, with concurrent increased morbidity.
b. Lack of prescribing control due to non existence of Interface management system which was launched in 2010, but still is not fully operational.
c. No direct contribution of beneficiaries-Exploitation of moral hazard.
d. Policy susceptible to Colloquial evidence especially regarding new expensive products.
e. Pharmaceuticals in the private sector are regulated only at price level.
f. There is a duplication of high cost hospital services in Cyprus, which have high running costs, but are not fully utilized.
g. The above remark is augmented by low value perceived by beneficiaries of the public sector. This was an undisputable finding of a recent study (Andreou, Pashardes & Pashourtidou, 2010) which examined the value for money regarding beneficiaries of Public Sector. Under the hypothesis that all health care systems want to gain more health for the same amount of money, the perceived value of the

Health system was assessed. The most important finding is presented in the figure 2 (p18).

h. Preventive programs are underfunded. Preventive programs apply usually to beneficiaries, while the financial burden of many diseases is entirely shifted to the MoH.
i. There are no quality indicators. As a result, MoH cannot assess any Health Policy, and consequently arbitrary decisions are taken regarding abortion or carry-over of them.

2.3.2. Goals of HTA

According to the terms of reference, the HTA should constantly upgrade, change and improve clinical guidelines. Currently, guidelines exist in the majority of therapeutic areas. In addition, it must define performance indicators and assess effectiveness of medicines along with limitation of the use of newly launched technologies to therapeutic areas for which there is sufficient documentation of efficacy and safety. Terms of reference also include the re-evaluation of high expenditure monopoly medicines which contribute disproportionately to the overall cost. Finally, it categorizes evidence deficit in areas where certain technologies are destined and ways to fill this along with disinvestment decisions. (Difficult to promote since low price of obsolete products manipulates authorities) (Petrou, 2011; MoH, 2006).

2.3.3. Criteria for inclusion of a medicine in the formulary-is HTA fitting in the picture?

The Drugs' Committee decides upon reimbursement of a product and its consequent inclusion in the formulary. Committee assess drug request based on five main pillars:

1. Prevalence and epidemiology of the disease (Prioritization of resource allocation).
2. Comparative effectiveness according to common practice.
3. Economic evaluation, primarily Budget Impact Analysis and to a lesser degree substantial cost-effectiveness studies (no inclusion of indirect data).
4. Appraisal of medicine by other HTA agencies (NICE).
5. Existing competitive medicines in the formulary (table 5).

The breadth and the quality of data is assessed. As in other small countries, the goal is to foster best practices instead of developing ones. As assessment of pharmaceuticals is a context- free and context-sensitive issues (Goeree et al., 2011) several caveats lurk in the transferability of data, which may be flawed owing to:

a. Demographic Heterogeneity.
b. Costs. Difference in pricing, reimbursement rates and between negotiating power of health prices will lead to cost divergence between countries.
c. Health care practices/ Different efficiency factor between health systems.
d. Cultural differences and social values between different populations (Velasco et al., 2010).

The Drugs Committee assesses medicines based on several indicators. These include cost per QALY, LYG, progression free and overall survival, and disease specific measures such as Psoriasis Area Severity Index (PASI) and American College of Radiology (ACR). Number needed to Treat (NNT) approach was implemented in the assessment of smoking cessation products. This is also implemented for competitive medicines which have significant price difference (e.g. different ATC 3 categories) and tender solely based on price, will have virtually no effect.

HTA implementation has not always been very successful in broadening the health scope and in certain cases overlooked one intrinsic factor, interrelation to Health Policy (Drummond & Kanavos, 2008). MOH implemented a public campaign to create awareness among public for the prevention of cervix cancer, however the only available vaccine was not approved by Drug's Committee. Moreover, as the complexity factor of the therapeutic regime increases, such as in the immunosuppressive ones, the assessment of m-TOR inhibitors was lengthy and both Marketing Authorization Holders strongly objected to the outcome.

Table 5

Criteria for HTA

Criteria	Importance	Comments
Disease Prevalence	Major	Easy to assess
Guidelines of NICE	Major	Transferability of data has to be checked for major divergences.
Efficacy Data	Major	Clinical effectiveness must be assessed
Budget Impact Analysis	Dominant	May conflict with cost-effectiveness approach
Off-label Use	Medium (unless specific trends documented)	Difficult to assess, may compromise actual medical need. Interface management will address this issue.
Cost- Effectiveness	Major (Difficult to apply a country specific study for each medicine)	A basic economic analysis is performed.
Impact on spending for other medical interventions	Medium	Incorporation of non pharmaceutical interventions Interface management may enable control. Difficult to assess

2.3.4. Prescription Guidelines and Preapprovals

The Drugs Committee has successfully implemented controlled prescription of certain medicines. The majority of its guidance specifies the definition of line of treatment for each product pertinent to patient profile, exceptions, and further requirements such as serum marker levels, expected duration of treatment and indication of medication failure. Statins were one of the most successful examples. The introduction of prescription guidelines for statins (including preapproval for high potency statins) concomitantly with the introduction of generic simvastatin, was successful in avoiding the 're-allocation of demand', as observed in Belgium (2007 to 2011: Consumption expressed in Defined Daily Dose: increased by 52%; Cost decreased by 48%).

Similar guidelines were elaborated for the prescription of all oncology medicines, insulin glargine, rosiglitazone, cinacalcet and darbeopetin alpha. For the majority of these products a preapproval is also necessary, usually with the obligation for submission of relevant laboratory documentation. The details of the patients are filed. Indication based guidelines were elaborated for the ARB. Different protocols were compiled for Hypertension, Congestive Heart Failure and Diabetic Nephropathy. In oncology medicines with significant uncertainty and high cost, on the grounds of lack of effectiveness data. Drug's Committee has adopted exceptions for compassionate use of cancer drugs in a small target group population in which benefits may not be sufficiently captured. Criteria are as following:

1. Patient´s life expectancy is less than 24 months.
2. There is sufficient data that the treatment will extend life at least for an additional 3 months compared to current treatment.
3. There is no alternative treatment with equal effectiveness available.
4. The target group is a small patients´ population (NICE, 2008).

2.3.5. Managed Entry Agreements in Cyprus

Risk sharing constitutes a new paradigm in adopting innovation in the pharmaceutical sector and it balances the interests of payers and industry (Espin, Rovira & García, 2009). Risk sharing schemes apply in case where the expected cost is significant or where uncertainly exists, contingent to the expected efficacy of the product and consequently to the net benefit of the company. In Cyprus, only price-volume agreements have been

scarcely applied, mainly due to human resources required for monitoring. Pemetrexed gained another indication of malignant pleural mesothelioma, in addition to the existing for NSCLC. By reason of the comparative effectiveness among all available treatments for NSCLC, an approach was set up which consisted of three scenarios. The prices incorporated expected efficacy of the product and the net benefit for the company. The addition of a new indication of Deferarisox and the increase of daily dose to 40 mg led to the dose capping agreement between Novartis and MOH. Based on this agreement, the MOH reimburses daily doses up to 30 mg (average 2160 per patient) while additional dosage burdens company. Company is obliged to provide free goods to MOH, based on the dose agreements. Currently, 38 patients are registered in this scheme which will last for 3 years, and data will be revised every six months to check for deviations.

2.3.6. Further Potentials for HTA in the New Financial Era

Cyprus has recently signed a Memorandum of Understanding with Troika (a term that is used to define the committee consisting of International Monetary Fund-IMF, European Union-EU and European Central Bank-ECB) in order to secure a life sustaining bail-out of 10 billion euro. As Troika's primary target is to enhance the efficiency of public governance, one important prerequisite for the Health Sector is the implementation of HTA for the 10 costlier pharmaceutical products. This provision will further leverage shift towards an integrated HTA system and several approaches are currently being considered, such as introduction of 2 HTA formats, according to the estimated Budget Impact (Light and full version), an approach currently implemented in many countries such as Netherlands (Stolk et al., 2009).

2.4. Evaluating health outcomes

The health related costs, both direct and indirect, can be measured. A hospital may easily assess all costs, but on the other hand it is really hard to assess health outcomes. The cost of an operation can be assessed but what about the outcome? Brazier (Brazier, 2007) underlines that health consequences are multidimensional, uncertain and disparate. Apart from the clear and undisputed biochemical results, such as serum creatinine, or white blood cells, there are many more dimensions that are deeply subjective and may not be repeatable or verifiable, such as social activities and ability to perform them.

Even the biochemical results may not lead to the same disease progress or recession, so there is a certain level of uncertainty. Likewise, the core of a health outcome is the ability to assess all aforementioned parameters. And just to make things worse, a response to an intervention is never taken for granted. If we consider that medical knowledge is limited, such as in rare diseases, sometimes conflicting, such as the use of erythropoetins (Bhatt, 2011) and occasionally even unexplainable as in the case of vitamins and cancer prevention (Klein et al., 2011), there is a high level of uncertainty rooted in the health outcomes. The real challenge of health economics is to minimize and transform all these data, including uncertainty, into robust data that will further shape the level of health care provided.

At this point, a measuring and valuing health framework must be distinctive. This is an area that has really sparked debate, due to perceptions towards what health really is and what is means to different individuals. A health economist must assess and express in money the value of an intervention to a patient, not the actual scope of the intervention. An effective intervention is assessed as such only if patients feel so. For instance, certain patients may appreciate a rather small, by medical standards, reduction in an annoying symptom, while they may disregard a significant improvement in an aspect which does not affect their daily activity. Because of the reason given, a short-sided patient may not appreciate a ground breaking and extremely precise LASIK operation for the reduction of short sight, especially if wearing glasses that fits their image. On the other hand, the same patient may find extremely helpful a 3 euro per vial over the counter preparation for dry eyes.

Another critical issue and a limitation as well is the inability to combine survival with other health status parameters (Newhouse & McClellan, 1998)**.** A lower survival rate study arm will possibly display a higher health status, simply because patients with lower health status passed away, as Brazier identifies.

2.5. Evidence-Based Medicine

Evidence-based medicine (EBM) is defined as "*the conscientious, explicit, and judicious use of the best evidence in making decisions about the care of individual patients" (*Sachett et al., 1996) Evidence Based medicine is not an intangible definition, but it is formatted by the accumulation of three skills as following (Mayer, 2004; Culyer, 2004; Walter et al., 2004; White, 2004).

Primarily it is imperative to have access to all available evidence and possess the ability to search medical literature *(Information Mastery).* Apart from merely having access, it is indispensable for a clinician to be able to search in an effective way. To this direction, the appraisal and interpretation of the data is of paramount importance (*Critical Appraisal).* Finally, all data must be transferable to the patient level and to the political decision-making level in a comprehensive, simple and explicable way *(Knowledge Translation).*

Other authors argue that Evidence-Based Medicine consists of four elements: Best evidence, Clinical situation, Patient Values and are bound together by Clinical Experience (Hoffmann, Bennett & Del Mar, 2010; Strauss et al., 2005). The pinnacle of evidence-based medicine are the randomised controlled trails, whose prominent features, such as the randomization and blinding process, the implementation of strict and specific inclusion criteria provide enough evidence that internal validity of the trial will be considerable (Sanson-Fisher et al., 2007).

All the aforementioned advantages are compromised by some limitations of a Randomised Controlled Trial (RCT). To begin with, cost is a significant factor which put off many researchers. Moreover, selection of competitor varies from country to country which ends up impairing data transfer across countries. In certain cases, several diagnostic tests are utilized which cannot be utilized in real life on grounds of cost, complexity or ethics issues. The duration of the study is still a major drawback and the use of placebo complicates further RCT. Finally, secondary factors, such as costs, are sometimes overlooked. The data of a RCT are defined as non-censored if the whole patient population was followed until the predefined duration of the trial or until death occurred. This occurs mainly in diseases which have a short term impact such as myocardial infarction or acute infections. Censored data, on the other hand, occur when patients are lost for follow up. This may involve administrative reasons (move to another area) or it may involve reasons related to the medical interventions such as intolerance of the active treatment. Different reasons for LTF (lost to follow up) constitute significant bias for the study.

Table 6
Centre of evidence based medicine-Levels of Evidence

Level	Therapy/ Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with > 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-value analyses ††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality	Retrospective cohort study or	Exploratory** cohort study	Retrospective cohort study, or poor follow-up	Analysis based on clinically

	RCT; e.g., <80% follow-up)	follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§§ only	with good††† reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases		sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on	Expert opinion without explicit critical	Expert opinion without explicit critical	Expert opinion without explicit critical appraisal, or based on physiology,	Expert opinion without explicit critical

	physiology, bench research or "first principles"	appraisal, or based on physiology, bench research or "first principles"	appraisal, or based on physiology, bench research or "first principles"	bench research or "first principles"	appraisal, or based on economic theory or "first principles"

Index

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.)
‡	See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
††	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
‡‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
†††	Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
††††	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1 - 5 years chronic)

(CEMB ,2009)

A critical step in the economic decision-making process is the selection of studies for the evidence synthesis part. It is imperative that high quality data are used, otherwise the risk of incorporation of bias and flaws in the model lurks. Consequently, all evidence must be summarized in a transparent and informative way, so that the quality of evidence is

clearly visible and it is rated consistently, systematically and unbiased. To this direction several tools have been introduced. The Center for evidence-based medicine has developed an algorithm that classifies scientific papers, with regards to the grade of evidence (CEBM, 2009). Systematic reviews and Randomized controlled Trials with narrow confidence interval provide the highest level of evidence and they yield applicable results (Table 6). The quality of each study is assessed on factors such as study design, consistency of the results and directness of the evidence. The overall quality of the evidence is pertinent to its potential effect by future data. In this sense, High quality evidence is defined as the body of evidence that further research is rather unlikely to change our confidence in the effect estimate and moderate quality evidence is defined as the body of evidence that further research is likely to have an important impact on our confidence in the estimate of effect and may change it. Lastly, low quality evidence is the body of evidence, for which our confidence in the estimate of effect is likely to change in view of further research.

2.6. Health Economics Evaluation

Definitely, Health is considered to be priceless. However, this infinity does not apply to the resources necessary to promote, maintain and enhance health. Consequently, health economic evaluations are used to create normative recommendations for the most efficient use and allocation of health resources, aiming to maximize the utility for the society. Fuschs (1998) identified 3 major economic points of view regarding health economics, which convey the need for implementation and dissemination of health economics:

a. Resources are scarce compared to actual human needs.
b. Resources have alternate uses. On a governmental and regulatory level, health has to compete with sectors such as Public Works, Education, Police, Defense and National Security, in order to attract as more funds as possible.
c. There is a varying degree of importance to what people need. Although health is considered to be to the top of the list, we generally make choices that clearly prioritize other needs over health.

Additionally, economic evaluation on a technical level, aims to define how to provide health care and how to minimize input for a given output (cost-minimization). On an

allocation level, economic evaluation elucidates what section of health care to fund and how to maximise output for a given input.

There are several reasons that explain the steady increase of health expenses. Introduction of newer and more expensive medical interventions poses a significant financial burden on the health systems. For instance, the monoclonal antibodies, due to their high specificity and selectivity are far more expensive compared to the standard therapy. In addition to this, Health Systems will have to accommodate an aging society. Life expectancy is keep rising, simultaneously with increased morbidity. At the beginning of the previous century there were 10 children for every person older than 65. In the 60's the ratio was 4 to 1 and in the 90's it plummeted to 2 to 1. The ratio is keep falling and it is not foreseen that there will be any reverse in this trend. It is estimated that every person older than 65 will cost to the Health provider 200,000 USD across his lifespan, according to Fuschs. At a percentage approach, elderly people consume around forty percent of all health care funds. At the same time, pensioners contribute less money to the Health funds owing to the progressive contribution system. Wrapping it up, more people live longer and cost more in order to sustain longevity.

Some authors argue that this is just the one side of the problem. William Baumol in 2012 used the term "Baumol or cost disease" in order to address his remarks. The cost disease refers to the faster increase of prices of healthcare inputs compared to other sectors of economy. As a result, the productivity growth in other economic sectors outpaces the corresponding input. For instance, the innovation in industry and manufacture, which is translated into standardization and automation, implies that less workforce will be needed to produce even more goods, ultimately reducing relevant costs. Standardization and automation are rather illusive goals in the healthcare setting, while concomitantly they are redundant features, very much alike in the niche of handmade cars, or exclusive gastronomy. Baumol classified industries according to their productivity compared to average in 2 categories: superior and inferior to average. He also mentioned that usually there is no transition among these categories, so the same industries linger in the same category. The inferior sector is also called stagnant sector and the integrated industries have a distinct characteristic: they need considerable amounts of labor which cannot be substituted by technology. These sectors are healthcare, education and even arts.

In a superior than average performing industry, we assume that an increase in productivity will lead to a corresponding increase of the wages, since the price of the produced item will remain the same. In certain non-stagnant sectors, such as the agriculture

sector, productivity increase (should) lead to increases in wages. In the stagnant sector, wages typically will tend to keep up with increases in other sector. However, if the productivity is less than wage increase, two options lay ahead: Price increase or decrease in profits. The former applies to the healthcare sector, because is a labor demanding sector. If economy stalls, it is certain that the corresponding increases in health care will freeze as well. If we compare the two sectors, stagnant and non-stagnant, one striking feature of the non-stagnant market is the steadily increasing affordability of the new products. Increased productivity increases Gross Domestic Product (GDP) and individual's purchase power. This leaves space for stagnant market to gain bigger market share. Appleby forecasted that by 2062, healthcare spending will represent up to 17% of GDP (UK), compared to just over 6% today (figure 4). At the same time, GDP will be 3 times higher, compared to current levels (Appleby, 2012). These carry some certain implications. Primarily, the poor will be affected. Furthermore, cost control in health, in conjunction with the above will probably lead to lower wages, or lower quality.

All the above, urge health economists to allocate resources across therapeutic domains, relying on specific, reliable, measurable and repeatable criteria. Walker (2001) promulgated four reasons why cost analyses are imperative in the Medical Decision Process:

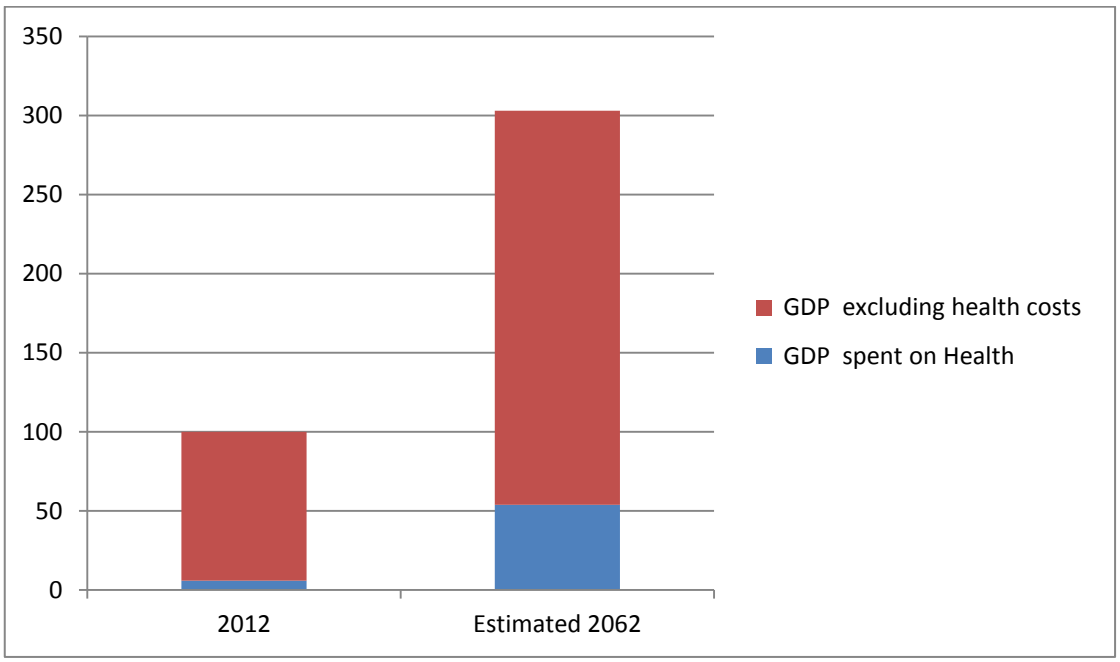
1. Cost monitoring will improve budgeting.
2. Identification of cost savings by improving efficiency of interventions.
3. Cost analysis gives a clear estimation of necessary resources to maintain a specific intervention. This is crucial In Health Systems such as in Italy and France, where a global budget (a budget with a hard cap that cannot be exceeded) is implemented in Public Medicine Expenditure.
4. It gives an inference of resources that are required in order to extend availability of a given intervention.

Health economics and cost-effectiveness studies are destined to assist all Regulatory Bodies to designate the intervention that will maximize the value of the money spent. Overall, the scope of health economics is to support the elaboration of equitable and efficient decisions. Equity is a fundamental pillar in health and it encompasses both timely access and continuity of care. It also safeguards that no other parameters, apart from patient's health needs, intrude in the provision of the necessary and indicated healthcare.

Currently, an increasing number of countries require the submission of cost-effectiveness studies as a prerequisite for the inclusion of a medicinal product in a formulary.

Figure 4

Health Expenditure and Gross Domestic Product



The economic evaluation of pharmaceuticals aims to:

a. Identify the optimum option among a number of options.
b. Better resource allocation among beneficiaries.
c. Save money (if feasible) (Mc Ghan, Rowland & Bootman, 1978).

A question frequently raised is why medical activity and drug prices need to be regulated. In the healthcare sector, the pharmaceutical prices are usually inflexible compared to other fields. They do not fall when there are changes in demand or production expenses and they are also inelastic to fiscal variations. This advocates Fuchs comment that "*market should not determine life or death"*. A prerequisite for economic evaluations is to get access to the high-grade of evidence data, a topic which is further commented on chapter 2.6.2

Economic evaluation carries some inherent limitations. Cost data are usually skewed (Baio, 2012). This means that distribution lacks normality and a significant proportion of

cost incurs to a small number of patients. Missing data is a common feature and obstacle in economic evaluations.

2.6.1. Effectiveness- Efficacy

Currently, Randomized Controlled Trials have been established as the gold standard and the mainstay in assessing the therapeutic effect of an intervention. There are several factors that contribute to the validity of a Randomized Control Trial, such as patients' profile, drug regimens and soft or hard clinical endpoints. A study designed to evaluate a hard clinical endpoint (i.e. reduction in MI or stroke) by reducing blood pressure is definitely more respected and more commonly cited, compared to a study which assess blood pressure reduction, that is a risk-factor for hard clinical endpoint. The former are even called "*landmark studies*" which emphasizes their legitimacy in the vast continuum of clinical trials. The 4S study is truly an icon in the field of statins, since it demonstrated, beyond any doubt, the beneficial effects of simvastatin in survival (Pedersen et al., 1994).

In addition to the above, the design of the trial may influence the generalizability of the trial. The eligibility criteria and the duration of the study comprise some of the design aspects of a trial that may (or may not) add credibility and convince policymakers that results may be extrapolated to the "real world" setting. A prominent example was the One million women study. This study was designed to evaluate the effect of the Hormone replacement therapy (HRT) on breast cancer, cardiovascular risk and deep venous thrombosis in women (Veral et al., 2003). Although the duration of the study was satisfactory, the age of women enrolled in the study raised criticism by many gynecologists who underscored that in the "real world", women at age of 60 are unlikely to experience menopause symptoms and, subsequently, ask for HRT. To sum up the foregoing, although the results were not disputed, the applicability was blatantly questioned. This applies to several studies performed in different patient's categories with different genotypes of infections. Hepatitis B field raised several concerns because the majority of studies took place in China and Mongolia, where the dominant form of infection is antigen negative. The results of telvibudine were satisfactory, but researchers cannot extrapolate these data to Europe, were the prevailing antigen is positive.

At this point, a line must be drawn to highlight the fundamental difference between *Efficacy* and *Effectiveness. Efficacy and effectiveness* are not the same variables, although are regularly perceived as such. Efficacy trials are designed and implemented under perfect conditions. Gross et al., (2002) stated that as many as 68 patients may be scanned in order

to recruit one single patient. Efficacy trials exhibit a high level of rigid criteria, and parameters such as concurrent medications and co-morbidity can be justified reasons for the patient to be excluded from the trial. On the contrary, Effectiveness trials are employed in real life conditions and are identical to what somebody would expect from the intervention in this average daily medical activity. Consequently, Effectiveness trials have less strict eligibility criteria. Clinical trials assess three types of outcomes: objective, subjective and health related. Effectiveness is usually measured by three measures: probability of surviving, mean survival time and mean quality adjusted survival time. Measuring the quality of life can be a very ambiguous task. Several tests have been developed in order to assist researchers assess quality of life. Some researchers raised the issue of negative quality of life. Admittedly there are some diseases, for which life sustaining interventions may lead to worse than dead QALY.

2.6.2. Grading Systems for Cost-Effectiveness Studies

Cost-effectiveness analyses comprise a significant tool in the allocation of constrained resources in health. In several countries, cost-effectiveness analyses are incorporated in the health policy decision-making process. Although this is not the case in Cyprus, we anticipate that due to MoU and the forthcoming introduction of NHS, Cyprus will follow in the steps of other countries, which rely heavily on economic evaluation. As a result, the quality of performance and reporting in health economic evaluation are in the spotlight. Many generic and disease-specific guidelines, checklists and recommendations have been published aiming to regulate this field. One of the most coherent, documented and substantiated is the grading system endorsed by Chiou et al., in 2003 (table 7). The differentiating factor of this grading system lies to the inclusion of a weight factor to each proposed criteria. Consequently, by assigning differing values as weights, this conveys the comparatively increased or reduced significance of the given criteria. The foreseen benefit is that differing weights demonstrate more discriminative power than equal ones.

Sound economic evaluations are founded on available data which are the core of this process. Specifically, the quality of data, either in the form of meta-analysis or data-synthesis, is major determinant and it preconceives the robustness of the economic evaluation and its ensuing value in the highly competitive resource allocation process. RCT are designed on regulatory approval grounds and can be of limited value in an economic evaluation since their duration is too small, the selection of competitors may not reflect current medical practice, while reported endpoints may not clinically relevant.

Table 7

Grading Systems for cost-effectiveness studies

Criteria
Was the study objective presented in a clear, specific and measurable manner?
Were the perspective of the analysis and reasons for its selection stated?
Were variable estimated used in the analysis from the best available source(i.e. RCT- best expert opinion- worst)
Was uncertainty handled by 1) statistical analysis to address random events? 2) sensitivity analysis to cover a range of assumptions?
Was incremental analysis performed between alternatives for resources and costs?
Was the methodology for data abstraction (including value health states and other benefits) stated?
Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that beyond1 year discounted (3-5%) and justification given for the discount rate?
Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?
Were the primary outcome measure for the economic evaluation clearly stated and were the major short term, long term, and negative outcomes included?
Were the health outcomes measures/ scales valid and reliable? If previously tested valid and reliable measure were not available ,was justification given for the measures/ scales used?
Were the economic model(including structure)study methods and analysis, and the components of the numerator and denominator displayed in a clear transparent manner?
Were the choice of economic model, main assumptions and limitations of the study stated and justified?
Did the authors explicitly discuss direction and magnitude of potential biases?
Were the conclusions/ recommendations of the study justified and based on the study results?
Was there a statement disclosing the source of funding for the study?

Chiou et al., 2003

Table 8

CHEERS Guidelines

ITEM	RECOMMENDATION
1	Identify the study as an economic evaluation, or use more specific terms such as "cost-effectiveness analysis" and describe the interventions compared
2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base-case and uncertainty analyses), and conclusions.
3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.
4	Describe characteristics of the base-case population and subgroups analyzed including why they were chosen.
5	State relevant aspects of the system (s) in which the decision (s) need (s) to be made
6	Describe the perspective of the study and relate this to the costs being evaluated
7	Describe the interventions or strategies being compared and state why they were chosen
8	State the time horizon (s) over which costs and consequences are being evaluated and say why appropriate
9	Report the choice of discount rate (s) used for costs and outcomes and say why appropriate.
10	Describe what outcomes were used as the measure (s) of benefit in the evaluation and their relevance for the type of analysis performed
11	Single study–based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data
12	Synthesis-based estimates: Describe fully the methods used for the identification of included studies and synthesis of clinical effectiveness data.
13	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base

	and the exchange rate
15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.
16	Describe all structural or other assumptions underpinning the decision-analytical model.
17	Describe all analytical methods supporting the evaluation
18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended
19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.
20	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.
21	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge

Therefore, the evidence synthesis has been developed with the goal to provide timely approximations by synthesising data from multiple resources in a policy relevant and specific context (Buxton et al., 1997). In the economic evaluation, much attention is given to consolidation of current guidelines and their update. In this context, the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) constitute a framework into transferring guidelines into useful reporting guidance (Drummond et al., 2013) (table 8).

To that end, Drummond identified ten parameters which are very important in economic evaluations and they cover the whole spectrum of a complete and thorough evaluation:

1. Was a well-defined question posed in answerable form?
2. Was a comprehensive description of alternatives given?
3. Was there evidence that effectiveness had been established?
4. Were all the important and relevant costs and consequences for each alternative identified?

5. Were costs and consequences measured accurately/appropriately?
6. Were costs and consequences valued credibly?
7. Were costs and consequences adjusted for differential timing?
8. Was an incremental analysis performed?
9. Was allowance made for uncertainty?
10. Did presentation/discussion of results include all issues of concern?

The economic evaluation is the comparison of alternative (and comparative) health interventions, concerning their clinical outcomes and costs. The costs and outcomes of health interventions are estimated by taking into consideration the natural course of the disease, the necessary resources which are utilized in order to address patient's needs and the actual health outcomes. There are two complementary approaches in an economic evaluation, modeling and clinical trials. Without doubt, randomized, double blind, placebo controlled trial display the highest credibility, however feasibility and time demands hinder its further dissemination among researches. Modeling combines data from several sources and it can circumvent these impediments. Ultimately, modeling can provide timely and tailored approximations to facilitate decision-making process, in the face of uncertainty (Barber & Thompson, 1998).

Economic evaluation is the comparative assessment of the costs and benefits of alternative health care interventions (Drummond et al., 1997). Economic evaluation has 5 techniques according to measurement indicators both for costs and health outcomes. In general, the core of the economic evaluation is the consent that health care provides are not supposed to deliver all available care. They should rather aim at providing the best value for money as possible, taking into consideration the available resources.This is described as the maximization of the societal value.

There are several determinants of the value of a certain intervention. More specifically, Nord in 1999 argued that the following have been adopted by several countries:

1. The number of people helped by the activity.
2. The severity of the patient's condition in terms of loss of quality of life.
3. The degree to which the service reduces symptoms and improves functioning.
4. The degree to which the service increases the patient's subjectively perceived quality of life.

5. The number of years the patient gets to enjoy improved health and/or quality of life (including increased life expectancy).
6. The age of the patient.
7. The distance in time until the gain in health materializes (future gains may be valued less than present ones).
8. The patient's responsibility for his/her own illness.
9. The patient's responsibility for caring for others.
10. The effect of care on a patient's productivity.

As a result, several variations of economic evaluation were developed and are critically assessed in the following chapters (table 9).

2.6.3. Cost-minimization analysis

A prerequisite for this analysis is that both (or more) therapeutic alternatives exert the same therapeutic effect. Consequently, all the relevant costs are compared so that the cheapest is selected. This is questioned by the intrinsic uncertainty of health outcome and their assessment. This is applied in different pharmacotechnical forms of the same active ingredient. Even in this case, it is not always the preferred method since different routes of administration are not considered equal in terms of drugs absorption, distribution, excretion and consequently effectiveness. In conclusion, this approach is rarely used (table 9).

Table 9

Types of economic evaluation

Method of Economic Analysis	Measurement of costs	Measurement of health outcome	Cost-outcome comparison
Cost-Minimization Analysis	Monetary	None	None
Cost-Effectiveness Analysis	Monetary	Natural Units	Cost per outcome unit
Cost–Utility analysis	Monetary	Utility Units	Costs per QALY
Cost-Benefit analysis	Monetary	Monetary	Net costs

2.6.4. Cost-effectiveness Analysis

Cost-effectiveness analysis (CEA) is the most widespread established economic evaluation Method (Cairns & Rushy, 2005). CEA can be used to assess only one outcome at a time and this is concurrently the benefit and short come of this method. Consequently, it cannot be used to compare 2 health care programs that have more than one clinical endpoint. For instance, it cannot actually asses the superior efficacy of infliximab in Crohn's disease versus a less oral potent drug, which nevertheless does not require an infusion which carries a 20% risk for potent anaphylactic reactions. Moreover, it cannot compare an intervention that improves 2 positive outcomes, because it cannot weight between the 2 outcomes. The task of CEA is to compare different methods that offer the same and unique endpoint (Zweifel & Manning, 2000). When using this method we make a statement that the clinical end point we want to compare is the same for both treatments. Additionally, the value of the chosen endpoint is given. Endpoints may be numerous and diverse, including blood pressure reduction, LYG (Life Years Gained), number of nodules detected and much more. It is apparent that this feature deprives the potential for comparisons and resource

allocation between disease groups. As Drummond mentions, there are "fairly restrictive boundaries" in the broader allocation of health care resources.

Cost-effectiveness models require information in order to be developed. The information needed is defined as the parameters of the model. There are different levels of parameters:

1. Parameters that are relating to analytical methods (e.g. the discount rate).
2. Parameters that illustrate the characteristics of a patient sample (e.g. age/gender composition or clinical characteristics such as disease severity/state).
3. Parameters that could, in principle, be sampled if an appropriate study were designed to collect the relevant data (Briggs, 2000).

2.6.5. Cost-Utility Analysis

Cost-Utility analysis (CUA) shares many aspects with cost-effectiveness analysis. The benefit is measured as a utility adjusted life year (QALY). If the quality of life is of major importance, then the CUA is the analysis of choice. The CUA actually refers to the level of satisfaction borne from the utilization of a specific health technology. It can be used to combine more than one dimension of life, such as the ability to move and resolution of discomfort, caused by the utilization of a specific intervention. In the MCMC model, and during transitions between several health stages, the total QALY is calculated based on the utility of each stage and the time that is spend on this stage**.** However, since utility is highly subjective, one of the limitations of CUA is that CUA is very time and resource intensive (Saha, 2001).

There is much controversy engulfing the classification of CUA. In the USA, CUA is perceived to be identical to CEA. Drummond suggests that CUA is a variation of CEA, with the only difference being the use of QALY as a health effect indicator (Neumann and Johannesson, 1994). The real advantage of CUA with QALY is the ability to rank all interventions in terms of monetary value per QALY. Although this may not be ethical, due to lack of equity and small Budget Impact analysis of some rare diseases, as discussed above, it gives us a certain overview of the optimum way resources should be allocated.

CUA with QALY as health status measurement are considered to be superior compared to CEA (Neumann, Zinner & Wright, 1997). As discussed earlier, CEA can integrate only one parameter of health, while QALY can incorporate a multifaceted health status using a single number (Ramsey et al., 2005). As a result, the incremental cost per QALY will be

the common parameter in comparison among different diseases (Sassi, 2006). The incremental cost-effectiveness ration (ICER) is emerging as a measure of cost-effectiveness of a new treatment, compared to the gold standard of therapy (Gold et al., 1996). ICER is the ratio of the mean difference in average cost the mean difference in average effectiveness. In this era, effectiveness is assessed by QALY (quality-adjusted life years), survival, patient response or other relevant clinical outcomes (Muenning, 2007).

2.6.6. Cost-Benefit Analysis

The cost-benefit analysis assess whether the benefit borne from a medical intervention outweighs the cost. It is expressed in ratio and any ratio larger than one indicates a positive yield. The larger the number, the more favorable is the intervention (Grauer, 2003). It is considered to be the most complete approach; however, one critical step of this approach is to transform all health gains in monetary value. Accordingly, several ethical dilemmas lurk and primarily the expression of a human life into monetary terms is an extremely delicate, disputing and ambiguous task and lies at the verge of engaging in an enormous and never ending process. This is the reason that Cost-Benefit Analysis is not used. Cost-effectiveness Analysis should be distinct from Cost-Benefit Analysis.

2.7. Willingness-to-Pay Threshold

The willingness-to-pay (WTP) is a term which describes the financial burden that the society is willing to undertake, for a patient to spend one year in a perfect health state (Culyer et al., 2007). The economic evaluations are extremely contingent to this threshold since, under an indefinite WTP threshold, potentially all products will be considered cost-effective. The definition of WTP threshold stems from the confluence of ethical, legal, medical and economical assumptions; consequently no explicit limits for the upper values of WTP exist. That is to say, the upper limit of the WTP threshold is up to the cohesiveness of each society to define, with regards to the financial and social state of this society, and to patient status as well.

Nevertheless, the process of adding a financial tag to the maximum amount somebody is willing to pay for health is controversial and it is, without doubt, conflicting to the “priceless” dimension of Health (Birch & Gafni, 2006). For instance, few people would hesitate to spend 50 euro to enter a lottery that carries a possibility of 0.05 to win. In

case they win, this will have an effect of 0.1 to their overall health status in the long term. Similarly, an amount of 50,000 euro as a ceiling to what somebody (or a Health system) can (or has to) pay is rather rational and justified. Consequently the debate about the threshold of WTP is relentless (Devlin, 2002). More precisely, the dilemma stands whether there should be "one fits all" or whether this ceiling should be adjusted vis-à-vis each disease or health status (Frew, Whynes & Wolstenholme 2003). Some authors suggest that it makes sense to cure more people with cheaper therapeutic options instead of treating fewer people with more expensive therapeutic options. Other authors argue for-a rather obsolete opinion- first comes first served". In UK, a relevant debate has been perpetuating and several conflicting rational opinions endorsed both approaches. National Institute of Clinical Excellence (NICE) rejects the use of an absolute threshold for judging the level of acceptability of a technology in the NHS for four reasons:

1. There is no empirical basis for deciding at what value a threshold should be set.
2. There may be circumstances in which NICE would want to ignore a threshold.
3. To set a threshold would imply that efficiency has absolute priority over other objectives (particularly fairness).
4. Many of the technology supply industries are monopolies, and a threshold would discourage price competition (Rawlins, 2004).

WTP has two sources (O'Brien et al., 2002). From an extra-welfarist perspective, it illustrates the ICER, which that has to be lower from current standard intervention's one, in order to be replaced. In the welfarist's approach, WTP denotes the amount that society is willing to pay and it is a combination of CEA and cost-benefit analysis, since health benefits are translated into monetary values.

NICE faced criticism about the QALY thresholds and there was much debate as an aftermath to a legal action of Pfizer against NICE. Towse, in 2009, stated that the threshold should be higher for two reasons: Primarily, it is difficult for people to make informed choices based on hypothesis and random knowledge, regarding a disease. Furthermore, the opportunity cost of an expensive QALY must be clarified. If an expensive treatment is rejected based on this feature, then what is the optimum investment of the corresponding amount? Raftery in 2009 responded to Towse and suggested that the Budget Impact Analysis should be included in the economic analysis. It is given the that opportunity costs are the foundation of the threshold and some interventions are displaced in order to

accommodate others. Specifically, he suggests that the growth in the NHS should precede any increase of the QALY. In this context, the *CHOICE* (CHOosing Interventions that are Cost- Effective) initiative was launched by WHO. This initiative aims to provide guidelines regarding resource allocation and cost-effectiveness analysis. They suggest that the GDP of each country can be utilized and formed as a willingness to pay benchmark (Murray, 2009; Sachs, 2001). A WTP threshold less than the gross domestic product (GDP) per capita represents a very cost-effective treatment. A WTP threshold less or equal to 3x GDP per capita represents a cost-effective treatment and comprises the threshold, at least for common conditions. Anything above this, is considered to be non-cost effective, although for some orphan drugs and rare disease, the relax of the upper limit up to 5x GDP can be justified, solely on solidarity grounds.

2.8. Quality Adjusted Life Years

2.8.1. Assessing QALY

The comparison between the gold standard of therapy and a new therapeutic intervention mandates the use of a common measurement tool across all interventions, since final efficacy endpoints vary immensely both across and within therapeutic categories. Consequently, any potential comparison between therapeutic options necessitates the use of a summary index measure of health outcomes that is common across all interventions in all disease areas. In this direction, the health related quality of life is assessed in order to deliver a globally endorsed factor such as QALY (Weinstein, 1988). Health utility describes qualities over health states.

The QALY was first used by Zeckhauser and Shepard in 1976 with the ambition to merge the duration and the quality of life in specific health state. The QALY is an indicator designed to combine and elucidate the attributes of CEA and CUA and it can enable comparison across therapeutic areas. It describes the number of years at full health that would be valued equivalently to the number of life years as experienced. QALY is calculated multiplying a person's life expectancy by the value of the health related quality of life. The QALY succeeded the development of a health status index, which was elaborated in the early 70's. Pliskin et al., (1980) underlined the 3 pillars of the QALY:

1. The utility independence between life expectancy (quantity) and life years (quality). Duration or expectancy of life is not related to quality of life. As a result, the value that is placed on each health state is not related either to the duration of the corresponding state, or to the sequence of the specific state. As a result a bad health state is valued the same regardless it lasted one month or 10 years, or regardless whether it occurred prior to or after a better health state.
2. The constant proportional trade-off between current and theoretical health stages (Describes how much many years a patient Is willing to sacrifice given that currently patient is in a health state < 1 in order to spend less years but in better health state of their remaining life expectancy.)
3. The risk neutrality (Patient does not show any preference towards either a shorter and better life expectancy or longer but worse life expectancy.)

A QALY is the year of life one can expect to live in perfect health. A QALY of 1 is a year spent in perfect health while a QALY of 0 is a year spent in extremely bad health. Some searches suggest that 0 corresponds to death. On the other hand, several other researches claim that certain conditions are worse than dead which implies that the range of QALY should include negative values as well, so that the range of QALY is from 1 to -1. Death state has also been an area of debate, as well as the definition of well-being. Death state is a verifiable, definite and irreversible state which carries 0 factor, regardless its duration (Benjamin and Busschbach, 2011), nevertheless people do not experience pain or anxiety. Currently, people in bad condition are reckoned to have 0 QALY, but in contrast to deceased they may experience pain, distress and anxiety. Without doubt, the optimal stage is difficult to measure.

In its simplest form a QALY can be represented a $QALY_G = T_1Q_1 - T_2 - Q_2$ (T represents number of years and Q represents health state values). If we consider discounting as well, as well as the inherent uncertainty, then the equation will be as following:

$QALY_G = \Sigma_h \Sigma_t \rho_{1ht} Q_{ht} - \Sigma_h \Sigma_t \rho_{0ht} Q_{ht}$ (ρ_{1ht}, ρ_{0ht} =*probability of being in the state h in time period t* $Q_{ht} = Q_h/(1+r)^{t,}$ *where r is the discount rate)*.

NICE recommends the use of the EQ-5D. In case when data are unavailable or unsuitable for the intervention which is being evaluated, there are some other generic instruments such as the Short Form 6D (SF-6D)(Sintonen 2001), Assessment of Quality of Life

(AQoL)(Hawthorne, Richardson & Osborne, 1999) Quality of Well-Being (QWB), and the Health Utilities Index (HUI) . In addition, some condition-specific measures (CSMs) are available which are used alongside or instead of generic instruments in order to track changes in symptoms and side effects that are disease specific(Brazier and Longworth, 2011). Several studies reached the conclusion that the different classification systems may deliver diverging health state values thus impeding comparative allocation process of resources (Brazier et al., 2004).

In certain cases, patients may not be able to report their personal health cases, particularly in diseases that alter cognitive function and the clarity of the respondents cannot be defined. This gap is filled by the introduction of a special version of the EQ-5D. In this context, NICE suggest that the mediator is one of the closest caregivers however there will be considerable uncertainty in subjective dimensions of health. This highlights the well documented difference between measuring health and valuing health. A health economist wants to know the perceived value of a certain patient for a specific health state.

Usually a QALY is assessed though a three step process. The first step is to describe the health states. This is the place where the generic based measures such as are EQ- 5D are utilized. This is usually done using generic preference-based measures which can be employed across different disease areas. This poses methodological challenges since there are many generic tools available, and there also several disease specific ones. What follows is the conversion of the resulting steps into a value, or coefficient, based on the preferences of a sample of the general population. There are several techniques which are implemented in order to highlight individual preferences. The time to trade-off (2.8.3.) is widely used and its goal is to reach a trade-off between the quality and the length of life. An alternative option is the standard gamble (2.8.4.), where patients are asked to choose between a certain outcomes and a gamble involving both a positive and a negative outcome (usually perfect health and death). Rating scales, such as the visual analogue scale (VAS) may also be used, but these are generally considered inferior to choice-based methods. NICE recommends the use of a set of tariff values estimated using the TTO for EQ-5D health states based on a study involving over 3,000 members of the UK population (Dolan, 1997).

The final step is to calculate the QALY gains associated with an intervention. In this step the duration of each health must be multiplied by the corresponding HRQL value for this specific health state. The resulting values are then summed according to the likely sequence of health states (with a discount rate applied to health states occurring in the future), estimated from primary data or by modeling the long-term benefits of treatment by

extrapolating from short-term data. The EQ-5D is the preferred measure of health. It possesses five major dimensions and in each one there are three sub-levels. Consequently this can deliver up to 243 unique health states, which a patient can classify himself:

1. MOBILITY

a. I have no problems in walking about

b. I have some problems in walking about

c. I am confined to bed

2. SELF CARE

a. I have no problems with self-care

b. I have some problems with self-care

c. I am unable to wash or dress myself

3. USUAL ACTIVITIES

a. I have no problems performing my usual activities

b. I have some problems with performing my usual activities

c. I am unable to perform my usual activities

4. PAIN/DISCOMFORT

a. I have no pain or discomfort

b. I have moderate pain or discomfort

c. I have extreme pain or discomfort

5. ANXIETY/DEPRESSION

a. I am not anxious or depressed

b. I am moderately anxious or depressed

c. I am extremely anxious or depressed.

If we take a look to the above classification, one can easily conclude that the QALY does not measure merely health, it evaluates well- being as well, although Grieve (Grieve, Grishchenko & Cairns, 2009) criticized EQ-5D for overlooking the element of vitality.

NICE has elaborated an approach that aims to set apart reporting and valuation of health, since they are overlapping utilities. As a rule, patients should directly report what they experience and during this process they should not be guided by the researcher since they may be guided, even subconsciously, due to the fact that health researchers are familiar with the cycle of the disease and they my anticipate a specific attitude, reaction or a certain

level of response during a perceived good or bad, health state. This is further impaired in cases that patients are not capable of reporting on their own health state.

At the same time, the use of QALY demonstrated certain weaknesses such as:

1. The inability to assess non-health benefits.
2. Unless a threshold is used, a random QALY does not give a clear and definite answer whether a new treatment should be introduced.
3. The QALY does not take into consideration how much people are willing to pay for certain products. For this reason it does not promote efficient use of scarce resources.
4. In certain cases, it is not feasible to distinguish a patient in good health from a patient in perfect health condition, since both classify themselves as being in the least severe condition.
5. The QALY does not promote Health equity. It is a distribution blind tool, since a random gain of a QALY amount is the same whether the patient is in poor, good or average health condition.

Since the QALY is borne according to number of years patients are going to live with the current health intervention, the addition of the discounting favors younger patients, compared to older ones, because of bigger life expectancy of younger patients (Harris, 1987). There is an ongoing debate on whether Quality should be assessed on a generic or a condition specific basis. It is apparent that a generic description tool enables comparisons among different fields, while a condition specific description tool will be more sensitive to a particular disease and it may lead to a more precise result .On the other hand, a condition specific description tool will overlook side effects, co morbidities, parameters that are not directly related to the condition.

Donaldson et al., (2011) drew some very important conclusions on the social value of the QALY. They argue on the Social Value of a QALY, which is a project initiated by NICE aiming to explore the optimum QALY value, which has been a field of debate as mentioned above. In this project, the social value of the QALY was assessed by three pathways. The first one involves modeling from the willingness-to-pay values which are utilized by the Department for Transport for life saving projects. This is in line with the perception that Health competes with other departments in order to attract more funds. In this approach the willingness-to-pay divided by the small number of life saved will deliver

the value of preventing a fatality (VPF). This VPF will be similar to a QALY since it entails all budget constraints, which are a feature of society's budget allocation. Indeed, it is crucial to highlight that the individual's income is not a part of this equation, a fundamental attribute to Health policies.

A second approach was to assess QALY given certain health states which includes recurrent stomach pains and head pains. Patients were asked a standard gamble question which included return to full health for the rest of one's life (better outcome) or worse outcome which was death. The WTP was also asked.

The third approach aimed to highlight the way people other's people's health states and relevant needs. The question raised is whether a QALY gained by a person in very bad health has the same value as a QALY gained by a person in relatively good health. Other dimensions of this pursuit are the QALY gained by very young and very old people and comparison to the QALY gained by people of a productive age. A way to assess this was the definition of a specific number of people with a certain disease that are judged equivalent to 100 people of different health state with the same characteristics, given that they reach the same QALY gain. If the number is less than 100, it means that the former group is valued higher compared to the latter (Person trade-off).

A variation of the aforementioned approach is the discrete choice experiment. The difference lies to the variation of health gains and consequently the responder was asked to choose one scenario over another. This project delivered 3 different levels of QALY (table 10).

Table 10

QALY and health condition

Basic modeling approach	Value of a QALY (GBP)
Life saving	70,000
Life –extending	35,000
Quality of life extending	10,000

As seen above, it is apparent that lifesaving procedures should carry a higher QALY, a practice which was adopted by NICE. This project reached some other conclusions, which must be underlined as well:

1. There are many QALY types, according to the above table (table 10).
2. There are different weighting of QALY by characteristics of beneficiaries. This means that patients, in whom a specific treatment is highly effective, should not overrun patient groups that display a moderate therapeutic outcome. Certain exceptions apply, such as Norway, that perceives that treating a few severely ill patient is just as valuable as treating a larger pool of patients with less severe disease. However, numbers still matters and unless the "a few" and "larger" is defined, the decision-making process can be a very ambiguous and conflicting process.
3. There are several health states that are quite serious which can actually force people to trade them in standard gamble, but are not severe enough as judged by an unaffordable WTP amount.

Some researchers raised the issue that QALY may not be the optimum indicator for certain diseases, such as cancer. This is of major importance because the cancer drugs comprise the cost-drivers in the pharmaceutical sector and they pose a significant financial burden to health systems worldwide. These low volume and high price medical interventions are insensitive to small changes in health state. This crudeness fails to notice impactful, yet small, changes that actually greatly influence the quality of life of a cancer patient. Another particularity of a cancer patient is that health gains are usually small, regardless the degree that the patient perceives them. This is described as "indifference to health quality at short duration". Moreover, Time-to-Trade off was designed given a 10 year framework. In certain cancer types, patients' survival spreads only to several months, thereof findings cannot be extrapolated. Miyamoto et al., (1988) found that when life expectancy is less than one year then patients are not willing to sacrifice any time, in order to gain superior health state.

Cancer interventions account as much as 25 % of the Technology Appraisals performed by NICE. NICE, after facing criticism following rejections to reimburse cancer drugs whose QALY's exceed upper limit, made an exemption in the inclusion of life-extending and end-of-life treatments. The indications include renal cell carcinoma, hepatocellular carcinoma and multiple myeloma. The two arguments that support this decision is the small target group population (which implies the Budget Impact Analysis is positive) and that the benefits may not be sufficiently captured in the reference case. Certain criteria apply as following:

1. Patient´s life expectancy is less than 24 months.
2. There is sufficient data that the treatment will extend life at least for an additional 3 months compared to current treatment.
3. There is no alternative treatment with equal effectiveness available.
4. The target group is a small patient´s population.

Apart from cancer patients, there is growing literature that suggests society may place a higher value on QALY's gained by some patient categories that are perceived to be either more important to others (people with dependants) or those with poor health (Devlin and Sussex, 2011). In conclusion, QALY offers several advantages such as:

a. Evaluation of health interventions with several outcomes and different side effects.(i.e. a very effective psoriasis treatment, with a high risk of renal side effects, compared to a less effective but safer alternative)
b. Comparison of treatments for the same condition, but with different outcome. (i.e. two statins with the same indications and side effects, but with statistically significant different reduction of total cholesterol levels.)
c. Ability to compare diverse health interventions for a broader spectrum of diseases and feasibility to make health decisions with a bigger perspective across several medical specialties (i.e. comparison of a liver transplant program and a chemotherapy regimen for hepatocellular cancer).

2.8.2. QALY and time

Time is taken into consideration when assessing a QALY, either in the form of discounting for future data, or in the form of assessing longer time periods in good or bad health (Raven et al., 2011). However, time perception by patients has not been taken into consideration yet. Time is a highly subjective parameter however the way we perceive it may deviate among individuals with concern to specific disease, gender and age. What is common is the perception that time passes more slowly in a bad health condition and cancer is disease that distorts time perception. Lastly, several neurological diseases, such as dementia and ADHD alter perception of time (Laarhoven et al., 2011).

2.8.3. TIME TO TRADE-OFF (TTO)

Time to trade-off (TTO) is one of the most important tools in the elicitation of health state utilities. It is applied to the second step of a QALY calculation and it involves asking patients to quantify the relative amount of money that they are willing to sacrifice, in return for a better health state. It asks patients to choose between 2 options:

1. *x* health state for an *I* period of time, followed by death or
2. Perfect health for a shorter period of time (< *I).*

TTO opposes to EQ-5D and SF-6D, which are classification systems and as such, they cover an array of diseases (Arnensen & Trommald, 2005). Specifically, as described above, this feature of EQ-5D hinders the ability to track down details of the health condition. In addition to this they do not capture dynamic health states such as pain. Moreover the utilities created by TTO represent cardinal values, while the corresponding values by standard gamble (2.8.4.) are based on the expected utility theory. TTO has a threshold which can be defined as the severity level that from beyond patients are willing to start trading, regardless the acknowledgement that their current state is suboptimal.

The values of TTO are computed by dividing the duration of the state of full health at the point of indifference by the duration of the valuated health state. The more time patients are willing to trade, the lower the value is assigned to the health state. Time to trade-off is perceived to be less susceptible to bias and definitely it is easier for patients to understand (Dolan et al., 1996). Another characteristic is that it does not assume that distributions will be linear.

2.8.4. Standard gamble

The standard gamble is another approach of preference instrument. The theory of standard gamble is substantiated and it is perceived to be the cornerstone of assessing preferences, due to theoretical econometric assumptions it satisfies about the most appropriate choice of preference instrument. Standard gable differs from TTO due to the inclusion of risk (TTO is perceived to be risk-less) (Bleichrodt, 2002) and on the assumption of non-linearity (Bennett, 1996).

2.8.5. DALY (Disability Adjusted Life Years)

DALY is another approach to measure effectiveness. It represents the sum of years of life lost as a result of premature mortality and years that are lost due to disability, diseases and injuries (Airoldi & Molton, 2009; Anand & Hanson, 1997). One of its attributes is being comparable across diseases, in the same format of a QALY. Consequently i.e. 5 DALY's lost due to cancer can be compared to 2 DALY's due to heart failure. DALY is founded on the international ICD classification. One DALY represents the loss of one year in full health**.** DALY is calculated taking into consideration the duration of disability and the exact disease or injury**.** Since it calculates the premature mortality, the Life Expectancy at age of birth is included in the calculation. In this context, an injury of a 25 year worker will be assessed as following:

-25 years old. Life expectancy for a 25 year old male is 77.2 (Census, 2011). YLD will include the duration of the injury. If we assume that the disability will be lifelong, then the duration according to the life expectancy is weighted according to the severity of the injury. If we assume that this injury carries a 0.66 weight factor, then 52.2*0.66 will deliver the DALY which in our case is 34.4.

-In the same accident, there was a fatality of a 20 year old worker. Then the total DALY will include the Life Expectancy of a 20 year old male which is 76.8. The life expectancy is 56.8 which is translated into 56.8 YLL's. The total DALY in this case is 34.4 plus 56.8, a total 91.2 DALY

2.8.6. Cost of Illness ANALYSIS (COI)

Cost of illness refers to the impact of a disease or health condition on the overall Health Costs. It consists of direct and indirect costs. Usually direct costs include doctor fees, drugs etc while indirect costs include morbidity and mortality costs, which as a rule of thumb do not burden the health care payer.

2.8.7. Discounting

In the majority of health economic approaches (except Budget Impact Analysis) all costs are discounted. The reason is that a decision made today, along with the interrelated expenditure, may demonstrate an effect in the long-term. In general, all people have a positive approach of time preference. This means that people would prefer to attain a

utility today than tomorrow. Regarding costs, individuals prefer that cost incur at a later stage. At this point we have to separate costs and effects pertinent to discounting. It is commonplace for costs to incur earlier than health gains, as in the case of vaccination and transplantation, whose effects occur at a later stage. Therefore, a gap exists in the comparison of today's cost with utility bourn tomorrow. In addition to this, it is essential to be able to compare health states that occur in different time periods. For instance, two competitive therapeutic approaches may deliver similar results with a significant time-lapse, which will have a differing impact on current expenditure. This approach does meet the opportunity cost concept which states that utilities borne in the future have to be weighed against current therapeutic options. Two major facts support the theory of discounting:

a. Time preference: More people would accept less money today instead of receiving more money in the future.
b. Opportunity cost: Less money can be invested by society and allow growing at a rate of interest less money can be invested by society and allowed to grow at a compound rate of interest to yield the money required for future costs.

Discounting is globally accepted as a corrective tool however certain issues are yet to be clarified. There is much dispute regarding the optimum discount rate and whether to discount health benefits, apart from costs, especially when health benefits are expressed with monetary values. Regarding the latter, there is much controversy whether to use the same rate to discount costs and benefits**.** Discounting is calculated as following:

$$PV = \sum_{t=1}^{T} \frac{C_t}{(1+r)^t}$$

PV is the current value in *t* years and *r* is the discounting percentage. For instance the current value of 1000 USD in 4 years will be 792USD, under the assumption that the discounting rate is 6 %. Another term is the Equivalent Annual Cost (EAC). EAC is defined as the $EAC=PV/ (1-1/ (1+r)^n /r)$. Discounting is of particular importance when comparing treatments, whose effects and relevant occur in different time periods. As an illustration, a comparative cost-effectiveness analysis between a major operation and a continuous long term drug treatment would be unfavorable against the treatment, owing to the time-lapse between payment and appearance of medical benefits. Specifically, the need

for discounting is prominent in vaccination programs that deliver their benefit across the life span of individual, while the cost incurs at the early stages. Nevertheless, discounting of the utilities in the long term, may render vaccines non cost-effective. Consequently, a common belief is that discounting is unfair against future generations. In order to counterbalance, it was suggested that future costs should be differentiated between intragenerational and intergenerational costs and an equity weight factor should be set for each function. Some other researchers suggest the introduction of a regressive discount factor, aiming to smaller impact of distant utilities compared to the close ones (Smith & Gravelle, 2000). Costs are usually discounted with a different rate than discount rates of utilities.

2.9. Modeling for Economic Evaluation

In view of the aforesaid limitations and inherent flaws of the pharmaceutical market, modeling may assist by providing valuable data apropos the cost-effectiveness status of medicines. Accordingly, this will enable policy-makers to define which product is cost-effective, whether the acquisition of new data would minimize uncertainty and if it is cost-effective to ask for more data. Ultimately, it can make possible the setting of a price which would render the product under assessment as cost-effective.

The modeling is classified as a reductionist methodology, since it can break down complex health states into simple ones, thus enabling a better understanding of the disease sequence. In return, this simplicity will enhance the decision-making process (Caro, 2012). Additionally, modeling is useful in case where is infeasible, costly, or impractical to carry out a real life experiment. As a result, modeling is currently implemented in many disciplines, where uncertainty dominates and it is defined as a "mathematical framework representing some aspects of reality at a sufficient level of detail to inform a clinical or policy decision" (Roberts et al., 2012).

Modeling serves primarily the following targets (Sculpher, Fenwick & Claxton, 2000; Roberts et al., 2012; Philips et al., 2006):

1. Modeling enables identification of important factors, among several ones.
2. Modeling allows combination of data from several sources and evidence synthesis. This will facilitate merging of data from studies with diverse clinical end points and

it lead to more robust results and recommendations. The most important data are economic, epidemiological and international data.

3. Modeling can create economic data in clinical trials, whose design did not make provision for collecting economic data.
4. Modeling can create cost- effectiveness data between actual competitive products, for which no direct clinical data exist. Currently new products choose either a placebo for the control arm or an outdated treatment for phase 3 trial. For instance (Moreland, 1997) etanercept choosed a placebo comparison arm for its PHASE III trials, which does not align with actual needs. In the Medical Decision process, physician and payers seek for cost-effectiveness comparison between etanercept and infliximab or adalimumab but definitely not placebo.
5. Modeling can give answers to long-term health questions. Usually, studies last for a limited time, due to human and financial resources that must be utilized. In this context, a surrogate clinical end point may be achieved in relatively short time, such as blood pressure reduction, nevertheless hard end clinical end points such as primary and secondary prevention of Myocardial Infarctions are long term goals and would need a bigger duration of the clinical trial (Mandelblatt et al., 2012). As a result, researchers do not know whether the health benefits are sustainable in the long term, or whether they will dissipate. Furthermore, the life years saved make greater impact and are a more meaningful term compared to 1 week or one month survival rate (Buxton et al., 1997).Only a handful of studies lasted for extensive time periods. Well known is the Framingham Heart Study, which is an observational and not an interventional study. Another example was the Million Women Study, which was designed to study the impact of Hormone Replacement Therapy on morbidity and mortality in postmenopausal women.
6. Modeling allows representation of the complexity of the real world in a more understandable way. A health economist may not be aware of the etiology, symptoms and clinical manifestations of a disease. He/she may not fully comprehend how patients and doctors feel regarding the progress of the disease. Modeling will present data in such a simple way that decisions taken will be fully justified and not arbitrary or emotionally derived (Karnon et al., 2012).
7. Modeling will outline and clarify certain areas of uncertainty (Weinstein, 2003).
8. Modeling may enable extrapolation of data from a single study.

Nevertheless, modeling is not always a straightforward procedure. There are a large number of documented reasons elucidating why the results of economic studies may not be transferable between different places and times, as Drummond (Drummond and Pang, 2001) stated in 2001:

1. *Variation of Methods.* Currently there is a wide spectrum off methods regarding clinical conducting clinical trials. Consequently, this hinders direct comparison, or data transferability.
2. *Intervention context and intervention costs*. Prices differ, not only from country to country, but within the same country as well. Volume price agreements, claw backs, economy of scale which is more prominent in bigger than smaller countries, different capita per head and different pricing procedures affect the homogeneity of prices. Given this, data must be converted before transferred. Jansen (Jansen et al., 2001) emphasized this in the L.I.O.N study. This multi-center study showed that terbinafine was the most cost-effective medicine for onychomycosis in 5 European countries (UK, Germany, Iceland, Italy and the Netherlands), while in Finland the competitive medicine, intraconazole, was more effective than terbinafine, due to the different pricing and prescription patterns. Moreover, several trials include endpoints that are not applicable in everyday practice due to cost and need of interventional procedures such as MRI, ultrasonograph and endoscopy.
3. *Clinical trials and decision models* .Clinical trials, with real patients, and decision modeling deliver complimentary data. However, these data are not exactly similar and sometimes merging these data may lead to design errors.
4. *Validity of extrapolation of data.* A straightforward linear relationship between a marker, such as blood pressure, and a clinical endpoint is not always given. Allosteric effects, saturation of binding proteins and other biological reactions contribute to this feature. One well known paradigm is calcitonin, which is indicated for treatment of osteoporosis. Effectiveness of calcitonin on Bone Mineral Density, which has a definite and strong correlation with prevention of osteoporosis, was rather weak compared to the more potent biphosphonates. Salmon calcinotonin was commercially available at 200 mcg. Marketing Authorisation Holder of calcitonin decided to run a clinical trial in order the test the hypothesis that 400 mcg of calcitonin was more effective on increasing BMD, compared to 200 mcg. The results however were frustrating when researches came

across to a placebo effect of calcitonin, as administrated at 400 mcg (Chestnut, 2001).

2.10. Bayesian Theory

Thomas Bayes (1702-1761), an English mathematician, was the first to introduce the Bayesian Theory, which was named after him. In contrast to the frequentist approach, which defines data as random while parameters are fixed, Bayesian Theory believes that parameters are not fixed and they follow a probability distribution. In this sense, it is a common belief that the Bayesian approach may enable us to overcome real problems such as missing data or latent variables, while its utilization is facilitated by the introduction of user-friendly software. Spiegenhalter (Spiegenhalter et al., 1999) defined Bayesian as the "the explicit quantitative use of external evidence in the design, monitoring, analysis, interpretation and reporting of a health technology assessment". Finally, the Bayesian approach can be quite effective with smaller cohorts, while frequentists rely on large groups.

But what's Bayes theorem? Let's assume that f is an unknown quantity which can be the survival rate of a patient or positive true results. The probability of each possible value of f is denoted by $p(f)$. At the same time we do have some other reliable data (y), whose like hood of occurrence depends on f. This dependence can be described by a probability $p(y/f)$, which is actually the probability of y for each possible value of f. Our endpoint is to assess the new probability for different values of f, in view of the evidence y. Bayes's theorem says $p(f|y)=p(y|f) \times p(f)$. The usual term for $p(f)$ is the **prior**, for $p(y|f)$ the **likelihood**, and for $p(f|y)$ the **posterior**. Bayes theory says that posterior distribution is proportional to the product of the prior times the likelihood.

Bayesian modeling has 3 aspects: Computation, Incorporation of historical information and inference on complex functions of parameters (Spiegenhalter, 2004). The economic evaluation of medical and pharmaceutical interventions relies mainly on models and it is estimated that 90% of cost-effectiveness analyses of vaccination programs have used modeling approaches (Kim et al., 2010). Their primary target is to resolve uncertainty about the history of a disease and the resources required to cope with the impact of the disease, including human and financial ones. In this context, the p –value, as derived through the frequentist approach, has been a long-standing method to prove whether an intervention works. In its most common form, that is $p<0.05$, it actually conveys the

message that there is only a 5% chance that the null hypothesis (no effect) is true. This is somehow oxymoron because concomitantly you presume that something is true and present a percentage of how much is likely to be wrong. Spiegenhalter (Spiegenhalter et al., 1999) demonstrated the deceptive properties of p value (table 11). A diverse number of clinical trials may demonstrate the same p value but at the same time huge differences may exist. Accordingly, the sample size cannot be adequately taken into perspective when p value is calculated.

Goodman (Goodman, 2005) tried to compare p value and Bayes factor, as seen in table 12. Bayesian inference is gaining more attention in the medical field. In Bayesian statistics, the current knowledge, which is called prior, is modeled to create the posterior probabilities. Moreover, researchers may define the range of the expected values, lower and higher. Bayesian inference is described as being subjective.

As a result, biases are not unlikely to exist. Frequentist statistics produce data which are rigid, either being statistically significant or not. "*The standard use of probability describes long-run frequency properties of repeated random events. This is known as the frequency interpretation of probability and so both Fisherian and Neyman–Pearson schools are often referred to as 'frequentist. We have allowed probability to refer to generic uncertainty about any unknown quantity, and this is an application of the subjectivist*" (Spiegenhalter, 2000). Another short-come of the conventional statistical analysis is the inability to integrate any available information both at the design and at the analysis phase of a trial. This leads to a disruption of the sequence of data and it rather isolates this trial. In Bayesian statistics, data are more appealing (Wainwenn et al., 2000) because instead of being dichotomized into being significant or not, they are classified.

Table 11

p-value and sample size

Number of patients	Proportion preferring A	p-value
20	15:5	0,04
200	115:86	0,04
2,000	1,046:954	0,04
2,000,000	1,001,445:998,555	0,04

Nevertheless, physicians in their everyday practice are subjective. Physicians prescribe medicines based on their perception that they posses, pertinent to the effectiveness of the products and to the patient's condition. This comprises the most difficult aspect of Bayesian analysis, which is the transformation of an informal opinion into a mathematical prior. A proper Bayesian modeling usually consists of 6 to 7 steps. One of the most rational and complete approach is described by Ntzoufras (2009). To begin with, the main variance of problem (X), as well as covariates and relevant data must be identified. It's equally important to classify the distribution of the problem (X). Then the prior distribution must be constructed. Finally, the likehood is reached. Kadane (Kadane, 1995) underlined internally consistency as the most important feature of Bayesian methodology. The inclusion of the same prior and likehood functions will deliver the same posterior distribution. Furthermore, all these data are made public and consequently they are subject to criticism. This extroversion requires justification of prior which is done through many ways, such as citation. Unavoidably, the "subjective" Bayesian prior can, at the contrary, generate a beneficial communication channel between author and readers.

Table 12

Bayes factor and p-value

P value	Bayes Factor
Non-comparative (either significant or not)	Comparative
Observed and hypothetical data	Only Observed data
Evidence only negative	Evidence negative or positive
Alternative hypothesis implicit data-dependent	Alternative hypothesis explicit data independent
Sensitive to stopping rules and study design	Insensitive to stopping rules and study design
No formal justification or interpretation	Formal justification and interpretation

A form of consensus in prior is generally required if the assessment is going to be accepted by a broader audience. In case that there is little assumption and this is usually the case in innovative or orphan drugs, for which there are limited, if any at all data, distribution features a very wide dispersion, accentuating that possible values could have significant differences. On the other hand, a very low dispersion and low range indicates a wealth of knowledge about prior data and signals a strong understanding of the environment, on behalf of the researcher.

2.10.1. Likehood possibilities and Bayes Factor

Bayes factor transforms prior to posterior odds: Numerically, it may vary from zero to infinite. The exact definition is $p(y/H_0)/p(y/H_1)$. H_0 and H_1 indicate the 2 hypotheses that specify the probability of observing y. Spiegenhalter (2004) elaborated a scale of Bayes factor based on the strength of evidence that they produce (table 13) .

Table 13

Bayes factor and strength of evidence

Bayes Factor	**Strength of evidence in favor of H_0 and against H_1**
>100	Decisive
32 to 100	Very Strong
10 to 32	Strong
3.2 to 10	Substantial
1 to 3.2	"Not worth more than a bare mention"

2.10.2. Prior in Bayes Theory

Prior is the process of incorporating existing data or opinions regarding the effectiveness of an intervention in our statistical model. In contrast to the general perception, it is not obligatory that the priors must be defined in advance. Cox (1999) mentioned that since prior is not a time dependent parameter, but a state dependent parameter, it could be defined even after the actual data are set. Prior does not refer to time, but to a specific situation. In addition to this, there is much debate about how correct prior distribution is. A prior distribution is a belief, and as such, it entails a certain degree of bias. Undoubtedly, a

prior distribution will entail some unknown parameters, especially if we include several studies. The inclusion of several studies will lead to overrun of prior by the actual and the more data we insert to the study, the less important the prior becomes. The name 'prior' implies a sequential relationship, but it cannot be ruled out that a prior distribution is set on after seeing the results of a study. This emphasizes the true nature of prior distribution which is not to set directions but rather to give a "yardstick against which a surprising finding may be measured" (Grieve, 1994).

It is given that the data supporting a hypothesis should align with clinical endpoints, so is crucial to identify data that carry a reasonable validity level. Prior setting must express and satisfy the needs of the individual who is an expert. If the Health Technology Assessment is going to be submitted to a regulating authority such as NICE or QWIVC, then prior should demonstrate a high level of evidential or consensus support. The true function of prior distribution is to be transformed into posterior rather than producing the posterior. However, it is possible to use posterior values in order to check their origin prior values, which may be unknown. Conjugate (or conjugacy) priors refer to the state in which priors and posteriors belong to the same distributional family. This enables researches to interpret prior parameters as a prior sample (table10). At certain cases, it is possible that no prior values are available. In this case, a non-informative or vague prior is utilized. Kadane and Wolfson (1998) stated that a Bayesian Analysis must be coherent and consequently valid. However, elicitation of prior lurks several perils that may hinder the Bayesian process:

1. Availability. Easily accessed or recalled events are usually more easily utilized compared to data which occurred a long time ago, or are not easily accessed because of barriers such as language, different institutions e.t.c.
2. Adjustment and anchoring. This described the tendency to exploit an initial prior. What follows a good first prior is usually a similar judgment.
3. Overconfidence. If we are very confident about a first prior, then this will lead to very tight distribution.
4. Conjunction fallacy. Conjunction fallacy describes the assumption that specific conditions are more probable than a single general one. In Bayesian theory this describes the tendency to delegate a higher probability to an event, simply because it is related to an event with lower probability.

5. Hindsight bias: This describes the assessment of prior which occurs after the expert saw the data. Although prior can be set after the event occurred, this may alter the objectivity of the expert.

Kadane came up with several procedures to overcome some, if not all, of the aforementioned hurdles. Asking predictive rather than structural questions is one of the most commonly used tactics. In this case, the expert is given various values of the predictor variables, instead of having to set his own values.
Likehood ratio is the weight of evidence. In Health, priors' distribution is supported by clinical data and consequently validity is adequate.
Posterior odds = Likehood ratio x prior odds.

2.10.3. Source for prior setting

There are several approaches to Bayesian thinking and four levels of them are primarily implemented:

1. The **empirical** Bayes approach demonstrates the approach in which a prior distribution from multiple experiments
2. The **reference** Bayes approach describes the interpretation which is given to conclusions expressed as posterior distributions
3. The **proper** Bayes approach describes the use of informative priors which are based on available evidence and conclusion are summarized by posterior distributions without incorporation of utility functions
4. The **decision-theoretic** or 'full' Bayes approach, in which explicit utility functions are used to make decisions based on maximizing expected utility.

2.11. Statistical Distributions in probabilistic decision analytic models

A distribution indicates how the probability of a random variable is distributed. This depends mainly of the form family of distribution.
Normal Distribution is of pivotal importance in the statistical analysis. Is has the expression $Y \sim N [\theta, \sigma^2]$ which describes the assumption of a normal distribution with mean denoted as θ and variance as σ^2. Standard deviation is denoted by σ. The possibility of the Y is denoted as

$$p(y) = \frac{1}{\sqrt{2\pi}\sigma}\exp\left(-\frac{1}{2}\frac{(y-\theta)^2}{\sigma^2}\right); \qquad -\infty < y < \infty.$$

Normal distribution is a continuous probability distribution with a bell shaped density function. One key characteristic of a normal distribution is the fact that 95% of the possible values of a variance lies within two standard deviations. It is a characteristic of normal distribution that 95 percent of the possible values for a variable lie within two standard deviations. On the grounds of the following reasons, the normal distribution is considered to be one of the most important probability distribution in statistics:

1. It is a tractable distribution which means that a large number of results involving this distribution can be derived in explicit form.
2. Normal distribution follows the principles of central limit theorem, which states that under normal circumstances the sum of almost all variances is normally distributed
3. The bell shape of the normal distribution which is explained by the central limit theorem makes it a very easy to use and comprehend distribution.
4. Standard Normal distribution has mean value of zero and a variance of one N (0, 1), however it can assume any price form negative to positive infinity.

According to the central limit theorem, many distributions can be considered as normal distributions given the sample size is very big (Armitage, Berry & Matthews, 2002).
One important attribute of normal distribution is the ability to preserve their normality either when added or when subtracted. If we have 2 distribution then their sum will have mean equal to the sum of their mean and variance equal to the sum of the 2 variances. In health, normal distribution is applied in certain health conditions which can be measured on a continuous scale in nature. These include blood pressure, cholesterol and age.

Binomial Distribution

Binomial Distribution is the sampling distribution of the success cases, given that there is a θ possibility to achieve so. It is associated with two mutually exclusive outcomes, which in health can be success or failure. The total number of successes comes from a number of Bernoulli trials.

Poisson Distribution

Poisson Distribution is applied in cases that we want to count cases occurring over time, or per unit of time, such as admission to emergency care units, or number of heart attacks per month. Cases are represented by a discrete variable Y. Y~Poisson (θ) express a Poisson distribution with the following properties: $P(y/\theta)=\theta^{y}e^{-\theta}/ y$

Gamma Distribution

Gamma Distribution is a continuous probability distribution with two parameters. It exhibits one scale parameter and one shape parameter. They are defined by a shape parameter (α) and a scale parameter (β). It is also utilized as a probability model for time estimation.

Lognormal Distribution

Lognrormal distribution belongs to continuous probability distributions. It ranges from zero to infinity and due to the log nature it cannot carry negative values. It's defined by the mean and standard deviation, denoted by σ .It's suitable for skewed data, such as costs and ratios.

Dirichlet Distribution

A dirichlet distribution is a multinomial distribution and can be utilized to represent multinomial data with numerous categories. It's defined by (α) and represented by Dir (α).

2.12. Decision Making in Health

Decision-making in health is a complex process, which engages all social stakeholders and health professionals such as payers, physicians and patients. Decision-making in health is defined as a specific, confining and qualitative process; an art in the face of adversity. Although the access to pharmaceuticals is considered to be a right, which interrelates with the classification of pharmaceutical products as social goods (Trebilcock, 1993),

pharmaceuticals constitute commodities of a multibillion dollar industry. As such, pharmaceuticals are subjected to the 4 Ps context, which consists of price, promotion, politics and patients. Consequently, the prescribing of pharmaceuticals, despite being a typical, throughput and rather quick process, is the outcome of the elaboration of clinical guidelines, their consequent implementation and it comprises the micro-level policy making. We have to take into consideration the diverse, usually conflicting, perspectives of different stakeholders and how these match in order to elaborate and enact the health policy. This is aggravated, not only by diverging opinions but by the asymmetry information possessed by the involved parties. Given this, apart from the guidelines, the interpretation of the term "good prescribing" must be thoroughly assessed. Indeed, there are many key players in the decision-making process and each one gives a different meaning to what constitutes "good prescribing". Social stakeholders are interested in cost saving while on the contrary, the pharmaceutical industry focus primarily on profit maximization. Physicians pay attention to safety and efficacy ratio and although they are classified as the actual customers of the industry, they neither pay nor consume the medicine. Patients tend to prefer new medicinal products, since they perceive them more effective compared to older products. Patients are also influenced by secondary characteristics of the medication such as colour and taste.

As a result, the diverging interests of involved stakeholders can be bridged through the implementation of Evidence-Based Medicine (Moshialos, Mrazek &Walley, 2004). This must be bundled with ethical and juridical arguments as well.

Smith (2010) identified 8 issues that a decision analysis must integrate:

1. What is the broad specification of the problem faced and its context? How might a decision analysis help?
2. Who is the Decision-Maker with the authority to enact and the responsibility for the efficacy of any chosen policy?
3. Who will scrutinize the Decision Maker's performance? In particular who will audit her assessment of the structure and uncertain features of her problem (sometimes of course this might be the Decision Maker)?
4. What are the viable options the Decision Maker can choose between?
5. What are the agreed facts and the uncertain features that embody a plausible description of what is happening? In particular what is the science and what are the

socially accepted theories that inform the decision process? Is expert advice required on these issues and if so who should be asked?

6. What are the features associated with the process on which the decision or policy impinges that are uncertain? How and to what extent do these uncertainties impact on the assessed efficacy of a chosen policy? How compelling will these judgments be to the auditor? Who knows about this interface?
7. How are the intrinsic and uncertain features that determine the efficacy of any given policy related to one another? Who can advise on this? Who judgments can be drawn on?
8. Where are the sources of information and data that might help reduce uncertainty and support any assertions the Decision-Maker wants to make to an auditor? How might these sources be supplemented?

2.13. Decision trees

A decision tree comprises a decision model and is considered to be among the most essential tools in decision-making process. A decision tree is a predictive model, which simulates the progression of a sequence, such as a specific health condition. In the health decision-making context, decision trees are of fundamental value since they portray the possible transitions between health states, the different outcomes, the possibilities for each stage and the relevant costs. The value of decision relies to their inherent attribute to show real and measurable results, which will further enhance the decision-making process, minimising shortfalls and misjudgements. The application of Bayes theory in a decision tree will lead to introduction of a prior possibility to each step of the decision tree. Decision trees must be simple enough in order to be comprehended; nevertheless they must include all relevant steps which will lead to robust results.

2.13.1. Markov Model

The economic decision models have been increasingly utilized to assess health interventions. Among them, Markov decision models are among the most powerful tools that can be used under uncertainty. The almost epidemic prevalence of chronic risk factors, such as hypertension, has established Markov models as important tools for planning health care programs. A Markov Model is a form of decision-analysis that represents

processes, in which there are transitions in and out of mutually exclusive outcome rates that vary with time (Hsieh & Meng, 2007). It is a natural approach to transitions between discrete health states over time, for example, the progression over stages of a disease (Carreras et al., 2012). The Markov Model is of paramount importance in decision-making in Health and using a Monte Carlo simulation can create robust data regarding cost-effectiveness studies. Primarily Monte Carlo is a simulation method for probability modeling. Due to the technological advances, especially in the domain of information technology, the dissemination of MCMC simulation has been significantly enhanced. In health economics, the most essential feature of Markov models is that they take into consideration both the use of resources and the outcomes.

Simulation relies on certain guidelines in order to deliver robust data and increase credibility. Relevance is important and it implies the integration of previous data or assumptions, as in Bayesian Theory. Specifically, the law of big numbers and the central limit theory state that if a simulation is adequately designed and enough iterations are performed, then the results will be reliable and the noise will be minimal.

Markov chain is a stochastic process. As such, a Markov Model has well-defined properties:

a. Transition rates between the states are invariant with time (table 14).
b. The time spent in a given state follows an exponential distribution
c. The times in successive states are independent (figure 5).
d. The probability to transit from one state *α,* to another, *b, is* independent of the time spent in state *α.*
e. The probability to transit from one state *α*, to another state *b*, is independent of the past states before (Uhry, 2010).

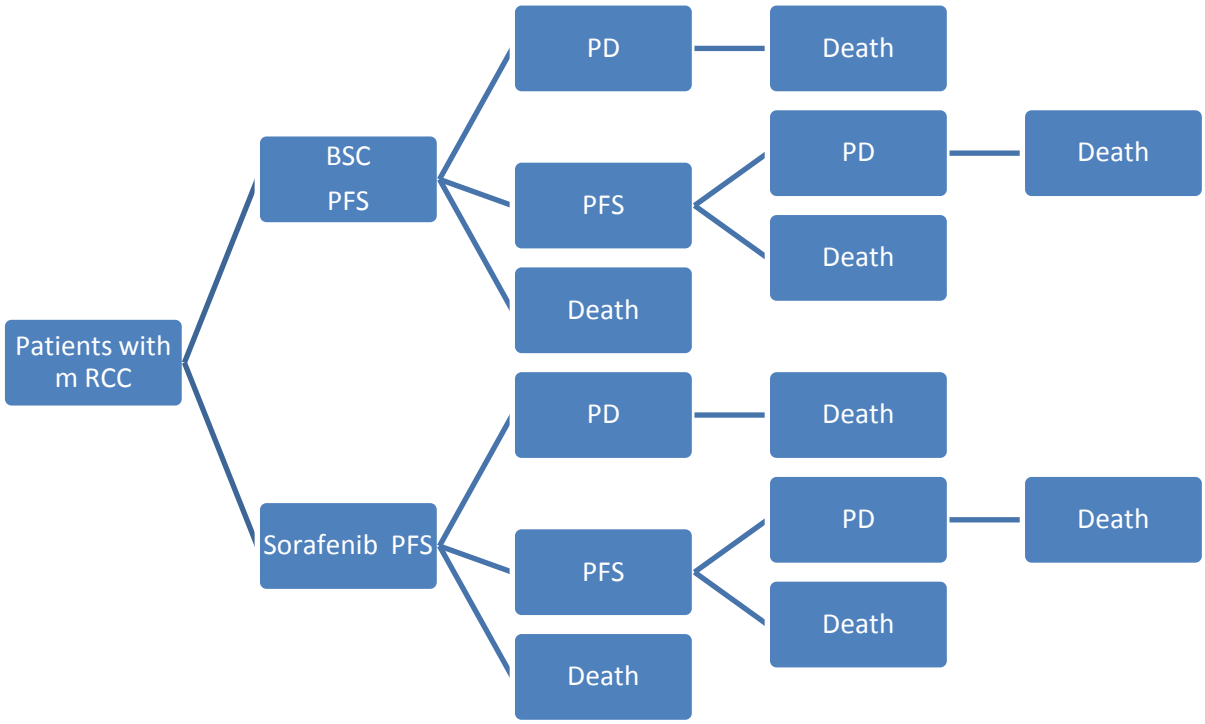
Table 14

Transition Probabilities between Markov Model Stages

	Asymptomatic	**Progressive**	**Death**
Asymptomatic	Tpr_{11}	TPr_{12}	1- (Tpr_{11} +TPr_{12})
Progressive	0	TPr_{22}	1- TPr_{22}
Death	0	0	0

Figure 5

Markov Model



Moreover, it should be highlighted that MCMC are memory-less, hence the probability of moving out or in a health state, is not related to any previous health state that the patient experienced (Spiegelhalter et al., 1999). This is described as the Markovian Assumption (Kemeny, 1976). Markov chain can be classified in 2 primary categories: discrete and continuous time. Discrete-time Markov chains and transitions occur at fixed points in time and we work with transition probabilities. Continuous time Markov chains whereby transitions can occur at any point in time and we work with transition rates. The Markov model follows the next decision-making process (Sato & Zouain, 2010):

1. Structure: The Markov model must sufficiently reproduce the possibility of prognosis that individuals may undergo, and the impact that treatment and health programs have on this prognosis. In this situation, the individuals are usually patients with a specific health condition, but may be healthy or asymptomatic, as in prevention campaigns.

2. Evidence: The Markov model provides an analytical structure in which relevant evidence for the study may be defined. This could be obtained through the model and through the entry parameters.
3. Evaluation: The Markov model provides a mean of translating relevant evidence into cost estimates and comparison of the impact of the options under comparison. The main types of study are cost-effectiveness, cost-benefit and cost-utility. The best option must be treated based on the evidence available.
4. Uncertainty and variability: The Markov model enables an evaluation of numerous types of uncertainty, including those related to the model and the entry parameters. The models must also provide flexibility to characterize heterogeneity through several subgroups of individuals.
5. Future research: The Markov model, through the evaluation of uncertainties, it is possible to identify priorities for future research, which will produce evidence to re-evaluate the issue in the future.

Ideally, a perfect setting should include destination state and the precise time that each transition occurs. The decision for reach treatment should be taken based on current health state and not base on the previous step the patient was. As a result, the endpoint of Markov decision process is the identification of the optimum treatment for each step, which includes even severity of disease classification. Gilks et al., in 1993 published one of the first papers which demonstrated the use of MCMC in the medical decision-making process.

The striking difference between Markov models and other models of economic evaluation in Health lies in the state of a patient during a specific moment in time. The impact of a given health problem is related to the time period it occurs. Markov Models can take this into consideration and it is effective when the risk involved is going over time. These ongoing risks have certain implications. Primarily, there is significant uncertainty with regards to the exact time the event will occur. This will exert differential impact on costs, utilities and disutilities. Additionally, there are certain medical states that usually occur more than once. A decision tree, in contrast to the Markov Model, cannot not track down these repetitive events (Sonnenberg, 1993).

The “Time” variable is clearly associated with the probability of a patient progressing through certain states in a series of separate time periods. In Markov models, these periods are called “cycles” and a disease is divided in distinct cycles, which have the

same duration. Probabilities refer to the transition between these states. The duration of these cycles depends on the disease and on the interventions that are being evaluated, and may be monthly or annual cycles. With regards to disease pattern, cycles in chronic diseases usually represent one year, while for acute conditions (i.e. infection) this period is reduced to a week. From an economic evaluation perspective, costs are restrained within each cycle. An exemption is cost-utility studies, in which the value represents the utility associated to each cycle. The average amount of time that a patient spends on the various states of the model is then weighted by cost or utility, which will be used to calculate the expected costs and outcomes. The transition rate between succeeding states is determined by the probability of the transitions. Thus, by determining the use of resources and outcomes in health, it is possible to evaluate these factors associated to the disease and the intervention that is performed. Primarily, it is fundamental to define the different states of the disease. The first stage in the construction of a Markov model is the definition of the different states of the disease. These states must represent the important clinical and economic effects of the disease, and all relevant effects should be included in the model. Each state must be assigned with its own utility. If we know the time spent in each state, we will be able to calculate the quality adjusted life expectancy of the patient.

One important consideration is that these stages of disease are mutually exclusive, because the patient cannot be in more than one state of the disease at the same time. The first state is defined as asymptomatic and indicates that the patient suffers from the disease, but is not experiencing its consequences and the risk of death is not higher than in someone who does not have the disease (Anderson, 1991; Bremaud, 1999). From this state of the disease, the patient may move towards the stage of "death", based on the probability of transition or progression of the disease. In disease progression state, the patient starts to experience the health impairments with an increased risk of death caused by the direct result of the disease on all other causes of mortality. The absorbing state is a state in the model from which it is technically impossible to move out, and an example is death. The utility value of death state is 0 and usually there is only one such state. At this point, the MCMC will converge to its stationary distribution. However, if the researcher wants to classify different causes of death, more than one dead state can be applied (Puterman, 1994).

A temporary state is another special feature of Markov Model, which denotes the existence of some specific states that are linked though a transition process between them. These states are also called tunnel states and their utility is to apply to health states, which

last less than a cycle. These may represent higher post-operative mortality, which will be normalized a couple of months after the operation. As a result of its short duration, it cannot be distinguished as a unique health state (Petitti, 2000). The backward arrows indicate the possibility of the patient remaining in this state or, if the model allows based on the therapeutic condition under study, it is possible to include improvements in the clinical conditions of the patient, as in the case of disease remission.

The probabilities of transition are considered in each cycle of the model, and they are represented in a matrix of the type "n χ n". The sum of probabilities of transition of each cycle must be equal to 1 (one), because there is only one state in each discrete moment of time. Thus, the probability of remaining in the same state is given by the value 1 (one) minus the probability of transition.

2.13.2. Monte Carlo simulation

The Monte Carlo simulations are stochastic techniques and they are based on the use of random numbers. They rely on repeated sampling and they are of particular interest in health due to their ability to operate even in cases with great uncertainty. As a rule of thumb simulation models must meet the following criteria:

1. Relevance. Observations must be generated through carefully selected data which must be applicable in the context of the specific model. These data may include previous reported data or even an expressed belief by a specialist
2. Diagnostics. Several methods have been created in order to check the stable state of a simulation, due to the existence of noise in any run.
3. Stability. The *c*entral limit theorem and the law of large numbers reassure that a well-designed and executed simulation, which will have enough iterations, will give some useful and reliable data (Dagpunar, 2007).

The central limit theorem describes the characteristics of the population of the means (Kallenberg, 1997), and it implies that an infinite number of parameters will deliver an equal mean of the total mean populations to the mean of the parent population, from which the sample were extracted. Consequently, the standard deviation of the sample means, which equals the standard error of the population mean, is smaller than the population mean and is equal to the standard deviation of the population divided by the square root of

the sample size. The variance of the sample means is the variance of the population divided by the sample size. Finally the distribution of means will tend to reach a normal distribution pattern as the size of samples increases. If we take all the above into consideration, it is extracted that the average data of each given measurement will tend to form a normal distribution. Furthermore, if we have variables which are not correlated, and their combination delivers a specific variable, then this variable has the random error of the primary variables normally distributed, as the number of the primary variables increases (Kendall, Liang & Wang, 2005).

The law of big numbers is of equal importance in the function of simulations. The law of large number suggests that by increasing the trials of a random process, then the expected values will reach actual ones. Consequently, a big number of iterations will mimic actual life evolution and prevalence of the specific variable and its effect .In health models, Monte Carlo is combined with Markov Model in order to create a distribution of values. There are 2 primary methods for MCMC methods: Metropolis –Hastings and Gibbs Sampling. Metropolis Hastings algorithm was introduced by Nick Metropolis in the 50's and was generalized by Hastings in the 70's (Hastings, 1970). Metropolis Hastings was introduced in order to overcome the obstacle of obtaining samples from complex probability distribution. Given that we have a distribution $\rho(\theta)$ with $\rho(\theta)=f(\theta)/K$ and K is a normalising constant which is difficult to calculate. Metropolis-Hastings allows to use any value given that it satisfies $f(n_0)>0$. With this value n, we can get a candidate value from the distribution; a common way to apply this is to add a mean zero normal deviate. By using the value (n) we can sample a candidate point out of a proposal distribution. A proposal distribution is denoted by q (n1, n2). This candidate point is the probability of having a value of n2 after we have set a previous value of n1. The candidate point will enable us to calculate density at that point and at the current point as well. This will lead us to $\alpha=\rho(n)/\rho(n_{t-1})$ which can be expressed as $\alpha=f(n)/f(n_{t-1})$.

What happens next is that if the density ($\alpha>1$) increases after this jump, then this will lead to the acceptance of the candidate point. However, if we notice a decrease in the density ($\alpha<1$), this will lead to rejection of the candidate point. Should this happen, then the proper step is to repeat this algorithm starting from the set of a candidate point, which again must satisfy the $(n_0) > 0$(Robert and Casella, 2010).

Primarily two conditions apply to Metropolis Hastings Algorithms .Firstly, this algorithm must be symmetric, thus satisfying the q(n1,n2)= q(n2,n1) .In addition to this, it must be highlighted that normalizing constant cancels out due to the elaboration of the

ratio of 2 different values of n (Dupont, 2009) . All the above will lead us to the $\alpha=\min\left(\frac{f(n)}{f(n_{t-1})}, 1\right)$. This is a Markov Chain, and according to Markov principles transition from one stage to the other depends only to the current state and not to the history. Markov Model carries some innate drawbacks, which are the tolls paid for some of its features. Some researchers describe Markov Model as "memoryless", which is attributed to the fact that once a patient shifts to another state, then model cannot "remember" where patient came from (Hiligsman, 2009).

2.13.3. Gibbs sampling

Gibbs sampling refers to a simulated Markov Chain Monte Carlo chain, which is used for the estimation of a sequence of observations from multivariate probability distribution. It is most useful when direct sampling is complicated. Gibbs sampling was first conceived by J.W.Gibbs in early 1900's and Geman brothers further refined in 1984 (Geman & Geman, 1984) . Given that we set a large amount of simulated values, then the distribution of the sample will be as close as possible to actual one. In its simple form, Gibbs sampling is similar to Metropolis Hastings algorithm. In more complex problems it enables researches to sample from a big variable set. One major difference of Gibbs sampler compared to the Metropolis algorithm is that in the Gibbs sampling process only one parameter is allowed to change. Gibbs is applied when the joint distribution is an unknown quantity, in the presence of known conditional distribution of the variables.

2.13.4. Common distributions and their denotion in winbugs

Dnorm (μ, τ) stands for the normal distribution with parameters μ and $\tau=1/\sigma^2$.
WINBUGS specifies normal distribution with mean (μ) and precision τ instead of mean and standard deviation.
Dbin (p, n) is the binomial distribution. It specified the distribution of successes in *n* given observations .p stands for parameters and usually it represents a proportion.
Dbeta (a, b) is a beta distribution with parameters a and b. It applies for unknown quantities that range between 0 and 1.
Dgamma (a, s) is the gamma distribution. It is a very flexible distribution and it applies for unknown quantities from 0 to infinite.

Table 15

Common Distributions

Expression Distribution Usage		
dbin	binomial	r ~ dbin(p ,n)
dnorm	normal	x ~ norm(mu, tau)
dpois	Poisson	r ~dpois(lambda)
dunif	uniform	x ~ dunif(a, b)
dgamma	gamma	x ~ dgamma(a, b)

2.13.5. Incremental Cost-Effectiveness Ratio

In the quest to further elaborate and capitalize on the QALY tool, several other parameters must be defined. Among these the incremental cost-effectiveness ratio (ICER) has emerged as the most significant tool. ICER denotes the additional investment that is needed in order to achieve one additional unit of health and it actually constitutes the policy interpretation of the economic analysis by comparing 2 or more therapeutic approaches. ICER effectiveness plane was first constructed by Black (1990) and it is divided in 4 quadrants which can be identified as in a map. The North-east quadrant contains more effective and costlier approaches. South east contains a new treatment that dominates the old one (more effective and cheaper). The North-west quadrant contains a less effective and costlier new treatment which is dominated. The South-west quadrant contains a less effective but also cheaper new treatment. South-East and North-West quadrants are self-explanatory.

The limit of the ICER is the λ, which stands for the maximum amount society is willing to pay for one extra unit of health. The Incremental Cost-effectiveness Ratio is Δc/Δe. Δe is the difference in effectiveness between the two comparative drugs, while Δc is the cost difference between the two treatment, which encompass not only

pharmaceutical costs, but medical and other costs as well. ICER has, by definition, a Gauchy distribution, due to being the ration of 2 asymptomatic variables. Consequently, it has no mean value and variance is indefinite. If we substitute Δe with 1/NNT then ICER is NNT x Δc .The rationale of *number needed to treat* lies to measurement of clinical effectiveness with binary outcomes and it represents the number of patients that have to been treated with a new therapy, compared to the gold standard, in order to benefit one additional patient (Cantor & Ganiats, 2012). Some authors have suggested the introduction of the NNE (Number Needed to Expose) and EIN (Exposure Impact Number).
ICER is reckoned to offer several advantages especially in defined budget and in presence of mutually exclusive treatments:

1. Rank least and more effective intervention within each disease.
2. Calculate ICERs; eliminate dominated.
3. Recompute ICERs and re-rank by ICER (lowest to highest).
4. Starting with lowest ICER, keep buying until money is gone.
5. Highest ICER you can afford is the *shadow price*.

Alternatively, ICERs are calculated, the dominated are eliminated and then we recalculate. All treatments with ICER less than the defined WTP threshold are purchased. More exclusive and efficient insurers have higher thresholds.

The standard point estimate of the ICER is $\rho=\Delta c/\Delta \varepsilon$, which is the average cost divided by average effectiveness (Gafni and Birch, 2006) and directly influences the decision process. If one product is cheaper and more effective than a competitive-mutual exclusive one-, then this state is called dominance and the product is approved for reimbursement. If the product concerned is more expensive and less effective, we can conclude that it is dominated and consequently rejected. ICER plane comes into real perspective when one product is concurrently more expensive and more effective, or less expensive and less effective. In these two cases, all resources and especially willingness to pay threshold and magnitude of the additional cost, or money saved, have to be evaluated and put into perspective.

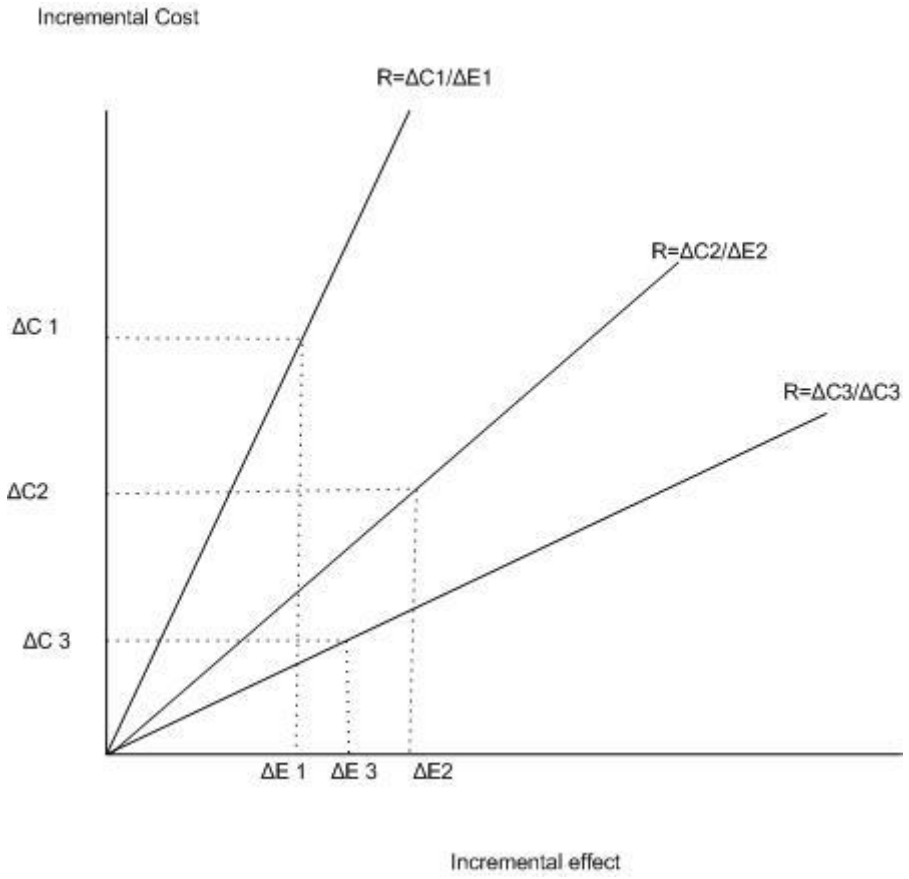
O'Brien et al., in 1994 argued that, if possible, all data should be stochastic and randomly sampled from population of the target group. As a result, costs and treatment effects will be defined from the same patient sample. This led to the need to characterize the uncertainty of ICER and to the development of approaches to illustrate uncertainty of

ΔE and ΔC. Moreover, O'Brien et al., demonstrated that in the NE quadrant, which depicts one usual case of a more costly and more effective product, it's possible to demonstrate uncertainty with 95% confidence intervals for the numerators and denominators of cost-effectiveness ratio separately. However, it is not possible to do this for the ICER, which is partially imputed to its discontinuous distribution (Wilan & Briggs, 2006). This problem is illustrated as "the close-to-zero problem" which illustrates the neighborhood of zero in the denominator, that makes a formula for the variance of the ICER obstinate and it was first reported by O'Brien (1994). Quadrant II accommodates treatments that cost less and are more effective compared to the benchmark, which rather rarely occurs in real life settings. If we observe great health gains (big denominator), then unavoidably the ratio will be close to zero (Mullahy & Manning, 1995). On the other hand, large cost savings on the numerator will create a ratio with a negative infinity. This was highlighted by Stinnet and Mullahy (1998) who commented on an ICER which was reported by the Panel on Cost-effectiveness analysis. This panel referred to a strategy to fortify grain acid with folic acid which led to a cost-effectiveness ratio of -13,000 USD. The interpretation of these findings by the authors was that it "resulted in cost savings of about 13,000 USD accompanying every QALY gained." Authors raised the following issue: "Is it better to save 13000 USD per each QALY or is it better to save 6500 USD per QALY gained?" The answer is not straight forward. If we reach the 13000 USD savings on the grounds of significant cost savings then the answer is yes. However, if we reach the same number through decreased effectiveness, then the right answer is no. O'Brien presumes that a negative correlation exists between cost and effectiveness. This can be explained by the following facts: The lower confidence limit of the ICER is given by the ratio of this lower confidence limit of cost and the upper confidence limit of effectiveness. This is the best case scenario. Respectively the Upper confidence limit of ICER is given by the ration of the Upper confidence limit of cost and the lower confidence limit of effectiveness, which is the worst case according to O' Brien (O'Brien & Briggs, 2002). Given the aforementioned reasons, the combination of these 2 approaches will give natural worst and best limits. Even more, it makes the assumption that cost and effectiveness are independent variables and that each confidence interval is calculated with no consideration of the confidence interval of other measures. The ratios can be derived from the "box" which is formatted by the maximum and minimum values in the confidence interval of each measure, namely northwest and southeast. The confidence interval as measured by the "box" is approximately 90%.A corrective approach is to use smaller confidence intervals

for both cost and effectiveness, which does not eliminate the risk for a wider than 95% confidence interval (figure 6).

Figure 6

INCREMENTAL EFFECT



(Briggs and Fenn, 1998)

Taylor's approximation is another approach to the definition of ICER's confidence interval. Taylor's method can be used to estimate the variance function of two random variables, which in this case are cost and effectiveness differences.

Taylor's method is utilised under the assumption that ICER has a normal distribution (table 16). Consequently, an ICER without a normal distribution may lead to false confidence intervals. Van Hout (Van Hout, Gordon & Rutten, 1994) argue that cost and density function have an elliptical shape and that Δc and Δe follow a normal distribution. Rationale behind lies to the assumption that generally more effective treatments cost more. The Confidence Ellipse method offers the advantage over the box method that allows for covariance between the numerator and denominator. In contrast to the box method which accepts as a principle that cost and effect are two independent variables, the confidence

box accepts that these two variables are interrelated. The joint density is constant at the elliptical lines on the CE plane. It is also documented that the joint probability density is constant if Q, the correlation factor, is constant as well. As a result, this ellipse will deliver over 95% of the integrated probability to give a confidence surface analogous to a confidence interval. If there is a positive correlation between cost and clinical effectiveness then the confidence interval will be smaller. On the other hand, if there is a negative correlation, then the confidence interval will be wider.

Another method which is founded on the assumption that Δc and Δe follow a joint density distribution is the Fieller method. The advantage over Taylor's method is that it takes into consideration the skew of the sampling distribution of the ratio estimator (Polsky et al., 1997). Researchers elaborated the cost-effectiveness plane, as pictured above in order to investigate the meaning of cost-effectiveness analysis. Δc is plotted on the vertical axis and Δe on the horizontal axis. Δc = vt- vs and it represents the cost difference between intervention t and s. Δe = ST (τ) − SS(τ) = πT – πS and it represents the absolute risk reduction of intervention t versus intervention s. According to definition of NNT, 1/ Δe is the number needed to treat in order to avoid a clinical event. NNT can be interpreted more easily. For instance if there is 0.1 difference in 1 year survival probability between 2 treatments, the we can estimate that 10 patients (1,/0.1) have to be treated with the more effective therapy in order to prevent one death. In the SE section, it's obvious that Δc<0 and Δe >0 and therefore treatment is dominated by standard. At the contrary, in the NW section, Δc >0 c and Δe <0 are indicators that treatment is more costly and less efficient and consequently it must be rejected, at a health policy coverage level. Regarding the other two sections, SW and NE, cost and effectiveness of the intervention must be taken into consideration in order to tag the intervention as cost-effective or not. Dowie in 2004 raised some concerns regarding cost-effectiveness, clinical effectiveness and cost. ICER located in the SW quadrant delivers the message that the new intervention is less effective and cheaper compared to the standard treatment. ICER will be positive, but what´s the proper way to interpret this? Is cost-effectiveness merely a strong variable that should overrun all other aspects, or exceptions must be endorsed in order to eliminate bias that may lead to inadequate medical treatment? For instance, a new intervention produces one more QALY at 15,000 GBP more compared to the current standard. Willingness to pay (λ) is 40,000 GBP, which leads to a positive ICER and the new intervention is accepted. In the same concept, the same dilemma applies to an intervention that loosed one more QALY at a saving of 15,000 GBP. We do accept that the gain of a QALY at a cost of

15,000 is justified and a common place. To a large extent, one should argue that the loss of a QALY at a saving of 15,000 GBP should be rejected, since this amount will not generate enough other benefits to the patients, in order to make up for the benefits (for instance the extra QALY) that the standard treatment already provides. But the controversy lies within the notion of the new intervention that loses one QALY at a saving of 45,000 GBP. So, if are willing to spend 40000 for an extra QALY, is it proper and legitimate to save 45000 in order to spare one for another patient?

O'Brien et al., based on their empirical review of willingness to pay and willingness to accept studies in a variety of fields, concluded that the 'selling price' of a QALY is higher than its 'buying price'. They suggest that the CE threshold is kinked at the origin of the CE plane.

The meaning of this finding is that it will take a greater amount of savings in order to make up for a lost QALY, than the amount to pay on order to gain one QALY. The former is called Willingness to accept (WTA) and it´s located in the SW quadrant (figure 7). Consequently, based on O´Brien, the λ line should be as in figure 7.

This pattern was classified by Thaler in 1980 as the *endowment effect* (Thaler, 1980) which describes the natural tendency of people to demand much more in order to give up something (in our case a QALY) than they would be willing to pay to acquire it.

Special caution must be paid in the negative ratio, which may have been derived from opposing data. A QALY lost at a cost of 5,000 GBP will have the same ratio as a QALY gained at 5000 GBP savings. As a result, a negative ICER is not a reliable tool in the decision-making unless the specific corresponding quadrant is indicated.

ICER faced criticism for the following reasons: Negative values are meaningless, while ICER is not a reliable concept when difference in effectiveness are near zero, since this will lead to excessive and unjustified values of ICER (Moreno et al., 2010). Additionally, it has little sensitivity when difference in cost are near zero as well and direction of increasing ICER is opposite in the NE & SW quadrants.

Table 16

Methods for calculating ICER

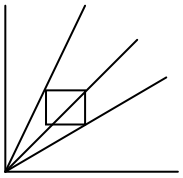
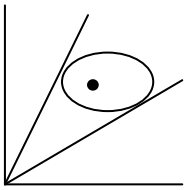
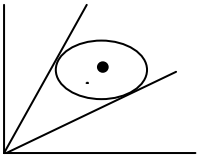
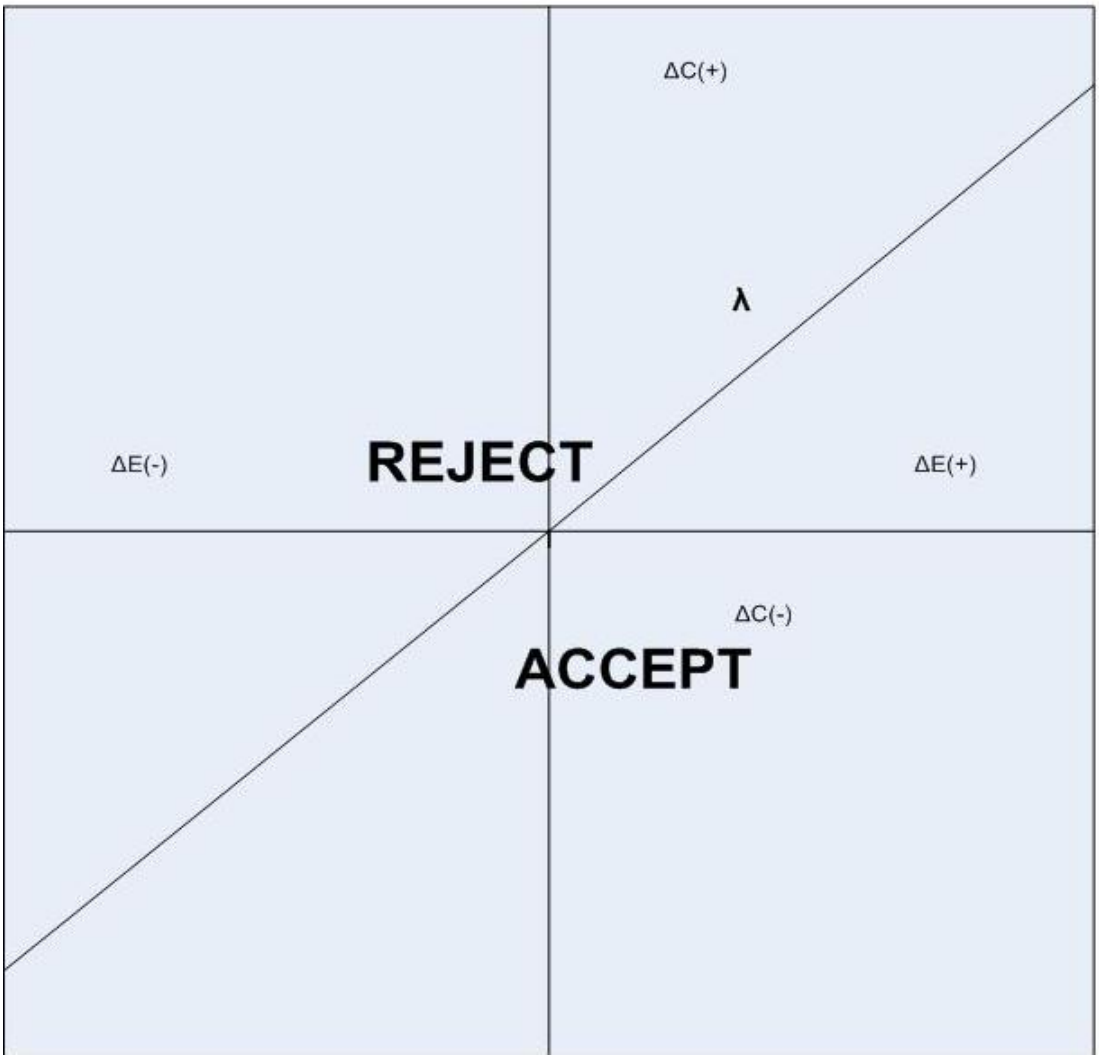
Method for calculating CI for ICER	Principal	Limitation	
Box method O' Brien	Uses the confidence interval around the cost and effectiveness estimates, to compute the confidence interval	Does not account for covariance between cost and effectiveness May create CI larger than 95%	
The Taylor Series	It can estimate the variance of a function between 2 random variables by taking into account the respective covariance between these 2 variances	If ICER is not normally distributed, then confidence interval may be misleading	
Fieller's	It enables to overcome limitation of Taylor Series(normality of ICER distribution). It follows the assumption that cost and effectiveness follow a bivariate distribution .It takes into account skewness of data	Bivariate normality may be difficult to justify, especially when sample is small	
The confidence Eclipse	Takes for granted that there is an elliptical shape of ρ(Δc ,Δ e)	Acts only approximately	

Figure 7

ICER PLANE



2.14. Incremental Net Health Benefit (INHB)

Claxton and Ponnett in 1996 were among the first to introduce the concept of INHB. The INHB is considered the alternative ICER since units are in dollars and the result and impact can be clearly defined and comprehended. In addition to this statistical inference is easy (linear combination of cost and effect estimates) and no ambiguity exists about quadrants. It is also important to underline its ability to compare more than 2 interventions. Foremost, INHB does not have the uncertainty of negative λ, while it delivers the net effect in effectiveness unit and not in monetary values. The incremental net benefit enables decision-making and it is defined as: INB $=\Delta e - \Delta c/\lambda$. The cost of the intervention is

divided by the value of one effectiveness unit. However, in order to perform an INB calculation, we need some prerequisites as following:

1. Δe
2. Δc
3. V(ˆΔe) estimated variance of Δe
4. V(ˆΔc) estimated variance of Δc
5. C(ˆΔe; ˆΔc)

The average INHB of a medical intervention is the net benefit, (which is assessed in units of health instead of monetary values) after the adoption of a specific intervention compared to investing the relevant resources to marginally cost-effective intervention. Decisions usually involve 2 or more health interventions and a policy maker has to make the most legitimate decision. The incremental NHB of a treatment X_1 compared to treatment X_0 is:
$(\Delta e_1-\Delta c_1/\lambda)-(\Delta e_0-\Delta c_0/\lambda) =(\Delta e_1- \Delta e_0)-(\Delta c_1-\Delta c_0)/\lambda$
A distinction has to be made between INHB and NMB. If we multiply the Δe with the value of one effectiveness unit (λ) and subtract the Δc, this will give us $\Delta NMB= \lambda.\Delta e - \Delta c$. Many authors (Stinnett & Mullahy, 1998) suggest that the utilization of INHB of a program at λ, which denotes the amount a decision maker is willing to pay in order to gain an additional unit of effectiveness, provides significant advantages over ICER. The Net Health Benefit at λ is the difference between the health gain derived from a given health intervention and the health gain that justifies this cost. In contrast to the ICER approach, the INHB does not eliminate dominated programs according to which quadrant they are located in. The INHB takes zero prices when λ takes the CER of that specific program. The net benefit is defined as NHB =e –k/λ. For 2 programs the incremental NHB is defined by the = (e1-e2)-(k2-k1)/λ. The INHB of these 2 programs (1, 2) intersect at only one point. This specific point is the ICER of the 2 programs. The implementation of the INHB illustrates the health gain which is expected to occur after programme 2 is launched, instead of programme 1, with the health gain needed to justify the additional cost. Finally, the sampling distribution of both ΔNMB and ΔNHB are continuous.

2.15. Uncertainty

While cost effectiveness analysis through modeling have contributed significantly to rational and evidence based decision- making, the interpretation of the results is pertinent

to the uncertainly of the model. Uncertainly is defined as the lack of explicit knowledge or significant fluctuations in the value range of variables. As a result, an inapt structure of a model can potentially nullify the results of the economic evaluation. This uncertainly comprises a pervasive topic in health care and is divided (or deals) to 4 distinct areas:

1. Variability in sample data: this is about the inherent variability that exists in the parameters of interest between patients within a specific population and it is attributed primarily to genetic and racial traits.

2. Generalisability and transferability of results to another population cohort, when using efficacy data from other health care settings.

3. Extrapolation of data. This occurs when authors try to extrapolate from short to long term outcomes.

4. Analytical Methods: This deals with the methodological flaws of the system and its structure. Methodological choices derive from different approaches regarding the process (Briggs, Sculpher & Buxton, 1994).

Moreover, the uncertainty can be divided between disease-centred and patient-centred. This includes a bundle of issues such as prognosis and disease course, natural variability, causal explanation and the possibility that the wrong data were used, such as costs and measurement of health outcomes.

The above topics highlight the likelihood that resources allocated to a specific intervention do not lead to optimum return on investment, which could have been achieved with a different approach. Uncertainty can be assessed by describing the range and likehood possible values and by creating a statistical model which will describe the distribution of this model, which assess the new intervention. This distribution will give answers to whether this new approach is more or less cost-effective, or whether more research is needed. Although there is still room for errors, it clearly strongly correlates with the likehood to generate more health for the same amount of money spent. In addition to this, these distributions also indicate which interventions to avoid since they will generate less health gains. Also, the ability to set apart health gains generated by different interventions is critical. Uncertainty is driven by a magnitude of underlying reasons. As described in the Bayesian Analysis above, utilisation of data borne out of clinical trials will minimise uncertainty. Briggs (Briggs & Gray, 1999) clearly set apart deterministic

sensitivity analysis (which is defined by variation of the model's inputs) compared to probabilistic sensitivity analysis (which is defined by the relative likehood regarding the range of unknown parameters). Different approaches to sensitivity derive from the varied sources of uncertainty. Currently there are 4 sources of Uncertainty:

a. *Chance Variability* represents the unavoidable uncertainty which will affect the outcome of a given intervention. It's a random error which connects the cause and the outcome and it may alter the underlying value, upwards or downwards.
b. *Heterogeneity* describes the variation between individuals which can be attributed to specific characteristics of individuals (age, sex, weight, height) that can be tracked down, or are attributed to characteristics that cannot be described (such as patient characteristics (Briggs, 2000). Deterministic sensitivity analysis is useful in the former analysis to see how expected outcomes vary between identifiable subgroups, possibly followed by probabilistic averaging over population subgroups according to their incidence.
c. *Parameter Uncertainty* is related to the definition of the right values of the parameters, which can be allocated in two categories:
    a. States-of –the-world describes parameters that under certain condition could have been accurately measured. These parameters usually are defined by distributions, and they are subject to probabilistic sensitivity analysis.
    b. Assumptions are quantitative judgements which are utilised in the model and are the results of consensus between stakeholders. Discount comprises the most common assumption, since it has to be mutually agreed upon and it varies among countries. Nevertheless, they are still a source for methodological uncertainty and deterministic analysis may check the sensitivity by using different values.
d. *Ignorance* describes the uncertainty due to lack of knowledge regarding disease course, possible flares, remissions, reoccurrences and prognosis.

An economic modeling entails many assumptions. There are so many variables and unavoidably this may lead to a great level of uncertainty which is inevitable. Genuinely, credibility of economic model rests to its validity.

Uncertainty is categorized as being either first or second order (Stinnet & Paltiel, 1997). First order effect embodies the inherent nature of a trial, which is never taken for

granted even in cases where overwhelming data exist. One common method to minimise first order effect is to increase sample size. In the modeling era, the capability to simulate thousands of patients and all possible health states clearly eliminates first order effects. Second order effects are more important in cost-effectiveness analysis.

Primarily, uncertainty may be caused by programming or syntax error. Secondly, logical checks and right program selection may help overcome this issue. There are several parameters that may influence the uncertainty level. These included parameters that are related to the analytical methods such as the discount percentage, parameters that describe disease status and severity such as blood glucose and cholesterol levels and parameters that could be sampled according to Briggs (2000).

Ultimately all the evidence derived out of cost-effectiveness analysis, will lead to the complicated process of decision- making. Usually, actions are not reversible since there is limited time or it's not feasible to overturn a health state. Moreover, heterogeneity exists among different groups of individuals. This process is dynamic, since new products emerge, obsolete technologies are abandoned or withdrawn and consequently this affects the policy. In the light of uncertainty, Health Agencies have developed reimbursement schemes, which provide that reimbursement depends on individual's health outcome (risk sharing projects) or it's impermanent and more data are needed for a definite appraisal.

These remarks led to evolution of policies that stretch beyond approval or rejection. In the light of uncertainty, one option is to delay or postpone reimbursement until robust data are available (patient access schemes) that intend to alleviate the impact of decision uncertainty. These schemes reduce the effective price of an intervention, there increasing the possibility of being cost-effective for the current health setting technology. The patient access schemes serve another target: ability to gather real life data, which will further reduce uncertainty. Methodological uncertainty refers to optimum not only of the analytical methods but to the use of cost and benefits and how to define them in the model. Structural level uncertainly follows the methodological uncertainly, at least as they occur over time. Structural uncertainty can be described as the quality level of the modeling. Proper selection of competitors, inclusion or exclusion of clinical trials, patient's sample and population of the study may minimise structural uncertainty. Lack of evidence may further complicate structural uncertainty.

During the probabilistic analysis phase the variability factor arises. Variability is the difference between patient's responses that can be attributed to chance. Although variability can be explained on heterogeneity basis, homogenous groups as well

demonstrate variability. Parameter uncertainty is the uncertainty about true values of parameters used as inputs in the analysis (O' Brien & Briggs, 2002).

2.15.1. One-way sensitivity Analysis

In the context of existing uncertainty, researchers want to be aware of the likely impact stemming out of using the wrong value on the final outcome, by assessing the sensitivity of the model to this specific parameter. One way sensitivity analysis is the variation of one value in the model by a given amount and assessment of the impact on model's final results. This analysis is considered as adding further layers of uncertainty to the process of assessing cost-effectiveness. Although is well accepted method, it is really difficult to define which parameters must be included in the analysis and the relevant range that has to checked. Additionally, there is ongoing dispute about the interpretation of the results and the clinical/economical complications that these create (Willan & O'Brien, 1996). One way sensitivity analysis is the simplest form of sensitivity analysis. By varying one value in the model (within a specific range "highest to lowest"), it is feasible to assess impact on results. The range of the variation can be defined according to the confidence interval. As a result, a researcher may identify parameters that exhibit biggest impact on results. A tornado diagram is a very useful way to display results. An one-way sensitivity may also define a threshold, since in certain cases it is useful to identify a certain level (such as the willingness-to-pay), given certain variations in the inputs (Briggs, Sculpher &Claxton, 2006).

2.15.2. Multiway sensitivity Analysis

While one-way sensitivity analysis is useful in demonstrating the impact of one parameter variation in the model, sometimes it is imperative to highlight the relationship of more than one parameters on the final outcome. This requires the concomitant variation in 2 or more parameters. For instance, inclusion of another patient cohort will cause a variation of certain inputs, which in turn may influence total cost.

2.15.3. Expected Value of Perfect Information

The Bayesian Statistical Decision theory has enabled the development of new methodological approaches to further minimise uncertainty. Expected value of Perfect Information (EVPI) enumerates the opportunity loss that is related with the uncertainty of the model and underlines the opportunity cost of wrong decision. The concept of expected has acquired a pivotal role in the health economics domain since the selection of a specific product is done of the axis of the expected value. EVPI quantifies the amount that decision makers should pay in order to eliminate all uncertainty of the model (Ades & Claxton, 2004) which could be achieved only by an indefinite large sample.

The EVPI is defined as a secondary endpoint of a probabilistic sensitivity analysis and it indicates whether we should further continue research and at which cost. This is done through setting of an upper limit on the societal returns to future research. It is imperative to underline that wrong reimbursement decisions ensue to loss of health gains and waste of financial resources. The Expected value of perfect information is the difference between the expected net benefit of perfect information, without uncertainty and current information, with uncertainty. EVPI represents the expected gain in benefit by resolving all uncertainly in the spectrum of the evidence that constitute the decision. In the economic analysis, uncertainty is denoted by the cost-effectiveness plane, cost-effectiveness acceptability curve and confidence regions and intervals of both ICER and Net benefit (O'Brien & Briggs, 2002).

We must also emphasize the existence of EVPPI (Expected value of partial perfect information) which represents the expected gain in health benefits by resolving some sources of uncertainty. When the WTP is relatively low and the technology is not cost-effective, then the accumulation of further information is casts doubts whether it can alter the taken decision. EVPI increases proportionately with the WTP threshold. In case that the EVPI is higher that the WTP, then the technology is assumed to be cost-effective. From a health policy perspective, this means that any new data are not expected to alter the cost-effectiveness status of the technology as the WTP increases. It's implied that the higher the WTP threshold, the lower the uncertainty level becomes. The same applies for EVPI. If we set a very high WTP (Claxton, 2004), this will lead to the increase of EVPI. This is caused by the declining rate of uncertainty decision. EVPI will reach its highest value when the ICER matches WTP threshold. This point is characterized by high uncertainty since there is no clear indication whether to adapt or reject the new technology.

In a decision model with unknown parameters θ, which denotes the value of t (comparative treatments parameter), the net benefit of treatment t under θ value is defined by the $B(t, \theta)$. The net benefit of treatment t is $B(t, \theta) = \lambda U(t, \theta) - C(t, \theta)$, where λ is the willingness- to-pay threshold, C denotes the cost and U the utility created. In this context the optimal decision, in the context of existing information is the one that delivers the highest net benefit max$t$ $E\theta B(t, \theta)$. At this point the values of θ are not known and in this context the net benefit of a decision under perfect information is reached by averaging the joint distribution of θ as following: $E_\theta max_t B(t, \theta)$. This leads to the

EVPI = $E_\theta max_j NB(j, \theta)$ - $max_j E_\theta NB(j, \theta)$ (Ades , Lu & Claxton, 2004;Welton et al., 2012).

The Bayesian-decision theoretic approach has been utilised in order to enable the assessment of Expected value of information and expected value of perfect implementation. Based on our model for the cost-effectiveness, we explore the uncertainty by determining EVPI. This clearly indicates whether is it cost-effective to pursue further evidence and how much we should spend it order to achieve so. Through the utilisation of a Bayesian decision-theoretic approach, the framework establishes cost-effective health care provision and the maximum returns to investment in further research (through the expected value of perfect information) and implementation efforts (through the expected value of perfect implementation).

Currently, at least theoretically 3 major questions must be answered prior to a reimbursement decision:

1. Indubitably, cost-effectiveness is the primary question that has to be addressed.
2. In the face of uncertainty, one question that has to be addressed is whether is justified to pursue further research, and whether there are indications that by collecting more evidence we able be able to support our hypothesis.
3. The final question relates to investment of strategies that will further help dissemination of the selected health policy.

Although we documented that cost-effectiveness analysis remain the holy grail of reimbursement process, EVPI emerges as an important and complementary approach system's objective is to maximise health gains.

2.16. Pricing of Pharmaceuticals

Cost-effectiveness of pharmaceuticals depends on two attributes of each product; effectiveness for the patient and costs incurred to the system, both direct (cost of the product) and indirect (other pharmaceutical, medical and societal benefits and costs). Effectiveness can be assessed by different approaches such as QALY, and disease specific instruments. The pricing of pharmaceuticals, as a major approximation in the cost-effectiveness analysis of pharmaceuticals is a complex procedure and currently there is a diversity of approaches, even among European Countries. In Cyprus, prices of pharmaceuticals have been relatively high and this may lead to compromised access of patients and may also jeopardize sustainability of health funding structure. This is more prominent is patent protected products. It is reckoned that payers (Health systems, Governments and Insurance agents) are under significant pressure from social stakeholders in order to provide continuous access to affordable and innovative treatments. At the same time, Countries want to protect pharmaceutical industry in order to sustain their research and development project, in particular for unmet medical needs (Kanavos & Vandegrift, 1997). The protection of the pharmaceutical industry is very important for Cyprus; albeit for another reason since exports of pharmaceutical is a powerhouse in Cyprus' economy. Specifically, they constitute the second highest value sector, consequently it is apparent that Health Authoritative must secure low prices without adversely affecting sustainability of this industry. Cyprus applies External Reference Pricing (ERP) for the pricing of pharmaceuticals. ERP uses a basket of prices of the same product in other countries, in order to set local price. ERP constitutes an easy system to apply, thus it suits smaller countries with reduced resources. Under certain conditions, it can lead to quick results as well. Companies try to overcome the barriers of ERP by adopting a single price for a specific product, launching products first in high price countries and at a later stage to low-priced countries and reaching confidentiality agreements with payer, in order to minimise impact on pricing. Programs such as rebates and discounts were applied, which grant payer some financial benefits, diverting spill-over effects on pricing. Setting a single price is not feasible since it will hinder access to low cost countries.

ERP has some drawbacks as well. As mentioned earlier, confidentiality agreements may distort the transferability of data. Moreover, some countries have implemented several risk sharing schemes, which link reimbursement to outcomes, for that reason actual price may be significant lower.

In the public sector, pricing is done through tendering. Tendering is an aggressive form of pricing and reimbursement. Despite its short term potency, many authors raised severe concerns regarding the impact on industry sustainability. Tendering was proved to be potent, but contextually is a sensitive process and it can contribute as a cost-containment tool only within a strict and specific framework.

3. METHODOLOGY

This chapter presents, describes and discusses the methodological pillars of the study. Initially, this chapter delineates the literature review. In the second part, this chapter depicts all parameters of the economic model. The second part begins with the decomposition study, promulgates the construction of the economic model and the definition of its variables. Emphasis is given to the Markov Model, along with the elucidation of its structure and integral functional parameters. Finally, the concept of elaborating innovative pricing schemes is outlined.

3.1. Research Design

The principal topic of this study, that is the economic evaluation of pharmaceuticals, is based on the Bayesian inference (Spiegenhalter, 1999). Firstly, a probabilistic Markov model was constructed to simulate disease progression. Markov Models enables the input of the significant parameters engaged in a dynamic change through a transition matrix, which is achievable in average software.

Nevertheless, several important stages must precede. Firstly, a systematic review is a prerequisite, aiming to gather, analyse, assess and present all related literature spanning from health technology assessment to economic evaluation in Cyprus. This facilitates a better understanding of the operational framework, identification of weaknesses and accentuation of opportunities.

For the reason that one of the goals of this study is to contribute both to theory and policy, as a value-added position paper, the deliverables must convey a corresponding value. In this context, we conducted a decomposition study, which elucidated the key cost-driving elements of Cyprus' pharmaceutical market. Consequently, by exploiting and scrutinizing these findings, we selected the pharmaceutical product, which was be set as the subject of this economic evaluation. The selected product must meet some criteria such as budget impact, significant sales forecast, limited number -if any-alternative options, and clear medical need for its indicated health condition.

3.2. Operational background of HTA and economic evaluation in Cyprus

Initially, a detailed, precise and thorough evaluation of the operation framework is incumbent. An extensive literature review was performed to assess the current state of economic evaluation in Cyprus and in Europe. The primary objective is to delineate current state of this sector in Cyprus, in order to be able to further lay out the pillars of the study. Foremost, a strength, opportunity, weakness and threat analysis was performed. This is coupled with a critical assessment of HTA and economic evaluation in the context of Cyprus' health care sector. Going a step further, current thesis assess the current pricing and procurement method of public health care sector, that is tendering .This serves as a benchmark for the pricing section of this thesis.

3.3. Assessment of current pricing and procurement method

Cyprus' pharmaceutical sector is a unique case among European country in the sense that it relies exclusively on tendering. Since tendering is utilised as the main pricing and reimbursement method only in Malta, Cyprus and Iceland, scarce data exist apropos its effectiveness, and even less regarding its methodological and conceptual foundation. In this context, the impact of some significant variables, such as clinical value of the products (innovation level), patent status, administration setting and sales volumes, are defined.

3.3.1. Methods and Data

In order to assess the impact of tendering on value reduction (weighted price reduction) and mean price reduction, we extracted the sales of 2011 from the official procurement list of MOH. We selected 178 products, with corresponding value of 49.3 million euro, approximately 50% of total public pharmaceutical expenditure. The selection criteria of these products were set as their value, volume and clinical importance. Following this, we identified the official pharmacy procurement prices (wholesale) and tendering price for the same product, including strength and package. Two products that did not carry wholesale price were excluded. As a benchmark, the official pharmacy procurement price was set, that is the wholesale price, and as endpoint the tendering price, which is the winning bidding price for each product procured by the public sector. We defined the value

reduction (weighted price reduction) as the reduction in expenditure achieved by use of tendering prices compared to the corresponding expenditure under official the pharmacy procurement price-the wholesale price-for the same volume of products (strength and package). We also defined the mean price reduction as the difference between the tendering price and the wholesale price, for the same products. The mean price reduction refers to the mathematic average reduction of all prices of tendered products, while value reduction takes into consideration the quantity. We assessed both since anecdotal sources suggest that usually products that bid for larger quantities are willing to submit lower prices, which leads to linearity between total volume and price reduction.

We analyzed the reductions in value and prices for the total sample and for three partially overlapping subgroups as following: Generics, Branded and the top-twenty products in value. Generics are segregated under the assumption that generic medicines can create higher savings for a health System as seen in other tendering countries. Generic substitution has been a significant approach for cost-containment in many countries and, in particular, the generic-mature markets have reported very steep price reductions. Generic companies are not burdened with R&D expenses; thus they can offer very low prices.
Another subgroup consists of branded products. For branded products, there is no clear evidence considering effect of tendering. Prices of branded products, in contrast to prices of generics do not represent only production costs, but they have to subsidy R&D costs as well.

The final group includes the top twenty products in value. This niche of medicines consists of highly innovative branded medicines which are already included in the Branded products analysis, with limited-if any alternative options at all-and there are no clear indicators whether tendering exerts a significant effect on this cost-driving category (Godman et al., 2011). This was an issue raised by official stakeholders who indicated that they perceive tendering as inefficient in this category, due to the monopoly status of products. Furthermore, pharmaceutical marketing (including potential benefits) strengthens patient's and physician's brand loyalty and makes the non-inclusion of these medicines in the formulary very complicated. For the aforementioned reasons, it is appealing to explore the impact of tendering of this specific cohort which constitutes approximately 27% of public sector's pharmaceutical expenditure. The normality property of the values will be tested with Shapiro-Wilk normality test.

The second part of this approach is to test which variables influence price reduction in tendering. For the scope of this study, we identified seven potentially exploratory

variables that may influence outcome of tendering and are associated either to intrinsic attributes of the product or to extrinsic product's attributes stemming out of its positioning and its uptake in the market. Primarily, innovation is significantly intertwined with pricing of pharmaceuticals (Garattini, Cornago, & De Compadri, 2007). In order to assess interaction of innovation with price reduction through tendering, we will adopt the ASMR (*Amelioration du Service Medical Rendu,- Improvement of Medical Benefit)* classification of HAS santé in France. In France, pharmaceutical products are assessed by the Commission of Pharmaceutical evaluation, based on five pillars:

1. Efficacy and Safety.
2. Position of the medicine in the therapeutic strategy and the existence or absence of therapeutic alternatives.
3. Severity of the disease.
4. Type of treatment: preventive, curative or symptomatic.
5. Public Health Impact.

After the assessment is concluded, each product is awarded a Medical Benefit level ASMR classification ranging from I to V as following:

1. ASMR I major improvement (new therapeutic area, reduction of mortality).
2. ASMR II significant improvement in efficacy and/or reduction of side-effects.
3. ASMR III modest improvement in efficacy and/or reduction of side-effects.
4. ASMR IV minor improvement.
5. ASMR V no improvement.

Tender type is also another important variable and currently, three types of tendering are applied in the Cyprus Health Setting (table 17). INN sole asks for a specific medicine, by its INN name. There is no virtually competition in this setting so we do not anticipate any significant price reduction. This however has to be counterbalanced by law provision which may reject the procurement of a product should Drug's Committee decided that submitted price is high. INN group refers to the procurement of several products of a specific therapeutic category such as aromatase inhibitors and anti TNF agent and the elaboration of treatment guidelines based on the results. This is applied to agents that are considered to possess class effect and therefore cheapest product is set as a therapy while

Table 17

Tender Types in Cyprus

Terms of Tendering	INN sole	INN group[3]	INN alternative
Key characteristic	Asking for only one pharmaceutical product. (i.e *bortezomib* for multiple myeloma)	Asking for several products with the same indication (e.g.anti TNF agents for RA) Classified protocol is elaborated based on the tender outcome (Cheapest product gets first line treatment, second cheapest product gets second line treatment) Currently infliximab is first line therapy, *adalimumab* second line and *etanercept* third line for Rheumatoid Arthritis	Asking for one product among several competitive ones Hypertension: *irbesartan* or *candesartan* or *valsartan* or *telmisartan* or *losartan* or *eprosartan*
Target group	Orphan, individualized (requiring therapeutic blood monitoring) innovative and highly specialized medicines	High drop-out rate and specialized medicines such as Anti TNF and aromatase inhibitors	Usually high volume primary care products which demonstrate class effect (statins, Proton Pump inhibitors, Angiotensin Receptor Blocker)

[3] In the INN group all products are included in the formulary, in different treatment lines according to bidding price .In the INN alternative only the product with the lowest price is included in the formulary

the other products are set in subsequent treatment lines, according to prices. Finally INN alternative is applied in high volume primary care products which are perceived to be interchangeable such as statins, angiotensin converting enzyme (ACE) inhibitors, non-steroid anti-inflammatory drugs (NSAIDS), and proton pump inhibitors (PPI) (e.g. omeprazole or lansoprazole) and asks for only one product (usually among 3 or more). Additionally, we will assess impact of value and volume of sales, hospital or outpatient administration, patent status, and wholesale price.

3.3.2. Statistical Analysis

For the statistical analysis, we used a beta regression since conventional regression analysis based on normal-error models are not suitable when outcome is bounded, either by proportional or by percentage. Beta regression is a generalization of logit regression and due to inclusion of percentage as an outcome, as in our case the price reduction, is a better option since it is more flexible and can assume different shapes including left or right skewness. It is also similar to generalised linear models and it employs a parameterization of the beta distribution in terms of its mean and a precision parameter (Schmid,2013). As a result, we assume that price reduction follows a beta regression as following: *pricereduction=interc+a*Innovation+b*hospital/outpatient + c*patentstatus +d*wholesaleprice* + e*volume + f*value+g*tendertype*

We applied these for 5 different categories: for the entire market, for products that carry an ASMR classification, for branded products only, for generic products only and for high value medicines (products with sales more than 1,000,000 euro yearly value of sales)

3.3.3. Data Management

We collected official sale from MOH of year 2011 and we selected 178 products with sales of 49 million euro, corresponding to approximately 50 % of annual pharmaceutical expenditure. Sampling was done through a stratified sampling process based on several stratums such as volume, value and therapeutic importance. Medicines refer to a specific dosage form, strength and pack size of a specific molecule. Among the selected products, 101 were assigned an ASMR status (Le Pen, Priol & Lilliu, 2003). A product with more than one indications is possible to carry 2 ASMR classifications which may vary, based on

efficacy for each indication. For the aforementioned reasons, we picked the ASMR classification for the indication of the respective product in Cyprus.

3.4. Decomposition of pharmaceutical sales in Cyprus

The second stage of this thesis is the selection of a product/ category which will be used in the context of the economic evaluation. In chapter one, it's outlined that the scope of this thesis is to contribute both in theory and practice. This presupposes that results should not be only be flawless, but aligned to current needs of Pharmaceutical sector of Cyprus. This is the core of the economic evaluation and the reason for not randomly selecting one product. On the contrary, we wanted to choose products which embed the primary reason for carrying out an economic evaluation, as discussed earlier. We designed a decomposition study which elucidates which factors dominate medicine's sales in Cyprus and which products are of particular interest in view of their fast uptake, clinical importance and budget impact. For the scope of the decomposition study we requested the official pharmaceuticals sales from MoH for the period from 2005 to 2011. Decomposition study will reveal which products are the cost-drivers and demonstrate significant budget increase.

As previous authors demonstrated (Gerdtham, Johannesson & Jonsson, 1993; Gerdtham, Johannesson & Gunnarsson, 1998) and further perpetuated by Dubois (2000) and Lambrelli (2011), expenditure is the joint result of three important factors: Price of drugs (Pr), Quantity of drugs (Q) and Product-mix Residual (r) (i.e. switch from cheap to more expensive medicines or vice versa). Quantity of drugs dispensed can be further decomposed in order to clarify whether increase of quantity was caused by more frequent visits to doctors, issuing of more prescriptions by the doctors and increase of beneficiaries.

Prescriptions= Prescription/ Visits x Visits/ Beneficiaries x Beneficiaries

This study accentuates the integral dynamics in prescribing of pharmaceuticals and goes beyond quantity and prices. Quantity would remain the same, if all patients switch to a match cheaper alternative product. In this case, total expenditure would decrease as well. However, we would observe the same expenditure reduction if consumption was also reduced. This leads to uncertainty regarding causality of expenditure reduction. This gap in decomposing expenditure to its primary elements can be addressed by introduction of the residual, a factor which comprises all involved variables and in a simple approach indicates whether patients switch to expensive or cheaper product. According to the following

equation expenditure, residual represents the difference in money spent which cannot be explained by volume and price alone. Taking all the above into consideration, residual can be used to identify changes among selection between competitive products. Residual bigger than 1 (or 100 percentages wise) indicates a shift to more expensive products, while a residual smaller than 1 (or 100 percentage wise) indicates a shift to cheaper products.

We will use the Defined Daily Dose, a statistical measure of drug consumption introduced by World Health Organization, to calculate quantity (WHO, 2013) (table 18). Although other authors use package, package size variability may alter analysis.

$$Exp=Q*Pr*r$$

$$r = \left[\frac{Qp1+Qcomp1}{Qp2+Qcomp2}\right] * \left[\frac{Pp2*Qp2+Pcomp2*Qcomp2}{Pp2*Qp1+Pcomp2*Qcomp1}\right]$$

Exp=expenditure

r= residual

Qp1=Quantity of product 1 in the baseline year (year 1)

Qcomp1=Quantity of competitive product in the baseline year (year 1)

Pp1= Price of product 1 in baseline year (year 1)

Pp 2= Price of product one in year 2

Qp2=Quantity of product 1 in year 2

Pcomp2= Price of competitive product in year 2

Qcomp2= Quantity of competitive product in year 2.

We also divided pharmaceutical market into Anatomic Therapeutic Chemical (ATC) categories, as seen in table 18, which divides active substances into different categories according to their therapeutic, pharmacological and chemical classification and the organ or system target. These categories are further classified in groups at five different levels. This will allow us to track down changes in product and disease level. We faced a dilemma regarding ATC L01 category which contains the majority of oncology cost-drivers, primarily the two most important categories with a significant annual increase rate (BPI, 2011): Monoclonal Antibodies and Protein Kinase Inhibitors. Another significant characteristic of this category is that after patent expires, its "generic" products will be defined as biosimilars and their pricing pattern is expected to be quite dissimilar, compared to existing generics, in view of the more strict regulatory framework that govern

these agents (Kozlowski et al., 2011). This category is not defined by DDD since the dosage is highly individualized. German Institute of Medical Documentation and Information (DIMDI) suggested a L01 DDD classification (DIMDI, 2013). Upon consultation with key oncologists in Cyprus, we deemed fit to foster L01 classification in our analysis. In general, antineoplasmatic agents are the core of any pharmaceutical expenditure analysis due to their budget impact and high price increase of these agents which according to some authors, doubled in a decade (Fojo & Grady, 2009). Real expenditure will be calculated

Table 18

ATC classifications

Code	Contents
A	Alimentary tract and metabolism
B	Blood and blood forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genito-urinary system and sex hormones
H	Systemic hormonal preparations, excluding sex hormones and insulins
J	Antiinfectives for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculo-skeletal system
N	Nervous system
P	Antiparasitic products, insecticides and repellents
R	Respiratory system
S	Sensory organs
V	Various

by dividing the actual (nominal) expenditure by the Consumer Price Index (CPI), which is calculated by Cyprus Statistical Services, thus adjusting for inflation. We will also use the term of relative price index, which can be calculated by dividing the Pharmaceutical Price Index (PPI) by the CPI. In the index, prices of 2005 were set to 100. In addition to this, we extracted visits to public health care doctors, number of prescriptions issued by public doctors and number of beneficiaries from 2005 to 2011, from annual reports of MoH. All aforementioned data refer to almost 85% of the population. This includes the majority of cost-drivers medicine such as monoclonal antibodies, oncology and neurology products which are dispensed almost exclusively from public pharmacies. We excluded ATC V category, a category which contains various products such as diagnostic agents, since these products vary greatly in the dosages used and consequently there are no DDD.

In order to analyse trends of the Cyprus public pharmaceutical market, we used the residual approach to identify which trends dominate Market. The next step is to examine to which extent beneficiaries visit, products per prescription and total number of beneficiaries influence pharmaceutical expenditure. By identifying market forces and prescribing market, further research can be performed in the most important sectors and agents.

3.5. Pharmacoeconomic Evaluation

The economic evaluation of this thesis is conducted through a probabilistic Bayesian Markov Model which simulates disease progression (Briggs & Schulpher, 1998) with the aim to compare various realisations of the economic aspects of the model versus the current best supportive care (standard therapy). A Markov model can be applied both at a cohort and an individual level (Brennan, Chick & Davies 2006). In our case, the Markov Model (figure 8) describes the evolution of disease between health states in a stochastic way based on transition probabilities (Gilks , Richardson & Spiegelhalter, 1996) which depend only on the current state of the process. Therefore, Markov Model can provide a more compact representation, compared to alternative options, in a repeated set of outcomes (Barton et al., 2004).

A cohort-based Markov model employs transition probabilities between successive health stages. Each stage is associated with relevant costs and health utilities (Sonnenberg & Beck, 1993). We defined 3 non absorbing health states, namely: Progression-free survival (PFS), Progression disease (PD) and death. Patients begin from PFS state, after their diagnosis with metastatic RCC is confirmed, as seen in figure 8. Each cycle lasts for

one month, due to the low expected survival of these patients and transition occurs within one month period. Prior distributions were extracted from a landmark clinical trial and they were verified by two local oncology experts.

The cost-effectiveness approach (Roberts et al., 2012) of the above model carries out the optimal properties of the Bayesian decision theoretic approach as pointed by several authors (Cooper, Sutton & Abrams, 2004; Talias, 2007; Moreno et al., 2012). The model was synthesized in the Winbugs software package (Bayesian inference Using Gibbs Sampling) suitable for analyzing complex statistical models (Spiegenhalter et al., 2003) and the R package BCEA (Baio, 2012) (Bayesian Cost-Effectiveness Analysis) to do all the economic evaluation process after the Bayesian model has been run. The R2winbugs programme was also utilised in order to call Winbugs from R. Winbugs is a freely available software which is capable of performing complex Bayesian analysis, as in the case of Markov Model. Foremost, it allows for custom made statistical codes, thus enabling the development of statistical modeling according to needs and goals of the researcher. Additionally, there are several packages, such as the BCEA, which further upgrade Winbugs' capabilities. Finally, Winbugs allows a visual inspection of the model, which minimises potential errors that can undermine the reliability of the results. Time horizon was set to 10 years, a period during which all patients will transit into 3rd state, and the discount rate was set at 3.5%. Since there is no official economic evaluation of medicines in Cyprus, the average discount rate, according to literature, was used. The literature review of the paper was be performed as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009)(figure 9). This Thesis also conforms to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines regarding economic evaluations (Drummond, 2013) (Table 19).

Figure 8

Markov model for second line m RCC.

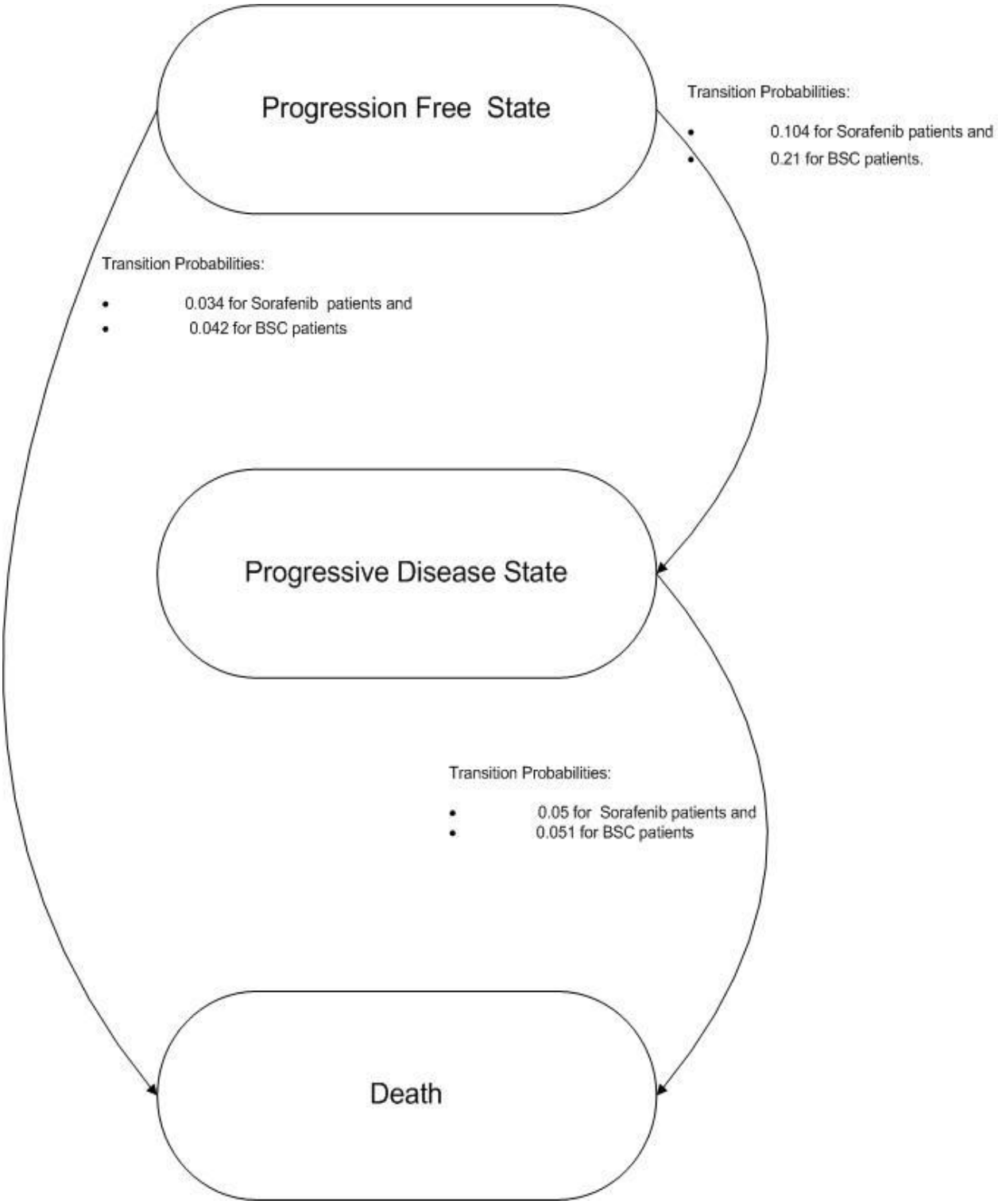


Table 19

CHEERS guidelines

ITEM	RECOMMENDATION	INPUT
1	Identify the study as an economic evaluation, or use more specific terms such as ‘‘cost-effectiveness analysis’’ and describe the interventions compared	Cost effectiveness and Value based pricing of Sorafenib compared to best supportive care
2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base-case and uncertainty analyses), and conclusions.	Done
3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Definition of ICER and VBP for Sorafenib Definition of a price that reflects added value and utility of sorafenib treatment
4	Describe characteristics of the base-case population and subgroups analyzed including why they were chosen.	Patients presented with metastatic RCC (as per indication)
5	State relevant aspects of the system(s) in which the decision(s)need(s) to be made.	Cyprus Public Health Care Sector

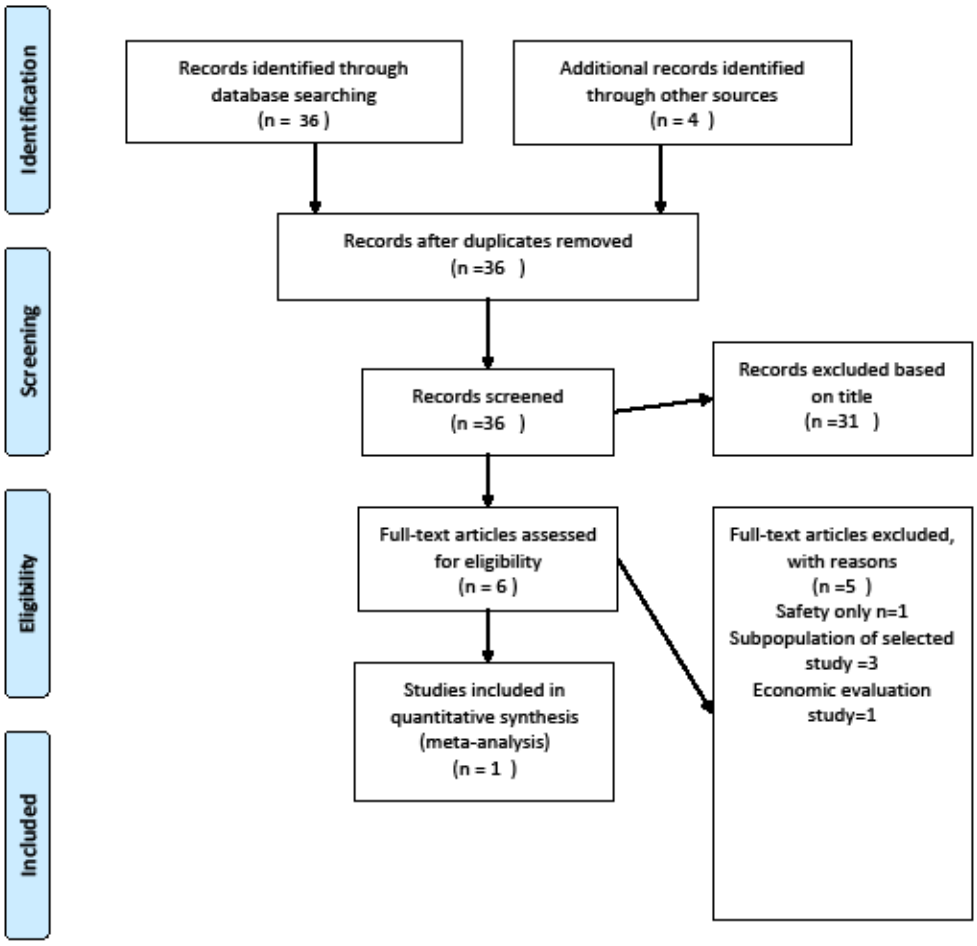
6	Describe the perspective of the study and relate this to the costs being evaluated	Costs from Payer perspective in Cyprus
7	Describe the interventions or strategies being compared and state why they were chosen	BSC vs sorafenib, a new product for this indication
8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate	Time horizon is 10 years, by the end of this period all patients will transit into 3 stage (death)
9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	3.5 % as per literature
10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	QALY due to its universal acceptance
11	Single study–based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	A high quality low bias clinical trial (Escudier)
12	Synthesis-based estimates: Describe fully the methods used for the identification of included studies and synthesis of clinical effectiveness data.	N/A
13	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe	In the Methodology section

	primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate	In the Methodology section
15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	In the Methodology section.
16	Describe all structural or other assumptions underpinning the decision-analytical model.	In the Methodology section
17	Describe all analytical methods supporting the evaluation.	In the Methodology Section
18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to	Table 21-23

	show the input values is strongly recommended.	
19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Results
20	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Sensitivity analysis was performed
21	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge	In the Results section

Figure 9

Flow Diagram of literature review as per PRISMA guidelines



We performed a literature review using mesh terms: Sorafenib" "Carcinoma, Renal Cell" and "Randomised Controlled trial" (Figure 9). The literature review tracked down 36 studies eligible for inclusion. We identified only one study that compares sorafenib with BSC, which was also the unique study for Best Supportive Care (BSC) (Escudier et al., 2007). TARGET trial is a large phase 3, high quality and low bias study trial. This is a multicenter, multinational, randomised double blind clinical trial and it was also used for the assessment of sorafenib by NICE (Thomson et al., 2010). This study demonstrated the survival benefit of sorafenib over BSC, lasted for one and a half years and recruited 903

patients with renal cell carcinoma that was resistant to standard therapy. Eighty three percent of recruited patients received cytocine therapy as first line therapy. The median age

Table 20

Clinical Effectiveness Data

	Sorafenib	**BSC**
Progression Free Survival (PFS) (months)	5.9	2.8
Overall Survival (OS) (months)	19.3	15.9

of patients in this trial was 58 years. Sorafenib was significantly superior compared to BSC for both PFS and overall survival (OS) (Table 20): For PFS, the hazard ratio (HR) was 0.51 (95% confidence interval [CI]: 0.43–0.60), and for OS, the HR was 0.72 (95% CI: 0.54–0.94). Based on the Progression free and Progression disease duration, we estimated the transition probabilities which were incorporated in the Markov model, according to the following approach:

Risk of an event (1 month) = [1-(0.5)^(1/median time to event)] (Miller and Homan, 1994; Purmonen et al., 2008)

This can be easily derived through the equations:

$P=1-e^{-R}$ and *R=-ln[0.5]/(Time to event/number of treatment cycles)* (Cooper , Sutton and Abrams, 2002)

Monthly transition probabilities to progressive disease were defined as:

_ 0.104 for Sorafenib patients and,

_ 0.21 for BSC patients.

Monthly death probabilities (from progression free state) were defined as:

_ 0.034 for Sorafenib patients and,

_ 0.042 for BSC patients.

Monthly death probabilities (from progressive state) were defined as:

_ 0.05 for Sorafenib patients and,

_ 0.051 for BSC patients.

In order to incorporate uncertainty in the model, we expressed these probabilities as beta distributions (Gelman & Rubin, 1995; Briggs et al., 2002). Beta distribution is defined as beta (α, β) and α denotes number of patients that transit to next stage while β is the

total sample size minus number of patients who shift to the next disease stage (Carreras et al., 2012; Briggs, 2000). We set the time horizon as a decade by the end of which all patients will shift into 3rd stage. On the grounds of the absence of any official guidance regarding technical parameters, we set the discounting rate at 3.5% according to current practice in UK (NICE, 2013) and Sweden (LFN, 2013).

The probability of progression and probability of death follow a beta distribution. Cost distribution of general medical and other pharmaceutical costs (excluding sorafenib cost) was assumed to follow a gamma distribution and method of moments (Hall, 2004) was applied in order to estimate parameters of this distribution. The assumption is that if there is a random sample from a gamma distribution $X_1\ X_2\ X_3\ \ldots\ldots X_n$, α and β are the unknown parameters of gamma distribution, then the expected value equals $E[X]=\alpha\beta$ and $E[X^2]=\alpha\beta^2+\alpha^2\beta^2$. Thence, we have to find the moments estimators by solving the two following equations:

$\frac{1}{n}\sum_{i=1}^{n} Xi = \overline{X}=\alpha\beta \quad \frac{1}{n}\sum_{i=1}^{n} X_i^2 i = \alpha\beta^2 + \alpha^2\beta^2$. The solution results to:

$\alpha = (\overline{X} / \beta)$ *and* $\beta = [\{(1/n)\ \sum_{i=1}^{n} x_i^2 - \bar{x}^2\}/\ \bar{x}]$.

The pharmaceutical costs are denoted by a uniform distribution as per the recommended (approved) daily dosage. Utilities distributions also follow a beta distribution. Other costs are assumed to follow a gamma distribution since they are non-normally distributed, highly skewed and demonstrate kurtosis (Briggs et al., 2003). Method of moments was applied in order to estimate parameters of this distribution.

The Markov Model was loaded with an initial cohort of 1000 patients. Patients are supposed to be on the first cycle of the disease. In order to ensure stability of the program the first 50000 iterations were discarded. The convergence of the model was assessed through the trace plots of samples and the standard error of the results.

3.5.1. Health State Utilities

In the context of economic evaluations, health state utilities are of paramount significance. Specifically, they are linked to each health state and determine the health gains of the product (Drummond et al., 1997). We used QALY, in view of its universal acceptance. In this notion, specific health states will be assigned to each Markov state of the disease.

We adopted the health state utilities as reported by Thomson (Thomson et al., 2010) which were assessed through the use of UK EQ-5D: health state utilities of 0.76 (s.e. 0.03) for PFS and 0.68 (s.e. 0.04) for PD. Since utility value is defined between 0 and 1, we assume that they follow a beta distribution. The parameters of the beta distribution are defined as following (Briggs, 2002; Ara & Weiloo, 2012):

$$\mu=\frac{\alpha}{\alpha+\beta} \qquad \sigma^2=\frac{\alpha\beta}{(\alpha+\beta)^2(\alpha+\beta+1)}$$

$$\alpha = (\frac{1-\mu}{\sigma^2} - \frac{1}{\mu}), \qquad \beta = \alpha(\frac{1}{\mu} - 1\ )$$

(μ=mean, σ=variance)

_ Progression Free State (153.26, 48.4),

_ Progressive disease state (91.8, 43.2) (table 21)

3.5.2. Health resource utilization and costs

In Cyprus, cancer patients are entitled to free medical care by the Ministry of Health. Therefore, we relied on the local guidelines and we used the latest publicly available costs (Ministry of Health). In Cyprus, medicines are procured through tendering; as a result prices vary compared to the wholesale ones. All health resource utilization rates and costs will be derived from Pharmaceutical Price lists and the Medical Law, which contains all costs for medical activities which are available in public hospitals.

For our analysis, we used the tender price, since final assessment of a product, especially apropos to the introduction of new products and accordingly, economic analysis is performed with the tender price. In Cyprus, there are no other patient access schemes or Managed Entry Agreements (MEA) that may further influence prices. Moreover, palliative care is provided by Non-Government Organisations, therefore costing is rather complex but also significantly lower compared to private sector prices. To this direction, we made a provision for costing with current private sector prices in the sensitivity analysis.

Based on the costs as reported in the literature and current practice in Cyprus, we calculated costs related to m RCC treatment in Cyprus (Table 22-24).

Table 21

Distribution of costs and utilities for Sorafenib patients

	Cost (euro) 2012	Type of Distribution	Distribution parameters (α, β)
Cost of Sorafenib	2880	Uniform	(2880,3000)
Medical and other pharmaceutical cost in Progression free stage	357	Gamma	(1714, 4.8)
Cost in the progression stage 1st and 2nd month	1499 [4]	Gamma	(7196, 4.8)
3nd Month and further on	770	Gamma	(3696, 4.8)

[4] Provides that patients will continue sorafenib for one month after progression until diagnosis is confirmed.

Table 22 Distribution for costs in the best supportive care patients

	Cost (euro) 2012	Type of Distribution	Distribution parameters (α, β)
Medical and other pharmaceutical cost in Progression free stage	1048	Gamma	(5031, 4.8)
Progression stage	770	Gamma	(3696, 4.8)

Table 23 Pharmaceutical costs

PRODUCT	Cost per Tab (euro) 2012	Monthly Cost	Dosage
SORAFENIB 200mg	24 eur		
Losartan 50 mg	0.06 per pill	1.8	o.d
Amlodipine 5 mg	0.02 per pill	0.6	o.d
ACE inhibitors	0.02 per pill	0.6	o.d
Opiods			
Morphine10 mg/ml	0.36	54	5-20 mg per 4 hours
Morphine 10 mg tab	0,07	4.2 -54	Up to 100 bid
Morphine 20 mg	0.33	19.8 -99	20 b.i.d.
Morphine 30 mg	0.19	11.4-34.2	30 b.i.d
Fentanyl 100mcg/hr	19	190	1 patch every 72 hours
Fentanyl 25 mcg	5.4	54	1 patch every 72 hours
Fentanyl 50 mcg	10.43	104.3	1 patch every 72 hours
Ondansetron 8 mg	0.66		Per Need

Table 24

Health services utilization and costs

PARAMETER	Sorafenib	BSC	Hospitalization (Daily-cost in euro)	Blood tests (Full blood count, liver function SGPT SGOT and creatinine-cost in euro)
PFS			€135	€157 Monthly
Consultation	1 specialist 40 eur	1 GP 20 eur		
CT scan	€256 (every 3 months)	€256 (every 6 months)		
	Annual costs related to hypertension 3 visits 60 eur			
PD				
Consultation	1 GP 2 nurses 1 psychologist 70 eur	1 GP 2 nurses 1 psychologist 70 eur		

3.5.3. Sensitivity Analysis

A one way sensitivity analysis was performed to identify which variables-and to which effect-influence the outcome of the economic evaluation. This includes costs of the product, medical and other pharmaceutical costs, PFS and OS, utility values, time horizon of the study and discounting.

3.5.4. Therapeutic area under evaluation

Based on the results of the decomposition study, we focused on ATC L01 products, that is products for oncology use. This will render our findings salient for health authorities, which are actively pursuing cost-containment approaches. We selected Sorafenib, a product that embeds all attributes that we have defined, such as high current and forecasted expenditure and absence of interchangeable products. Sorafenib is indicated for renal cell cancer and liver cancer. In this analysis, we focus on renal cancer which accounts for the majority of its cases. Renal cell carcinoma (RCC) is a highly vascular cancer type that originates in the lining of tubulins in the kidney. It is usually asymptomatic, and this impairs outcomes since patients present at a later stage. In general, prognosis of metastatic renal cell cancer (mRCC) is poor. Survival rate for tumor <4 cm is around 90–95%. Even for larger tumors that are limited to the kidney, thus without venous invasion, prognosis is still favorable and 5-year survival is around 80–85%. Tumors that have extended through the renal capsule out of the local fascial investments usually lead to 60% 5-year survival (National Comprehensive Cancer Network Guidelines for Kidney Cancer, 2013). Since RCC is asymptomatic, if the patient presents with metastasis to the lymph nodes, this is translated to a poor prognosis, and 5-year survival is 5–15%. Metastasis to other organs such as lung and liver leads to even lower 5-year survival. Median age at diagnosis is 65 years. Prevalence of RCC rose significantly during the last decades, and it is estimated that the rate of increase is 2% annually. This is due to better diagnostic procedures such as Computerised Tomography scan and MRI and also because of increase in risk factors such as obesity, hypertension and dietary habits (McLaughlin & Lipworth, 2000). It affects more males than females and the ratio is 1.5:1 (Wingo, Tong & Bolden, 1995). In Cyprus, it is estimated that around 40 cases are diagnosed every year (MoH, 2010). Chemotherapy and radiation have not delivered significant health gains. The novel therapeutic category of tyrosine kinase inhibitors has shown promising results in treating advanced RCC (Thompson-coon et al., 2010). Still and all, their relatively high cost impairs further

therapeutic penetration and uptake in some countries, especially in the present context of economic crisis. Sorafenib is a small molecule that inhibits tumor cell proliferation and tumor angiogenesis and increases the rate of apoptosis in several tumor types (Chang et al., 2007). On a molecular level, it inhibits the receptor kinase activity of VEGF receptor 1, 2, 3, the serine–threonine kinases Raf-1 and B-Rad and platelet-derived growth factor receptor b (Wilhelm et al., 2004). Furthermore, it targets the transforming growth factor a. In renal cancer, it was shown that increased production of VEGF and the mutation of the tumor suppressor gene VHL are involved in the process of RCC. There is no single follow-up treatment for all patients. A tailored approach is needed for each patient as size, stage and grade of tumor define the risk of relapse and disease progression.

3.5.5. Willingness-to-Pay Threshold

The Willingness-to-pay threshold (WTP) is a monetary amount which illustrates the higher limit that each society is willing to pay for a patient to spend one year in a perfect health state. This threshold has not been defined in Cyprus, nevertheless the outcome of any pharmacoeconomic evaluation is highly pertinent to the hypothetical limits of resources that society is willing to allocate to medical interventions. In this sense, we tried to set a WTP threshold for Cyprus. It is important to underline that due to the low prevalence of RCC, sorafenib was granted an orphan status (EMEA, 2007). According to the European Medicines Agency, a medicine must meet the following criteria in order to be awarded the status of orphan drug:

1. It must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating.
2. The prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify.
3. The investment needed for its development.
4. No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

This provides several advantages to the marketing authorization holder, such as 10 years of protection from market competition and provision for a centrally assessed procedure for

obtaining marketing license in the EU that allows companies to make a single application to the European Medicines Agency. In addition, orphan drugs are usually exempted from strict reimbursement rules. The monopoly power, either actual or artificially created, of marketing authorization holders of orphan drugs translates to high prices for this market niche. Societal values and solidarity principle confront with financial capacity of Health Agencies and Payer to fund these products. With this backdrop, we adopted the recommendations of WHO (Murray, 2000) regarding utilisation of multiplies of Gross Domestic Product (GDP) per capita as a proxy for WTP threshold. In 2012 the estimated GDP per capita current prices was 20,517 euro (IMF, 2011); accordingly we define the WTP threshold at 61,551 euro. Since sorafenib is an orphan drug, we will also use the highest recommended level (5 x GDP).

3.6. Value-Based Pricing

The Value-based pricing scheme constitutes a paradigm shift from volume to value. The aim is to convert the health benefits that the product delivers, which exceed the health benefits displaced in the broader health system and society in light of the additional cost incurred (Camps-Walsh , Aivas & Barratt, 2009), into monetary value. The core of value-based pricing is the incorporation of the product's value into its price in the concept of a holistic and integrated pathway. It also safeguards access to effective and innovative drugs by setting a price that reflects the utility created (Brown, Brown & Sharma, 2005). From an industry perspective, this establishes a clear motive to pursue innovation, which will be rewarded accordingly. From a payer's perspective this leads to optimality of available resources. Taking all the above into consideration, we designed a conceptual pilot study to assess practicability of adopting value-based pricing in Cyprus, from a payer's perspective. The scope of this study is to explore the feasibility of setting a price based on value. We track down all issues, positive and negative, stemming out of this process. Due to the fact that value-based pricing is a new approach, several methodological and conceptual limitations exist. They include:

1. The determination of affordability thresholds and overall affordability.
2. The relative lack of identifying, measuring and valuing additional health benefits.
3. Conversion from value to price.
4. Data aggregation in heterogeneity population.

5. Inherent challenges of measuring and comparing utilities of different types, different diseases and different stages of the same disease.
6. Time lapse between availability of clinical data and best practice development.
7. Ambiguity regarding optimal approaches of late external benefits that cannot be captured in the short term analysis (Kanavos et al., 2010).

Factors such as disease status and stage, bioethical arguments, inclusion or not of societal costs, uncertainty of results, robustness and reliability of clinical data infiltrate value definition and currently there is an ongoing debate regarding the actual definition (Sussex, Towse & Devlin, 2013).Therefore, by capitalising on the previous findings, we explore the potentials for defining Value-based prices in Cyprus.

4. FINDINGS

This chapter aims to present the findings of this study and address the research questions that were raised in the previous chapters.

4.1. Results of the tendering study

In the total combined sample, a 60.6% value reduction (weighted price reduction) was achieved through tendering ($p<0.000$, $z= \_11.32$, Wilcoxon Signed ranks test), that is a 39.39% mean reduction of prices (Table 25). In the generic segment, 94.85% value reduction (weighted price reduction) was achieved ($p<0.000$, $z= \_7.219$ Wilcoxon signed ranks test). This is a mean price reduction of 62.97%. Branded products reached a 33.4% ($p<0.000$, $z=\_8.723$ wilcoxon signed ranks test) value reduction (weighted price reduction) and a mean price reduction of 25.99%. The subgroup of top 20 products in value demonstrated a 29% value reduction (weighted price reduction) ($p<0.000$, $z= \_3.932$ wilcoxon signed ranks test) and 23% mean price reduction (Table 25). The Wilcoxon signed ranks test was preferred due to non-normality property of the values, which was verified through the Shapiro–Wilk normality test ($W=0.971$, p-value=0.0009 for distribution of Wholesale prices and $W=0.963$, p value= 0.0001) for the distribution of tendering prices. In the same sample, we explore the relationship of several attributes with price reduction. Primarily, we are interested in the correlation of value in the final price of the products, which will serve as a proxy for the remaining study. For the statistical analysis we used a beta regression since conventional regression analysis based on normal-error models are not suitable when outcome is bounded, either by proportional or by percentage. Beta regression, due to inclusion of percentage as an outcome, is a better option and can assume different shapes, including left or right skewness. It is also similar to generalised linear models and it employs a parameterization of the beta distribution in terms of its mean and a precision parameter.

Table 25 Tendering Results

	Branded	Generic	Top twenty Products [5](value)	All products
Value Reduction (Weighted price reduction)	33,4% (p<0.000, z=-8,723)	94,85% (p<0.000, z=-7,219)	29% (p<0.000, z=-3,932)	60.6 % (p <0.000, z=-11,32)
Average price Reduction	25.99% (p <0.000, z=-8.48)	62.97% (p < 0.000 z=-6.90)	23,18% (p <0.000 z=-3.91)	39,37% (p < 0.000 z=-10.85)
Standard Error of Price Reduction	2.14	3.03	4,63	2,29
Median Price Reduction	19.53	68.2	18.30	32,28
Standard Deviation of Price Reduction	22.22	25.18	20.22	29,5
Sample Variance of Price Reduction	493.92	634.17	408.89	871.96
Kurtosis of Price Reduction	-0.04	0.01	1.775	-1.27
Skewness of Price Reduction	0.92	-0.90	1.463	0.324
Range of Price Reduction	88.76	97.70	74.32	97.70
Minimum Price Reduction	0	0	1,44	0
Maximum Price Reduction	88.76	97.70	75.76	97.70
Confidence Level(95,0%)	4.25	6.04	9,22	4.52
Count	107	69	20	176

[5] Top 20 products are already included in the Branded products.

Therefrom, we assume that price reduction follows a beta regression as following: pricereduction=interc+a*Innovation+b*hospital/outpatient + c*patentstatus +d*wholesaleprice* + e*volume + f*value+g*tendertype +er. We applied these variables for 5 different categories:

1. For the entire market.
2. For products that carry an ASMR classification.
3. For branded products only.
4. For generic products only.
5. For high value medicines (products with sales more than 1,000,000 euro yearly value of sales).

One consistent finding across all market segments is the non-correlation of innovation status with price reduction. Price reduction is indifferent to innovation status. Higher wholesale prices are statistically significant related to a higher price reduction, while a notable finding is the negative correlation of total sales value to price reduction, except in the cohort with ASMR assigned status. This conflicts with another consistent finding across all categories, namely significant correlation of volume with price reduction.
Tendering by alternative (procuring only one out of several competitive products) is related to statistically significant price reductions in all but one categories (products assigned an ASMR innovation status). Tendering by group demonstrated statistically significant correlation with price reduction only in the total sample while tendering by INN (monopoly products) did not correlate with significant price reductions. In the total sample, outpatient medicines are related to statistically significant impact on price reduction. This also occurs in the generics only category (table 26). Generic status had an undisputable strong impact on price reduction which was consistent across all subcategories as well. Levels of pseudo R square were satisfactory in all analysis indicating that model fit the data well.

Table 26

Tendering Variables Results

	Tendering type	Innovation status	Outpatient/ Hospital Medicines	Branded/ Generics	Volume	Value	Wholesale prices
Total Sample (No ASMR status)	Tendering alternative *p=05.59e-05 Tendering group *p=0.045	N.S	Outpatient *p=0.002	Generic *p=0.001	*p=4.84e-14	*p=0.000156 negatively correlated	*p=0.0005
Sample with Innovation status	Tendering alternative *p=0.0019	N.S	N.S	Generic *p=1.67e-06	*p=0.000496	N.S	*p=0.000570
Generic	N.S	N.S	Outpatient *p=3.21e-08	N/A	*p=8.67e-10	*p=0.00018 negatively correlated	*p=0.028
Branded	Tendering alternative *p=0.000216	N.S	N.S	N/A	*p=7.75e-08	*p=0.04 negatively correlated	*p=0.01
Products with value more that 1,000,000 yearly	N.S.	N.S	N.S	N.S	*p=2.2e-16	*p=2.2e-16 negatively correlated	*p=2.2e-16

4.2. Results of the Decomposition study

The decomposition study covered the entire public pharmaceutical market for 7 years. In the last year, public pharmaceutical expenditure was 104.5 million euro. Decomposition study had several endpoints. Nominal expenditure increased by 53%, while real expenditure (adjusted by CPI) increased by 31%. Prices increased by 4%, while real prices after adjusting for inflation, decreased by 11%. Quantity of drugs dispensed increased by 55%.

Table 27 Expenditure on pharmaceuticals 2005-2011

	2005	2006	2007	2008	2009	2010	2011
Nominal expenditure (euro)	56,816,678	61,346,056	70,657,952	76,406,384	0.00	85,881,311	87,092,919
CPI	100	102.49	104.92	109.82	110.18	112.86	116.57
Real expenditure (euro)	56,816,678	59,852,752	67,340,356	69,571,030	0	76,094,876	74,710,843
Drug expenditure index	100	105.34	118.52	122.44		133.93	131.49
Relative Prices index	100	96.58	97.68	97.70	98.51	98.67	104.08
Real Prices Indices	100	94.22	93.09	94.22	89.40	87.42	89.28
Quantity(DDD)	199,130,868	208,325,558	239,979,532	261,105,237		289,644,555	310,168,521
Quantity Index	100	104.61	120.51	131.12		145.45	155.76
Residual	1	1.06	1.05	0.99		1.05	0.94

Quantity and prices only partially explained the increase in real-drug expenditure.This gap is breached by product-mix residual, which measures shift of prescription patterns between cheaper or more expensive products. Residual is -5.5%, indicating a shift to cheaper products (Table 27).

Table 28

Residual based on ATC categories

ATC Category		RESIDUAL						
		2005	2006	2007	2008	2009	2010	2011
	A	1	1.16	1.34	1.34		1.43	1.61
	B	1	1.04	1.37	1.07		0.99	1.02
	C	1	0.92	0.77	0.64		0.57	0.44
	G	1	0.93	0.82	0.74		0.68	0.58
	H	1	0.85	0.91	0.97		0.87	0.7
	J	1	0.79	0.77	0.61		0.53	0.52
	L	1	1.23	1.23	1.17		1.36	1.2 (1.12 if L01 is excluded)
	M	1	1.14	0.60	0.58		0.62	0.58
	N	1	1.03	1.01	1.03		1.08	0.92
	R	1	1.06	1.03	0.87		1.15	1.16
	S	1	1.04	1	0.89		0.99	0.78

Likewise, this may also point out a shift to older products or generic ones. Therefore, the next step is to assess each ATC category individually (Table 28). ATC C category is displaying a very low residual -55%, with a DDD increase of 58%, while ATC A displays the highest residual 62%, with a 71% increase of DDD. ATC G had a DDD increase of 11% and a negative residual -42%, ATC J had a 66% DDD increase, which stabilized in 2010, along with a negative residual -48%. Oncology products in ATC L category have a residual 20% with an increase of DDD 82%, which falls to 10% should we exclude L01. ATC L01 demonstrates the highest residual 80%, underlining that the prevailing prescribing pattern is the introduction of new and more expensive medicines (table 29). Total value of L01 cluster in 2005 was 5,948,235 euro and total quantity was 71,225 DDD. In 2011, the equivalent value was 14,714,730 euro and the amount was 93,813 DDD. Real expenditure increase was 147%, while increase in DDD was 31%. Upon inflation adjustment, real expenditure increase is 112%. ATC R has 16% residual along with a 72%

DDD increase, while all other categories have negative residuals. In contrast to other EU countries, overall utilization of pharmaceuticals as expressed by the number of prescriptions seems to be stable (Table 30). Indicatively, we observed only a marginal increase in prescription rate for the period 2005–2011.

Table 29

L01 ATC category

L01 oncology cluster	2005	2006	2007	2008	2010	2011
Nominal sales value (euro)	5,997,801	8,808,349	12,420,976	13,336,491	16,709,686	14,746,195
CPI (Consumer Price Index)	100	102.49	104.92	109.82	112.86	116.57
Real sales value(euro)	5,997,801	8,593,933	11,837,775	12,143,401	14,805,567	12,649,715
Drug expenditure Index	100	144.47	199.01	204.15	248.9	212.66
Prices index	100	96.58	97.68	97.7	98.67	104.08
Real prices indices	100	94.22	93.09	94.22	87.42	89.28
Quantity (DDD)	71225	77284	78574	85394	89551	93813
Quantity index	100	108.5	110.3	119.8	125.7	131.7
Residual	1	1.40	1.92	1.79	2.24	1.79

Table 30

Decomposition of prescription issues by Public Health Care Sector 2005-2011

Year	Prescriptions Number index	Prescription/visits index	Visits/population index	Population index
2005	100	100	100	100
2006	100.78	89.40	110.66	101.86
2007	96.11	102.20	87.80	104.35
2008	96.03	91.46	98.02	107.11
2009	100.27	88.32	103.12	110.09
2010	102.86	83.71	108.85	112.87
2011	107.63	84.17	110.36	115.8

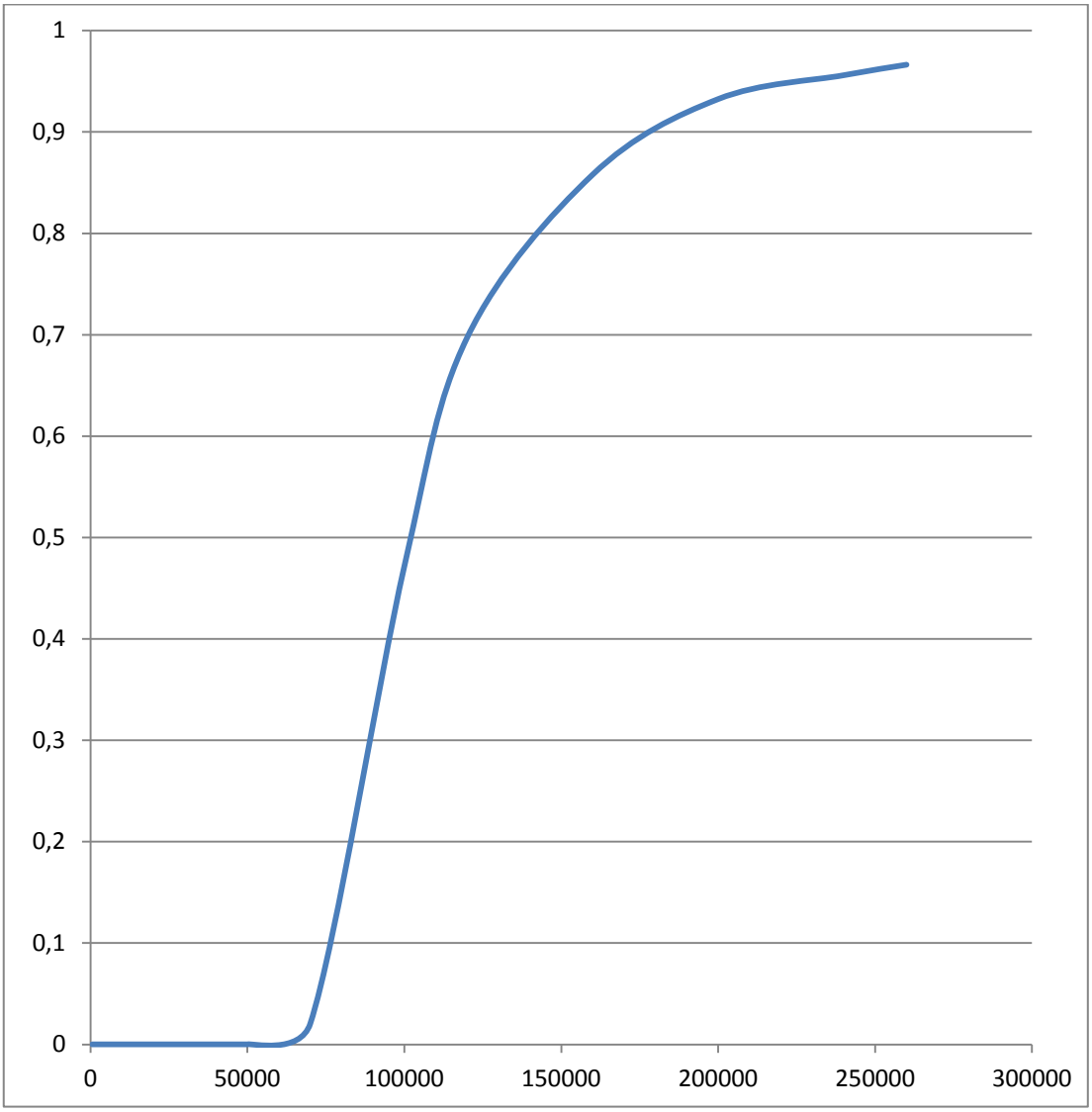
4.3. Pharmacoeconomic Evaluation

For the scope of the economic evaluation of sorafenib, the Markov Model was loaded with an initial cohort of 1000 patients. Patients were supposed to be on the second line of treatment with sorafenib with an indication of metastasis. We discarded the first 50000 iterations to ensure stability of the model. Convergence of the model was significant and was assessed through trace plots of samples and standard error of the results. According to our results, sorafenib has a probability of 0 % to be cost-effective at a threshold of 61,551 euro (figure 10). In Cyprus, there is no official willingness to pay (WTP) threshold (Petrou & Talias, 2013) and under the WHO recommendations (Murray et al. ,2009), WTP threshold should be defined three times per Gross Domestic Product (GDP) per capita current prices (IMF, 2011) (2011: 20517 euro). Nevertheless, as described in Chapter Three, sorafenib is an orphan drug. This would justify its assessment under a higher WTP threshold, due to the small patient pool. By capitalising on this, coupled with WHO WTP recommendations, sorafenib carries a 47 % probability to be cost-effective under a 100,000 euro WTP threshold, which is five times the GDP per capita. Treatment with sorafenib

leads to an average increased cost of 16,450 (CI: 12,520-21,000, sd =2170). Mean cost per sorafenib patient is 23780 eur (20010-28220). Mean QALY gain per sorafenib patient is 0.639 while mean QALY per patient in Bsc was 0.478. ICER of sorafenib versus Bsc was found to be 102,059 euro (figure 11).

Figure 10

Probability of sorafenib being cost–effective at different WTP thresholds



X axis: WTP threshold
Y axis: Probability of being cost-effective (0-1 range)

4.3.1. Validation of the model

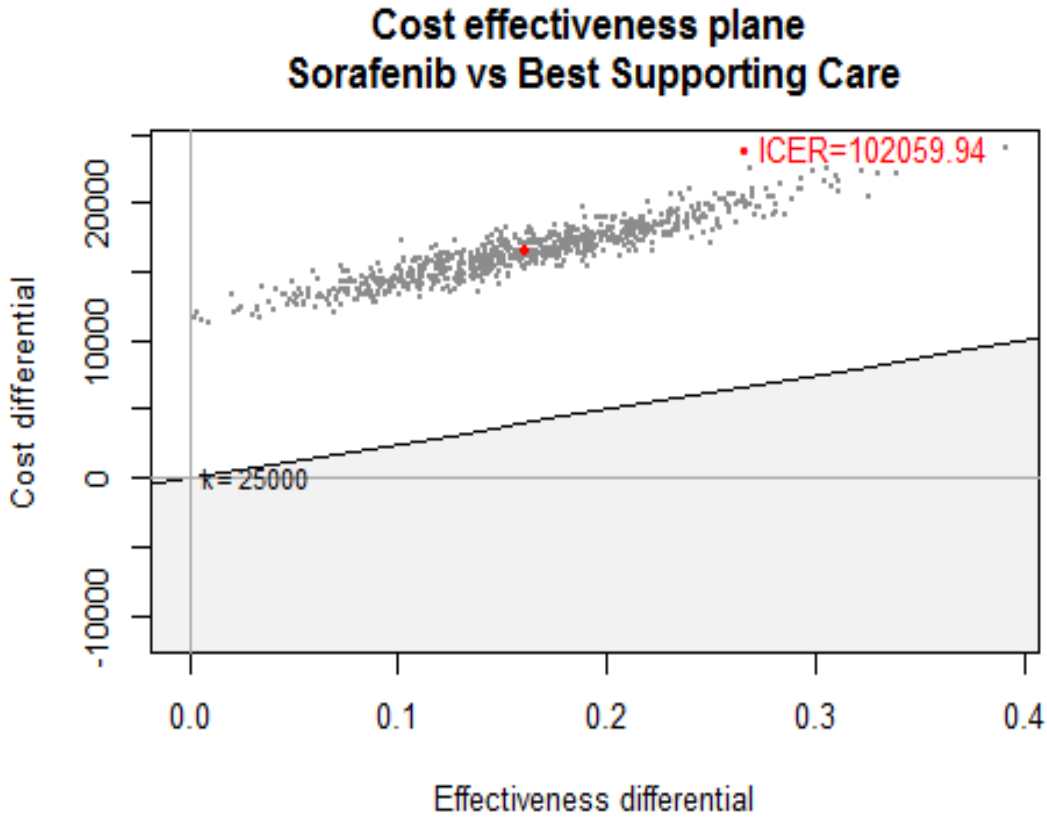
The validation of the model is of paramount importance, since if left unchecked can lead to technically induced uncertainty and wrong results. The model was checked visually and the number of patients transitioning to each state was tracked and was compared with data of the referenced study. Foremost, the convergence of the model was assessed through visual observation of the plots. In addition to the above, the PFS and OS of the simulation were compared to the actual corresponding input data. No differences were spotted and we can conclude that are results are robust and reliable.

4.3.2. Sensitivity analysis

In Chapter Three, the value of the sensitivity analysis has been described. In this notion, we performed one-way sensitivity analysis (table 31) and applied several assumptions in order to define the range of parameters that may influence outcome. Price of sorafenib was reduced to 50% which is a common approach in many risk sharing schemes (Espín, Rovira & García, 2011). Discounting varied from 0 to 5% since there is no established level in Cyprus. Utility and effectiveness also varied. Model was also checked for convergence.

Figure 11

ICER plane



X axis: QALY
Y axis: Cost (euros)

Table 31

Sensitivity Analysis

Parameter	Baseline Value	Sensitivity Analysis	Reason	ICER	BASE CASE
Sorafenib price	2880 (per month)	50% reduction	Patient access schemes	45,558	101,857
TIME HORIZON	10 YEARS	5 YEARS		102,173	101,857
Discounting	3.5	0		72,672	101,857
Discounting	3.5	5		115337	101,857
QALY	0.76 – 0.68	0.7 – 0.6	No explicit data	112218	101,857
QALY	0.76 – 0.68	0.8-0.7		97,396	101,857
Increase of PFS 10%			Clinical uncertainty	95722	101,857
Increase of PFS and OS 10%			Clinical uncertainty	91293	101,857

The sensitivity analysis shows that cost-effectiveness parameters are particularly sensitive to effectiveness, mainly OS, and cost of the product. Other medical and pharmaceutical cost variations have minimum influence on ICER.

4.3.3. Expected value of perfect information (EVPI)

Many authors suggest that the use of EVPI in economic evaluation of pharmaceuticals is superior to conventional approaches since it gives information pertinent to the impact of adopting the wrong therapeutic option (Welton et al., 2012). EVPI denotes the difference between a decision reached under perfect information compared to a decision reached under available (flawed) information. We must emphasise that eradication of parameter uncertainty would be feasible only under an infinitely large sample (Oostenbrink et al., 2008).

Decision-making between two mutually exclusive health care interventions is critically relied upon each intervention's net Benefit, should we want to maximise health utility in the context of a specific budget (Ades, Lu and Claxton, 2004). Net benefit (B) in a decision model with unknown parameter B (t,θ) (B=net benefit of treatment, t is the number of treatments, if parameters reach θ value (Claxton & Possnet, 1996) is linked to the cost(C) and utilities(U) as following $B = \lambda U(t,) - C(t,\theta)$ (λ represents willingness to pay threshold). The optimal decision given current information, is the decision that yields the highest expected net benefit $EVPI = E_\theta max_t B(t,\theta), - max_t E_\theta B(t,\theta)$.Based on these equations we conclude in our study, EVPI reaches its maximum value at 30880 at the point that INB is 0, which indicates that there is a strong possibility of 50% of taking the wrong decision and uncertainty peaks. Given that are annually 40 new cases of RCC in Cyprus, total amount spent should be less than 1,235,200 euro annually, which should justify further research to minimise uncertainty.

4.4. VALUE-BASED PRICING

Treatment with sorafenib results to an incremental gain 0.1605 QALY per patient, compared to BSC. This would lead to 16996 euro cost per sorafenib patient (CI 95%: 13140-18950) compared to 7336 euro per patient on best supportive care (CI 95%: 6327.0-8468.0). Our Value-based pricing approach indicates that under a 60,000 theoretical WTP Threshold, the price of sorafenib should be set at 1816 euro per package, a price notably lower compared to current price. Under current price (2880 per package) the Incremental Cost-Effectiveness Ratio (ICER) is 102,879 and the health gains cost 16470 euro additional per patient (Table 32).

Table 32

WTP threshold levels and corresponding value-based price of Sorafenib

	Willingness to pay Threshold	20,000	40,000	60,000	>100,00
Cost of sorafenib arm		10620.0 (CI 95% 9022.0-12490.0)	13760 (CI 95% 11680.0-16290.0)	16996 (CI 95%14370.0-20120.0)	23806.0 (CI 95% 20,000 - 28220)
Cost of bsc arm		7336.0 (CI 95%: 6327.0-8468.0).	7336.0 (CI 95% : 6327.0-8468.0).	7336.0 (CI 95% : 6327.0-8468.0).	7336.0 (CI 95% : 6327.0-8468.0).
Incremental QALY gains		0,1605 QALY	0,1605 QALY	0,1605 QALY	0,1605 QALY
Incremental Cost		3284	6424	9630	16470
VBP of sorafenib		810	1325	1816	2880

Table 33

Sensitivity Analysis of Value-Based Pricing

Parameter	Baseline Value	Sensitivity Analysis	New Price	ICER	BASE CASE
Sorafenib price	1816 (per month)	50% reduction	908	24,190	60,00
TIME HORIZON	10 YEARS	5 YEARS	1860	60,266	60,000
Discounting	3.5	0	2455	45,279	60,000
Discounting	3.5	1.5	2124	51,025	60,000
Discounting	3.5	5	1695	67,203	60,000
QALY	0.76 – 0.68	0,836 0.748	2013	54,738	60,000
QALY	0.76 – 0.68	0.684- 0.612	1711	66,863	60,000
Medical and other pharmaceutical costs		Increase 20%	1926	57,407	60,000
Medical and other pharmaceutical costs		Decrease 20%	1802	62,282	60,000
Decrease of PFS 10%			1655	68,853	60,000
Decrease of PFS and OS 10%			1580	72,374	60,000
Increase of PFS and OS 10%			2030	53,300	60,000
Increase of OS 10%			1905	58,329	60,000
Increase of PFS 10%			1987	55,701	60,000
Decrease of OS 10%			1790	62,695	60,000

4.4.1. Sensitivity analysis of value-based pricing

We performed one way sensitivity analysis. ICER was proved to be significant sensitive to the price of sorafenib, while medical and other pharmaceutical had a minimum impact on ICER. ICER is also sensitive to utilities and to PFS while it is less sensitive to OS (Table 33).

5. DISCUSSION

5.1. Overview of previous Chapters

5.1.1. The research Topic, Purpose and Research questions

In the context of the pharmaceutical market, which is inherently flawed, the utilization of high quality, evidence-based data is incumbent in order to enable the efficient and highly competitive allocation of scarce health resources. This should concomitantly occur with safeguarding the timely access of patients to the necessary medicines, maintaining equipoise between maximising utility gained and minimising waste, rewarding innovation and abiding by the fundamental principles of health: equity, quality and solidarity. With this backdrop, the main purpose of this thesis is to assess the current pharmaceutical market in Cyprus; explore the Health technology assessment domain (HTA) and the cost-effectiveness analysis context in Cyprus; propose a conceptual and technical framework through the introduction of innovative pharmacoeconomic modeling and elaborate on pioneering approaches in pricing of pharmaceuticals through incorporation of value, as defined through Health Technology Assessment, in the price of the product. Research questions were defined as following:

1. Is Health Technology Assessment a substantial and reliable tool for introduction of new products in the formulary list of publicly reimbursed pharmaceutical products?
2. How to define cost-effectiveness profile of medicines?
3. What is the value of current pharmaceutical assessment and reimbursement policy?
4. What is the potential of pharmaceutical pricing based on its value, as defined by clinical outcomes (along with exploration of new approaches for integration of value in the price of the product)?
5. Exclusive or adjuvant positioning of economic evaluation in decision-making?
6. What is the cost of acquiring perfect information? Many researchers point the expected value of perfect information which elucidates the cost of taking a wrong decision. It represents the costs which are justified to spend in order to reach perfect information.
7. How to define willingness to pay thresholds?
8. How to perform sensitivity analysis?
9. How to explore and assess uncertainty of the model?

10. How to define the technical parameters of the model such as time horizon, discounting and distributions of the model?

5.1.2. Review of the literature

An extensive literature review was performed, in order to acquire thorough and technical acquaintance, by accessing and assessing all state-of-the-art data in the fields of health economics, HTA, pharmacoeconomics, pharmaceutical pricing, Value-Based pricing, Expected value of perfect information, sensitivity analysis, Markov Model and Bayesian statistics. The literature review accentuated both the importance of evidence-based decision-making, and it also underlined the methodological, technical and medical impediments in doing so. It also highlighted the barriers to the dissemination of evidence-based medicine. Finally, the introduction of VBP in European Countries has stalled due to several methodological and political issues, nevertheless this does not cancel out the theoretical advantages that VBP yields. This also prescribes strict observance to caveats lurking in this domain.

5.1.3. Methodology

The specific study used an array of approaches. Primarily, this thesis used a step-up approach to critically assess the Cyprus pharmaceutical market, highlight strengths, weaknesses, opportunities and threats which laid the foundations for the subsequent part. The following part of the study assessed the impact of current pricing and reimbursement method of public health care sector. Further scrutinizing on this topic, we explored the impact of several variables in the tendering prices of pharmaceuticals, through the use of a beta-regression. In the next part, we utilised a decomposition study, which facilitated a deeper and comprehensive understanding of prescribing patterns and dynamics of Cyprus market. This consequently led to the identification of cost-drivers products in Cyprus market, whose further economic evaluation would be of value both on theoretical and on practical level as well. A Markov Model Bayesian pharmacoeconomic model was utilised to simulate disease progression for the economic evaluation and the VBP study. The pharmacoeconomic model was validated and checked for its stability and internal validity. Several methodological approaches were utilised to construct and evaluate the model such as the method of moments. Finally, the technical parameters such as discounting and time horizon have been defined, in line with reported ones.

5.1.4. Findings

The main findings of this thesis are delineated below:

1. This thesis is the first to explore the correlation of tendering prices with the level of innovation, volume, value, interchangeability, administration and patent status. The most important finding is the lack of any correlation of tender-defined prices with the innovation status of each product. Tendering is an aggressive form of pricing and reimbursement, which can serve a health system, but it overlooks the innovation status of the product. This infers that some utility is lost in health's closed system.
2. This is the first study to report on the prescribing patterns, cost-drivers and the dynamics of Cyprus pharmaceutical sector. The primal prescribing pattern in Cyprus' pharmaceutical sector is the introduction of new-and significantly more expensive- oncology treatments. The affordability for these newer agents was feasible due to savings generated by massive generic substitution of products whose patent has expired. It also contradicts the assumption that polypharmacy and increase of beneficiaries are the main factors for the increase in pharmaceutical expenditure.
3. An economic evaluation model, through the use of Markov Model, can enhance decision-making by indicating the cost-effectiveness profile of a product in Cyprus context. Since cost-effectiveness of a product is a relative term, highly contingent to fiscal conditions and disease severity, we defined several willingness-to-pay thresholds. In our case, we used the highest level, since our product was assigned an orphan product status.
4. Markov Model can give answers to the expected value of perfect information which is a clear indicator of how, if, and at which cost, future research can further minimise uncertainty by elucidating several blurred aspects of the specific health condition contingent to the pharmaceutical agent under evaluation. This may be more relevant to decision makers, since it tags a price to uncertainty, which it may be multifactorial.
5. It is feasible to contemplate a pioneer pricing scheme, which provides for alignment of price to the clinical and societal value of the product. We propose an innovative scheme which can align the price to the real clinical value of the product, a finding which is relevant not only for Cyprus but for a global audience as

6. well. This can minimise uncertainty for the payer, while accelerating introduction of products in the market. This is important for public health, while it is vital for conditions without any potent alternative agents.

5.2. Discussion of Findings

5.2.1. Tendering

The tendering attains significant financial benefits, nevertheless its efficacy, which is highly remarkable in certain categories such as generics, cannot be perceived as a panacea of soaring health expenditure. The willingness-to-submit lower price, on behalf of the Marketing Authorisation Holder, diminishes as sales value of each product increases. This can be partially imputed to an elaboration of a strong brand loyalty that can shield the product from further price reduction. In the same context, the innovation level does not correlate with price reduction. Consequently, Tendering is a potent tool, however it is also a blunt tool for high value products, which are also the key cost-drivers. This epitomises our suggestion that tendering should be complemented by more sensitive and pioneering pricing and reimbursement tools.

5.2.2. Decomposition Study

In the conundrum of the pharmaceutical market, which is defined by a myriad of pharmaceutical products further segregated by innovation and interchangeability status, class-effect, unique indications and therapeutic categories, the task of tracking-down prescribing patterns of physicians is often perceived as a Sisyphean task. To this direction, the decomposition tool can serve as a tool to reach the core of physicians' prescribing pattern and highlight the lurking trends. Usually, Health Agencies publish either volume or value data of pharmaceuticals sales: neither of these can grasp the magnitude of the pharmaceutical market, while they may convey flawed and biased data. Any decision reached on low quality data will eventually disseminate and magnify input flaws, thus escalating to implementation of erroneous policies. Ultimately, this can deprive utility from the population.

The decomposition study surpasses these impediments by capitalising not only on value, but on volume, population, inflation, prices and price index, number of prescriptions for competitive products and most importantly, on the prescribing patterns of physicians.

Ultimately, decomposition tool can hold out as a blueprint the actual dynamics of the market. In this thesis, the decomposition study underlined that in the Oncology sector the dominant prescribing pattern was the switch to more expensive products. This prescribes strict observance to focus on oncology products, since a pillar of this thesis is to contribute to health policy making in Cyprus, potentially acting as a pretext for reform. Of equal importance, the decomposition revealed that the increase of prescribed medicines in primary care occurred primarily due to the increasing number of beneficiaries and was not caused by the prescribing pattern of physician, thus disputing a common perception about polypharmacy as a major determinant of pharmaceutical sales evolution. Even more, some other ATC categories, such as ATC C (cardiology products) demonstrated a substantial value decrease, with concomitant volume increase. This accentuates a highly efficient policy, which must be carried over. Finally it proves that in this case, only the decomposition method, through the use of the residual could convey a precise depiction of this specific cohort market forces, in which apparently both volume and value utilised as explanatory variables would be of no avail.

5.2.3. Statistical Analysis

In order to generate estimates of cost-effectiveness analysis and value-based pricing, the relevant parameters were synthesized in a modeling which consists of three distinctive health stages that simulate the disease progression. We used common and clinically meaningful endpoints, namely progression-free and progressive health states. This enabled us to combine data from several sources: high quality effectiveness studies, quality of life studies, local data and prices from Cyprus. All these divergent factors were embedded in the model. Some authors argue that use of published data in phase III studies illustrate a theoretical and not practical situation since these results are the best case scenario and not pertinent to the real needs of practicing physicians. As a result, while the stand-off between efficacy and effectiveness data is prominent, published data from RCT carry the second highest grade of scientific evidence. Efficacy data of the model were derived from a literature review, while expert opinion data were utilised for costing in Cyprus' context. The Markov model can be of significant value in combining all available data, constructing a disease-simulating process and delivering cost, effectiveness and cost-effectiveness results. It is a transparent process and can make highly accurate predictions, although more accuracy comes at the cost of more complexity, which compromises the ability of

decision makers to fully grasp the deliverables of the modeling process (Weinstein et al., 2003). Markov model provides flexibility, by allowing the input of data from several sources. In our case, Markov Models was based on a probabilistic approach with use of non-informative priors.

The external consistency and validity of the model is also of utter importance. It is often depicted that modeling is a black box, which infers that its validation is of great necessity. This can be achieved by extensive visual observation of the model (observing number of patients transitioning between health states and convergence of the model) and by comparing inputs with outputs (progression free survival from literature review compared to actual progression free survival as reported by the study). External validity can be also arraigned by comparing data with corresponding ones from other studies, nevertheless this should be performed with caution. Among different countries, significant disparities occur in cost, health structures, efficiency of the system and health policies, which may exert a variable effect on outcomes.

Although modeling based processes and approximations are considered to be inferior to real life cost based trials, someone must also weigh their costs, complexity, duration, regulatory impediments and applicability as well (Claxton et al., 2002). Well-structured randomised controlled trials are still the benchmark of informed decision-making, however their tailored utility is faint and the conducting of a custom-built RCT, pertinent to a decision-making dilemma is implausible. As a result, when there is a need to combine data, modeling is the process of choice. In this direction, a model-based analysis epitomises the amalgamation of statistical inference and evidence synthesis process, can contribute to the rational decision- making process and can elucidate several domains with ingrained uncertainty. Internal validity of the model is essential to ensure that the definition of transition probabilities between health states holds clinical validity.

5.2.4. Evidence Synthesis

One vital part of modeling is the identification, selection, and assessment of the available evidence. The researcher must access, scrutinize and critically assess a disproportionate body of evidence and ultimately filter the clinically meaningful ones. This is performed as a systematic review, which stands as the core of the decision synthesis. In this direction, the researcher can be guided through the use of structured quality assessment forms, which can also make the procedure more transparent. The quality of inclusion criteria is also

peremptory; too strict or too loose criteria may distort the final outcomes. In our case we identified only one trial through the body of evidence, which was assessed through the Cochrane risk of bias and CHEERS guidelines. In case that no actual data exist, meta-analyses and meta-regressions can be utilised to summarise and analyse data. The uncertainties of the efficacy and cost data were embedded in the decision model through the use of efficacy parameters. The selection of the distributions was based on the nature and value range of each parameter, presence of kyrtosis and other technical characteristics.

5.2.5. Economic evaluations and Policy implications

Normal market forces are usually frail or even absent from pharmaceutical market and consequently competent authorities must allocate scarce resources based on high quality data. In this thesis, we substantiate the use of economic evaluation as a decision-making tool. Decision-makers are confronted with several interventions and the utter goal is to maximise health outcomes, in the context of budgetary constraints and the highly competitive resource allocating process across therapeutic areas.

The innovation in the pharmaceutical sector is rare and it is disproportionately rewarded. Indicatively in France, 92% of all registered products in 2011, when compared to gold standard, were assessed as delivering minor or no incremental added value effect, while only two products were assessed as potentially offering more than minor added value (Bastian, 2013;Walker et al., 2009). This has to be interpreted along with the significantly higher prices of new products, compared to existing ones; this price gap does not reflect the health gains (Lu & Comanor, 1998).

As a result, new treatments are definitely expensive, but their real value has provoked significant debates. This gap is breached by economic evaluation, a process that assesses which treatment provides the greatest benefit for the money spent (or invested).
This study aims to position itself as a starting point and act as a pretext for reform for a National policy in economic evaluation, an issue highlighted by the Memorandum of Understanding between Cyprus Republic and a team of international lenders (MoU, 2013). To our knowledge, this is the first study to report cost-effectiveness analysis germane to Cyprus pharmaceutical market and present a coherent, holistic, integrated framework, at the confluence of technical and theoretical crossroads. We must underline that a decision analytic model comprises a decision-making tool that can be utilised at a specific point in time. Due to the dynamic nature of the pharmaceutical market, there is a constant

production of data, which must be critically-and unabatedly-assessed. Indeed, decision analytic models have a limited applicability period since new data may require the update of the model and its outgrowth policies. In our case, we compared sorafenib to BSC. It is anticipated that in the next 5 year, two more products will compete for reimbursement in the field mRCC, thus the need for the comparative assessment of these products with sorafenib will be overwhelming. What matter the most is the alignment of the decision analytical modeling with the contemplation of a national health policy. Decision analytical models, should not lag health policy, but they must be integrated. On the contrary, decision analytical models should preferably precede elaboration of health policy, or just be an integral part of it, in order to maximise the benefit stemming out of it.

The oncology medicines demonstrate the highest increase rate, due to the small life expectancy of patients and consequent social solidarity, which are interweaved with unmet medical needs, poor tolerance and effectiveness of existing agents and increasing prevalence of cancer. In this sector, decision-making is intertwined with social, economic, medical and legal issues. In this conundrum, cost-effectiveness analysis can provide objective results that can catalyze decision-making process and most importantly, enhance a rational allocation of resources.

Cyprus is experiencing the aforementioned issues as well, which currently are exacerbated due to the financial crisis. This constitutes an exemplary reason to shift to, and bolster the support for a rational, unbiased, objective and transparent decision-making framework. In the context of m RCC, we performed a cost-effectiveness analysis of sorafenib versus BSC in the second-line treatment of mRCC from a payer's perspective in Cyprus, in the context of varying WTP thresholds, capitalising on a decision analytic approach. It is found that it is not cost-effective; however its orphan status that can justify reimbursement on an individual basis for certain patients who meet strict criteria. These criteria should entail, but not limit to, poor prognosis, small patient cohort and budget impact constraints. Additionally, the introduction of novel Managed Entry Agreements, such as risk-sharing schemes, and integration with aforementioned criteria may create a framework of a high potency, cost-containment reimbursement policy, especially in high value, low volume biotechnology products. In Cyprus, from a payer perspective, the cost-effectiveness analysis proved that Sorafenib is associated with excessive costs, which in the current financial era of Cyprus do not fit, suggesting that it is not a cost-effective product. It is shown that the cost of sorafenib dominated the cost decomposition of mRCC therapy. Hoyle et al., (2010) have also demonstrated that sorafenib is not cost-effective

compared with BSC, from NHS perspective in UK. We performed this study from a payer's perspective of Cyprus; nevertheless, we believe that results are transferable to other EU countries. Cyprus implements an external reference-based pricing scheme and according to the terms of reference of competent authority, prices of medicines are set at the average of EU countries. Therefore, the findings represent the average EU countries, since the cost of sorafenib dominates the cost-effectiveness analysis. At this point, we must draw attention to the orphan drug status of sorafenib and the high complexity level of orphan drugs reimbursement. Even the addition of an orphan indication at an existing commonplace indication for a product already in market, can lead to a considerable price increase, as with the case of sildenafil, whose new orphan indication led to a six-fold increase of its price(Simoens, 2011). The high prices of orphan drugs stem out of their monopolistic status and are aggravated by:

1. Aforementioned market exclusivity.
2. Lack of alternative interventions that result to low bargaining power of payers.
3. R&D costs are high but have to be redeemed through a small patient cohort.

In addition, owing to the lack of information and great uncertainty ingrained in the field of rare diseases, health agencies are under significant pressures from patient associations in order to reimburse new orphan drugs (Picavet et al., 2011). However, under current cost-effectiveness WTP thresholds, almost collectively all orphan drugs would be excluded from the conventional reimbursement pathways, which blatantly opposes to the principles of social solidarity regarding vulnerable groups. This debate led several agencies, such as NICE, to issue methodological guidance to regulate this field. Indicatively, NICE provides that uncertainty of orphan drug's effectiveness should be dealt with the introduction of a weight factor (NICE, 2010) since it is generally accepted that people value more treatments that target patients with worse and debilitating health states. Usually, the criteria of weight factors include the severity of the disease (life threatening or not) and health outcome (resolution, stabilization, decrease of progression rate or symptomatic relief). Moreover, poor prognosis, small patient cohort and budget impact constraints were some issues raised by NICE, which led to granting exemption from the WTP threshold for orphan drugs. This is in line with findings of other authors as well as addressing that severity and not prevalence of a disease constitute a legitimate reason for accepting a premium in health finance. All aforementioned exceptions should be incorporated into pragmatic health

budgets constraints, reaching equilibrium between financing very expensive treatments for a small patient cohort and maintaining a good coverage of more common (primary health care) products (Desser et al., 2010).

In view of the above, several innovative approaches to reimbursement of these products can be considered as adjuvant schemes to economic evaluations. Risk sharing is one of the new approaches in limiting growth in pharmaceutical expenditure and was introduced in the last decade (Scherer, 2000). It serves as a binary scheme. The core of the scheme is the interrelation of coverage and payment to the clinical outcomes. Indicatively, savings up to 34.6% were achieved, as in the case of Italian Sorafenib risk-sharing scheme (Espin, Rovira & Garcia, 2011). Some other authors suggested auctions of patents for orphan drugs. This guarantees, at least, a minimum reward for the innovator and payer pays a potential marketing authorization holder through the progressing stages of R&D.

The findings of this thesis should also be interpreted in the scope of the Memorandum of Understanding (MoU), which Cyprus has contracted with a committee consisting of International Monetary Fund, European Commission and European Central Bank, commonly known as Troika, in order to secure a life-sustaining bailout loan of 10 billion Euros. In the context of this MoU, Cyprus has to meet several conditions of Troika, and primarily the steadily increasing rate of public pharmaceutical expenditure has to be constrained. Troika highlights the importance of proper economic evaluation of pharmaceuticals. Current financial situation of Cyprus and the implementation of MoU urges for cost reduction in Health. Pharmaceutical sector is estimated that will face fund reductions up to 20%. This will mandate prioritization of needs and the need for informed decision-making will be based on robust data with high rating of evidence. Although a proper comparative agent should be axitinib or everolimus, current financial situation literally prohibits introduction of new products. This may also occur in other countries that have been struck by financial crisis. Thereof, we believe that this paper goes beyond its primary objective and can actively serve the aforementioned goals by leveraging change toward a functional cost-effectiveness and HTA programs.

5.2.6. Value-based pricing

Health care costs are rapidly expanding. Several cost-containment approaches such as price reductions, internal price referencing, tendering and risk-sharing have been applied extensively. Despite being undisputedly potent in the short-term, tendering and the price

reduction approach lack selectivity and both oversee product's innovation level and particularities of involved patient categories. On the other hand, risk sharing schemes were implemented to tackle uncertainty primarily for short-term and due to their binary evaluation context (accept or decline reimbursement) they tend to benefit insurer, while major concerns encompass their long-term sustainability (Carlson, 2009). Given these facts, these schemes cannot be considered as a long-term approach. Other current pricing schemes such as EPR do not promote innovation, while some authors argue that EPR leads to high prices of medicines which are not aligned to their value.

In this context, Value-based pricing is a paradigm shift that distributes risk among payer and industry and offers measurable value to payers and can be utilised as a valuable tool. It has been an elusive target for many researchers while it has been depicted as the holy-grail of pharmaceutical policy. Our approach substantiates that value-based pricing is a feasible approach in Cyprus Health sector. The definition of the maximum price, which will fairly incentivize the marketing authorization holder, while it will not impair the allocative efficiency of the system, is a major contribution to health policy, nested in a flawed market. To this end, Value-based pricing will accelerate access of patients to much-needed products, saving time from negotiations, which in several cases are futile. In this bottom-up approach, Value-based pricing guarantees that the benefits the reimbursed product yields do not displace health benefits in the broader health sector. Ultimately, these costs can be considered to represent value for money. Nevertheless, several practical issues were raised during the procedure that have to be tackled before value-based pricing is disseminated. We identified only one clinical study, whose design matches current practice in Cyprus, nevertheless this would not be the norm for the majority of drugs. Marketing authorization holders run randomised controlled trials for regulatory purposes, whose design deviates from real life settings owing to comparator choice, exclusion and inclusion criteria, patient population, duration of the trials, setting, outcome measures and duration. Assessing data and synthesizing relevant models for economic evaluation raise substantially the complexity factor and this constitutes value-based pricing a lengthy, labour and expertise demanding process. It would demand strong support and commitment by the government and mainly a multidisciplinary pool of people with the appropriate health economic, statistical and epidemiological skills. A small country such as Cyprus may struggle to maintain the necessary human resources required especially given current financial recession. Another obstacle emerging from size of Cyprus deals with maximum output capacity. A proper economic evaluation may span up to one year, and it is doubtful

whether current Health context can support more than one committee. Therefore, relevant output capacity of this committee will be low and full market coverage is illusive. In conclusion, it is expected that given that such a committee is assembled, it can focus only on selected products, with significant disease or budget impact. This could create inequalities among pharmaceutical market and create 2 tier products. Cyprus, due to its small size and remote location, is classified as a non-attractive small pharmaceutical market (Value for Money, 2007). A distinct characteristic of this market is the existence of low competitive forces, which tend to shift monopoly power to supplier. Supplier's monopoly power is also augmented by entry barriers, such as obligations of marketing authorization holder to supply summary of product's characteristics in Greek, along with Greek labelled packages. Being a small market deters the development of alternative supply chains, such as parallel imports, which could have compromised dominant position of a single supplier. To sum up the foregoing, we would need to assess potential exit of pharmaceutical industries from Cyprus, in case of price reductions. However, this has to be weighed against a much faster introduction of the pharmaceutical products to the formulary.

The conclusions of this thesis extend beyond Cyprus' boundaries and take a global stand in the quest for efficient, scientifically endorsed, and potent pricing schemes. Since value-based pricing schemes reached a stand-off, our conclusions and recommendations can invigorate the interest and motivate more research in this domain, under the light of our findings.

Sorafenib has two indications, renal and liver cancer. Under proposed value-based pricing, this will create severe implications since potentially Sorafenib will carry 2 prices, which will further increase complexity factor of reimbursement process. This may lead to a weighted value-based pricing, based on estimated utilization data.

The establishment of a WTP threshold remains uncharted territory for many countries primarily due to ethical reasons and the decision-making is performed on the basis of unpublished pertinent thresholds. The cost-effectiveness analysis has an ingrained comparative and limiting attribute, since all medicines would be cost-effective under an infinitely large WTP threshold. For the value-based pricing study, we adopted the recommendations of WHO, which provides that the multiplies of per-capita domestic product can be utilised as economic threshold. More importantly, this approach takes into consideration the financial capacity of each country. According to this approach, the highest WTP threshold equals three time per capita domestic product; anything above this

is considered to be non cost-effective. In this notion, the human and the financial resources could create more health utility if they are diverted to other therapeutic territories. This is in line with the differential price concept and, in contrast to the external price reference scheme, it allows the affordability of each country to be a constituent factor in the pharmaceutical pricing process. Some authors take a step forward and suggest the introduction of varying thresholds level: each one addressing a specific health state under the condition that the entangled ethical and legal concerns can be addressed. A higher WTP threshold would probably suit better health conditions with greater burden of illness, such as rare and orphan diseases, end of life treatment, highly innovative products and medicines that exhibit wider societal benefits, such as benefits to carers (Medicines, Pharmacy and Industry Group, 2011). Many authors argued about potential extra weight of QALY in end of life treatments (Towse, 2009) while others debate that even a QALY at the end of life actually varies according (NICE, 2009) to the way it was obtained, with gain in palliative care being superior (Mason, Jones-Lee & Donaldson, 2009; Pinto-Prades, Fernando-Ignacio & Corbacho, 2012) to gains in life expectancy. Since all health programs actually compete for funds it is possible that this diversity may be beneficial for some patients and injurious for others. Ginette Camps-Walsh (2009) suggests 5 different categories of threshold within NHS which differentiate acute, chronic, paediatric, rare and end of life diseases. The categories above have varying degrees of treatment options and as a result, each category has diverse unmet medical needs.

Capitalising on this, we adopted the highest WTP threshold, on account to the orphan drug status of sorafenib. The above issue is also linked to utilisation of different health state measure tools. It is accepted that available health state measurement tools (Hemmett et al., 2004) can deliver varying results and it's also substantiated that patients in different stages of the same disease have diverse perception of time (Maor et al., 2001) and health state preferences (Hanneke, 2011). These findings create further complications pertinent to the selection of endpoints of the study (Overall survival or Progression free survival) which must be consonant, in order to ensure homogeneity among potentially comparative products. Comparator selection and specifically the base care product, is of unparalleled significance. In a time series setting, the price of future products will be a step-up dependant based on past and current value-based prices. In our case, we compared Sorafenib to BSC, with BSC being the base case product. Upon future introduction of Axitinib, its price will greatly depend on price of Sorafenib and there will be notable differences between Sorafenib' s reference (2880 euro) and Sorafenib' s value-based price

(1816 euro).The level of complexity will further rise given that in oncology regimens, it is not rare to encounter expensive products, apart from primary ones, which are given as adjuvant or to cure side effects. It's still unknown how to address this issue regarding products that were priced ex post and products that will be priced ex ante. Another decisive task is to express all values into money: Some authors suggest the net-benefit while other authors argue for the use of multi-criteria decision analysis, by using weight value for each benefit type (Devlin & Sussex, 2011). Value-based pricing is expected to engage R & D companies in a quest for really innovative products, but it may deter companies from investing into territories, in which marginal benefits are anticipated (Kanavos et al., 2010). Another pending issue is the pricing of equivalent products and the concern that this will impede further price competitions which have led to massive reductions in some therapeutic categories, such as statins (Hughes, 2011). As proved by our analysis value-based pricing does not result in high pharmaceutical prices when society's WTP is known and under a specific context it can be considered a cost-containment tool (Persson, 2011). This does not come under surprise since oncology products on the grounds of their innovative mode of action status, high R & D costs and considerable failure rates ask for higher prices. In our study we transferred health utilities from published study. Value-based pricing framework in other countries, such as Germany provides that a product gets a provisional price, and afterwards "real life effectiveness data" (Kielstra, 2012) are gathered, which will be utilized to set a value-based price (Greiner, 2011). For new products this preferably has to be carried out in national level. This is in line with other approaches which provide that new products get a price based on an ex ante evaluation while existing products get a price based on a rolling ex post evaluation (McGuire, Raikou & Kanavos, 2008).

In addition to the above, there are several intertwined regulatory and political issues on Value-based pricing, such as the value of a potential breakthrough treatment for cancer. Given that cancer in Cyprus costs annually more than 200 million euros, the capital worth of an innovative treatment that would cure cancer would be subject to a corresponding WTP threshold; having said that Government would never accept to define such a high price. In addition to this, the rationale of aligning the price to the costs or the suffer that has been averted, is an unfamiliar approximation among public, in contrast to supply and demand defined prices. Finally another regulatory issue is the introduction of the generics. The price of the generics is substantially lower, while its value is the same. This is primarily a regulatory issue which merits additional research. Nevertheless, by the time

that a product loses its patent, it is already considered to be a cash cow and the financial expectations from the MaH are marginal.

5.2.7. Expected Value of Perfect Information

The findings of this study corroborate the value of EVPI in the decision-making process a uncertainty-reduction tool and a gauge for targeted future research. In the previous sections, we delineated the need to maximise health outcomes given the budget constraints in health care sector. The presence of uncertainty, as discussed earlier, leads to a finite probability that the decision is wrong. It is essential to further analyse and scrutinize this probability in order to reduce waste, by adopting the wrong therapeutic approach. Previous studies used the sensitivity analysis, an approach that indicates which factors and to which extent, affect the outcome of the economic evaluation. In our study we performed a sensitivity analysis, which highlighted which variables influence outcome. This is important since it underlines which factors can lead to over or under estimation of outcome.

The EVPI takes a step forward and quantifies the expected opportunity loss which is associated with uncertainty. In our case the sensitivity analysis showed that cost-effectiveness parameters are particularly sensitive to effectiveness, mainly overall survival, and cost of the product. Other medical and pharmaceutical cost variations demonstrate minimum impact on ICER. EVPI reaches its maximum at the point that INB is 0, that is 30880 euro. At this point, there is a strong possibility of 50% that the wrong decision is reached, which maximises uncertainty. EVPI serves as an upper limit proxy for what is perceived to constitute an acceptable societal return for future research. The decision for future research does not depend only on the EVPI but is also subject to whether product is cost-effective or not. Another significant attribute of EVPI is that it takes into consideration the specific population. In our case, since we know the prevalence or m RCC in Cyprus, we estimate that the total EVPI for the Cyprus population is 1,235,200 euro. This both exemplifies and simplifies the decision-making process, by conveying the necessary funds for further research. Low values of EVPI should be treated with caution, since they may indicate perfect knowledge; consequently any future research would not add any value. Having said that, low values of EVPI may indicate that due to the uncertainty of the model, any future research would not be any value. EVPI could also be of value when comparing sub-cohorts (age, disease status etc).

5.3. Recommendations for future research

The current study has led to significant findings. At the same time it raised several other issues that merit additional research, mainly in the context of decision- making and technical parameters of the modeling process.

To begin with, tendering for pharmaceuticals was proved to be a potent pricing and reimbursement approach. This attribute has to be weighed against some potential drawbacks, such as exit of failed bidders from the market, which would lead to oligopoly. Oligopoly in a regulated market, as the pharmaceutical, would shift market power towards the seller and any further savings potential would be diminished. Taking this into consideration, the qualitative relationship between number of bidders and rate of price decrease. In addition to this, it would be meaningful to assess if a minimum number of bidders should be set.

In the second place, our findings in the tendering study would justify more research pertinent to the insensitivity of price reduction to innovation status of the product. We proved that initially MaH submits lower prices, while as sales value is increasing, efficacy of tendering wanes. This also could justify more research, connecting the dots between increasing sales and regressive price reduction.

The decomposition study of pharmaceutical sales had only minor, in any limitations, that would need further research. Nevertheless, since our study covered a seven year period, which was characterised by significant changes in the market, a continuation of this study would perfectly make sense, given that changes occurred during financial crisis and consequent austerity measures and memorandum-impelled reforms. This would answer the question whether crisis exerted a beneficial neutral or negative effect on the prescribing patterns of physicians. Furthermore, it can potentially clarify if privatization in health occurs, that is the shifting the reimbursement operational mode to out-of pocket payments.

Economic analysis is a highly dynamic field and more research is imperative. This can serve two-fold: verification of current practices and elaboration of pioneer tools that will evolve this field. Introduction of new products mandates designing and conducting newer studies, which will include current and newer agents. Furthermore, the uncertainty of the economic evaluation, regardless its causality, is a topic that has only recently emerged in the spotlight. In this sense, evolvement of current approaches, such as sensitivity analysis and EVPI, would deserve more studies in order to be optimised. EVPI can be further disintegrated into its integral elements, thus constituting the effort for

minimising uncertainty more focused, targeted and eventually effective. Nevertheless, this intertwines with inherent limited capacity to fully comprehend biological complexity of human body, causes and trajectories of diseases. As a result, causality of uncertainty and its consequent fragmentation in small segments which can be easily analysed, would be beneficial.

As discussed earlier in this thesis, economic evaluation carries some drawbacks, which could suffice future research. To begin with, negative values of ICER are meaningless, while ICER is not a reliable concept when difference in effectiveness are near zero, since this will lead to excessive and unjustified values of ICER(Moreno et al., 2010). Lastly, it has little sensitivity when difference in costs are near zero, as well as when direction of increasing ICER is opposite, in quadrants NE & SW.

In the context of economic evaluation, the quality-adjusted life year (QALY) as a monetary solution which is utilized as the denominator of cost-effectiveness ratio, facilitated the comparison of resource efficiency utilization in health production. Despite its global acceptance, QALY still entails several assumptions and limitations, which could be the subject of future research. Indicatively, there are several concerns whether all QALY's are equal or discrepancies exist contingent to disease severity, estimated survival, age and sex. In addition to this, the conundrum of providing small health gains to bigger patient cohorts or large health gains to fewer people, must be solved. Also, the introduction of QALY weights could be considered. Finally, the QALY theory assumes that the patient's preferences for paths of transitioning between health states can be approximated by toting up the time-weighted preferences for the fragments of that path, as per the patient's preferences.

Furthermore, the introduction of newer metrics, in addition to the existing ones can make economic evaluation accessible to a wider audience, who do not posses technical expertise.

Future research should capitalize on the findings concerning VBP and enhance research in this topic, primarily by addressing the ethical concerns espousing the dilemma of setting a price-tag to human life. Spending a lot of money for a small pool of patients, attaining marginal health gains it is a highly sensitive topic which interlaces with the principles of equity and solidarity. This is multidiscipline issues and a consensus is rather unlikely to reach. In addition, the long term effect of VBP merits additional research, especially compared to other pricing schemes such as external reference pricing and tendering.

The Definition of a VBP is pertinent to willingness-to-pay threshold, which is the confluence of ethical, societal and financial cohesion of a society. This may culminate in a stand-off; however it may also lead to a constructive work in this field and explicate several tangled and dysfunctional areas of our health policy sector. In any sense, by capitalising on our methodology, more insight can be gained for the optimum prices of several products with significant uncertainty and strong budget impact.

5.4. Limitations

Study has some limitations. It is possible that patient population of the study differs compares to the local patient population. Secondly, it is likely that patients in daily practice present at a later stage and it is also probable that their health condition is worse, in comparison to the population of the study.

Transition between health stages are confirmed by laboratory and imaging techniques in the study and are protocol driven, while in real life they are mostly defined by presence of symptoms, that substantiate progression.

Lastly, the selection of other therapeutic options is contingent to formulary while in clinical trials adjuvant treatment are protocol defined and available to all patients.

5.5. Summary

The main purpose of this study was to explore Health technology assessment (HTA) and cost-effectiveness analysis context in Cyprus; propose a conceptual and technical framework through the introduction of innovative pharmacoeconomic modeling and elaborate pioneering approaches in pricing of pharmaceuticals through incorporation of value, as defined through health technology assessment in the price of the product.

The first part of the thesis studied the current pharmaceutical sector. A multivariate analysis revealed which factors and to which extent affect outcome of public pricing and reimbursement scheme. The most important findings were the lack of correlation between value of the product and its final price.

The next step defined the key cost-drivers of Cyprus pharmaceutical market. The decomposition study revealed that oncology sector is characterised by a shift of prescribing to new and more expensive products.

Findings must be interpreted in the context of a coherent and integrated health policy, while they also create stimulus for future research.

Economic evaluation of pharmaceutical can be of value for Cyprus health care sector and can solve some complex resource allocating issues. The use of Markov Model is a scientific robust approach that can serve well this topic.

5.6. Conclusions

Decision-making in health is a specific, confining and qualitative process; an art in the face of adversity. It is of utter importance that decision-making in Health occurs, nested in the perspective of evidence based medicine. In the pharmaceutical market, several tools have been proven to elucidate current situation, identify areas of strength and weakness and minimise threats. The use of decomposition facilitates the classification of cost-drivers and the ensuing economic evaluation can answer the question whether is it justifiable on grounds of health economic theory to adapt this therapeutic option.

The final conclusion is the feasibility to align the price of the product to its clinical value. In addition to this, the estimated value-based price of Sorafenib is significantly lower, which is in line with findings of other authors (Dranitsaris, 2012).

Although many issues are still pending, the notion of economic evaluation should enter the collective consciousness of decision makers. The incorporation of value and affordability into the product's price is a thematically ambitious concept which comprises an essential rationale for its further dissemination. Prior to this, the pharmaceutical sector must be fully understood and clarified using the right statistical tools and high-grade of evidence data. This also implies that all aspects must be illuminated. The industry and health authorities must engage in a mutual beneficial dialogue to further define and refine these innovative schemes.

REFERENCES

Abboud, C., Berman, E., Cohen, A., Cortes, J., DeAngelo, M., Deininger, M.,.....& Salem, Z. (2013). The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. *Blood, 121*(22), 4439-42.

Adèr, H.J., Mellenbergh, G. J., & Hand, D. J. (2008). *Advising on research methods: A consultant's companion*. Huizen, The Netherlands: Johannes van Kessel Publishing.

Ades, A.E., Lu, G., & Claxton, K. (2004). Expected value of sample information calculations in medical decision modeling. *Medical Decision Making, 24* (2), 207-27.

Anand, S., & Hanson, K. (1997). Disability-adjusted life years: a critical review. *Journal of Health Economics, 16*(6), 685–702.

Andreou, M., Pashardes, P., & Pashourtidou, N. (2011). *Cost and value of health care in Cyprus.* Nicosia: University of Cyprus. Available from: http://www.ucy.ac.cy/data/ecorece/DOP02-10.[Accessed August 18].

Airoldi, M., & Molton, A. (2009). Adjusting life for quality or disability: stylistic difference or substantial dispute? *Health Economics 18* (11), 1237–1247.

Anderson, W.J. (1991). *Continuous-time Markov chains. An applications-oriented approach.* New York: Springer-Verlag.

Antoniadou, M. (2005). Can Cyprus overcome its health care challenges? *Lancet, 365* (9464), 1017–20.

Appleby, J. (2012). Rises in healthcare spending: where will it end? *BMJ, 345,* 7127.

Ara, R., & Weiloo, A. (2012). Using Health State Utility Values in Models Exploring the Cost-Effectiveness of Health Technologies. *Value in Health, 15* (6), 971–974.

Arickx, F., Bormans, V., Leveque, F., Mortier, M., Soete, E., & Vanhaeren, E. (2009). *Public Tendering for off Patent Medicines in Belgium—The Simvastatin Case*. Brussels, Belgium: RIZIV.

Armitage, P., Berry, G., & Matthews, J. (2002). *Statistical methods in medical research* (4th ed). Oxford: Blackwell Publishing.

Arnensen, T., & Trommald, M. (2005). Are QALYs based on time trade-off comparable? A systematic review of TTO methodologies. *Health Economics, 14* (1), 39–53.

Baio, G. (2012). *Bayesian methods in health economics*. USA: Chapman Hall, CRC.

Barber, J. A., & Thompson, S.G. (1998). Analysis and interpretation of cost data in randomised controlled trials: review of published studies. *BMJ*, 317 (7167), 1195-1200.

Barber, N. (1995).What constitutes good prescribing? *BMJ,* 310 (6984), 923-925.

Bastian, A. (2013). *THE FUTURE OF ONCOLOGY: THE EUROPEAN MODEL*? Washington: Bridgehead Seattle.

Battista, R.N., & Hodge, N.J. (1995). The development of health care technology assessment: an international perspective. *International Journal of Technology Assessment in Health Care, 11* (2), 287–300.

Baumol, W., & Bowen, W. (1966). *Performing Arts, The Economic Dilemma: a study of problems common to theater, opera, music, and dance.* New York: Twentieth Century Fund.

Baumol, W., De Ferranti, D., Malach, M., Pablos-mendez, A., Tabish, A., & Wu, L.G. (2012). *The Cost Disease: Why Computers Get Cheaper and Health Care Doesn't.* Yale: Yale University Press.

Benjamin, C.M.B., & Busschbach., J.V. (2011). Toward a more universal approach in health valuation. *Health Economics, 20* (7), 864–875.

Bennet, K.J. (1996). *Measuring health state preferences and utilities: rating scale, time trade-off, and standard gamble techniques*. In Spilker B. *Quality of life and pharmacoeconomics in clinical trials* (2nd Edition, Chapter 27). Philadelphia: Lippincott-Raven.

Beral, V. et al. (2003). Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet, 362* (9382), 419-427.

Bhatt, D. L. (2011). Evaluation of agents to reduce infarct size. It can be quite REVEALing. *JAMA, 305* (18), 1908-1909.

Bleichrodt, H. A. (2002). New explanation for the difference between time trade-off utilities and standard gamble utilities. *Health Economics, 11* (5), 447–456.

Bickerdyke, I., Dolamore, R., Monday, I., & Preston, R. (2002). *Supplier-Induced Demand for Medical Services*, Productivity Commission Staff Working Paper: Canberra.

Birch, S., & Gafni, A. (2006). Information created to evade reality (ICER): things we should not look to for answers. *Pharmacoeconomics*, *24* (11), 21-31.

Black, W.C. (1990). The CE plane: a graphic representation of cost-effectiveness. *Medical Decision Making*, *10* (3), 212-214.

B.P.I. (2011). German Association for Pharmaceutical Industry (BPI e.V.) Pharma Data.; Available from: www.bpi.de/fileadmin/ edia/bpi/Downloads/Internet/ Publikationen/Pharma-Daten/Pharmadaten %202011%20EN.pdf [Last assessed March 2013].

Brazier, J., Roberts, J., Tsuchiya, A., & Busschbach, J. (2004). A comparison of the EQ-5D and SF-6D across seven patient groups. *Health Economics*, *13* (9):873-884

Brazier, J., Ratchliffe, J., Tsuchiya, A., & Salomon J. (2007). *Measuring and valuing Health benefits for Economic Evaluation*. Oxford: OUP.

Brazier, J.E., & Longworth, L. (2011). An introduction to the measurement and valuation of health for NICE submissions. *NICE DSU Technical Support Document 8*. Available from http://www.nicedsu.org.uk

Bremaud, P. (1999). Markov chains, Gibbs Fields, Monte Carlo simulation and queues. New York: Springer-Verlag.

Briggs, A., Sculpher, M., & Buxton, M. (1994). Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. *Health Economics, 3*(2), 95–104.

Briggs, A., & Fenn, P. (1998). Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. *Health Economics, 7* (8), 723–740.

Briggs, A., & Sculpher, M. (1998). An introduction to Markov Modelling for economic evaluation. *Pharmacoeconomics, 13* (4):397-409.

Briggs, A., & Gray, A. M. (1999). Handling uncertainty when performing economic evaluation of healthcare interventions. *Health Technology Assessment*, *3* (2), 1–134.

Briggs, A. (2000) .Handling Uncertainty in Cost-Effectiveness Models. *Pharmacoeconomics, 17* (5), 479-500.

Briggs, A.H., Goeree, R., Blackhouse, G., & O'Brien, B.J. (2002). Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. *Medical Decision Making, 22* (4), 290–308.

Briggs, A. (2002). *Probabilistic Cost-Effectiveness Modelling: Overview of Methods and Challenges with an interactive Illustration.*. Paper presented at the 7th Annual ISPOR Meeting , Rotterdam , The Netherlands. USA: ISPOR.

Briggs, A., Nixon, R., Dixon, S., & Thompson, S. (2003): *Parametric modelling of cost data: some simulation evidence*. CHEBS seminar.

Briggs, A., Sculpher, M.J., & Claxton, K. (2006). *Decision Modelling for Health Economic Evaluation.* Oxford: Oxford University Press.

Brown, M.M., Brown, G.C., & Sharma, S. (2005). *Evidence-Based to Value-Based Medicine.* Chicago: AMA Press.

Buxton, M.J., Drummond, M.F., VAN Hout, B.A., Prince, R.L., Sheldon, T.A., Szucs, T., & Vray, M. (1997). Modelling in economic evaluation: An unavoidable fact of life. *Health Economics*, *6* (3), 217-227.

Cairns, J., & Rushy, J.F. (2005). *Economic Evaluation*. Berkshire, England: Open University Press McGraw-Hill Education.

Camps-Walsh, G., Aivas, I., & Barratt, H. (2009). *How can value-based pricing improve access to and adoption of new treatments*? 2020health.

Cantor, S., & Ganiats, T. (2012). Incremental Cost-Effectiveness Analysis: The Optimal Strategy Depends on the Strategy Set. *Journal of Clinical Epidemiology*, *52* (6), 517–522.

Carlson, B. (2009). Satisfaction Guaranteed: Or your Money Back. *Biotechnology Healthcare, 6* (4), 14–22.

Caro, J.J., Briggs, A.H., Siebert, U., Kuntz, KM, & ISPOR SMDM. Modelling Good Research Practices Task Force (2012). Modelling good research practices. *Medical Decision Making*, *32* (5), 667-677.

Carreras, G., Baccini, M., Accetta, G., & Biggeri, A. (2012). Bayesian probabilistic sensitivity analysis of Markov models for natural history of a disease: an application for cervical cancer. *Italian Journal of Public Health, 9 (3),* 7537-7539.

CBI Market Information Database. (2010). CBI MARKET SURVEY :The Pharmaceutical Market in Cyprus [pdf] Available at ⟨www.cbi. nl/?pag=85&doc=5177&typ=mid_document⟩;

Ministry of Interior, Census (2011). http://www.census.gov/compendia/statab/2011/tables/11s0103.pdf

Chang, Y.S., Adnane, J., Trail, P.A., Levy, J., Henderson, A., Xue, D.,.....& Wilhelm, S. (2007). Sorafenib (BAY 43-9006) inhibits tumor growth and vascularization and induces tumor apoptosis and hypoxia in RCC xenograft models. *Cancer Chemotherapy and Pharmacology*, *59* (5), 561-574.

Chatterji, S., Ustün, B. L., Sadana, R., Salomon, J., Mathers, C., & Murray, C. (2002). *The conceptual basis for measuring and reporting on Health Global Programme on Evidence for Health Policy.* Discussion Paper No. 45 World Health Organization.

Chesnut, C.H. , Silverman, S., Andriano, K., Genant, H., Gimona, A., Harris, S..... & Baylink, D. A. (2000). Randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. *American Journal of Medicine, 109* (4), 267-76.

Chiou, C.F., Hay, J.W., Wallace, J.F., Bloom, B.S., Neumann, P.J., Sullivan, S.D., Yu, H.T.,.....& Ofman, J.J. (2003) . Development and validation of a grading system for the quality of cost-effectiveness studies. *Medical Care, 41*(1), 32–44.

Claxton, K., & Possnet, J. (1996). An economic approach to clinical trial design and research priority setting. *Health Economics, 5* (6), 513-524.

Claxton, K. (1999).The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *Journal of Health Economics*, *18* (3), 341–364.

Claxton, K., Ginnelly, L., Sculpher, M., Philips, Z., & Palmer, S. (2004). A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme. *Health Technology Assessment, 8* (31), 1–103.

Cooper, N.J., Sutton, A.J., & Abrams, K.R. (2002). Decision analytical economic modelling within a Bayesian framework: application to prophylactic antibiotics use for caesarean section. *Statistical Methods in Medical Research, 11* (6), 491-512.

Cooper, N.J., Sutton, A.J., & Abrams, K.R. (2004). *Decision analytical economic modelling within a Bayesian framework. Technical report 02-03*. Department of Epidemiology and Public Health; University of Leicester, UK:

Culyer, A.J., & Lomas, J. (2006). Deliberative processes and evidence- informed decision making in healthcare: do they work and how might we know? *Evidence and Policy, 2* (3), 357-371.

Culyer, A., McCabe, C., Brigss, A., Claxton, K., Buxton, M., Akehurst, R., Sculpher, M., & Brazier, J. (2007). Searching for a threshold, not setting one: the role of the national institute of health and clinical excellence. *Journal of Health Services Research and Policy*, *12*(1), 56-58.

Dagpunar, J. S. (2006). *Simulation and Monte Carlo With applications in finance and MCMC*. Sussex, UK: Wiley.

Desser, A.S., Gyrd-Hansen, D., Olsen, J.A., Grepperud, S., & Kristiansen, I.V. (2010). Societal views on orphan drugs: cross sectional survey of Norwegians aged 40 to 67. *BMJ, 341*(4715), 1-6.

Devlin, N. (2002). *An introduction to the use of cost-effectiveness thresholds in decision-making: What are the issues*? In A. Towse, C. Pritchard, & N. Devlin (Eds.), *Cost effectiveness thresholds: Economics and ethical issues* (pp. 16–24). London: Kings Fund and Office of Health Economics.

Devlin, N., & Sussex, J. (2011). *Incorporating multiple criteria in HTA*. Office of Health Economics Office Incorporating multiple criteria in HTA.

Dias, S., Welton, N. J., Sutton, A. J., & Ades, A. E. (2013). Evidence Synthesis for Decision Making 1: Introduction. *Medical decision making, 33* (5), 597-606.

DIMDI (2013). A.T.C *classification with defined daily doses*. Available from: www.dimdi.de/ static/en/klassi/atcddd/index.htm [Last assessed March 2013]

Dolan, P., Gudex, C., Kind, P., & Williams, A. (1996). Valuing health states: a comparison of methods. *Journal of Health Economics, 15* (2), 209-31.

Dolan, P. (1997). Modelling valuations for EuroQol health states. *Medical Care, 35*(11), 1095-108.

Donaldson, C., Baker, R., Mason, H., Jones-Lee, M., Lancsar, E., Wildman, J., Bateman, I.,.....& Smith, R.(2011). The social value of QALY: raising the bar or barring the raise? *BMC Health Services Research*, *11*(8).

Dowie, J. (2004). Why cost-effectiveness should trump (clinical)effectiveness: the ethical economics of the South West quadrant. *Health Economics, 13* (5), 453–459.

Dranitsaris, G. (2012). The application of pharmacoeconomic modelling to estimate a value-based price for new cancer drugs. *Journal of Evaluation in Clinical Practice,* 18 (2), 343–351.

Dranove, D. (1988). Demand inducement and the physician/patient relationship. *Economic Inquiry,* 26 (2), 251-298.

Drummond, M. (1992). Cost Effectiveness guidelines for reimbursement of pharmaceuticals: Is economic evaluation ready for its enhanced status? *Health Economics, 1* (2), 85-92.

Drummond, M., Sculpher, M., Claxton, K., Stoddart, G.L., & Torrance G.W. (1997). *Methods for the economic evaluation of health care programmes*. Oxford Medical Publications, 2nd edition. Oxford: Oxford University Press.

Drummond, M., & Pang, F. (2001). *Transferability of economic evaluation results*. In *Economic Evaluation in Health Care: Merging Theory with Practice*, Drummond M, McGuire, A. (eds). Oxford: Oxford University Press.

Drummond, M., Kanavos, P., & Sorenson, C. (2008). *Ensuring Value for Money in Health Care: The Role of Health Technology Assessment in the European Union*. Denmark: World Health Organization on behalf of the European Observatory on Health Systems and Policies.

Drummond, D.H., Petrou, S., Carswell, C., Moher, D., Greenberg, D., Augustovski, F., Briggs, A., Mauskopf, J., & Loder, E. (2013). Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluations publication guidelines task force. *Cost Effectiveness and Resource Allocation*, *11*(6).

Dubois, R.W., Chawla, A.J., Neslusan, C.A., Smith M.W., & Wade, S. (2000). Explaining drug spending trends: does perception match reality? *Health Affairs, 19* (2), 231-9.

Dylst, P., Vulto, A., & Simoens, S.(2011). Tendering for outpatients prescription pharmaceuticals: what can be learned from current practices in Europe? *Health Policy, 101* (2), 146-52.

Dylst, P., Vulto, A., Godman, B., & Simoens, S. (2013).Generic medicines: solution for a sustainable drug market? *Applied Health Economics and Health Policy*, *11* (5), 437-43.

Dupont, W. (2009). *Statistical Modelling for Biomedical Researchers A Simple Introduction to the Analysis of Complex Data*. Cambridge: Cambridge University Press.

Efron, B. (1979). Bootstrap Methods: Another look at the jackknife. *The Annals of Statistics*, *17* (1), 1-26.

EMEA EU/3/04/207. Available from www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2009/11/human_orphan_000064.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d12b

Escarce, J., & Pauly, M.V. (1998). Physician opportunity costs in physician practice costs functions. .*Journal of Health economics, 17* (2), 129-151.

Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M., ...& Bukowski, R.M. (2007): Sorafenib in advanced clear-cell renal-cell carcinoma. *New England Journal of Medicine*, *356* (2), 125–134.

Espín, J., Rovira, J., & García, L. (2011). *Experiences and Impact of European Risk Sharing Schemes Focusing on Oncology Medicines.* Grenada, Spain: Andalusian School of Public Health.

FDA (2014). Drug Safety Communication: *FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines* available at http://www.fda.gov/Drugs/DrugSafety/ucm376389.htm last assessed in November (2014).

Fojo, T., & Grady, C. (2009).How much is life worth: cetuximab, non-small cell lung cancer, and the $440 billion question. *Journal of the National Cancer Institute, 101* (15), 1044-8.

Frew, E.J., Whynes, D.K., & Wolstenholme, J.L. (2003). Eliciting willingness to pay: comparing closed-ended with open- ended and payment scale formats. *Medical Decision Making, 23* (2), 150–159.

Friedman, D. (1991). Should Medicine be a Commodity? An Economist's Perspective Rights to Health Care. *Philosophy and Medicine*, 38, 259-305.

Fuchs, V.R., & Zeckhauser, R. (1987). Valuing health - a 'priceless' commodity. *American Economic Review, 77* (2), 263-8.

Fuchs, V. (1998). *Who is going to live Health, Economics, And Social Choice. Economic Ideas Leading to the 21st Century.* Singapore: World Scientific Publishing.

Gafni, A., & Birch, S. (2006). Incremental cost-effectiveness ratios (ICERs): The silence of the lambda. *Social Science & Medicine*, 62 (9), 2091–2100.

Garattini, L., Cornago, D., & Compadri, P.(2007). Pricing and reimbursement of in-patent drugs in seven European countries: a comparative analysis. *Health Policy, 82 (3),* 330-9.

Gelman, A., Carlin, J., Stren, H., & Rubin, D. (1995). Bayesian Data Analysis. London: Chapman & Hall.

Geman, S., & Geman, D. (1984). "Stochastic Relaxation, Gibbs Distributions, and the Bayesian Restoration of Images". *IEEE Transactions on Pattern Analysis and Machine Intelligence, 6* (6), 721–741.

General Audit recommendations for rational medicines procurement, 2011. Available at http://pdf.politis-news.com/pdf/pdf?-A=257761,pdfview.html&-V=pdfarchivefullpaper Last assessed on November 17, 2011.

General Guidelines for Economic Evaluations from the Pharmaceutical Benefits Board (LFNAR 2003:2); 2003. Available at http://www.tlv.se/Upload/English/ Guidelines-for-economic-evaluations-LFNAR-2003-2.pdf.] last assessed on August 2013.

Gerdtham, U.G., Johannesson, M., & Jonsson, B. (1993). Drug expenditure and new drug introductions: the Swedish experience. *Pharmacoeconomics, 4* (3), 215- 25.

Gerdtham, U.G., Johannesson, M., & Gunnarsson, B. (1998). The effect of changes in treatment patterns on drug expenditure. *Pharmacoeconomics, 13* (1), 127-34.

Gilks, W. R., Clayton, D. G., Spiegelhalter, D. J., Best, N. G., McNeil, A. J., Sharples, L. D., & Kirby, A. J. (1993). Modelling complexity: Applications of Gibbs Sampling in medicine. *Journal of the Royal Statistical Society, 55*(1), 39–52.

Gilks, W.R., Richardson, S, Spiegelhalter, D.J. (1996). *Markov Chain Monte Carlo in Practice*. London, UK.: Chapman & Hall/CRC.

Godman, B., Sakshaug, S., Berg, C., Wettermark, B., & Haycox, A. (2011). Combination of prescribing restrictions and policies to engineer low prices to reduce reimbursmenent costs. *Expert Review of Pharmacoeconomics & Outcomes Research*, *11(1)*, 121-9.

Goeree, R., He, J., O'Reilly, D.l., Tarride, J.E., Xie, F., Lim, M., & Burke, N. (2011). Transferability of health technology assessments and economic evaluations: a systematic review of approaches for assessment and application. *Clinicoeconomics and Outcomes Research, 3,* 89–104.

Gold, M.R., Siegel, J.E., Russell, L.B., & Weinstein, M.C. (1996). *Cost- effectiveness in Health and Medicine*. New York: Oxford University Press.

Goodman, S. (2005). Introduction to Bayesian methods I: measuring the strength of evidence. *Clinical Trials, 2*(4), 282-90.

Grauer, D.W., Lee, J., Odom, TD, Osterhaus, J.T., & Sanchez, L.A. (2003). Pharmacoeconomics and Outcomes: Applications for Patient Care, Second Edition. Kansas City: American College of Clinical Pharmacy.

Greiner, W. (2011). *Germany's drug pricing after AMNOG – What comes next*? Ppaer presented at the 7th American & German Healthcare Forum, Minneapolis. Germany, University of Bielefeld.

Gridchyna,I., Aulois-Griot, M., Maurain, C., & Begaud, B. (2012). How innovative are pharmaceutical innovations? The case of medicines financed through add-on payments outside of the French DRG-based hospital payment system. *Health Policy*, *104*(1), 69-75.

Grieve, A.P. (1994). Bayesian approaches to randomized trials – discussion. *Journal of the Royal Statistical Society, Series A, 157*, 387–416.

Grieve, R., Grishchenko, M., & Cairns, J. (2009). SF-6D versus EQ-5D: reasons for differences in utility scores and impact on reported cost-utility. *European Journal of Health Economics,* (10)1, 15-23.

Gross, C.P., Mallory, R., Heiat, A., & Krumholz, H.M. (2002). Reporting the recruitment process in clinical trials: who are these patients and how they get there? *Annals of Internal Medicine*, *137*(1), 10-6.

Gyatt, G., & Evidence-Based Medicine Working Group (1992). Evidence-based medicine: a new approach to teaching the practice of medicine. *JAMA, 268*(17), 2420-2425.

Guyatt, G., Oxman. A.D., Akl, E.A., Kunz, R, Vist, G., Dahm, P.,..... Schünemann, H.J. (2011). GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology, 64(4),* 383-394.

Hall, A.R. (2004). *Generalized method of moments*. NY, USA: Oxford University Press.

Harris, J. (1987). QALYfying the value of life. *Journal of Medical Ethics, 13*(3), 117-123.

Hastings, W.K. (1970). "Monte Carlo Sampling Methods Using Markov Chains and Their Applications". *Biometrika, 57*(1), 97–109.

Hawthorne, G., Richardson, J., & Osborne, R. (1999). The Assessment of Quality of Life (AQoL) instrument: a psychometric measure of health-related quality of life. *Quality of Life Research*, *8*(3), 209-224.

Hemmett, L., Holmes, J., Barnes, M., & Russell, N. (2004). What drives quality of life in multiple sclerosis? *QJM*, *97*(10), 671–676.

Hilden, J. (2008). Budget Impact Analysis and Its Rational Basis. *Medical Decision Making, 28*(4), 460-1.

Hiligsman, M., Ethgen, O., Bruyère, O., Richy, F., Gathon, H.J., & Reginster, J.Y. (2009). Development and Validation of a Markov Microsimulation Model for the economic evaluation of Treatments in Osteoporosis. *Value in Health, 12*(5),687-96.

Hoffmann, T., Bennett, S., & De Mar, C. (2010). *Evidence-based practice across the health professions.* Sydney: Elsevier.

Hoyle, M., Green, C., Thompson-Coon, J., Liu, Z., Welch, K., Moxham, T., & Stein, K. (2010). Cost-effectiveness of sorafenib for second-line treatment of advanced renal cell carcinoma. *Value in Health, 13*(1), 55-60.

House of Parliament 3.06.010.01.646, 26 March 2012, Issue Raised by member of Parliament Hadjiyiannis, Kyriakos (2012). available at ⟨http://www. parliament.cy/parliamentgr/008_02/chronological/008_02_IA. htm⟩ [last assessed on July 2014].

Hsieh, H.M, & Meng, V.M. (2007). Decision Analysis and Markov Modeling in Urology. *The journal of urology, 178*(5), 1867-1874.

Hughes, D. (2011). Value-based pricing incentive for innovation or zero net benefit? Pharmacoeconomics, *29*(9)731–735.

International Monetary Fund (2012). Cyprus: GDP per capita, current prices. Available from: www.imf.org/external/pubs/ft/weo/2013/01/weodata/weorept.aspx?sy=200&ey=2012&scsm=1&ssd=1&sort=country&ds=.&br=1&c=423&s=NGDPRPC%2CNGDPPC%2CNGDPDPC& grp=0&a=&pr.x=101&pr.y=3

Jacobson, P. (2005).Single-payer health insurance works best. *Policy options September.*

Johnston, A., Belitsky, P., Frei, U., Horvath, J., Hoyer, P., Harold, H.,.....& Nashan, B. (2004). Potential clinical implications of substitution of generic cyclosporine formulations for cyclosporine microemulsion (Neoral) in transplant recipients. *European Journal of Clinical Pharmacology 60*(6), 389–95.

Kadane, J. (1995). Prime time for Bayes. *Controlled clinical Trials, 16*(5), 131-318.

Kadane, J., & Wolfson, L. (1998). Experiences in elicitation. *The Statistician, 47*(1), 3-19.

Kallenberg, O. (1997). *Foundations of Modern Probability*. New York: Springer-Verlag.

Kanavos, P., & Vandegrift, M. (1997). Health policy versus industrial policy in the pharmaceutical sector: the case of Canada. *Health Policy*, *41*(3), 241–60.

Kannavos, P., Seeley, L., & Vandoros, S. (2009). *Tender systems for outpatient pharmaceuticals in the European Union: Evidence from the Netherlands, Germany and Belgium.* London School of Economics.

Kanavos, P.K., Nicod, E., Espin, J., Van, D., & Aardweg, S. (2010): *Short- and Long-Term Effects of Value-Based Pricing vs. External Price Referencing*. Brussels: LSE Health - London School of Economics, Andalusian School of Public Health.

Kanavos, P., Taylor, D., Manning, J., & Carr, M. (2010). *Implementing Value Based Pricing for Medicines: An introduction.* London: University of London.

Karnon, J., Stahl, J., Brennan, A., Caro, J.J., Mar, J., & Möller, J. (2012). Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force–4. *Medical Decision Making 32*(5), 701–711.

Kemeny, J.G., & Snell, J.L. (1976). *Finite Markov Chains*. New York: Springer Verlag.

Kendall, W.S., Liang, F., & Wang, J.S. (2005). *MARKOV CHAIN MONTE CARLO Innovations and Applications*. Singapore: World Scientific Publishing.

Kielstra, P. (2012). Reinventing biopharma: Strategies for an evolving marketplace. The value challenge. *Economist intelligence Unit.* Available at http://www.quintiles.com/~/media/library/white%20papers/reinventing-biopharma-the-value-challenge.pdf

Kim, S., Goldie S.J., & Salomon, J.A. (2010). Exploring Uncertainty in economic health interventions: The example of rotavirus vaccination in Vietnam. *Medical Decision Making, 30* (5), E1-E28.

Klein, E.A., Thompson, I.M.Jr, Tangen, C.M., Crowley, J.J., Lucia, M.S., Goodman, P.J., ...Baker, L.H. (2011). Vitamin E and the Risk of Prostate Cancer: Results of The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA, 306*(14), 1549-1556.

Kozlowski, S., Woodcock, J., Midthun, K.., & Sherman, R.B. (2011). Developing the nation's biosimilars program. *New England Journal of Medicine, 365*(5), 385-8.

Jansen, R., Redekop, W.K., & Rutten, F.F. (2001). Cost effectiveness of continuous terbinafine compared with intermittent intraconazole in the treatment of dermatophyte toenail onychomycosis: an analysis of based on results form the L.I.O.N. study. Lamisil versus intraconazol in onychomycosis. *Pharmacoeconomics, 19*(4), 401-410.

Laarhoven, V.H.W., Schilderman, J., Verhagen, C.A., & Prins, J.B. (2011). Time perception of cancer patients without evidence of disease and advanced cancer patients in a palliative, end-of-life-care setting. *Cancer Nursing*, *34*(6) 453-63.

Laing, R., & Buysse, I. (2010). *Impact of the Economic Crisis on the Global Pharmaceutical Sector*. Paper presented at Financial Crisis and Global Health Conference, Utrecht. Geneva: WHO.

Le Pen, C., Priol, G., & Lilliu, H.(2003). What criteria for pharmaceuticals reimbursement? An empirical analysis of the evaluation of "medical service rendered" by reimbursable drugs in France. *European Journal of Health Economics, 4*(1), 30-6.

Leopold, C., Habl, C., & Vogler, S. (2008). Tendering of Pharmaceuticals in EU member states and EEA countries (online).Available at ⟨http://ppri.oebig.at/Downloads/…/Final_Report_Tender- ing_June_08.pdf⟩.

Lichtenberg, F.R. (2005). The impact of new drug launches on longevity: evidence from longitudinal, disease-level data from 52 countries, 1982–2001. *International Journal of Health Care Finance and Economics, 5*(1), 47-73.

Light, D. (2010). American Sociological Association. Pharmaceuticals: a market for producing 'lemons' and serious harm, analysis finds. *Science Daily*

Lindsey, J. K. (1999). Discussion of some statistical heresies. *The Statistician*, *48* (1), 1-40.

López-Casanova, G., & Puig-Junoy, J. (2000): Review of the Literature on reference Pricing. *Health Policy, 54*(2), 87–123.

Lu, Z.J., & Comanor, W.S. (1998). Strategic pricing of new pharmaceuticals. *The Review of Economics and Statistics, 80*(1), 108-118.

M.S.J Iacovides, Ltd. (2001) vs Republic of Cyprus Case 415/99;15June.

Maor, Y., King, M., Olmer, L., & Mozes, B. (2001). A comparison of three measures: the time trade-off technique, global health-related quality of life and the SF-36 in dialysis patients. *Journal of Clinical Epidemiology, 54*(6), 565–570.

Mandelblatt, J., Schechter, C., Levy, C., Zauber, A., Chang, Y., & Etzioni, R. (2012). Building better models: if we build them, will policy makers use them? Toward integrating modeling into health care decisions? *Med Decision Making 32*(5) 656-9.

Mar, J., Sainz-Ezkerra, M., & Miranda-Serrano, E. (2008). Calculation of Prevalence with Markov Models: Budget Impact Analysis of Thrombolysis for Stroke. *Medical Decision Making, 28*(4), 481-90.

Marshall, D.A., Douglas, P.R., Drummond, M.F., Torrance, G.W., Macleod, S., Manti, O., Cheruvu, L., & Corvari, R. (2008). Guidelines for conducting pharmaceutical budget impact analyses for submission to public drug plans in Canada *Pharmacoeconomics, 26*(6), 477-95.

Mason, H., Jones-Lee, M., & Donaldson, C. (2009). Modelling the monetary value of a QALY: A new approach based on UK data. *Health Economics, 18*(8), 933–950.

Mayer, D. (2004). *Essential Evidence Based Medicine*. UK: Cambridge.

Maynard, A., & McDaid, D. (2003). Evaluating health interventions: exploiting the potential. *Health Policy, 63*(2), 215-26.

McAlister, F.A., Laupacis, A., Wells, G.A., & Sackett, D.L. (1999).Users' guides to the medical literature XIX applying clinical trial results B. Guidelines for determining whether a drug is exerting (more than) a class effect. *JAMA, 282*, 1371–7.

Mcguire, A., Raikou, M., & Kanavos, P. (2008). Pricing pharmaceuticals: Value based pricing in what sense? *Eurohealth,* 2008, *14*(2)3–5.

McLaughlin, J.K., & Lipworth, L. (2002). Epidemiologic aspects of renal cell cancer. Seminars in Oncology, *27*(2), 115-23.

McGhan, W.F., Rowland, C.R., & Bootman, J.L. (1978). Cost-benefit and cost-effectiveness: methodologies for evaluating innovative pharmaceutical services. *American Journal of Hospital Pharmacy, 35*(2),133-40.

McGuire, T. (1990). *Physician Agency. In Handbook of Health Economics*, Volume 1, Edited by A.J. Culyer, and J.P. Newhouse. North Holland: Elsevier.

Medicines, Pharmacy & Industry Group, Department of Health: A new Value-Based Approach to the Pricing of Branded Medicines. London;2011. http:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_122793.pdf last assessed on April 2014.

Merkur S., & Moshialos, E. (2007). A pricing policy towards the sourcing of cheaper drugs in Cyprus. *Health Policy, 81*(2-3), 368–375.

Meyer, F. (2011). *Outlook and challenges for the future A French perspective*. France: HAS.

Miller, D., & Homan, S. (1994). Determining transition probabilities: confusion and suggestions. *Medical Decision Making, 14*(1), 52-8.

Ministry of Finance. *Memorandum of understanding on specific economic policy conditionality*. Nicosia: Republic of Cyprus, 2013.

Ministry of Health .Pharmaceutical reform in Cyprus (2006).Available from: http://www.cyprus.gov.cy/moi/pio/pio.nsf/All/BEFF3C4943A9C69 6C2257127003D66A8?OpenDocument&print. [AccessedSeptember11, 2011].

Ministry of Health, Cyprus. Medical Institute and services law (1978-2000)

Ministry of Health (2010). Mecc Joint Registration Project. Cyprus Cancer Registry (CyCR). Nicosia: MoH.

Miyamoto, J.M., & Eraker, S.A. (1988). A multiplicative model of the utility of survival duration and health quality. *Journal of Experimental Psychology*, *117*(1), 3-20.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., & The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*, 6(7):e1000097. doi:10.1371/journal.pmed1000097.

Moreland, L.W., Schiff, M.H., Baumgartner, S.W., Tindall, E.A., Fleischmann, R.M., Bulpitt, K.J.....& Weinblatt, M.E. (1999). Etanercept therapy in rheumatoid arthritis: a randomized controlled trial. *Annals of Internal Medicine 130*(6), 478-486.

Moreno, E., Giron, F.J., Vazquez-Polo, F.J., & Negrin, M.J. (2010). Complementing information from incremental net benefit: a Bayesian perspective. *Health Services and Outcomes Research Methodology,10*(1),86–99.

Moreno, E., Giron, F.J., Vazquez-Polo, M.A., & Negrın, M.J. (2012): optimal healthcare decisions: the importance of the covariates in cost-effectiveness analysis. *European Journal of Operational Research, 218*(2), 512-22.

Moshialos, Mrazek, M., & Walley, T. (2004). *Regulating Pharmaceutical In Europe: Striving for efficiency Equity and Quality*. Brussels: European Observatory.

Motzer, R.J., Michaelson, M.D., Redman, B.G., Hudes, G.R., Wilding, G., Figlin, R.A.....& Rini, B.I. (2006). Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *Journal of clinical oncology, 24*(1), 16-24.

Muennig, P. (2007). *Cost Effectiveness in Health: A Practical Approach*. 2nd Edition. USA: Jossey-Bass.

Mullahy, J. & Manning, W. G. (1995). *Statistical issues in cost–effectiveness analysis*. In: Sloan, F. (ed.) *Valuing Health Care*. Cambridge: Cambridge University Press.

Murray, C.J., Evans, D.B., Acharya, A., & Baltussen, R.M. (2000). Development of WHO guidelines in generalized cost effectiveness analysis. *Health Economics, 9*(3), 235-5.

National Comprehensive Cancer Network. (2013). *Guidelines for Kidney cancer*. Available from: www.nccn.org/professionals/physician_gls/pdf/kidney.pdf

National Institute for Health and Care Excellence. (2005). Citizens Council Report Ultra Orphan Drugs. National Institute for Health and Clinical Excellence.

National Institute for Health and Care Excellence. (2008). *Appraisal of macular degeneration(age-related)—ranibizumab and pegaptanib* (TA155).Availablefrom:http://www.nice.org.uk/ TA155.

National Institute for Health and Care Excellence. (2011). *Appraising end of life medicines*. Available from http://www.nice.org.uk/media/ 26E/43/Endoflifemedicines.pdf. [AccessedDecember17,2011]

National Institute for Health and Care Excellence. (2013). available at [http://www.nice. org.uk/media/955/4F/Clarification_to_section_5.6_of_the_Guide_to_Methods_ of_Technology_Appraisals.pdf] last assessed on August 2013.

Neumann, P.J., & Johannesson, M. (1994). From principle to public policy: using cost-effectiveness analysis. *Health Affairs (Millwood), 13* (3), 206–14.

Neumann, P.J., Zinner, D.E., & Wright, J.C. (1997). Are methods for estimating QALYs in cost-effectiveness analyses improving? *Medical Decision Making, 17* (4), 402–440.

Newhouse, J., & McClellan, M. (1998).Econometrics in outcomes research: The Use of Instrumental Variables. *Annual Review of Public Health, 19*, 17-34.

Nord, E. (1992). Methods for quality adjustment of life years, *Social Science & Medicine 34* (5), 559–569.

Ntzoufras, I.(2009). *Bayesian Modelling using WINBUGS.* USA: Wiley Publications.

O'Brien, B.J., Drummond, M.F., Labelle, R.J., & Willan., A. (1994). In search of power and significance: issues in the design and analysis of stochastic cost-effectiveness studies in health care, *Medical Care, 32* (2), 150-163.

O'Brien, J.B., Kirsten Gertsen, K., Willan, A.R., & Faulkner, A. (2002). Is there a kink in consumers' threshold value for cost-effectiveness in health care? *Health Economics, 11* (2), 175–180.

O'Brien, B.J. & Briggs, A.H. (2002) Analysis of uncertainty in health care cost-effectiveness studies: an introduction to statistical issues and methods. *Statistical Methods in Medical Research, 11* (6), 455-468.

OECD (2012). Health at a Glance: Europe 2012. Paris: OECD Publishing. Available at http://ec.europa.eu/health/reports/docs/health_glance_2012_en.pdf. [Last accessed December 2015].

Oxford Centre for Evidence-Base Medicine. (2009) Levels of evidence. available at http://www.cebm.net/?o=1025. [Last accessed December 2015].

Oostenbrink, J., Al, M.J., Oppe, M., & Rutten-van Molken, M.P. (2008). Expected value of perfect information: an empirical example of reducing decision uncertainty by conducting additional research. *Value in Health*, *11* (7), 1070-80.

Parmigiani, G. (2002). *Modeling in medical decision making. A Bayesian approach.* West Sussex: John Wiley & Sons.

Paris, V. M., Devaux, & Wei, L. (2010). "*Health Systems Institutional Characteristics: A Survey of 29 OECD Countries*", OECD Health Working Papers, No. 50, OECD Publishing.

Patz, R., & Junker, B .W. (1999). A Straightforward Approach to Markov Chain Monte Carlo Methods for item Response Models. *Journal of educational and behavioral statistics, 24* (2), 146-178.

Pauly, M.V. (1978). *Is medical care different*?" in Greenberg, W. (ed), *Competition in the Health Care Sector: Past, Present and Future*, Germantown, MD: Aspen Systems.

Peacock, S.J., & Richardson, R.J. (2007). Supplier-induced demand: re-examining identification and misspecification in cross-sectional analysis. *European Journal of Health Economics, 8* (3), 267-277.

Pedersen, T.R., et al. (1994). Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *The Lancet, 344* (8934), 1383 – 1389.

Persson, U. (2012). Value Based Pricing in Sweden: Seminar Briefing no12. London: Office of Health Economics.

Petitti, D.B. (2000). *Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis: Methods for Quantitative Synthesis in Medicine*. New York: Oxford University Press.

Petrou, P. (2011). *PHIS Hospital Pharma Report*; 2009. Available from: http:// phis.goeg.at/downloads/hospitalPharma/PHIS%20Hospital%20Pharma %20Report%202009%20Cyprus.pdf. [Accessed September 6].

Petrou, P., & Talias, M. (2013). A framework for applying health technology assessment in Cyprus: thoughts, success stories, and recommendations. *Value in Health Regional Issues, 2* (2013), 273–278.

Pharmaceutical Trading Co. Ltd. vs Republic of Cyprus,371/ 2000; 12March.

Philips, Z., Bojke, L.,Sculpher, M., Claxton, K., & Golder, S.(2006). Good Practice Guidelines for Decision-Analytic Modelling in Health Technology Assessment A Review and Consolidation of Quality Assessment. *Pharmacoeconomics, 24* (4), 355-371.

Picavet, E., Dooms, M., Cassiman, D., & Simoens, S. (2011). Drugs for rare diseases – orphan designation status influences price. *Applied Health Economics and Health Policy, 9* (4), 1-5.

Pinto-Prades, J.L., Fernando-Ignacio, S.M., & Corbacho, B. (2012). Valuing qalys at the end of Life. Seville, Spain: Andalusian Agency for Health Technology Assessment.

Pliskin, J.S., Shepard, D.S., & Weinstein, M.C. (1980). Utility functions for life years and health status. *Operations Research, 28* (1), 206–24.

Polsky, D., Glick, H., Willke, R., & Schulman, K. (1997). Confidence intervals for cost–effectiveness ratios: a comparison of four methods. *Health economics, 6* (3), 243–252.

Purmonen, T., Martikainen, J.A., Soini, E.J., Kataja, V., Vuorinen, R.L., & Kellokumpu-Lehtinen P.L. (2008). Economic evaluation of Sunitinib Malate in second line treatment of metastatic renal cell cancer in Finland. *Clinical Therapeutics, 30* (2), 382-92.

Puterman, M.L. (1994). *Markov Decision Processes*. New York: John Wiley and Sons.

Raftery, J. (2009). Should NICE ´s threshold range for cost per QALY be raised? No, .*BMJ, 338* (e185).

Ramsey, S.D., Willke, R.J., Glick, H., Reed, S.D., Augustovski, F., Jonsson, B, Briggs, A., & Sullivan, S.D. (2005). Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. *Value in Health, 8* (5), 521–533.

Raven, M.C., Gillespie, C.C., Di Bennardo, R., Van Busum, K. ,And . Elbel, B. (2012). Vulnerable Patients' Perceptions of Health Care Quality and Quality Data. *Medical Decision Making*, *32* (2), 311-326.

Rawlins, M. (2004). National Institute for Clinical Excellence and its value judgments *BMJ*, *329* (e 224).

Rhee, J. (2009). The influence of the pharmaceutical industry on healthcare practitioners prescribing habits. *Internet Journal of Academic Physician Assistants, 7* (1), 4.

Robert, C., & Casella, G.(2010). *Introducing Monte Carlo Methods with R*. Springer, NY.

Roberts, M., Russell, L.B., Paltiel, A.D., Chambers, M., McEwan, P., & Krahn, M. (2012). Conceptualizing a model: a report of the ISPOR-SMDM modeling good research practices task force-2. *Value in Health, 15* (6), 804-15.

Roemer, M.I. (1961). Bed supply and hospital utilization: a natural experiment. *Hospitals, 1* (35), 36-42.

Sackett, D., Rosenberg, W.M., Gray, J.A., Haynes, R.B., & Richardson, W.S. (1996). Evidence based medicine: what it is and what it isn't. BMJ, *13* (312), *71-2.*

Sachs, J.D. (2001). *Macroeconomics and Health: Investing in Health for Economic Development*. World Health Organization WHO Library Catalogue-in-Publication Data World Health Organization. Geneva, Switzerland: World Health Organization.

Saha, S., Hoerger, T.,Pignone ,M., Teutsch, S., Helfand, M., & Mandelblatt, J. (2001). The art and science of incorporating cost effective- ness into evidence-based recommendations for clinical preventive services. *American Journal of Preventive Medicine, 20* (3), 36–43.

Sammoutis, G., & Paschalides, C. (2011). Will the sun shine over Cyprus's national health system*? Lancet*, *377* (29).

Sanson-Fisher, R.W., Bonevski, B., Green, L.W., & D'Este, C. (2007). Limitations of the randomized controlled trial in evaluating population-based health interventions. *American Journal of Preventive Medicine, 33* (2), 155-61.

Sassi, F. (2006). Calculating QALYs, comparing QALY and DALY calculations. *Health Policy and Planning, 21* (5), 402-8.

Sato, R. C., Zouain, D. M.(2010). Markov Models in health care *Einstein*, 8(3Pt 1), 376-9.

Scherer, F.M. (2000). The pharmaceutical industry. In: Culyer, AJ, & Newhouse, J.P., editors. Handbook of health economics, (Chapter 25 p. 1297-338). North-Holland: Elsevier.

Schmid, M., Wickler, F., Kelly, Maloney, K.O., Mitchell, R., Fenske, N., & Mayr, A. (2013). Boosted Beta Regression. *Plos One, 8* (4).

Sculpher, M., Fenwick, E., & Claxton, K. (2000). Assessing Quality in Decision Analytic Cost-Effectiveness Models A Suggested Framework and Example of Application *Pharmacoeconomics*, *17* (5), 461-477.

Sigerist, H.R. (1941). *Medicine and human welfare*. New Haven: Yale University Press.

Simoens S, & Coster, D. (2006). *Sustaining Generic Medicines Markets in Europe.* Research Centre for Pharmaceutical Care and Phar acoeconomics: Belgium;April.

Simoens, S. (2011). Pricing and reimbursement of orphan drugs: the need for more transparency. *Orphanet Journal of Rare Diseases, 6* (42).

Sintonen, H. (2001). The 15D instrument of health-related quality of life: properties and applications. *Annals of Medicine, 33* (5), 328-336.

Smith, J. (2010). *Bayesian Decision Analysis.* Cambridge: Cambridge University Press.

Smith D., Gravelle H., *The Practice of Discounting Economic Evaluation of Health Care Interventions* CHE Technical Paper Series 19 available at http://www.york.ac.uk/che/pdf/tp19.pdf last assessed November 2015.

Sonnenberg, F. & Beck, R. (1993). Markov Models in Medical Decision Making. *Medical Decision Making*, *13* (34), 322-338.

Spiegelhalter, D., Myles, J., Jones, D., & Abrams, K. (1999). An introduction to Bayesian methods in health technology assessment. *BMJ, 319* (508), 12.

Spiegelhalter, D.J., Myles, J.P., Jones, D.R., & Abrams, K.R. (2000). Bayesian Methods in HTA review. *Health Technology Assessment, 4*(38), 1-130.

Spiegelhalter, D.J., Thomas, A., Best, N.G., & Lunn, D.(2003). "WinBUGS Version 1.4 Users Manual". MRC Biostatistics Unit, Cambridge, UK; Available from:www.mrc-bsu.cam.ac.uk/bugs/

Spiegelhalter, D., Abrams, K.E., & Myles, J. (2004): *Bayesian approaches to clinical trials and health-care evaluation.* West Sussex: John Wiley & Sons.

Spiegenhalter, D. (2004). Incorporating Bayesian Ideas into Health Care Evaluation. *Statistical Science*, *19* (1), 156-174.

Stinnet, A., & Paltiel, D. (1997). Estimating CE ratios under second-order uncertainty: the mean ratio versus the ratio of means. *Medical Decision Making*, *17* (4), 483-9.

Stinnett, A.A., & Mullahy, J. (1998). Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Medical Decision Making*, *18* (2), S68–80.

Stolk, A.E., de Bont, A., van Halteren, A.R., Bijlmer R.J., & Poley, M.J. (2009). Role of health technology assessment in shaping the benefits package in The Netherlands. *Expert Reviews of Pharmacoeconomics and Outcomes Research, 9* (1), 85–94.

Sackett, D., Straus S.E., Richardson S., Rosenberg, W., & Haynes B.R. (2005). *Evidence-based medicine: how to practice and teach EBM* . 3rd edn. Edinburgh : Elsevier Churchill Livingstone.

Suess, E.A., & Bruce, T. E. (2010). *Introduction to probability simulation and Gibbs sampling with R.* New York, USA: Springer.

Sussex, J., Towse, A., & Devlin, N. (2013). Operationalizing value-based pricing of medicines a taxonomy of approaches. *Pharmacoeconomics*, *31* (1), 1–10.

Talias, M. (2007). Optimal decision indices for R&D project evaluation in the pharmaceutical industry: pearson index versus Gittins index. *European Journal of Operational Research, 177* (2), 1105-12.

Thaler, R. (1980). Toward a Positive Theory of Consumer Choice. *Journal of Economic Behaviour and Organization*, *1* (1), 39-60.

Thompson-coon, J., Hoyle, M., Green, C., Liu, Z.., Welch, K.., Moxham, T., & Stein, K.. (2010). Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma:a systematic review and economic evaluation. *Health Technology Assessment*, *14* (2), 1-184.

Towse, A. (2009). Should NICE´s threshold range for cost per QALY be raised? Yes. *BMJ*, *338* (b181).

Trebilcock, M. (1993). *The Limits of Freedom of Contract.* Cambridge, MA: Harvard University Press.

Uhry, Z., Hédelin, G., Colonna, M., Asselain B., Arveux, P,, Rogel A., ...& Duffy, S.W. (2010). Multi state Markov Models in cancer screening evaluation: a brief review and case study. *Statistical Methods in Medical Research*, *19* (5), 463-86.

Value for Money Pharmaceuticals: Fostering Constructive Collaboration among Stakeholders. Cologne, Germany: Proceedings from European InnovationLeadership Network; 2007. Available at [http://www.tapestrynetworks.com/documents/Tapestry_European_Healthcare_Innovation_Leadership_Network_ViewPoints_Apr07.pdf] last assessed on April 2014.

Vandoros, S., & Kanavos, P. (2013). The generics paradox revisited: empirical evidence from regulated markets. *Applied Economics, 45* (22), 3230–9.

Van, Hout, B.A., AI, M.J., Gordon, G.S., & and Rutten, F.F.(1994). Costs, effects and C/E-ratios alongside a clinical trial. *Health Economics*, *3* (5), 309–319.

Vandoros, S., & Stargardt, T. (2013). Reforms in the Greek pharmaceutical market during the financial crisis. *Health Policy*, *109* (1), 1–6.

Velasco Garrido, M., Gerhardus, A., Røttingen, J. A., & Busse, R. (2010). Developing health technology assessment to address health care system needs. *Health Policy*, *94* (3), 196–202.

Vogler, S., & Zimmermann, N. (2011). Pharmaceutical policies in European countries in response to the global financial crisis. *Southern Medical Review, 4* (2), 69-79.

Vogler S, Zimmermann, N., Leopold, C., Habl, C., & Mazag, J. (2011). *Are hospital medicines prices influenced by discounts and rebates*? Poster presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Madrid. Spain: ISPOR.

Walker, D. (2001). Cost and cost-effectiveness guidelines: which ones to use? *Health policy and planning*, *16* (1), 113-121.

Walker, A., Booth, C., Brown, A., & Paterson, K. (2009). How much good do new medicines do? *Basic Clinical Pharmacology & Toxicology, 105* (Suppl. 1), 29.

Flynn, C.A., Shaughnessy, A.F., Slawson, D.C. (2003). *Information mastery: Evidence Based Family Medicine.* USA: Springer.

Al, M.J., & Van Hout, BA. (2000). A Bayesian approach to economic analyses of clinical trials: the case of stenting. *Health Economics*. *9* (7), 599-609.

Weinstein, M.A. (1988). QALY Is a QALY-Or Is It? *Journal of Health Economics,* 7 (3), 289-290.

Weinstein, M.C., O'Brien, B., Hornberger, J., Jackson, J., Johannesson, M., McCabe, C., & Luce, B.R. (2003). Principles of good practice for decision analytic modelling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices— Modelling Studies. *Value in Health, 6* (1), 9–17.

Welton, N.J., Sutton, A.J., Cooper, N.J., Abrams, K.R., & Ades A.E. (2012). *Evidence synthesis for decision making in healthcare.* West Sussex, UK: Wiley.

Wennberg, J., Barnes, B., & Zubkoff, M. (1982). Professional uncertainty and the problem of supplier-induced demand. *Social Science and Medicine*, *16* (7), 811-824.

White, B. (2004). Making Evidence-Based Medicine Doable in Everyday Practice. *Family Practice Management*, *11* (2), 51-58.

WHO Collaborating Centre for Drug Statistics Methodology. Available from: www.whocc.no/atc_ddd_index/ [Last assessed September 2013]

Wilhelm, S.M., Carter, C., Tang, L., Wilkie, D., McNabola A., Rong, H.,....& Trail, P.A. (2004). BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets

the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Research, 64* (19), 7099-109.

Willan, A.R., & O'Brien, B.J. (1996). Confidence intervals for cost-effectiveness ratios: An application of Fieller's Theorem. *Health Economics 5* (4), 297–305.

Willan, A., & Briggs, A. (2006). *Statistical analysis of Cost –effectiveness data*. Chichester UK: Wiley, World Health Organization. Geneva: World Health Organization.

Wingo, P.A., Tong, T., & Bolden, S. (1995). Cancer statistics. *A Cancer Journal for Clinicians, 45* (1), 8-30.

Zeckhauser, R.J., & Shepard, D. (1976). Where Now for Saving Lives? *Law and Contemporary Problems*, *40* (4), 5-45.

Zweifel, P., & Manning, W.G. (2000). *Moral Hazard and Consumer Incentives in Health Care*. In A.J. Culyer and J.P. Newhouse (Eds), *Handbook of Health Economics*. Boston: Elsevier.