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Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

ΣΧΟΛΗ ΟΙΚΟΝΟΜΙΚΩΝ ΚΑΙ ΠΟΛΙΤΙΚΩΝ ΕΠΙΣΤΗΜΩΝ

ΤΜΗΜΑ ΟΙΚΟΝΟΜΙΚΩΝ ΕΠΙΣΤΗΜΩΝ

Πρόγραμμα Μεταπτυχιακών Σπουδών

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«ΔΙΟΙΚΗΣΗΣ ΟΙΚΟΝΟΜΙΚΩΝ
ΜΟΝΑΔΩΝ»,

με κατεύθυνση τις «Μονάδες Υγείας»

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ΠΕΡΙΛΗΨΗ

Σκοπός: Στην παρούσα εργασία εξετάζονται οι τρέχουσες και προτεινόμενες μεθοδολογίες στην Αξιολόγηση Τεχνολογιών Υγείας (ΑΤΥ), με έμφαση στις διαδικασίες και μεθοδολογίες της NICE, σε μια προσπάθεια προσδιορισμού των τομέων βελτίωσης που θα μπορούσαν να εφαρμοστούν σε έναν οργανισμό Αξιολόγησης Τεχνολογιών Υγείας στην Ελλάδα.

Μεθοδολογία:. Δημιουργήθηκε ερωτηματολόγιο με σκοπό τη διερεύνηση των απόψεων ορισμένων βασικών ομάδων ενδιαφερόμενων (γιατροί, φαρμακοποιοί, επαγγελματίες του τομέα της υγείας και το κοινό) σε σχέση με την οργανωτική δομή και το ρόλο της Αξιολόγησης Τεχνολογιών Υγείας στην Ελλάδα, καθώς και τη δυνητική σχέση του με άλλους εθνικούς ή ευρωπαϊκούς οργανισμούς ΑΤΥ. Οι ερωτηθέντες κλήθηκαν επίσης να γνωμοδοτήσουν σχετικά με την εφαρμογή ορισμένων κοινωνικοοικονομικών κριτηρίων στην ΑΤΥ και, λόγω της συνάφειάς τους με τα προαναφερθέντα κριτήρια, την τοπική παραγωγή φαρμακευτικών προϊόντων. Τα αποτελέσματα που συλλέχθηκαν στη συνέχεια αναλύθηκαν με το λογισμικό IBM SPSS Statistics, v.25 (IBM, 2017).

Αποτελέσματα: Τα αποτελέσματα καταδεικνύουν το ενδιαφέρον των βασικών ομάδων ενδιαφερόμενων για έναν Ελληνικό οργανισμό ΑΤΥ, τμήμα ενός Ευρωπαϊκού δικτύου σε συνεργασία με άλλους εθνικούς οργανισμούς ΑΤΥ, που να είναι σε θέση να αξιολογήσει όλες τις θεραπευτικές παρεμβάσεις και όχι μόνο τα φαρμακευτικά προϊόντα. Για την αξιολόγηση, τα κοινωνικοοικονομικά κριτήρια βρέθηκαν λιγότερο σημαντικά για τους ερωτηθέντες σε σχέση με αυτά που αναφέρονται στη θεραπεία καθαυτή (ασφάλεια/ αποτελεσματικότητα της θεραπείας, σοβαρότητα της νόσου). Τέλος το 60% των ερωτηθέντων έδειξαν πρόθεση να πληρώσουν περισσότερο για ένα τοπικά παραγόμενο φαρμακευτικό προϊόν σε σχέση με ένα εισαγόμενο.

Συμπέρασμα: Παρά τις σημαντικές βελτιώσεις στη μεθοδολογία, τις συστηματικότερες προσεγγίσεις και τα βήματα προς ενοποίηση των οργανισμών ΑΤΥ στην Ευρώπη, διαπιστώθηκαν ορισμένα μεθοδολογικά προβλήματα η αντιμετώπιση των οποίων θα οδηγούσε σε βελτιστοποίηση της ΑΤΥ. Η αντιμετώπιση πολλών από αυτά τα ζητήματα δε θα είχε σημαντικό αντίκτυπο στην ΑΤΥ στην Ελλάδα λόγω του αρχικού σταδίου της, ωστόσο ορισμένες παρεμβάσεις θα μπορούσαν να έχουν σημαντική αξία σε οικονομίες με περιορισμένους πόρους, όπως αυτή της Ελλάδας.

Λέξεις κλειδιά: Ελλάδα, Αξιολόγηση Τεχνολογιών Υγείας, ΑΤΥ, CUA, cost utility analysis, CBA

ABSTRACT/EXECUTIVE SUMMARY

Scope: In the particular thesis current and suggested methodologies on Health Technology Assessment are evaluated with an emphasis on NICE's processes and methodologies, in an attempt to identify areas of improvement that could be applied to a Greek Health Technology Assessment organisation.

Methodology: A questionnaire was developed in order to explore the views of some key stakeholder groups (doctors, pharmacists, healthcare professionals and the public) with respect to the organisational structure and role of HTA in Greece and its potential relationship to other national or European HTA bodies. The respondents were also consulted on the applicability of a number of socioeconomic criteria in HTA and, due to its relevance to the above-mentioned criteria, local production of pharmaceuticals. The results collected were subsequently analysed with the software IBM SPSS Statistics, v.25 (IBM, 2017).

Results: The results indicate interest of the key stakeholder groups in a Greek HTA body, part of a European network, in collaboration with other national HTA bodies, able to evaluate all therapeutic interventions and not just pharmaceuticals. For the evaluation, socioeconomic criteria were found to be less important to the respondents than those referring to the actual treatment (safety/efficacy of the treatment, seriousness of the disease). Finally, 60% of the respondents indicated willingness to pay more for a locally produced pharmaceutical compared to an imported one.

Conclusion: In spite of the significant improvements of the methodological models, the more systematic approaches and the steps towards consolidation with regards to HTA in Europe, there are certain methodological issues that have been identified, which if addressed should lead to an optimisation of HTA. Resolving many of these issues cannot have a significant impact on HTA in Greece due to its embryonic nature, however, certain interventions could be of significant value to economies with limited resources, such as that of Greece.

Keywords: Greece, Health Technology Assessment, HTA, CUA, cost utility analysis, CBA

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ABBREVIATIONS AND ACRONYMS

ACD	Appraisal Consultation Document
API	Active Pharmaceutical Ingredient
ATY	Health Technology Assessment (Αξιολόγηση Τεχνολογιών Υγείας)
CA	Collaborative Assessment
CAGR	Compound Annual Growth Rate
CBA	Cost Benefit Analysis
CCA	Cost Consequence Analysis
CEA	Cost Effectiveness Analysis
CMA	Cost Minimisation Analysis
CRO	Clinical Research Organisation
CUA	Cost Utility Analysis
GDP	Gross Domestic Product
EC	European Commission
ECB	European Central Bank
ΕΟΠΥΥ	National Organisation for Provision of Healthcare Services (Εθνικός Οργανισμός Παροχής Υπηρεσιών Υγείας)
ΕΟΦ	National Organisation for Medicines (Εθνικός Οργανισμός Φαρμάκων)
EQ-5D	EuroQol 5 Dimension scale
ERDF	European Regional Development Fund
ERG	Evidence Report Group
EUnetHTA	European Network for Health Technology Assessment
FAD	Final Appraisal Document
FTE	Full-Time Equivalent
GDPR	General Data Protection Regulation
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio

IMF	International Monetary Fund
IP	Intellectual Property
JA	Joint Assessment
MA	Marketing Authorisation
MCDA	Multi-Criteria Decision Analysis
MoH	Ministry of Health
MoU	Memorandum of Understanding
NHS	National Health Service (UK)
NICE	National Institute for Health and Care Excellence
OECD	Organisation for Economic Cooperation and Development
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
VM	Value Metrics
WTP	Willingness To Pay

INTRODUCTION

It is common knowledge to those versed in Health Economics that no healthcare system can enjoy infinite resources and that therefore some form of prioritisation of resource allocation is necessary.

This fact is becoming more pronounced in Europe, where the social character of healthcare, one of the cornerstones of modern European societies, is threatened on one side by increased demands in healthcare expenditure -due to ageing population and new more expensive treatments, among others- and on the other side by the fiscal pressure from tight government budgets due to European integration requirements -and even more so since the financial crisis of 2008.

This has resulted in decision makers finding themselves under increasing pressure regarding resource allocation in healthcare, which has inevitably led to the development of a heterogeneous mixture of HTA bodies throughout Europe (M. Velasco-Garrido, R. Busse, 2005). In response to the fragmented landscape, there has been significant interest in recent years towards consolidation, with the most notable being the development of the European Network for Health Technology Assessment, or EUnetHTA (EUnetHTA (a), 2018).

Particularly in the case of Greece, the issue of tight fiscal control is even more prevalent. The inability of its governments to adequately manage their persistently high fiscal imbalances over decades was exacerbated during the financial crisis of 2008 which eventually led to the request for financial assistance from “troika”, a joint EC/ECB/IMF collaboration (Directorate-General for Economic and Financial Affairs, 2010). This assistance was provided on the basis of the government initiating significant reforms, however, further inability of subsequent governments to adequately manage these reforms and the resulting financial situation led to another two financial assistance programmes (Directorate-General for Economic and Financial Affairs, 2012), (Tsakalotos, Stournaras, & Dombrovskis, 2015).

Forced by financial situation and imposed reforms, Greece has recently initiated implementation of Technology Assessment in Healthcare, through the creation of a Health Technology Assessment committee (ΦΕΚ Α'/5/17.01.2018). Due to a combination of factors such as ageing population, tight fiscal controls and inefficiencies in Healthcare, Greece is amongst the countries that have a lot to gain from a successful implementation of Health Technology Assessment.

In the particular thesis current and suggested methodologies on Health Technology Assessment are evaluated with an emphasis on NICE’s processes and methodologies, in an attempt to identify areas of improvement that could be applied to a Greek Health Technology Assessment organisation. The

research hypothesis is whether Health Technology Assessment methodology has achieved maturity or if there is significant space for improvement.

In parallel, as HTA is a relatively new concept outside the field of Health Economics in Greece, a questionnaire was developed in order to explore the views of some key stakeholder groups (doctors, pharmacists, healthcare professionals and the public) regarding the organisational structure and role of such a Greek HTA body, together with its potential relationship to other national or European HTA bodies. Further to this, the respondents were also consulted about their views regarding the applicability of a number of socioeconomic criteria to such an evaluation and, due to its relevance to the above-mentioned criteria, local production of pharmaceuticals.

With Health Technology Assessment being an area of increasing interest in recent years by healthcare companies, government bodies and academia, identifying areas of potential improvement can have important repercussions, affecting from the cost of Healthcare interventions to the overall development of the HTA field and the implementation of new guidelines. It could also hopefully result in the Greek Health Technology Assessment body adopting more efficient methodologies, permitting better allocation of the anyway scarce healthcare resources and in parallel allowing the society to reap wider benefits for its investment.

CHAPTER 1: HEALTH TECHNOLOGY ASSESSMENT

Health Technology Assessment is "a form of policy research that systematically examines the short- and long-term consequences, in terms of health and resource use, of the application of a health technology, a set of related technologies or a technology related issue" (Henshall C, 1997). By definition, its aim is to provide reliable information in support of the decision making process in healthcare and as such, it is a multidisciplinary activity concerned with the medical, organizational, economic and societal consequences of implementing health technologies or interventions within the health system (M. Velasco-Garrido, R. Busse, 2005).

Health Technology Assessment can be applied to all therapeutic interventions, including clinical procedures, surgical interventions and diagnostics. However, many HTA bodies focus on pharmaceuticals and medical devices, since these are standardised technologies with clear ownership and with significant social impact, visibility and, more importantly, financial burden on healthcare systems (Danko, 2014).

1.1 Health Technology Assessment process

In order for a better understanding of Health Technology Assessment to take place, the typical steps followed during the assessment process by HTA bodies are described below. Due to the heterogeneous nature of HTA bodies throughout Europe, the exact assessment process varies from country to country (M. Velasco-Garrido, R. Busse, 2005). However, it can be argued that they tend to follow the same general principles, such as review of data by independent experts, capacity of comments/appeals by stakeholders etc. In parallel, there are efforts towards consolidating methods and processes of HTA bodies throughout Europe in an attempt to increase efficiency and knowledge sharing (EUnetHTA (a), 2018).

1.1.1 Single or Multiple Technology Appraisal by NICE

A description of the typical steps followed during a Single or Multiple Technology Appraisal by NICE can be seen in Appendix 1 (NICE, 2018). The evaluation process of a Single Technology Appraisal, where a single drug or treatment is assessed, involves the below steps:

- Once the appraisal is initiated, the company that has an interest in the new health technology is requested to produce a report of all relevant published and unpublished evidence. As it is usually a new technology that is evaluated, other involved parties will not be as familiar with it, which

is also why the particular report is then further utilised in the preparation of other documentation required in the appraisal process. In order for all evaluations to be comparable, the report has to include an analysis of results generated using specific "reference case" methods considered by the Institute to be appropriate, depending on the type of technology and disease area (NICE, 2013).

- In parallel, stakeholders are invited to take part in the appraisal as non-company consultees and commentators, which are requested to submit a statement on the potential clinical- and cost-effectiveness of a treatment. Consultees include national groups representing patients and carers, bodies representing health professionals, the company that manufactures the technology being appraised, the Department of Health, the Welsh Government, NHS England as a specialised commissioning group and clinical commissioning groups (NICE, 2019). Similarly, commentators include but are not limited to relevant comparator technology companies, Healthcare Improvement Scotland, any relevant National Collaborating Centres, research groups working in the area and others (NICE, 2019).
- The non-company consultees and commentators are also requested to nominate clinical, commissioning and patient experts, which are in turn requested to submit personal statements on the technology and its applications.
- At the same time, the Evidence Report Group (ERG, an independent academic centre commissioned by NICE) is requested to produce a review of the company report, evaluating the evidence presented.
- The consultees, commentators and the nominated clinical, commissioning and patient experts are requested to attend the appraisal committee and are given the below documents, having two weeks to evaluate them before they must meet to consider the evidence:
    1. The company report containing all relevant published and unpublished evidence, which is issued by the company that has an interest in the new health technology. Although the company has 8 weeks from assessment initiation to submit the report, it takes several years for the company to collect corresponding data, which are painstakingly prepared to maximise chances of approval. It goes without saying that these data are of extreme importance to the company, which relies on the particular results to recap its investment.
    2. The review of the above-mentioned report by the Evidence Report Group. The academic centre is given 8 weeks to prepare corresponding report, which is delivered to the company afterwards for fact checking before being sent to the appraisal committee. If the Evidence Report Group deems the evidence submission to have deficiencies, a letter of clarification is sent to the company, which must be replied to within 10 days.

3. A statement from non-company consultees on the potential clinical- and cost- effectiveness of the treatment. Although it is not clearly stated, non-company consultees appear to have 8 weeks to produce such a statement, given corresponding timelines.
4. Personal statements from patient, clinical and commissioning experts on the technology and how it should be used in the NHS in England. These statements will have to be submitted to NICE within 8 weeks, which then forwards them to the appraisal committee.
5. A pre-meeting briefing written by NICE's technical lead for the appraisal.
6. The scope of the appraisal and the list of consultees and commentators.

- Based on the outcome of the appraisal committee, a document is produced; either an Appraisal Consultation Document (ACD), if the use of the technology is not recommended or limited beyond the specification of the marketing authorisation, or a Final Appraisal Determination Document (FAD), if no ACD is needed.
- If an ACD was produced, it is sent out together with supporting documents to consultees and commentators, who have 20 working days to submit their comments on the draft recommendations. The ACD and supporting documents are also open for public consultation for 15 working days. The appraisal committee then meets again to prepare the corresponding FAD, taking into consideration any comments made in the meantime.
- Once a FAD is produced, it is sent out together with supporting documents to consultees and commentators, while the documents are also published on the NICE website. The consultees and commentators have 15 days to appeal against the final recommendations of the FAD; if appeals are received, an appeals process is followed otherwise the guidance is prepared for publication.
- The new guidance is finally published on NICE website and incorporated into NICE pathways, while a review date for the guideline is issued (at which point it is checked whether it needs updating).

A similar process is followed during a Multiple Technology Appraisal, which can also be seen in Appendix 1 (NICE, 2018). The main difference is that there are no companies directly involved and corresponding information is requested by the non-company consultees, which have a slightly longer time to collect it (14 weeks for preparation of report instead of 8 weeks given during Single Technology Appraisal). There is also another difference, a potential Stakeholder Information Meeting may be requested on week 8 for consultees and commentators, which does not take place during Single Technology Appraisals. As a result, the overall Multiple Technology Appraisal process is also longer by 17 weeks. Overall, NICE is pretty explicit providing detailed information regarding the assessment process including corresponding steps, contributions and timescales for all stakeholders (NICE (b), 2018).

1.1.2 Other HTA bodies and moves towards consolidation – EUnetHTA

With respect to other HTA bodies, there is significant fragmentation within the European Union. According to a report from the European Commission (Chamova & Stellalliance, 2017), from the 28 EU members + Norway[1] questioned regarding their HTA processes, 53 HTA organisations were found, all public bodies (in other part of the report 56 HTA organisations are mentioned). It should be noted that until May 2011, data were not available for Bulgaria, Cyprus, Greece, Lithuania, and Romania, due to lack of HTA organisations (Kleijnen, et al., 2011), in the meantime Bulgaria and Lithuania seem to have progressed further than Romania, Cyprus and Greece. Staffing of these organisations varied greatly, from no full-time employees dedicated to HTA activities e.g. for Slovenia to 604 total FTEs of permanently employed staff across the whole organisation for NICE (Chamova & Stellalliance, 2017).

Concerning the assessment of pharmaceuticals, from the countries that provided data (22 member-states and Norway) 10 countries perform Single Technology Assessments and 7 countries both STAs and MTAs, while respondents from Portugal and Sweden indicated that for the reassessment of pharmaceuticals they only perform MTA (Chamova & Stellalliance, 2017). Regarding duration of such assessments, it varies significantly depending on country and type of assessment performed, it has been observed, however, it usually takes longer for HTA organisations whose timeframe is not determined by the Transparency Directive (Council Directive 89/105/EEC, 1988) or who are not formally involved in pricing and/or reimbursement decision-making (Chamova & Stellalliance, 2017).

For topic selection for HTA, with the exception of the countries for which information is lacking (Romania, Cyprus and Greece) and 3 countries that indicated that there is no topic selection process, 20 countries indicate that they derive their topic suggestions from interested companies, 5 countries from hospital providers, 5 from clinical groups and 5 from patient groups. Finally, 21 countries utilised HTA to inform pricing decisions on pharmaceuticals, 9 countries also for medical devices and 7 countries for other technologies (Chamova & Stellalliance, 2017).

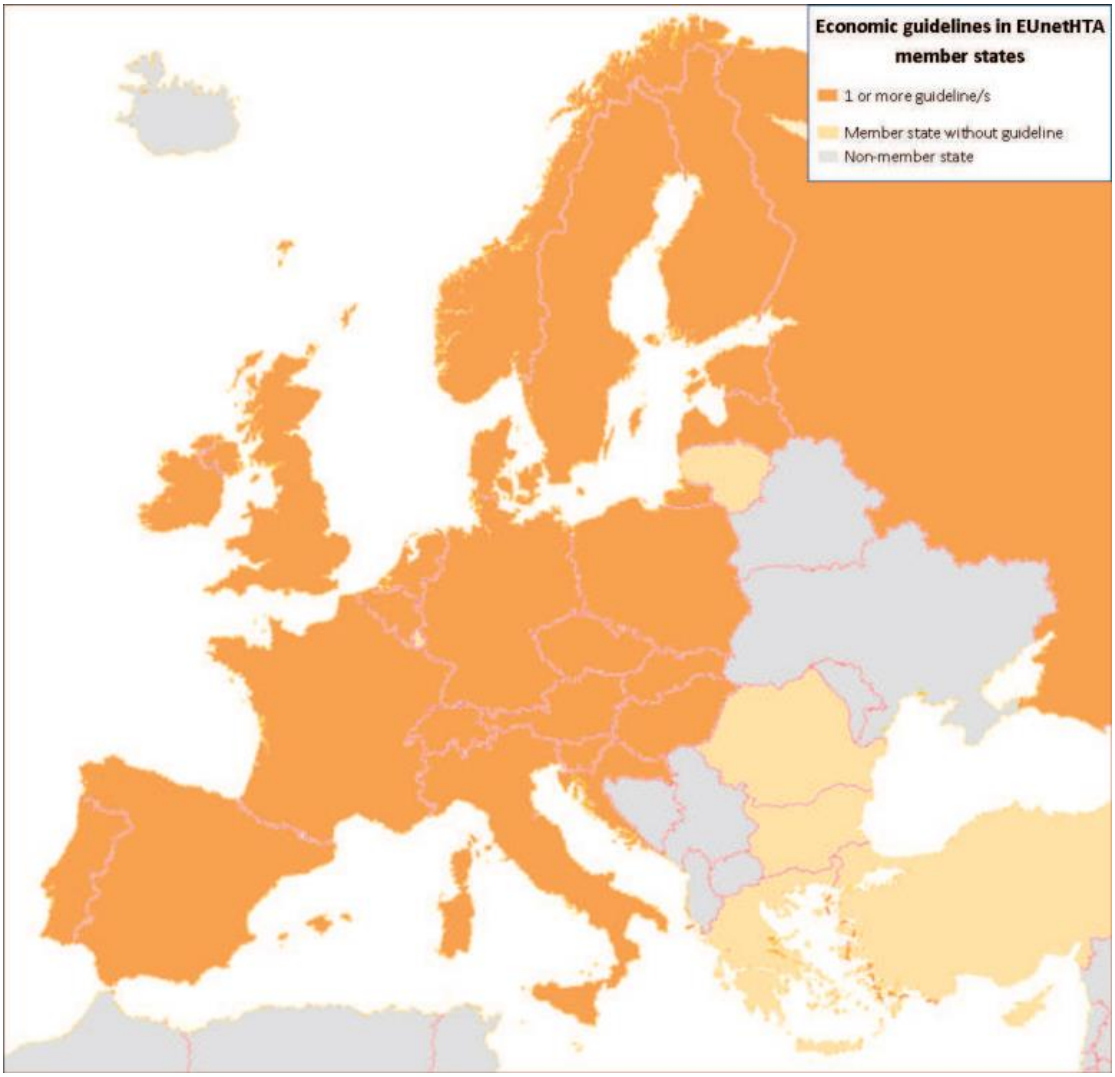
For the HTA process, 24 countries claimed that the interested company provides information on a technology to undergo HTA, of which 10 countries also indicated that an independent collection of evidence by the HTA body may also take place. For review of corresponding information, 13 countries

[1] Of the EU member-states and Norway only Greece and Romania did not respond to the questionnaire of the study and were therefore not included, while Cyprus stated that they are in a process of setting up a formal national HTA system, including development of appropriate legislation and structure to support the HTA production process(Chamova & Stellalliance, 2017). It should be noted however, that since then at least in the case of Greece some basic HTA organization has been established, as discussed later.

use a stop-the-clock mechanism in order to review the information, while this information is public for 9 countries, private for 7 countries and public with confidential information removed for 10 countries (Chamova & Stellalliance, 2017).

Due to the fragmented nature of HTA in EU, there is currently a systematic effort towards consolidating the European landscape. To that extent, EUnetHTA has been created, which consists of a network of government-appointed organisations, relevant regional agencies and non-for-profit organisations with interest in production or contribution to HTA in Europe (EUnetHTA (b), 2018). The aim of EUnetHTA is to promote collaboration among European HTA organisations at a national, regional and European level. The landscape regarding countries that are members and the corresponding availability of HTA economic guidelines is summarised on the below figure (EUnetHTA, 2015).

Figure 1.1: Map of EUnetHTA member states and which ones have Economic guidelines in place



Source: (EUnetHTA, 2015)

It should be noted that EUnetHTA has expanded beyond EU borders, with members shown to include Norway, Switzerland, Russia and Turkey, although the latter two are not currently officially listed in the partner organisations comprising the EUnetHTA network (EUnetHTA (g), 2018). Also, although Greece appears to not have an economic guideline in place for HTA, at least some basic guidelines have since been implemented, as discussed later. The same holds true at least for the cases of Bulgaria and Lithuania discussed above and Romania more recently (EUnetHTA (e), 2018).

EUnetHTA facilitates the efficient HTA resource use through the creation of a sustainable system of HTA knowledge sharing and guidelines that promote good practice in HTA methods and processes (EUnetHTA (a), 2018). Although such guidelines are currently consolidated views of non-binding recommendations, it appears that the EC is planning to use EUnetHTA as a centralised body for coordinating national HTA bodies, in a manner similar to the relationship between the European Medicines Agency (EMA) and national drug organisations (EMA, 2019).

As a result, a Guidance for Parallel Consultation has been introduced, where a company developing a new medicine can ask for scientific advice from regulators and HTA bodies in parallel, through a single gateway (EMA & EUnetHTA, 2019). This allows the company to receive feedback on evidence-generation plans to support decision making on both marketing authorisation and reimbursement through a streamlined procedure, with EUnetHTA facilitating the centralised recruitment of HTA bodies. It replaced the parallel scientific advice procedure, which required medicine developers to contact HTA bodies individually (EMA, 2019).

Apart from the parallel consultation process, EUnetHTA also performs Joint Assessments (JA), which involve evaluation by at least four EUnetHTA partners from different European countries. These are centrally coordinated Health Technology Assessments utilising EUnetHTA processes, guidelines and the HTA Core Model discussed later, and are subject to extensive review procedures to ensure high quality (EUnetHTA (f), 2018).

Finally, EUnetHTA Collaborative Assessments (CA) is another process mainly for non-pharmaceutical technologies. The main difference is that in contrast to the centrally coordinated JAs, CAs project management is performed in a decentralised manner (EUnetHTA (f), 2018).

1.2 Health Technology Assessment Methodology

In contrast to the defined processes followed during a Health Technology Assessment, the methodology employed and the evaluation criteria are much less defined. The policy-oriented nature of HTA requires it to provide reliable information, by means of assessment reports, to be employed in decision-making. It is therefore required from HTA to pass judgements on a broad range of issues ranging from the clinical effectiveness of the treatment and the quality of evidence to the costs relating to the treatment, which can be grouped to scientific value judgements and social value judgements (Rawlins, Barnett, & Stevens, 2010).

The part of the evaluation relating to the scientific value judgements is also known as Relative Effectiveness Assessment (REA), which is also a specific element of HTA focusing on the clinical benefit of the intervention and can be defined as the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice (Kleijnen, et al., 2011).

There are several guidelines addressing relative effectiveness assessment, like those published by EUnetHTA (EUnetHTA (c), 2018), (EUnetHTA, 2015), however, as these are quite specialised and require a certain degree of clinical expertise, they are considered beyond the scope of the particular thesis. Instead, an overview of such methodology is attempted through investigation of the decision factors involved in such evaluations, with more focus on cost effectiveness. Besides, it has been argued that "big data" may replace much of the work about clinical safety and efficacy in the future, while cost-effectiveness seems to be of increasing importance in Health Technology Assessments but also in methodology development (Banta, 2018). Finally, HTA can also include other socioeconomic aspects such as ethical, legal, social considerations etc. which are also marginally addressed here through the analysis of the decision components affecting such evaluations.

1.2.1 Decision components of HTA by NICE

NICE assesses the clinical, public health and cost effectiveness of interventions before deciding whether and how to recommend their use (NICE, 2008). The scope of the evaluation is first developed by the Institute, which defines the main technology of interest and its comparator(s), its expected place in the pathway of care and the patient group(s) related to the technology (NICE, 2013).

There are several decision components that play part in such evaluations. De Folter *et al* have tried to identify them based on the information obtained from 243 documents of NICE's medicines guidance, the results of which are summarised in Appendix 2 (de Folter, Trusheim, Jonsson, & Garner, 2018). It has resulted in the identification of 125 decision factors, which have been grouped into 8 main domains:

1) Clinical Effectiveness
2) Cost effectiveness
3) Condition
4) Current practice
5) Clinical need
6) New treatment
7) Studies
8) Other factors

From those, Clinical effectiveness and Cost effectiveness contain more than half of the decision factors, signifying their importance in the overall evaluation.

It should also be noted that some decision components are repeated among the different domains, indicating a level of interdependency, however, it may also indicate methodological inefficiencies, for example in the case of MCDA such an approach is explicitly avoided to prevent double-counting (Angelis & Kanavos, 2017).

With regards to cost-effectiveness Cost-Utility Analysis (CUA) is the preferred method of choice for NICE (NICE, 2013). The outcomes of an intervention are expressed in terms of QALYs, which is considered the preferred generic measure of health benefit, as it combines information on both life expectancy and health-related quality of life (NICE, 2013).

For QALY determination each health state within the time horizon of the intervention is given a utility value, ranging from negative (for states considered worse than death) to 1 (for state of best possible health). A value of 0 is equivalent to being dead. QALYs are derived by multiplying the duration of time spent in each health state with the utility value of the particular health state. The utility value should be given directly by the patients or their carer if unable to, in preference to healthcare professionals, by using a choice-based method such as EQ-5D, the preferred measure of health-related quality of life in adults (NICE, 2013).

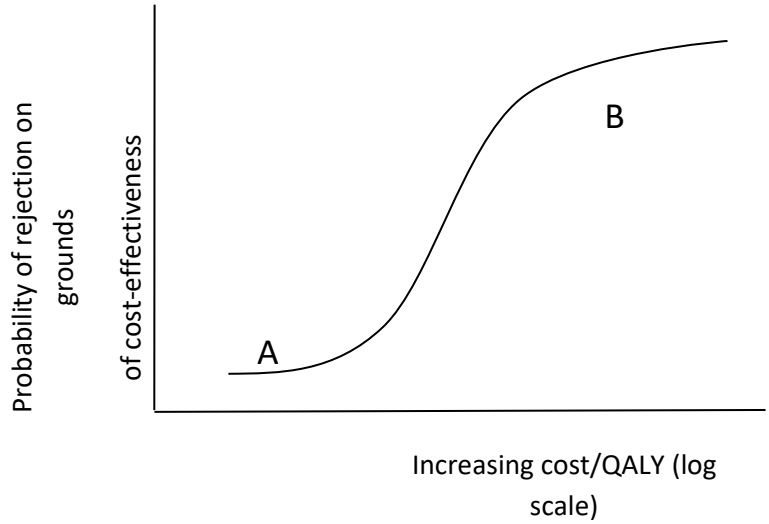
EuroQol 5 Dimension scale was first introduced in 1990 by the EuroQol Group (EuroQol, 2019). As the name implies, it consists of 5 dimensions of health: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression, with each dimension having 3 levels of severity (no problems, some problems, severe problems) (NICE, 2013). The EQ-5D is a standardised descriptive system validated in many patient populations, designed so that people can describe their own health-related quality of life (NICE, 2013).

With regards to the time horizon of the analysis, it has to be of sufficient length to accommodate all important differences in costs and outcomes between the technologies under evaluation and therefore it

is most commonly for the life-time of patients (NICE, 2011). Finally, in all calculations discounting is implemented at an annual rate of 3.5% on both costs and health effects (NICE, 2013). However, a lower discount rate of 1.5% has been recently suggested for QALYs since the welfare or utility associated with it does not decline as real incomes rise and therefore the 'wealth effect', or real per capita consumption growth element of the discount rate, is excluded (HM Treasury, 2018).

Once an intervention is deemed more effective than the comparator, the incremental cost effectiveness ratio (ICER) is calculated, as the ratio of the difference in the mean costs of the intervention *versus* the comparator (the next most effective alternative) to the differences in the QALYs. ICERs are expressed as cost per QALY gained (NICE, 2008). If there is strong evidence that the intervention is more effective and less costly that the comparator (i.e. it dominates the alternatives), the intervention is recommended (NICE, 2011). If it is more effective but more expensive, the probability that this technology is recommended depends on the ICER cost. NICE does not have an absolute threshold regarding the ICER cost, as this would discourage price competition, would mean that efficiency has absolute priority among other objectives (particularly fairness), would be difficult for such a threshold to be ignored if circumstances required it and finally there is no empirical basis for deciding at what value it should be set to (Rawlins & Culyer, 2004). Instead, such a threshold is more of a range, as shown below (Figure 1.1), where area A describes interventions with a cost below £20,000/QALY and area B interventions with a cost above £30,000/QALY (Rawlins & Culyer, 2004).

Figure 1.2: Relation between probability of a technology to be considered cost-effective and its ICER cost



Source: (Rawlins & Culyer, 2004)

As a result, interventions below £20,000/QALY are unlikely to be rejected on the grounds of cost-effectiveness. On the other hand, interventions above £30,000/QALY are more likely to be rejected unless other criteria shift the balance towards justifying such an investment; such criteria have been identified below (Rawlins, Barnett, & Stevens, 2010):

1) Severity of the underlying illness (often more generous consideration is given to the acceptability of an ICER in serious conditions)
2) End-of-life treatments (special value is given on treatments that life extension of reasonable quality at the end of life, even if this is for a few months. This is further discussed below)
3) Stakeholder persuasion (where patients and their advocates have been affecting the views of NICE's advisory committees)
4) Significant innovation (where the intervention produces a substantial, demonstrable and distinct benefit that may not have been adequately captured in the QALYs measured)
5) Disadvantaged populations (particularly poorer people and ethnic minorities)
6) Children (where the Institute gives 'the benefit of the doubt' to interventions aimed at sick children since compilation of the evidence and assessment of improvements is methodologically challenging for this age group).

Once an intervention is finally recommended and a new guidance is to be issued, NICE undertakes a cost impact assessment in order to help support those responsible for implementing guidance recommendations to estimate the net costs (or savings) for the purpose of informing budget setting (NICE, 2011). Cost impact considers the impact on budgets for one-off and recurring costs over a period of typically 3 – 5 years and for a defined population (NICE, 2011). The result of this analysis is the production of costing tools, which are published at the same time as the guidance.

It has been argued that in addition to examining newer technologies, the National Institute for Clinical Excellence (NICE), in conjunction with similar bodies in the Devolved Administrations, should examine older technologies and practices which may no longer be appropriate or cost effective; (Walness, 2002). It has also been suggested that NICE should actively make both disinvestment and investment recommendations (Culyer, et al., 2007). The basis of a cost-effectiveness threshold is about matching any investment in a new therapeutic intervention to a corresponding disinvestment, in order to increase the total health produced by the health service, and a programme of disinvestment guidance to balance the investment guidance is believed to have a positive impact on both NHS and the public (McCabe, Claxton, & Culyer, 2008)

Another issue worth addressing that relates to this threshold is that NICE since 2009 has been publishing a series of guidelines in which there is a move away from the essence of QALYs as a means to judge all interventions (Paulden, O'Mahony, Culyer, & McCabe, 2014). The first such amendment was a guidance

for life-extending, end of life treatments (NICE, 2009). According to this, in cases where a treatment is licensed for small populations for which the patient has a life expectancy of less than 24 months, while the treatment extends life by at least 3 months, an increased threshold of £50,000 per QALY is permitted, increasing the chances of such a treatment being recommended, in spite of its cost.

Furthermore, with the selective discounting amendment in 2011 it was considered appropriate to apply a discounting rate of 1.5% for health effects and 3.5% for costs, for treatment effects that are both substantial in restoring health and sustained over a very long period (at least 30 years) (NICE (b), 2011). Of course, as mentioned before, this has now been suggested for all QALYs (HM Treasury, 2018).

It has also been proposed to add two new "value elements", namely burden of illness and wider societal impact, which are not currently captured by QALYs as "modifiers" during the evaluation (NICE, 2014). Burden of illness is defined as "the loss (or shortfall) in quality and length of life, measured in QALYs, which occurs as a consequence of having a disease or condition, when compared to the QALYs that people would expect to have over the rest of their lives without the condition" (NICE, 2014). Similarly, wider societal impact is defined as "the loss (or shortfall) in a person's capacity to engage with society as a result of living with the disease or condition, compared with their capacity to engage with society without the condition" (NICE, 2014). The proposal suggest to replace the "end of life" modifier (which is maximum 2.5, thus setting the threshold from £20,000 per QALY to £50,000 per QALY) with a new set of modifiers which will take into account burden of illness and societal impact, setting a maximum cumulative weight of 2.5 in circumstances where all modifiers apply (NICE, 2014).

Finally, a higher threshold of £100,000 to £300,000 per QALY has been adopted by NICE for the evaluation of very rare diseases (NICE, 2017). In fact, in such cases, the more additional QALYs a medicine offers, the more generous the cost per QALY level it will need to meet, rising up to ten times the normal limit applied by NICE (NICE, 2017).

The above have resulted in criticism in that such interventions ignore the opportunity cost and raise fundamental equity issues that should be of concern to all NHS patients and other stakeholders (Paulden M. , 2017). Using programme budgeting data for the English NHS, it has been calculated that every £12,936 spent on new technologies (2008 expenditure, or a discounted central estimate of £13,724 for 2015) results in a QALY lost from NHS patients (Claxton, et al., 2015). Any expenditure per QALY above this threshold for new technologies results in overall QALY loss for NHS patients, therefore treatment for example of a very rare disease with the high threshold adopted by the corresponding guidance (NICE, 2017) can result in more than 20 times the health losses for the population compared to any health gains, raising equity issues for NHS patients (Paulden M. , 2017).

1.2.2 Other HTA bodies – EUnetHTA

As far as other organisations in the EU are concerned, there is significant differentiation in the types of evaluations and methodological approaches observed. In a questionnaire of the European Commission to the member-states and Norway (28 + 1 in total) regarding their HTA organizations, processes and methodologies, 16 countries were found to conduct Relative Effectiveness Assessments, 25 countries REAs together with economic evaluation and 13 countries full HTAs (Chamova & Stellalliance, 2017). The results are summarised below (Figure 1.2):

Figure 1.3: Scope of HTA: REA, REA and Economic evaluation, Full HTA

REA	REA and economic evaluation	Full HTA
Austria, Belgium, Bulgaria, Croatia, Denmark, France, ***Germany***, Ireland, **Lithuania**, Luxembourg, Netherlands, Poland, Portugal, Spain, Sweden, Norway	Austria, Belgium, Bulgaria, Croatia, **Czech Republic**, Denmark, Estonia, **Finland**, France, ***Germany****, **Hungary**, Ireland, Italy, **Latvia**, Luxembourg, **Malta**, Netherlands, Poland, Portugal, **Slovakia**, **Slovenia**, Spain, Sweden, ***United Kingdom*****, Norway	Austria, Belgium, Croatia, Denmark, Estonia, France, Ireland, Italy, Netherlands, Spain, Sweden, ***United Kingdom (Scotland)*****, Norway
15 MS and Norway	24 MS and Norway	12 MS and Norway

** - G-BA rules of porcedures has an option for including economic evaluation*

*** - It is only SHTG in Scotland that indicates full HTA as the scope of HTA perfomed by the organisation.*

Source: (Chamova & Stellalliance, 2017)

For their analysis, EUnetHTA has also created a pretty comprehensive review regarding the methodologies employed by its members (EUnetHTA, 2015). Of the 33 countries interviewed, 25 were found to have corresponding guidelines in place. Of these, 21 countries recommended the use of CUA as the main type of analysis (20 + 1 country which has not indicated method of analysis but claims QALY to be the preferred outcome measure), although in 5 guidelines it was stated that the choice of economic analysis should also depend on the characteristics of the technology, nature of the disease and data availability (EUnetHTA, 2015). In 3 guidelines, it was indicated that the CUA should always be

accompanied by a cost-effectiveness analysis (CEA) with costs per life-year gained as the outcome measure. As an exception to the above, in cases where life expectancy is improved without an effect on QoL, CEA was recommended with cost per life-years gained as the outcome measure instead of a CUA (EUnetHTA, 2015).

From the remaining countries, 4 supported the use of CEA as the main analysis, however, 2 of which indicated that the results from a CUA could be presented in an additional analysis. Switzerland did not recommend any specific outcome measure, but CUA ratios are explicitly mentioned as not so important. Finally, Germany preferred the use of outcomes from clinical studies such as mortality, morbidity, HRQoL and validated surrogates, although QALYs can be used in cases such as when no other measure of QoL is available (EUnetHTA, 2015).

Cost-benefit analysis (CBA), further discussed below, was also mentioned as a possible type of analysis in 5 countries, however, 4 others indicated that CBA was not recommended, 3 others that it should only be used as an additional analysis and 2 only for cross-sectorial public health interventions or when there was difficulty in utilising QALYs, respectively (EUnetHTA, 2015).

When there is no difference in clinical effectiveness between the alternatives, 14 countries suggested cost-minimisation analysis (CMA), which compares the cost per course of treatment of the alternatives. Finally, 1 country recommended the use of cost-consequence analysis (CCA) for evaluations of medical devices (EUnetHTA, 2015). CCA compares the costs and the consequences like CEA, however, it does not attempt to summarise the outcomes in a single measure (e.g. QALY, monetary terms), instead each outcome is shown in their natural units and it is left to the decision maker to determine whether the intervention is justified (Optimity Advisors, 2016).

With regards to EUnetHTA, it is focused on REAs with the aim that these are performed in parallel by several HTA bodies in different countries in a format that is easily applicable in the remaining countries, with the national bodies focusing on cost-effectiveness and socioeconomic criteria. This can better be seen through the HTA Core Model® it has developed for the production and sharing of HTA information (EUnetHTA (h), 2018). . The HTA Core Model® is organised in nine domains, which attempt to cover the multidisciplinary nature of HTA assessments and can be seen below (EUnetHTA, 2016):

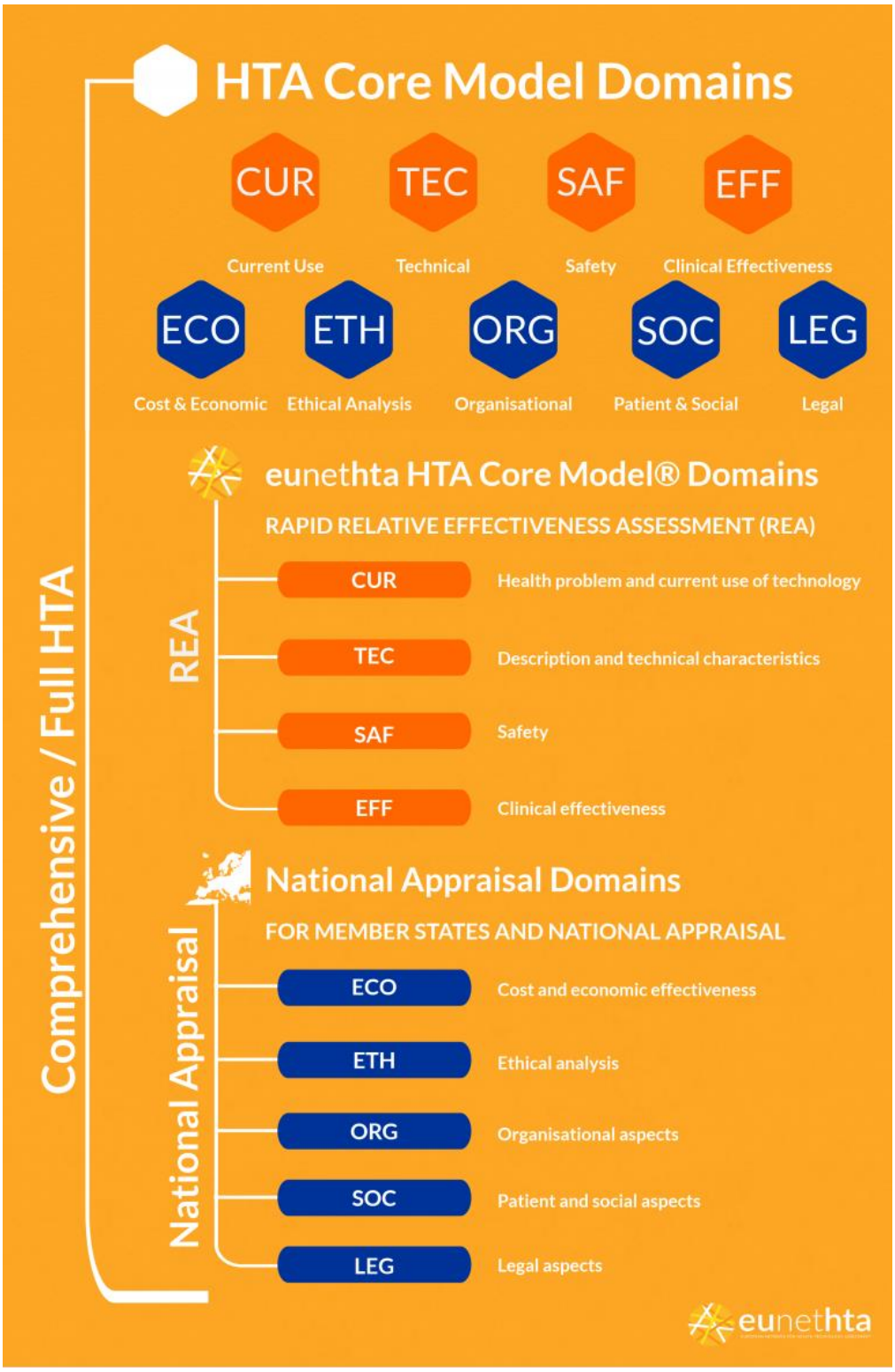
1) Health problem and current use of technology (CUR)
2) Description and technical characteristics of technology (TEC)
3) Safety (SAF)
4) Clinical effectiveness (EFF)
5) Costs and economic evaluation (ECO)
6) Ethical analysis (ETH)
7) Organisational aspects (ORG)

8) Patients and Social aspects (SOC)
9) Legal aspects (LEG)

Each domain contains a standardised set of HTA questions (the ontology) which allow users to define their specific research questions within a hierarchical structure, also allowing a common reporting structure for presenting findings in a standardised "question-answer pair" format. Each such item of information is also referred to as an assessment element. The Model also consists of specific methodological guidance facilitating the answering of these research questions (EUnetHTA, 2016).

According to the model, the first four domains are related to Rapid Relative Effectiveness Assessment, to be performed in a more centralised manner, while the remaining which are related to socioeconomic impact are of more relevance to national HTA bodies. An evaluation across all 9 domains constitutes a comprehensive/full HTA process, as can also be schematically shown in the below figure (EUnetHTA (d), 2018):

Figure 1.4: The EUnetHTA Core Model Domains



Source: (EUnetHTA (d), 2018)

1.2.3 Multi-Criteria Decision Analysis

As seen so far, there is a number of diverse criteria that have to be taken into account during a Health Technology Assessment, involving both scientific and social value judgements in order to reach a decision. This complexity creates inherent problems, which policymakers are typically quite bad at solving unaided (Baltussen & Niessen, 2006). It has therefore been suggested that Multi-Criteria Decision Analysis (MCDA), which permits the development of a multi-criteria approach to priority setting, should be ideally suited for HTA (Baltussen & Niessen, 2006).

MCDA is both an approach and a set of techniques for looking at complex problems that are characterised by any mixture of monetary and non-monetary objectives, with the goal of providing an overall ordering of options, from the most preferred to the least preferred one, in order to serve as an aid to thinking and decision making (Spackman, Dogson, Pearman, & Phillips, 2000).

MCDA establishes preferences between the options relating to these objectives by establishing a set of criteria that assess the extent the objectives have been achieved (Spackman, Dogson, Pearman, & Phillips, 2000). A performance matrix, or consequence table, is then typically prepared, in which each row describes an option and each column a criterion, so that their intersection describes the performance of the particular option against that criterion. The individual performance assessments are often numerical but can also be expressed as "bullet point" scores, or colour coding (Department for Communities and Local Government, 2009).

At this stage, the performance matrix can be used qualitatively in cases of dominance (when one option performs at least as well as another on all criteria and strictly better than the other on at least one criterion) or for subjective interpretation (where recorded performance levels are added across the rows to make some holistic judgment between options about which ones are better) (Baltussen & Niessen, 2006). However, in most MCDA techniques, modelling is performed, i.e. a numerical analysis is applied in the performance matrix, in two stages (Department for Communities and Local Government, 2009).

The first stage involves scoring, where each option is assigned a numerical score on a strength of preference scale (the higher the preference, the higher the score), for each criterion. In practice, scales from 0 – 100 are used, with 0 representing a real or hypothetical least preferred option and 100 a real or hypothetical most preferred option. Similarly, the second stage involves weighing, where the relative valuations of each criterion are defined by assigning numerical weights to it. Once relative score and weights have been determined the two components are combined to give the overall assessment of each option being appraised (Department for Communities and Local Government, 2009).

There are several MCDA approaches with regards to aggregating the data on individual criteria to provide indicators of the overall performance of options, which can be broadly classified in the below categories (Thokala, 2011):

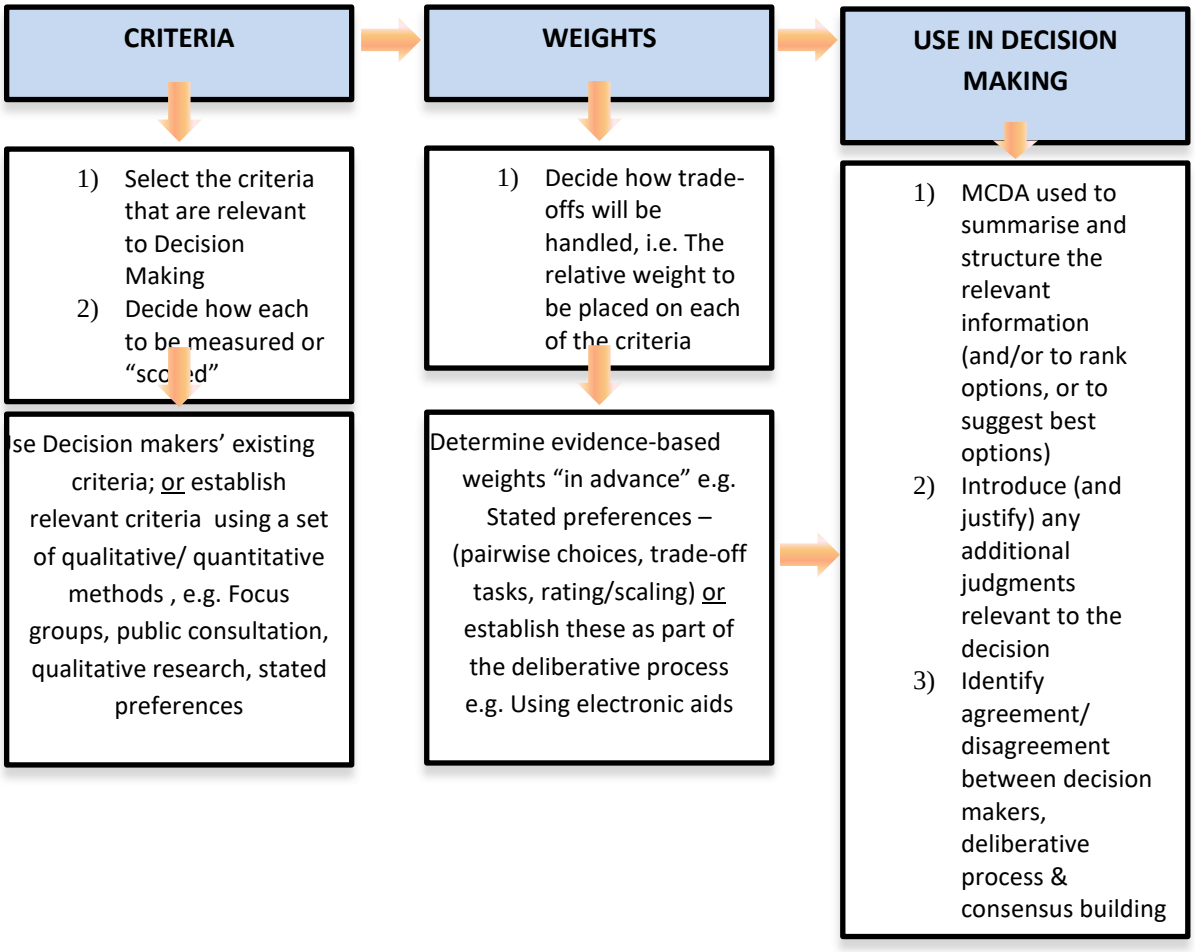
Value measurement models: This is the most commonly suggested MCDA methodological approach in HTA (Thokala, 2011). In value measurement models an overall value is constructed for each decision option by initially developing individual scores for each criterion. The importance of different criteria is measured by using the gain associated with replacing the worst outcome with the best outcome and multiplying this number with a number representative of the relative importance of each criterion. The overall value is then calculated by aggregating these partial value functions taking into account the relative importance of the different criteria (Thokala, 2011).

Outranking models: In this case the alternatives are compared pairwise against each criterion individually. The performance scores are utilised in the construction of a matrix of outranking relations from the individual scores on each criterion. The information across all criteria is then aggregated in order to establish the strength of evidence favouring the selection of one option *versus* the other. Although this approach is not widely used, it has been suggested as a suitable model for HTA, since HTA commonly performs a direct comparison of the key characteristics of the therapeutic interventions (Thokala, 2011).

Goal, aspiration or reference level models: In this approach emphasis is placed on attaining satisfactory levels of performance on each criterion, with preference given to criteria in order of importance. For each criterion there is a predefined desirable (or satisfactory) level of achievement (a goal) and an algorithm is used to identify the alternatives which satisfy the goals in the specified priority order. Provided the definition of value is clearly defined, it has been suggested that this approach could be implemented in value-based pricing to set the prices of 10 drugs/treatments such that the ICER is under the relevant cost-effectiveness threshold (Thokala, 2011).

Once the overall performance of each option has been evaluated, the structured information can be used to support decision-making, while the overall MCDA methodology is schematically represented below (Figure 1.5).

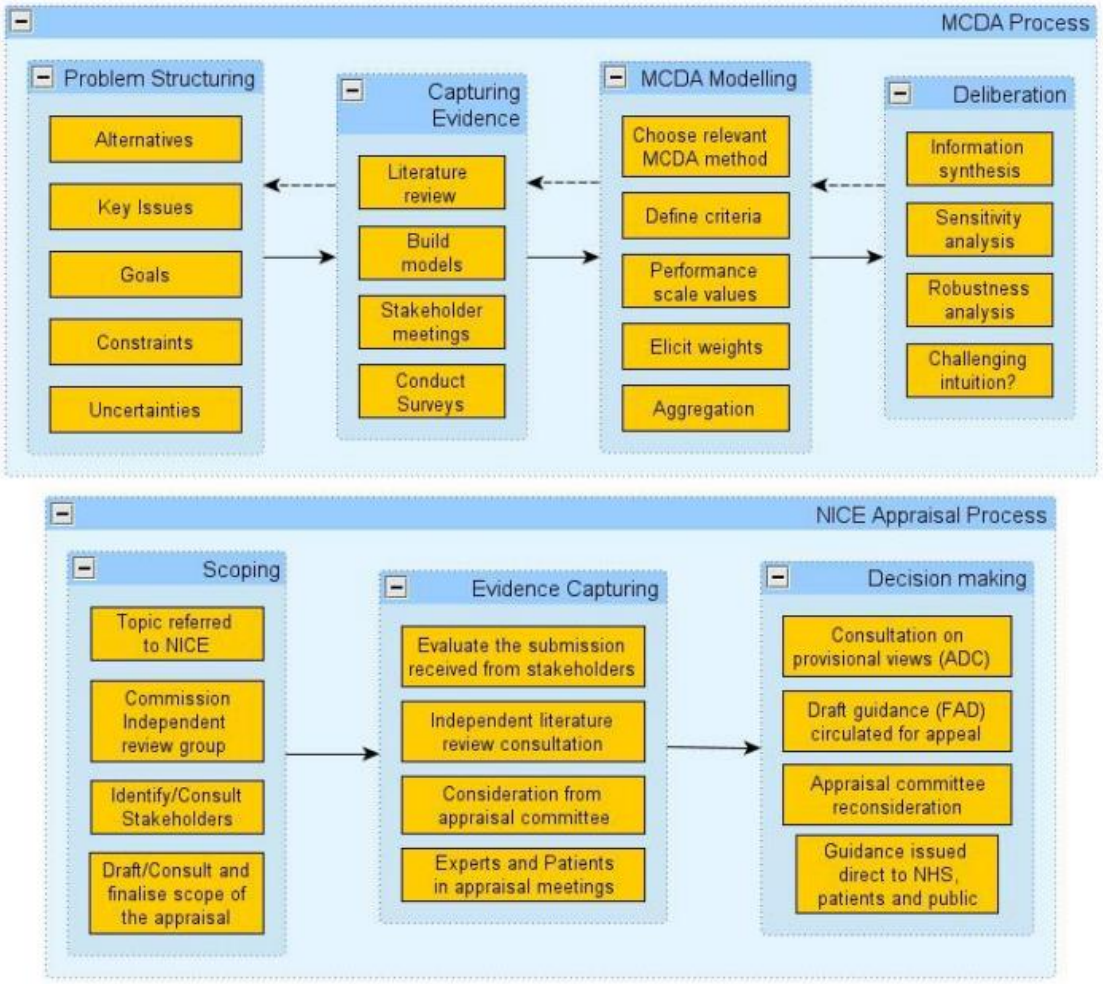
Figure 1.5: An Overview of MCDA methods



Source: (Delvin & Sussex, 2011)

In comparison to the existing NICE appraisal process, MCDA has been identified to have a similar process but with the addition of a formal mathematical approach to decision making (Thokala, 2011). While NICE utilises a deliberative manner with the employment of QALYs/ICER and other criteria for capturing and evaluating the evidence regarding the alternatives, under MCDA the evidence needs to be quantified and mathematical models are utilised to identify the best alternatives. This is also graphically represented below, where the similarities and differences between a typical MCDA and a NICE HTA process, can be readily identified (Figure 1.6).

Figure 1.6: MCDA and NICE technology appraisal process



Source: (Thokala, 2011)

From the above it can be deduced that MCDA could be a valuable tool in assisting NICE in decision-making during Health Technology Assessments. It has also been argued that it could be utilised more broadly in setting priorities in health, to indicate general perceptions on priorities without defining the allocation of resources in a precise fashion (Baltussen, Youngkong, Paolucci, & Niessen, 2010). Furthermore, the basic principles shown above are encountered in most HTA organisations and not just in NICE. Consequently, MCDA is already beginning to find its way into Health Technology Assessments, at least in the case of Sweden, Canada and Australia (Danko, 2014) and the implementation of MCDA as an aid in decision-making should be seriously considered for HTA in general.

1.2.2.1 The EVIDEM Framework

Currently the most widely used MCDA tool in healthcare, the EVIDEM framework stands for Evidence and Value: Impact on Decision Making and has been specifically developed as a practical framework to facilitate decision-making in terms of supporting the deliberative process, providing access to evidence, and enhancing the communication of decisions for HTA (Goetghebeur, et al., 2008).

It consists of three parts, the Core MCDA model, which is an MCDA performance matrix, also called Value Matrix (VM), a Contextual tool, adaptable to the context of each particular evaluation, used to effect the Core MCDA model and a "by-criterion" HTA report which compiles the available evidence for each criterion (Goetghebeur, et al., 2012).

The Core MCDA model was compiled with the criteria required for a Health Technology Assessment and was originally organised into four main clusters (Goetghebeur, et al., 2008). Within the model each individual criterion is given weights (on a scale from 1 – 5) depending on their importance, while during the evaluation each intervention is given a performance score for each criterion based on the available evidence synthesised in an HTA report covering each criterion individually. The scoring scale has defined anchors and scoring guidelines, it takes values from 0 – 3, with zero allowing to exclude a criterion that does not bring any value (Goetghebeur, et al., 2008). Once scoring is complete, the individual scores of each criterion are aggregated and an overall score for the intervention is calculated in an additive aggregation value measurement model (Thokala, 2011).

The clusters with the corresponding evaluation criteria employed in this method can be seen below (Goetghebeur, et al., 2008), while in brackets are the labels that were subsequently given to them (Goetghebeur, et al., 2012).

Disease impact cluster:

1) Disease severity (D1)
2) Size of population affected by disease (D2)

Intervention cluster:

1) Current clinical guidelines (C1)
2) Current interventions' limitations (C2)
3) Improvement of efficacy/effectiveness (I1)
4) Improvement of safety and tolerability (I2)
5) Improvement of patient reported outcomes, convenience and adherence (I3)
6) Public health interest (T1)
7) Type of medical device (T2)

Economics cluster:

1) Budget impact on health plan (E1)
2) Cost-effectiveness of intervention (E2)
3) Impact on other spending (E3)

Quality of evidence:

1) Adherence to requirements of decision-making body (Q1)
2) Completeness and consistency of reporting evidence (Q2)
3) Relevance and validity of evidence (Q3)

The value components that could be not readily incorporated into the matrix were listed as extrinsic components in the accompanying contextual tool, to be considered at the jurisdictional level or on a case-by-case basis. A typical contextual tool, as described in a subsequent field testing of the model with a public payer in Canada, regarding the HTA of tramadol, an opioid pain medication, can be seen below (Tony, et al., 2011):

Contextual Tool:

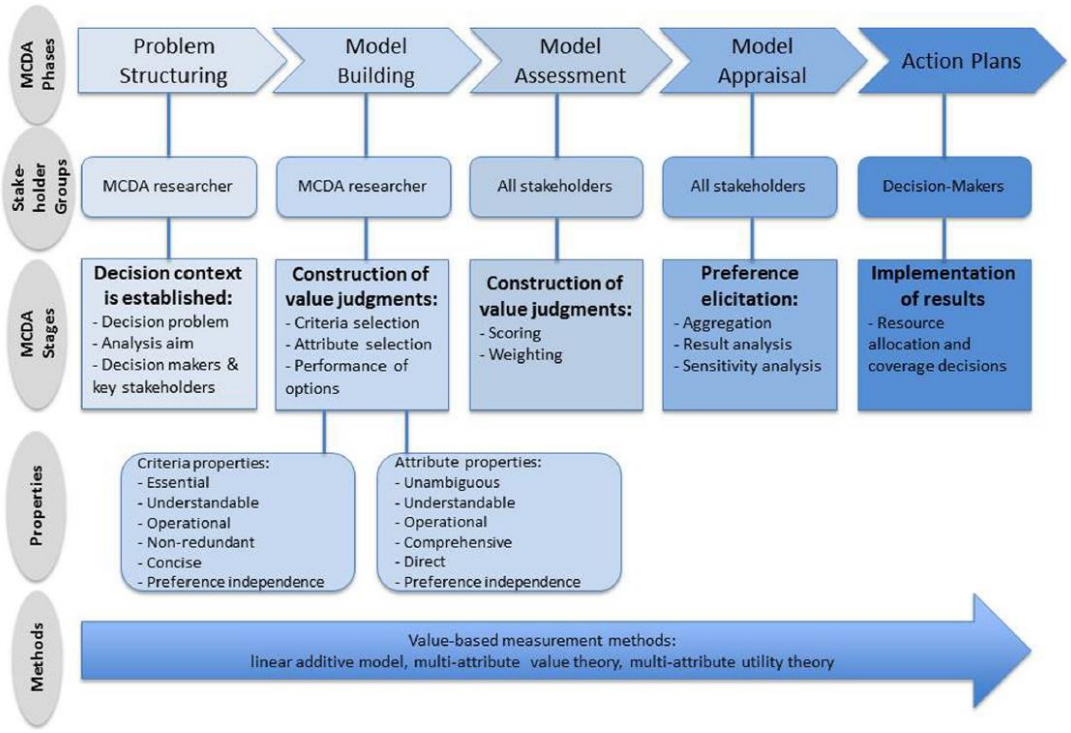
1. Goals of healthcare – utility (Et1) - (Utility of the treatment)
2. Opportunity costs – efficiency (Et2) - (Efficiency and potential opportunity costs)
3. Population priority & access – fairness (Et3) - (Fairness and access to care for opioid analgesics)
4. System capacity and appropriate use of intervention (O1) - (Risk of abuse)
5. Stakeholder pressures (O2) - (Pressures from the Canadian Pain Society to keep tramadol out of the controlled drug schedule)
6. Political/historical context (O3) - (Historical reviews of WHO on tramadol & Recommendations on tramadol from Canadian agencies)

The EVIDEM framework utilises the flexibility and comprehensiveness of MCDA without the need for complicated mathematical modelling. It separates the extrinsic from the intrinsic value components, providing a structured access to the evidence on which value judgements are made, thus also serving as a communication tool among and between stakeholders (Goetghebeur, et al., 2008).

1.2.2.2 The Advance Value Framework

The Advance Value Framework is another relatively new value framework developed for the implementation of MCDA principles in HTA (Angelis & Kanavos, 2017). According to this framework, the MCDA methodological process in the context of HTA can be divided into five distinct phases, in particular (1) problem structuring, (2) model building, (3) model assessment, (4) model appraisal, and (5) development of action plans (Angelis & Kanavos, 2016). This methodological process is represented below (Figure 1.7).

Figure 1.7: MCDA methodological process in the context of HTA



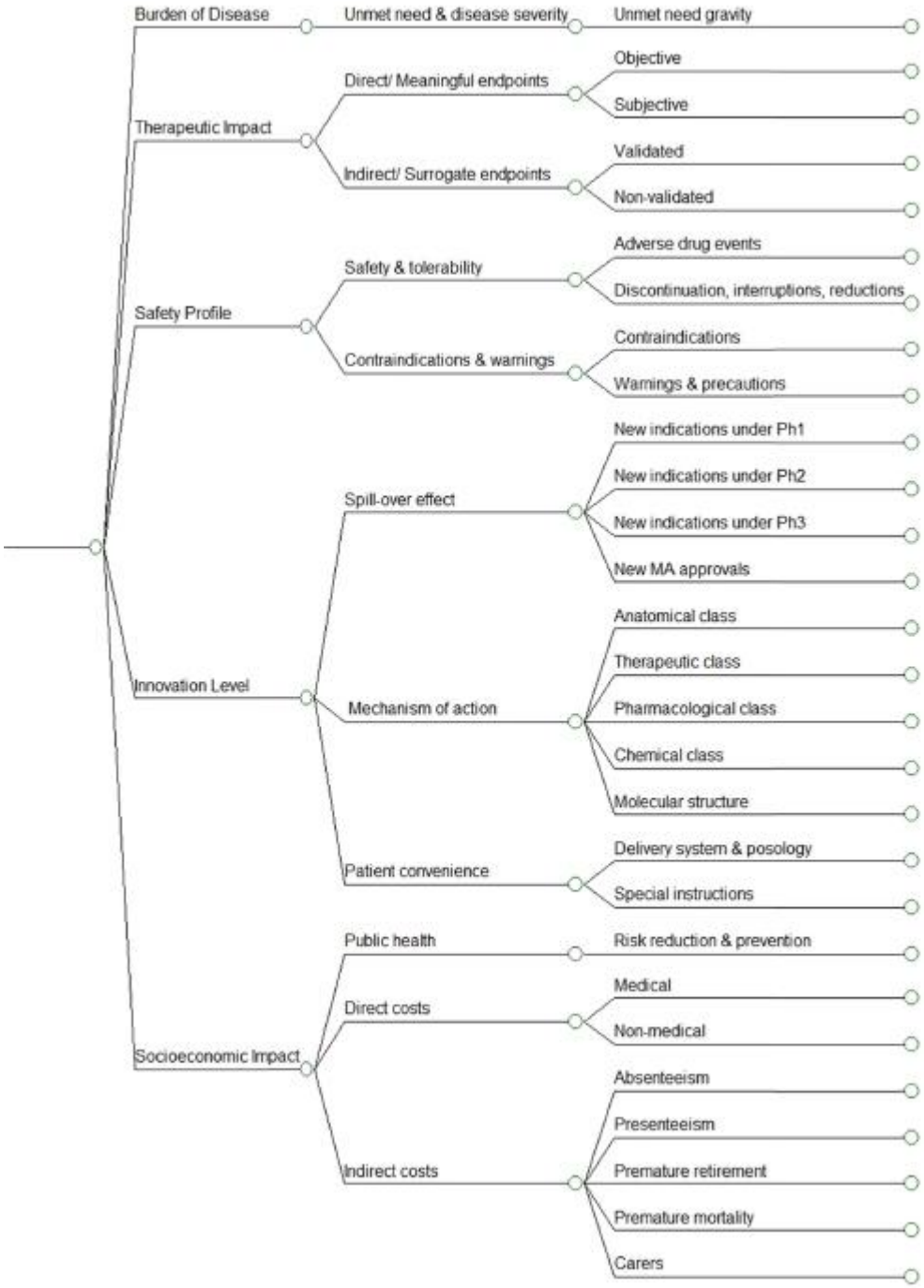
Source: (Angelis & Kanavos, 2016)

The framework places emphasis on problem structuring and even more so on criteria selection, as it is believed that the most important stages that act as the foundations to the analysis are the establishment of objectives and the definition of criteria and attributes (Angelis & Kanavos, 2016).

In the model, objectives and criteria are further decomposed into sub-objectives and sub-criteria, all structured in the form of a tree which is offering an organised overview of the values under consideration and is known as value tree. The sub-objectives and sub-criteria are further expanded in the tree, incorporating their attributes, which are the quantitative or qualitative performance measures associated with each sub-objective and sub-criterion (Angelis & Kanavos, 2016).

After a five-stage process that lasted from February 2013 – June 2016, which included systematic literature review in HTA, consultation with the experts, targeted examination of methodological/ grey literature, consultation with Advance-HTA partners and wider dissemination and consultation activities, the Advance Value Tree was created, which is shown below (Angelis & Kanavos, 2017).

Figure 1.8: The Advance Value Tree



Source: (Angelis & Kanavos, 2017)

As it can be seen, the model consists of 5 main criteria clusters (generic value domains), divided into 11 criteria, which are in turn separated into 28 sub-criteria or attributes. Care has been taken so that there is no overlap or double counting between criteria or attributes.

The framework does not take into consideration any extrinsic criteria, as it is believed that these do not relate to the "value" of the new medicine per se, instead relating to the particular health system under consideration (Angelis & Kanavos, 2017). Instead, any extrinsic criteria should be considered or incorporated on an optional basis depending on the decision context and problem in question, possibly through the application of other analytical frameworks, such as the Contextual Tool discussed in the EVIDEM framework (Tony, et al., 2011) in parallel to the Advance Value framework (Angelis & Kanavos, 2017).

As modelling technique, value measurement methods category is proposed, mainly because of the multiple decision contexts that they can be applied to and the simplicity of the value judgements required (Angelis & Kanavos, 2017). Similarly, in terms of aggregating, a simple additive model could be applied; however, the optimal combination of modelling techniques requires further research as it has not been evaluated (Angelis & Kanavos, 2017).

The Advance Value framework has several advantages; by bringing each criterion down to its attributes level the factors affecting each criterion can be deduced directly and criteria can be selected that will prevent from double counting of attribute values or criteria overlap (Angelis & Kanavos, 2017).

This approach is also preferred comparing to the EVIDEM framework since the presence of criteria domains and sub-criteria discussed in the Advance Value Framework is also in line with the actual findings regarding the evaluation criteria actually employed by NICE, as discussed above (de Folter, Trusheim, Jonsson, & Garner, 2018).

1.2.4 HTA and CBA

Cost-benefit analysis (CBA) is an analytical tool for economic assessment of interventions where a set of predetermined project objectives are evaluated by bestowing a monetary value to all positive

(benefits) and negative (costs) welfare effects of the intervention. These values are discounted and then totalled in order to calculate a net total benefit (Sartori, et al., 2015).

Cost-benefit analysis has so far limited application in HTA, although it is acknowledged that there may be cases where the application of CBA may be more appropriate than CUA (NICE, 2011). Such cases are usually healthcare interventions which often produce benefits to individuals that were not the target of the intervention or have other non-health benefits, examples being the drop in crime by programs targeting alcohol misuse or increase in the number of smokers trying to quit by programs aiming to protect non-smokers through the implementation of smoke-free legislation (NICE, 2011). In such cases, using QALY as a measure of benefit would impose serious limitations to the study due to the restriction of QALY to measure only health-related outcomes (life expectancy and HRQoL).

Another issue regarding CBA is the valuation of a health outcome, which is usually calculated through the estimation of the willingness to pay (WTP) of the patients or the general public for the given health outcome to be attained. Even if CBA is mentioned as an alternative method by several HTA bodies in EU, there are few guidelines available with recommendations on how to conduct studies for assigning monetary values to health outcomes and in general WTP is not recommended as one of the primary outcome measures in a health economic evaluation (EUnetHTA, 2015). In that respect, the EQ-5D, the preferred measure of health-related quality of life according to NICE, is standardised, widely used and validated in many patient populations (NICE, 2013).

Apart from the more extensive use and publication of cost-effectiveness methods compared with cost-benefit analysis, the limited use of CBA in favour of cost-effectiveness (and mostly cost-utility) analysis in Health Technology Assessment has also been attributed by NICE to the Institute's focus on maximising health gains from a fixed NHS and personal social services budget (NICE, 2013). However, although such a focus would maximise health outcomes within the limited NHS budget, this would not necessarily maximise the welfare of society within resources available, since a non-societal perspective may result in suboptimal resource allocation decisions and a corresponding loss in the total welfare of society. (Byford & Raftery, 1998). A societal perspective is therefore necessary for making optimal societal decisions (Drummond, Weatherly, & Ferguson, 2008).

Further to the above, cost-benefit analysis evaluates the benefit in monetary terms (in shadow values) and not in physical terms as in previous methods. If shadow prices are calculated accurately, this method can correct distortions due to market and state failures, so that it is more feasible to choose a project that maximizes net social benefit (Μέργος, 2007). In this case, the return calculated is a proper measure of the project's contribution to social welfare (Sartori, et al., 2015).

For this reason, in spite of the limited application of CBA in Health Technology Assessment, cost-benefit analysis is a technique used extensively for assessing the wider costs and benefits (Jonsson, B.,

2009). It should be noted that CBA is explicitly required, among other elements, as a basis for decision making on the co-financing of major projects by the European Regional Development Fund (ERDF) and the EU Cohesion Fund (Sartori, et al., 2015). A major project is defined as "an operation comprising a series of works, activities or services intended in itself to accomplish an indivisible task of a precise economic or technical nature which has clearly identified goals and for which the total eligible cost exceeds EUR 50 million" (Regulation (EU) No 1303/2013, 2018).

The EU cohesion policy has a distinct socioeconomic nature, since it aims to support job creation, business competitiveness, economic growth, sustainable development, and improve citizens' quality of life (European Commission, 2019). Any investments falling under the definition of major project must be contributing to the achievement of targets and objectives contained within the Europe 2020 strategy (Sartori, et al., 2015). CBA provides key support in assessing such contribution by evaluating the impact of each project to a number of evaluation criteria, in line with Europe 2020 targets. These evaluation criteria are summarised below (Sartori, et al., 2015):

1) Employment
2) Innovation
3) Climate change
4) Education
5) Poverty

With regards to Healthcare, most interventions under evaluation by HTA have a cost significantly higher than €50 million at a European level. It can therefore be argued that during socioeconomic evaluation such interventions should also be considered as potential investments and their wider impact on costs and benefits should be examined. This could be implemented by incorporating the evaluation criteria in line with Europe 2020 targets into the other socioeconomic criteria currently employed by HTA.

Due to the difficulty of adopting a social perspective in HTA and the fact that this may be in conflict with the narrower healthcare perspective, it has been argued that not all costs need to be considered equally important and that it may be useful to adopt a two-perspective approach as a standard, presenting one cost-effectiveness ratio following a strict healthcare perspective and one following the common societal perspective (Brouwer, van Exel, Baltussen, & Rutten, 2006). Further to this, it has also been suggested that a 'welfarist' societal perspective is not sufficient and that an intervention should be recommended if the benefits are greater than the costs from the perspective of all stakeholders necessary to deliver the intervention (Claxton, Sculpher, & Culyer, 2007).

It may therefore be necessary to develop a different approach relating to the societal perspective in HTA, where evaluation criteria covering the needs of all stakeholders are included. In the present thesis, this approach is further explored through a questionnaire, where people belonging to some key stakeholder

groups (doctors, pharmacists, healthcare professionals and the public) are consulted about some of these evaluation criteria and HTA in general.

CHAPTER 2: THE CASE OF GREECE

It is now common knowledge that Greece has been impacted more than any country in the world by the financial crisis of 2008. In the particular chapter the effect of the financial crisis to some key economic indicators is evaluated in an attempt to show the extent of the impact it had to the economy and consequently to the availability of Healthcare resources.

In order to obtain a perspective on the impact of the financial crisis in Greece, its main development indicators are compared *versus* the corresponding EU values and the average of such values of the other EU countries in the South (Spain, Portugal, Italy).

The impact of the financial assistance programs is then discussed with a focus in Healthcare measures requested, followed by a description of the role, processes and methodologies of the new HTA organisation in Greece.

2.1 Crisis and Austerity Measures

In order to obtain a better representation of the alterations in the economic indicators before and after the crisis, the Compound Annual Growth Rate (CAGR) is used, which is defined as the rate of return that would be required for an investment to grow from its beginning balance to its ending balance, assuming the profits were reinvested at the end of each year of the investment's lifespan (Murphy, 2019). Although it is an investing-specific term, CAGR has been found to be a useful tool for the evaluation of the overall picture over a time period, since it provides a constant rate of return over a time period, dampening the effects of variations observed during individual intervals. It is calculated as follows:

$$CAGR = \left(\frac{FinalValue}{InitialValue} \right)^{\frac{1}{TimePeriod}} - 1$$

Further to the above, the GDP for 2000 – 2018 for EU, Greece and the average of the other European countries in the South is summarised in the below table (Table 2.1). It can be seen that the crisis of 2008 affected all Europe, however, both the South and the rest of Europe returned to positive growth after 2 years of recession. On the other hand, it took Greece 9 years of continuous recession in order to record GDP growth. Similarly, although neither EU nor the South have still reached the GDP levels of 2008,

EU has 98.5% and the South 87.2% of the GDP of 2008. Greece in 2018 had slightly less than 62% of its GDP of 2008, signifying the impact the crisis had to its economy.

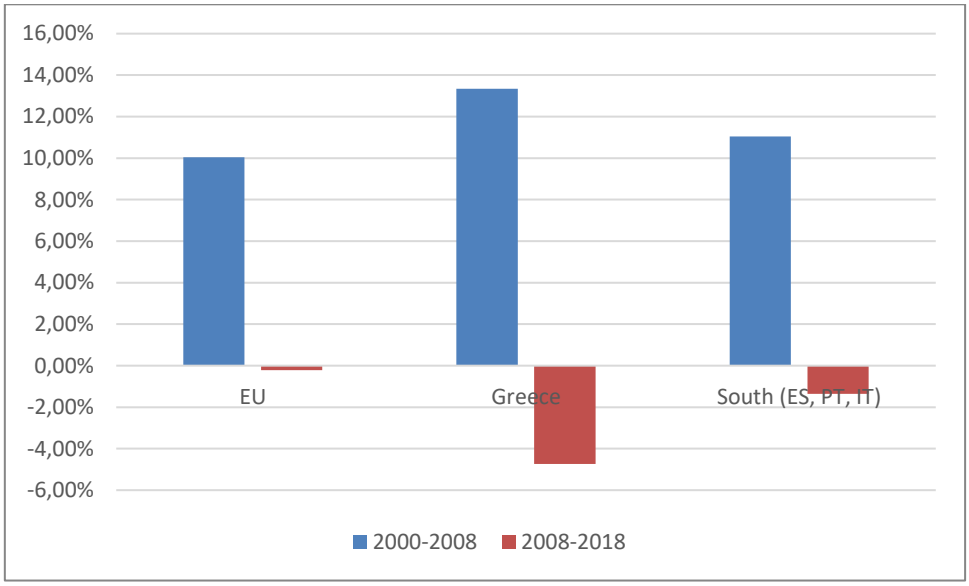
Table 2.1: GDP ($) for 2000 – 2018 in Greece, EU and the South

Year	EU	Greece	Average EU South (ES, PT, IT)
2000	8,910,186,780,352	130,133,845,771	618,507,034,273
2001	9,012,853,057,241	136,191,353,468	636,613,190,753
2002	9,827,530,204,796	153,830,947,017	701,961,733,484
2003	11,960,208,638,257	201,924,270,316	880,489,043,266
2004	13,808,952,935,800	240,521,260,988	1,019,019,229,368
2005	14,443,193,154,921	247,783,001,865	1,069,080,984,538
2006	15,408,596,680,554	273,317,737,047	1,138,584,081,880
2007	17,810,757,410,320	318,497,936,901	1,307,521,451,319
2008	19,163,615,271,292	354,460,802,549	1,429,250,711,391
2009	17,126,624,755,495	330,000,252,153	1,309,335,227,378
2010	17,009,600,166,106	299,361,576,558	1,264,992,812,436
2011	18,374,750,719,408	287,797,822,093	1,336,418,254,879
2012	17,316,993,527,215	245,670,666,639	1,208,403,428,508
2013	18,053,069,090,743	239,862,011,450	1,239,473,006,725
2014	18,669,297,250,216	237,029,579,261	1,252,757,833,802
2015	16,446,079,334,591	196,591,353,761	1,076,925,824,112
2016	16,553,075,746,192	195,222,443,513	1,104,325,616,856
2017	17,344,924,399,291	203,085,551,429	1,160,064,210,083
2018	18,748,572,435,144	218,031,844,584	1,246,023,354,477

Source: (World Bank, 2019)

Similarly, by comparing the % CAGRs of the corresponding economies, it can be seen that all EU countries enjoyed a significant GDP growth the years prior to the crisis with Greece having the best performance between EU and the average of the other European countries in the South (Figure 2.1). However, after the crisis, Greece also shows a much bigger reduction, approx. 3 times the reduction observed at the average of the other European countries in the South, while the rest of EU seems to have almost reached pre-crisis levels in its GDP.

Figure 2.1: GDP (% CAGR) for 2000 – 2018 in Greece, EU and the South (ES, PT, IT)



With regards to the per capita GDP, the results of which are summarised below (Table 2.2), in all cases, an increased per capita GDP is observed up to 2008. Greece in particular reached 95% of the per capita GDP of the average of the other European countries in the South, from 78.2% of that number in 2000. However, this picture is reversed after 2008, with Greece in 2018 having 69.3% of the per capita GDP of the average of Spain, Portugal and Italy.

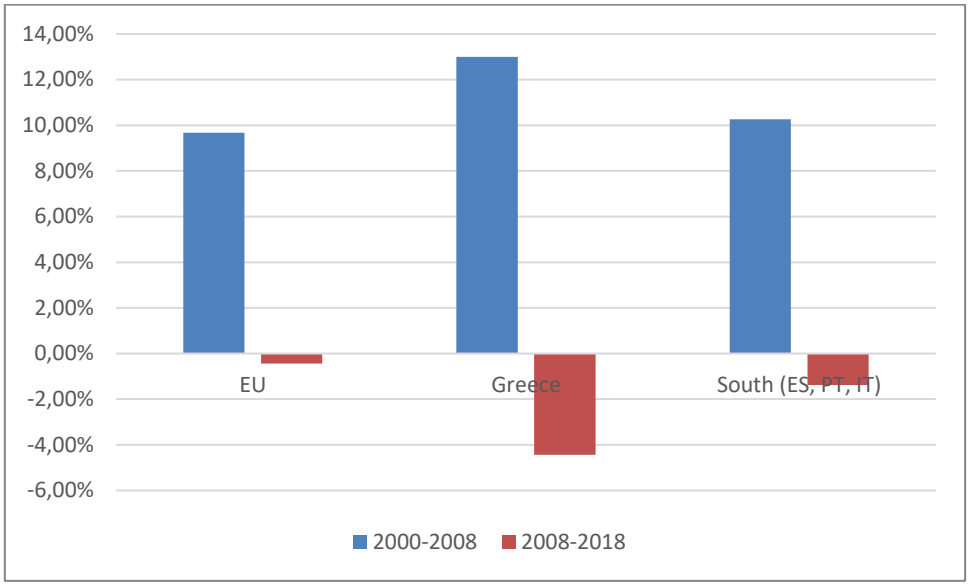
Table 2.2: Per Capita GDP ($) for 2000 – 2018 in Greece, EU and the South

Year	EU	Greece	Average EU South (ES, PT, IT)
2000	18250.3	12043.0	15410.1
2001	18430.6	12538.2	15817.9
2002	20045.9	14110.3	17366.1
2003	24306.2	18477.6	21551.9
2004	27951.8	21955.1	24712.9
2005	29120.3	22551.7	25751.6
2006	30950.6	24801.2	27238.3
2007	35636.4	28827.3	31062.7
2008	38198.6	31997.3	33678.4
2009	34035.8	29711.0	30791.6
2010	33729.2	26917.8	29708.2
2011	36457.4	25916.3	31122.1
2012	34284.5	22242.7	27985.1
2013	35635.9	21874.8	28733.6
2014	36736.6	21761.0	29032.5
2015	32265.1	18167.8	25080.2
2016	32379.6	18116.5	25810.2
2017	33864.2	18883.5	27218.3
2018	36531.7	20324.3	29329.3

Source: (World Bank, 2019)

The % CAGR of the per capita GDP between EU, Greece and the average of the other European countries in the South for 2000 – 2008 can also be seen below (Figure 2.2). The findings are similar to what was observed in Figure 2.1 with the %CAGR of the GDP. Before the crisis Greece performed better in the particular indicator, however, after the crisis Greece has performed significantly worse.

Figure 2.2: Per Capita GDP (% CAGR) for 2000 – 2018 in Greece, EU and the South (ES, PT, IT)



As expected, such a drastic decrease in GDP had a similarly drastic effect on unemployment, which is summarised below (Table 2.3). The unemployment in Greece had a significant reduction on the years before the crisis, dropping below the average of the countries in the South in 2008 and approaching very close to the European average (7.8% *versus* 7.0% for EU and 8.5% for EU South). During the first years of crisis, an explosion in unemployment is observed in Greece, reaching 27.5% in 2013, while at the same time the average of the EU countries of the South was 18.1%.

Table 2.3: Unemployment (%) for 2000 – 2018 in Greece, EU and the South

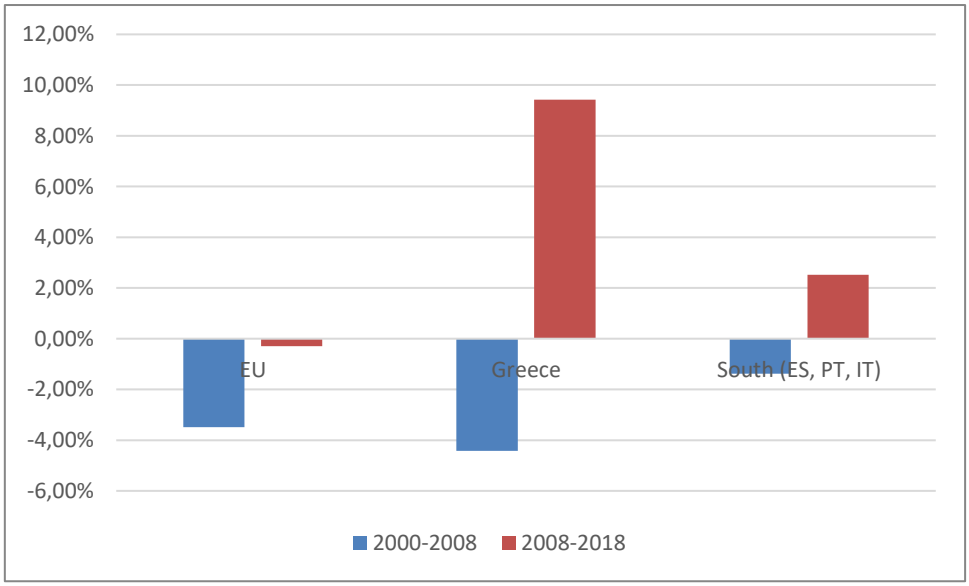
Year	EU	Greece	Average EU South (ES, PT, IT)
2000	9.30%	11.20%	9.50%
2001	8.60%	10.50%	7.90%
2002	9.00%	10.00%	8.30%
2003	9.00%	9.40%	8.80%
2004	9.20%	10.30%	8.40%
2005	8.90%	10.00%	8.20%
2006	8.20%	9.00%	7.60%
2007	7.10%	8.40%	7.40%
2008	7.00%	7.80%	8.50%
2009	8.90%	9.60%	11.70%

2010	9.50%	12.70%	13.00%
2011	9.60%	17.90%	14.10%
2012	10.40%	24.40%	17.00%
2013	10.80%	27.50%	18.10%
2014	10.20%	26.50%	17.00%
2015	9.40%	24.90%	15.50%
2016	8.50%	23.50%	14.10%
2017	7.60%	21.50%	12.40%
2018	6.80%	19.20%	10.90%

Source: (World Bank, 2019)

In the below figure the %CAGR for unemployment is observed (Figure 2.3). It can be seen that from 2000 – 2008 there was a reduction in unemployment throughout Europe, however, Greece had the highest rate, with over 4% average unemployment reduction per year. However, this has been completely reversed for 2008 – 2018, with an annual increase in unemployment in the case of Greece several times what was observed in the other countries of the South.

Figure 2.3: Unemployment (% CAGR) for 2000 – 2018 in Greece, EU and the South (ES, PT, IT)



The crisis also had a significant effect on government expenditure in Healthcare. Collapse in GDP and employment resulted in significantly fewer resources to the government, which adversely impacted Healthcare. The summary of Public per capita Health expenditure can be seen below (Table 2.4).

Furthermore, due to lack of available data the period under evaluation for these metrics is 2000 – 2016. As it can be observed, the effects are not obvious in 2008, as expenditure had already been budgeted from the previous year, first appearing in 2009 for Greece and in 2010 for the average of the other EU countries in the south. It should also be noted that EU did not show any reduction in Healthcare expenditure during the crisis, every year the per capita Health expenditure was increased compared the previous one, throughout the period under evaluation.

Table 2.4: Public per capita Health expenditure ($) for 2000 – 2016 in Greece, EU and the South

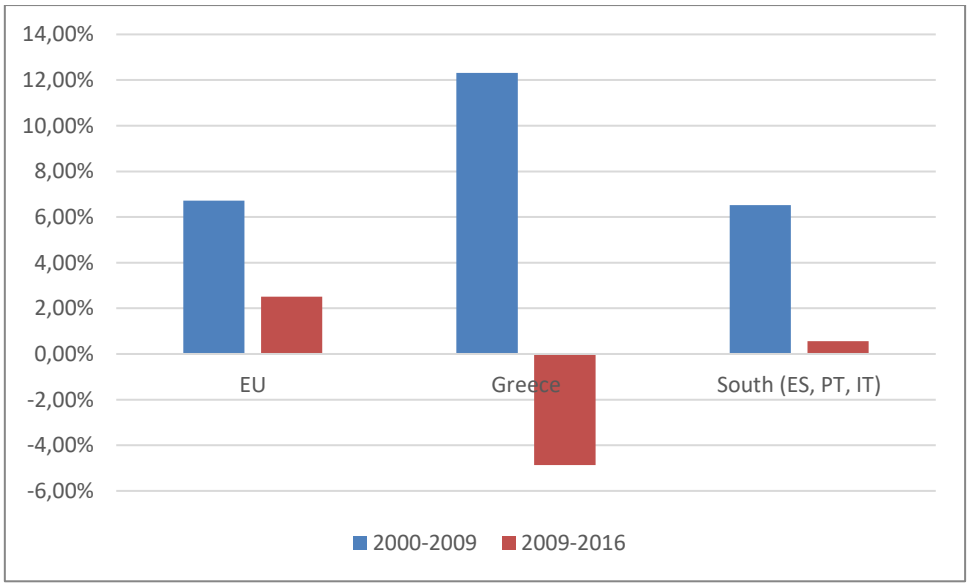
Year	EU	Greece	Average EU South (ES, PT, IT)
2000	1354.9	864.0	1219.0
2001	1458.6	1050.2	1299.4
2002	1564.8	1114.8	1384.6
2003	1642.1	1195.9	1467.5
2004	1722.9	1217.3	1568.6
2005	1819.7	1406.3	1673.8
2006	1980.3	1613.9	1812.0
2007	2077.2	1625.2	1878.8
2008	2240.3	1673.2	2040.2
2009	2431.4	1948.2	2153.0
2010	2496.4	1839.3	2165.9
2011	2571.2	1545.5	2117.9
2012	2618.5	1470.5	2062.5
2013	2774.0	1345.8	2086.7
2014	2852.1	1225.9	2102.9
2015	2909.8	1257.9	2155.6
2016	3040.1	1373.5	2239.3

Source: (World Bank, 2019)

The %CAGR public per capita Health expenditure for the same period (2000 – 2016) can also be seen below (Figure 2.4). As it can be observed, before the crisis Greece had a more than 12% annual growth in per capita Health expenditure, which was twice the rate of EU or the other European countries of the south, which had similar rates, clearly indicating a mismanagement of Healthcare funds before the crisis.

After the crisis the opposite extreme is observed; both EU and the south have a small increase in expenditure, however, significantly reduced compared to before the crisis. Greece on the other hand, has an almost 5% compound annual reduction in per capita Health expenditure for the seven years after the crisis under examination, which is bound to place significant strain to the Healthcare system.

Figure 2.4: Public per capita Health expenditure (%CAGR) for 2000 – 2016 in Greece, EU and the South



With regards to the Private per capita Health expenditure for 2000 – 2016, the results of which are summarised below (Table 2.5), a similar picture is observed, with all 3 indicators peaking during 2008. In all three cases, in 2016 the expenditure was lower than in 2008, while the private per capita Health expenditure was 95% more for EU, 70% for Greece and 102% more for the average of Spain, Portugal and Italy in comparison to 2000 values.

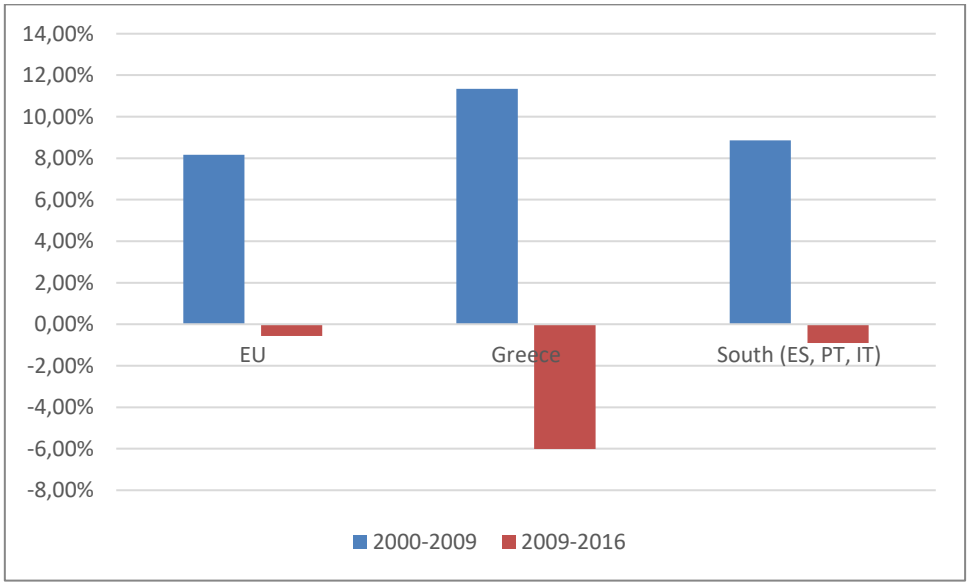
Also, the %CAGR private per capita Health expenditure for the same period (2000 – 2016) can be seen below (Figure 2.5). It is worth noting that all 3 indicators remain negative after the crisis, which means that overall people in Europe have kept reducing their private expenditure for Healthcare since 2008 and this indicator never recovered to its pre-crisis levels.

Table 2.5: Private per capita Health expenditure ($) for 2000 – 2016 in Greece, EU and the South

Year	EU	Greece	Average EU South (ES, PT, IT)
2000	334.7	345.8	329.6
2001	344.5	376.4	331.1
2002	384.8	467.8	360.3
2003	482.9	590.7	469.4
2004	560.7	693.7	546.4
2005	586.8	792.2	563.1
2006	607.2	823.4	600.9
2007	700.6	1015.1	682.7
2008	778.5	1272.2	765.2
2009	678.0	909.4	707.9
2010	670.8	816.3	687.5
2011	737.9	817.3	750.6
2012	703.4	671.5	709.0
2013	767.1	690.8	725.1
2014	787.1	708.4	747.2
2015	687.5	600.5	649.0
2016	651.4	589.2	664.2

Source: (World Bank, 2019)

Figure 2.5: Private per capita Health expenditure (%CAGR) for 2000 – 2016 in Greece, EU and the South



In the end, the total per capita Health expenditure for 2000 – 2006 in Greece, EU and the average of the three other EU countries in the south is summarised below (Table 2.6). Increase in expenditure was observed in all three cases before the crisis, which was more pronounced in the case of Greece, which surpassed the average of total per capita Health expenditure of Spain, Portugal and Italy for the years of 2007 and 2008. However, in the years after 2008 this number has collapsed for Greece and in 2016 the total per capita Health expenditure was 47% of the corresponding EU expenditure and 67% of the average in the south.

Table 2.6: Total per capita Health expenditure ($) for 2000 – 2016 in Greece, EU and the South

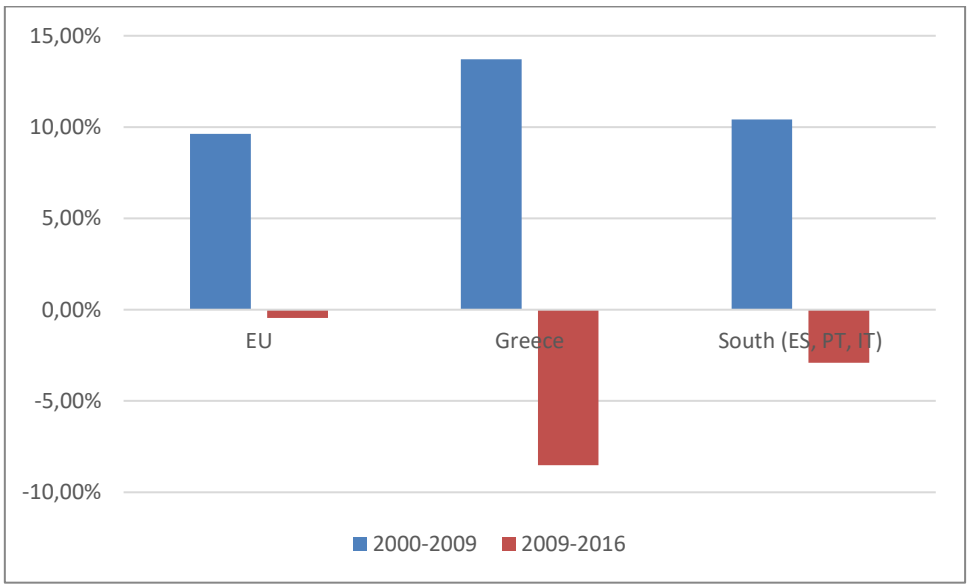
Year	EU	Greece	Average EU South (ES, PT, IT)
2000	1450.3	885.4	1163.5
2001	1497.6	1003.9	1206.1
2002	1673.4	1163.3	1342.8
2003	2088.0	1516.5	1732.2
2004	2410.6	1744.0	2051.9
2005	2546.7	2032.1	2167.3
2006	2706.0	2226.6	2290.3
2007	3091.9	2614.7	2581.4
2008	3425.7	3007.2	2926.6
2009	3315.6	2816.1	2839.3
2010	3261.2	2573.8	2735.4
2011	3511.9	2354.0	2831.4
2012	3323.8	1968.4	2544.7
2013	3559.2	1834.2	2595.1
2014	3668.4	1724.5	2616.1
2015	3206.1	1475.7	2261.8
2016	3211.4	1510.7	2309.8

Source: (World Bank, 2019)

Similarly, as can be seen by the %CAGR total per capita Health expenditure below (Figure 2.6), while the %CAGR before the crisis for EU and the south is in the region of 10%, in Greece expenditure has been increasing by 14% annually, almost 40% more than the rest of the countries in the south. On the other hand, after the crisis this number is being reduced approximately three times faster compared to the south. It should also be noted that %CAGR has remained negative in all three cases, which indicate that even in EU total per capita Health expenditure in 2016 is lower than what it was in 2008. Given the

fact that public per capita Health expenditure for both EU and the south has since surpassed its 2008 level, it also leads to the conclusion of Europeans having significantly reduced private spending in Healthcare after the crisis.

Figure 2.6: Total per capita Health expenditure (%CAGR) for 2000 – 2016 in Greece, EU and the South



From the above, it can be easily deduced that the significant growth observed in Greece before the crisis resulted in several indicators improving faster than the average of the other EU countries of the south. This prosperity also resulted in excessive expenditure in the Healthcare sector indicated by their significantly higher growth rate compared to the other EU countries in the south.

2.1.1 Healthcare inefficiency and MoUs

It is not surprising that the overall culture in the Greek Healthcare system had not been putting any significant value in cost-effectiveness prior to the economic crisis. The change in economic conditions meant that significant reforms were required in the shortest amount of time, in order for the Healthcare system to remain viable in the new environment. It is not surprising therefore that the current culture of healthcare reforms that is leading to the implementation of HTA in Greece has practically been forced through the MoUs signed with the creditors.

The first Memorandum (Directorate-General for Economic and Financial Affairs, 2010) and the consequent IMF funding request (Papakonstantinou & Provopoulos, 2010) had very limited references to health reforms, with more emphasis on computerization upgrades to hospitals, the introduction of duplicate accounting systems, their administration, budgets, etc.

With the failure of the first memorandum, the second request for funding brought significant changes, with much more specific and detailed reforms, with the text larger than twice that of the first memorandum (Directorate-General for Economic and Financial Affairs, 2012) (Papademos, Venizelos, & Provopoulos, 2012). For pharmaceutical spending, its main objective was to reduce it by at least 1,076 million euro in 2012, from 1.9% to 1.33% of GDP, with a further target of 1% of GDP (close to EU average) by the end of 2014.

In the third memorandum (Tsakalotos, Stournaras, & Dombrovskis, 2015) again a more limited description of the prerequisites is observed, as their volume is comparable to that of the first memorandum. On the other hand, a more detailed look at the prerequisites shows that they are based on the measures of the previous two memorandums, with many of the prerequisites specifying and extending the preceding measures.

2.2 HTA in Greece

Greece has recently joined the EU member states with a government body responsible for HTA, through the creation of a Health Technology Assessment committee. Although there was no explicit request regarding HTA by the joint EC/ECB/IMF collaboration providing financial assistance to Greece, the articles relevant to the committee have been part of Law 4512/2018, “Arrangements for the implementation of the Structural Reforms of the Financial Adjustment Program and other provisions” (ΦΕΚ A'/5/17.01.2018). The members of the Committee for the Evaluation and Reimbursement of Medicinal Products for Human Use, as is the official name of the committee, were appointed soon after (ΦΕΚ B'/365/26.06.2018).

The committee consists of 11 members including the chairman and vice-chairman and its work is supported by a secretariat of 10 full-time staff. In parallel, it can be assisted by external experts/evaluators, while it can outsource the preparation of a pre-evaluation report of the medicinal product under consideration to scientific institutions or academic centres. The committee is based on the grounds of the National Drug Organisation (ΕΟΦ); it is under the responsibility of the Minister of Health, while it is also taking over the responsibilities of the Positive Reimbursement List committee that had been set up previously (ΦΕΚ A'/6/26.01.2010).

According to the corresponding law, the committee is tasked with issuing an Opinion to the Minister of Health, following an evaluation of the Medicinal Products authorised and marketed in Greece. The opinion is to be utilised by the Minister in order to decide on the inclusion or removal of Medicinal products from the Positive Reimbursement list or the revision of the Positive Reimbursement list itself. The Minister of Health is entitled to reach a different decision to the committee's recommendations, provided that his decision is sufficiently justified, and this justification is based on the same evaluation criteria followed by the committee. Consequence to the above, the committee is only evaluating Medicinal products, while these products must have already received a Marketing Authorisation (MA) in Greece.

As far as the HTA process is concerned, the company that has obtained the Marketing Authorisation in Greece submits an application to the committee together with a dossier containing all supporting information and documentation. The application undergoes a preliminary evaluation and if this is positive, it is sent to the Committee for the Negotiation of Medicinal Products Prices, a new 9-member committee also created with the same law (ΦΕΚ Α'/5/17.01.2018), which is also planned to replace the existing Negotiation Committee of the National Organisation for Provision of Healthcare Services (ΕΟΠΥΥ) (ΦΕΚ Α'/31/02.03.2011), however, until the formation of the new committee, all responsibilities of the new law will be part of the responsibilities of the existing Negotiation Committee (ΦΕΚ Α'/5/17.01.2018).

The Committee for the Negotiation of Medicinal Products Prices is tasked with negotiating prices, discounts and rebates with the applicant companies. Based on these negotiations it creates a report with a justified opinion regarding the financial impact of the Medicinal Product under evaluation to Healthcare budget from the incorporation or maintenance of the particular Medicinal Product to the Positive Reimbursement List. The report is then sent to the Committee for the Evaluation and Reimbursement of Medicinal Products for Human Use, which is taken into account for the final recommendation of the committee to the Minister of Health.

If the application is successful, an abstract of the recommendation of the evaluation committee is published on the website of the National Drug Organisation. These abstracts contain as a minimum the rationale that led to the recommendation, while any information regarding trade secrets or private information has been previously removed (ΦΕΚ Α'/5/17.01.2018). The ministerial decisions are similarly uploaded online on «Διαύγεια» website according to the corresponding guideline and are considered to be in effect from the day they are uploaded (ΦΕΚ Α'/112/13.07.2010). These decisions are also published on the MoH website, while the results of any negotiations are not published.

In the event that the application is rejected, the applicant company is allowed to make an appeal; however, this can take place after at least 6 months from the above-mentioned decision. During such an

appeal, the applicant will have to also submit clinical and financial information and documentation justifying new substantive evaluation of the Medicinal Product. The whole process from the application for evaluation to the uploading of the final Ministerial decision should be completed within 180 days.

With regards to the HTA Methodology employed by the evaluation committee, the members of the evaluation committee and the external experts have full access to all information available for all Medicinal Products, in order to be assisted with their evaluation. It is optional for the committee to also take into account the evaluations and decisions of other HTA bodies in EU; however it is obliged to consider any evaluations performed by EUnetHTA. Regarding the basic criteria in use by the evaluation committee these are the below, as defined by the same law (ΦΕΚ A'/5/17.01.2018):

1) The clinical benefit, in relation to the severity and burden of the disease, the impact on mortality and morbidity indicators, as well as safety and tolerability data
2) A comparison with the already available drug treatments
3) The degree of reliability of clinical trial data
4) The cost/effectiveness ratio (it is possible that the Incremental Cost Effectiveness Ratio, or ICER, is employed in this criterion although it is not clearly mentioned)
5) The impact on budget (in conjunction with the justified opinion from the Negotiations committee)

Apart from the above, particularly for new Medicinal Products under patent, they can be evaluated and included into the Positive Reimbursement List only if they are already reimbursed by at least two-thirds (2/3) of the EU Member states that the product is already marketed. These must also be 9 Member states at a minimum where the product must already be marketed, from which a minimum of 6 Member states should have it on their reimbursement list. At least half of the countries reimbursing the drug must be among the ones that currently have a Health Technology Assessment institution (thus currently accepting UK, Austria, Belgium, France, Spain, Holland, Portugal, Sweden and Finland, although the particular list can change with a Ministerial decree). There are certain exceptions to the above rule, such as orphan drugs, drugs for thalassemia, certain vaccines, drugs based on human blood or blood plasma and biosimilars. Other exceptions include combinations of known Active Pharmaceutical Ingredients (APIs) that their prices are lower than that of the sum of the drugs containing the individual APIs and MA clones of Medicinal Products already on the Positive Reimbursement List.

It is clear from the above that the evaluation committee is not requested to perform full-fledged evaluations and is to rely instead on evaluations performed by HTA bodies on other EU Member states. This is also in line with the number of personnel allocated for such a task, since such evaluations should require significantly more resources than the ones available to the committee. Instead, it appears that the

role of the two committees is mainly to control the financial impact of new treatments to the Healthcare budget.

This is evident from the fact that both committees have to evaluate the budgetary impact, with the negotiation committee trying to secure the best possible price and providing the justified opinion to the evaluation committee, with the latter evaluating all other criteria together with budgetary impact to issue its recommendation. It is also apparent from the appeals process, where in contrast to other processes such as NICE's, it is deliberately slow, requiring the applicant company to not have their medicinal product reimbursed for at least six months, which forces the company to allow for more concessions during price negotiation.

In the questionnaire developed, the potential organisational structure and role of a Greek HTA body is explored further, together with its potential relationship to other national or EU HTA bodies, through the consultation of people of some key stakeholder groups (doctors, pharmacists, healthcare professionals and the public).

QUESTIONNAIRE METHODOLOGY

As HTA is a relatively new concept outside the field of Health Economics in Greece, a questionnaire was developed. The opinions of people belonging to some key stakeholder groups were requested with regards to HTA in general and the possibility of implementing socioeconomic criteria such as those assessing the contribution of major investment projects towards the achievement of Europe 2020 targets. Further to this, due to the continuous debate concerning local pharmaceutical production and its relevance to the above-mentioned criteria (as it directly affects 4 of the 5 criteria, namely local employment, innovation, education and poverty), the respondents were also consulted about their views regarding local production.

The questionnaire can be seen in Appendix III. It consists of 17 multiple-choice, close-ended questions, as follows:

1) A general question regarding the professional group the respondent belongs to.
2) A general question regarding the familiarity of the respondent with HTA.
3) A question with 10 sub-questions regarding a Health Technology Assessment organisation, its form and the kind of interventions it should be assessing.
4) A question with 6 sub-questions regarding the stakeholders that should be consulted during HTA.
5) A general question regarding the familiarity of the respondent with the potential existence of an HTA organisation in Greece.
6) A question with 5 sub-questions regarding the potential relationship of a Greek HTA organisation with corresponding organisations in other countries and in the EU.
7) A question requesting the respondent to weigh 6 criteria from a scale of 1 – 5 Likert scale (Likert, 1932) as to the impact they should have during a Health Technology Assessment. These were the main criteria proposed by the Advance Value Tree except that the socioeconomic impact was divided to social impact and economic impact, in order to be better understood by the respondents.
8) A question requesting the respondent to weigh 8 socioeconomic criteria from a scale of 1 – 5 as to the impact they should have during a Health Technology Assessment. These were the 5 criteria correlating to the Europe 2020 targets (employment, poverty, innovation, environment/climate change and education), the 3 sub-criteria of the socioeconomic group of the Advance Value Tree (direct costs, indirect costs, public health) and the hidden costs which are not mentioned in the Advance Value Tree. From these, poverty has been reworded to "improvement of access to treatment for patients of lower income" and public health to

"prevention of disease spread to other people in the society" (which is the only sub-group of public health) in order to be better understood by the respondents.

9) A closed question regarding preference between an imported and an identical locally produced pharmaceutical product.
10) A closed question regarding WTP for a locally produced pharmaceutical product in comparison to a given price for an identical imported pharmaceutical product.
11) A closed question regarding WTP for a locally produced pharmaceutical product in comparison to a given price for an identical imported pharmaceutical product.
12) A closed question regarding WTP for a locally produced pharmaceutical product in comparison to a given price for an identical imported pharmaceutical product.
13) A question about the sex of the respondent
14) A question about the age of the respondent
15) A question about the educational background of the respondent
16) A question regarding the year of experience of the respondent in the Health sector
17) A question regarding the job position of the respondent

The questionnaire was prepared with the Google Forms software, which gives the ability to have a link to the form of the questionnaire and can be easily sent to potential respondents *via* email, messaging applications or social networks. In spite of this, a significant number of questionnaires (more than 40) had to be printed to be filled by the respondents manually, as it was found to be more convenient to them.

The size of the questionnaire was decided to be such that could be completed within 10 minutes, in order not to be too difficult for respondents, particularly the ones not familiar with the Healthcare sector and to allow for maximum participation.

As target respondents, it was decided to have four groups: Doctors, Pharmacists, Other professionals working in the Healthcare sector (nursing, pharmaceutical companies etc.) and those with no relationship with the sector. The aim was to determine if there were any differing views among the particular groups, while the group with no relationship to the sector would also serve as a point of reference.

For reaching the respondents, the methods that were followed were word of mouth, phone calls/emails/messages to familiar respondents, which were also requested to enlist people they were comfortable with, social networks groups and finally professional organisations/ associations (from the latter, mostly associations of doctors, dentists and pharmacists and auditors of corresponding scientific journals).

Apart from the questions relating to demographic information, in all other questions where there was more than one choice to be made or contained several sub-questions, the order of appearance of each choice or sub-question was randomised, before being added to the questionnaire to minimise corresponding biases.

The main questions were sequenced according to the below pattern: First, there was an introductory question that defined which group the respondent belonged to, which was followed by the more general questions regarding HTA and its role and organisational structure in Greece. Subsequently, there were the questions relating to more specific questions regarding HTA with the evaluation criteria under consideration and the questions regarding local production of pharmaceuticals and corresponding costs, followed by questions relating to demographic information. In the end, there was an option to leave an email if interested in receiving feedback from the questionnaire once the study was complete, thus permitting people interested in the study and contributing to it to receive a report of the findings.

Due to the specialised nature of the questionnaire and the presence of respondents with no exposure in the Health sector, in all questions requiring "Yes/No" or "Agree/Disagree" for an answer a third option was also added, "I do not know" or "I do not have an opinion", respectively. This was done in order for any respondents who did not feel confident in replying to have the way to opt-out from such a question.

The questionnaire was pre-tested with colleagues and refined according to their recommendations, providing clarifications or rephrasing questions as required. During pre-testing the time required for questionnaire completion was also measured in an attempt to keep the time required for completion at under 10 minutes. The circle of pre-testing and questionnaire updating was repeated four times before the final questionnaire was launched.

The results collected were subsequently analysed with the software IBM SPSS Statistics, v.25 (IBM, 2017) and are presented in the following chapter.

RESULTS

The questionnaire results are organised in three sections; the first contains replies relating to HTA in general, the organisational structure and role of an HTA body in Greece and its potential relationship with other national and European HTA bodies. The second refers to the views of the respondents regarding evaluation criteria that a Health Technology Assessment should employ, together with questions regarding WTP for local production of pharmaceuticals *versus* the same product being imported. In the end, the demographic information of the respondents is presented, together with their professional relationship with the Health sector.

HTA in Greece

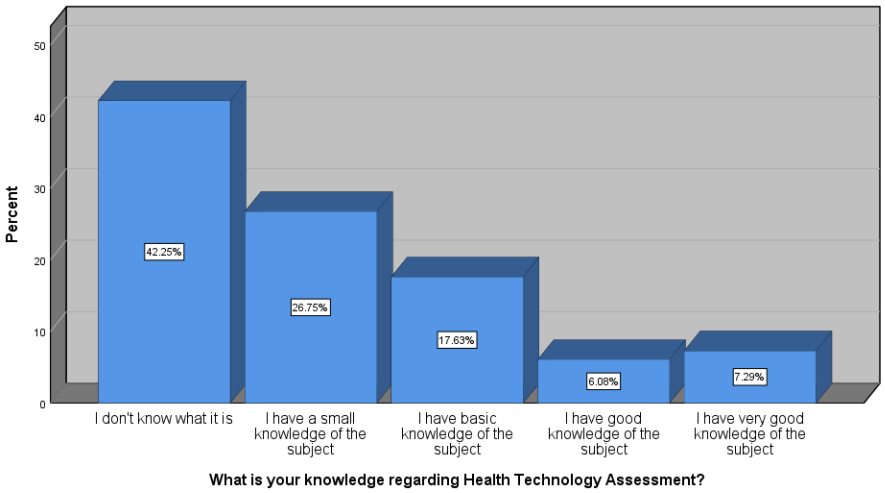
The first question relevant to HTA was enquiring about the respondents' familiarity regarding Health Technology Assessment. 42.2% replied that they have no knowledge on HTA, 26.7% that they had a small knowledge, with 31.0% having from basic to very good knowledge on HTA. The results are summarised below (Table 4.1, Figure 4.1).

From the results it can be deduced that 57.8% of the respondents have at least some small knowledge regarding HTA. Although it appears likely that with a large proportion of the respondents relating to the Health sector, they may be familiar with HTA, it is also as likely that a large proportion of the respondents claiming a small knowledge regarding HTA may in fact be quite unfamiliar with it.

Table 4.1: Responses regarding the familiarity of the respondents with Health Technology Assessment

Replies	Frequency	Valid Percent	Cumulative Percent
I don't know what it is	139	42.2	42.2
I have a small knowledge of the subject	88	26.7	69.0
I have basic knowledge of the subject	58	17.6	86.6
I have good knowledge of the subject	20	6.1	92.7
I have very good knowledge of the subject	24	7.3	100.0
Total	**329**	**100.0**	

Figure 4.1: Responses regarding the familiarity of the respondents with Health Technology Assessment



The second question relating to HTA begins with a small definition of Health Technology Assessment, in order to introduce HTA to all respondents, including the ones unfamiliar to it, so as to enable them to have a better opinion on subsequent questions. It then proceeds with a few sub-questions, which can be divided to three sub-groups, relating to the below questions:

1) What should be the organisational structure of a Greek HTA body?
2) Should it be governed by Public or Private Law?
3) What interventions should it be evaluating?

The obtained results are summarised in the below table (Table 4.2). In the first sub-group, 62.0% of respondents agreed that it should belong to the Ministry of Health, while 30.1% disagreed. Similarly, 80.5% agreed that it should belong to a centralised EU HTA organisation, while 10.9% disagreed. To the question if such an organisation should be independent, with own organisation and administration 53.2% agreed and 40.4% disagreed.

For the second sub-group enquiring whether the entity should be governed by private or public law, 43.5% of the respondents agreed on the organisation being governed by public law, 29.8% disagreed and 26.7% had no opinion on the matter. Regarding private law, 26.7% agreed, 52.9 disagreed and 20.4% had no opinion. Although the respondents seemed to favour the organisation to be governed by public law, opinions were quite divided. A large percentage claimed no opinion on the matter, much higher than in all other sub-questions, while even for public law, the total number agreeing was below 50%.

On the other hand, replies were much clearer on the third subgroup, as for most interventions (pharmaceuticals, medical devices, diagnostic products and therapeutic/ hospital interventions) >90% of the respondents agreed that they should be evaluated by an HTA body. Only differentiation has been the preventive medicine interventions, where 81.8% agreed and 11.6% disagreed about these interventions evaluated by a HTA body. Overall, however, there was wide acceptance in the belief that HTA should be performed for all such interventions.

Table 4.2: Responses to the question "An Organisation which determines the added value of a treatment in comparison to the existing ones, so that it can provide evidence-based information to the persons responsible for the determination of Healthcare policy, should:"

Replies	Agree	Disagree	I have no opinion
Belong to the Ministry of Health	62.0%	30.1%	7.9%
Belong to a centralised EU HTA organisation	80.5%	10.9%	8.5%
Be independent, with own organisation and administration	53.2%	40.4%	6.4%
Be an entity governed by Public Law	43.5%	29.8%	26.7%
Be an entity governed by Private Law	26.7%	52.9%	20.4%
Be evaluating pharmaceutical products	90.0%	7.3%	2.7%
Be evaluating medical devices	92.1%	5.2%	2.7%
Be evaluating diagnostic products	91.5%	2.1%	6.4%
Be evaluating therapeutic/ hospital interventions	90.3%	4.3%	5.5%
Be evaluating preventive medicine interventions	81.8%	11.6%	6.7%

For the third question, regarding the groups the HTA body should be inviting for consultation during an evaluation, health professionals organisations was the most favourable choice with 91.8% of the respondents in agreement and 6.4% disagreeing, followed by National Healthcare system providers where 78.4% agreed and 15.5% disagreed with their invitation. 76.0% of the respondents agreed for the patient organisation to be invited and 19.5% disagreed, while for companies whose products relate to the particular treatment 72.9% agreed and 24.0% disagreed to being invited for consultation. Finally, 47.4% of respondents agreed and 39.8% disagreed to the invitation of companies whose products relate with competing treatments and 40.7% of respondents agreed with 47.4% disagreeing to insurance companies being consulted during a Health Technology Assessment evaluation. For all of the above,

only for the case of insurance companies the number of respondents disagreeing has higher than that of the respondents agreeing to their participation.

Table 4.3: Responses to the question "During the evaluation of a treatment, the HTA organisation should be inviting for consultation:"

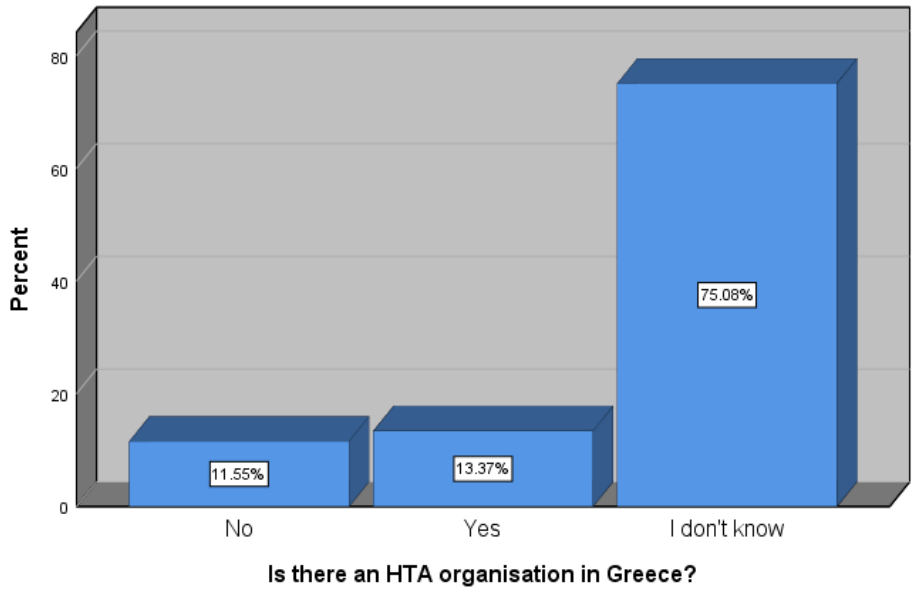
Replies	Agree	Disagree	I have no opinion
Patient organisations	76.0%	19.5%	4.6%
Health Professionals organisations	91.8%	6.4%	1.8%
Companies whose products relate with the particular treatment	72.9%	24.0%	3.0%
Companies whose products relate with competing treatments	47.4%	39.8%	12.8%
Insurance companies	40.7%	47.4%	11.9%
National Healthcare system providers	78.4%	15.5%	6.1%

The next question is about the existence of an HTA organisation in Greece, where the large majority of the respondents (75.1%) indicated that they were unfamiliar with its existence. 11.6% of respondents replied that there was an HTA organisation in Greece, while 13.4% that there was no such organisation. The results are summarised in the following table (Table 4.4) and are graphically represented below (Figure 4.2). It can be argued that this question may be a good indication regarding the familiarity of the respondents with HTA of the previous question, at least in relation to Greece.

Table 4.4: Responses to the question "Is there an HTA organisation in Greece?"

Replies	Frequency	Valid Percent	Cumulative Percent
Yes	38	11.6	11.6
No	44	13.4	25.0
I don't know	247	75.1	100.0
Total	**329**	**100.0**	

Figure 4.2: Responses to the question "Is there an HTA organisation in Greece?"



In the final question of this section, the respondents were requested to their opinion with regards to the relationship between a national HTA organisation and a corresponding EU organisation. The most positive response was observed to the sub-question if the evaluations of every national HTA organisations should be available to the remaining HTA organisations (91.8% agree, 4.3% disagree), followed by the sub-question if the national HTA organisation should be evaluating according to local epidemiological data (79.6% agree, 14.3% disagree). To the sub-question if the national HTA organisation should be part of an EU HTA organisation 69.9% of the respondents agreed with 20.7% disagreeing, while to the sub-question if the national HTA organisation should be able to make decisions independently from the EU HTA organisation 66.6% of the respondents agreed and 25.5% disagreed. In the end, to the sub-question if the main evaluation should take place by a HTA organisation of the EU 62.3% of the respondents agreed and 26.7% disagreed. The results are summarised below (Table 4.5).

Table 4.5: Responses to the question "What should be the relationship between a national HTA organisation and a corresponding EU organisation?"

Replies	Agree	Disagree	I have no opinion
The main evaluation should take place by a HTA organisation of the EU	62.3%	26.7%	10.9%
The national HTA organisation should be part of an EU HTA organisation	69.9%	20.7%	9.4%
The evaluations of every national HTA organisations should be available to the remaining HTA organisations	91.8%	4.3%	4.0%
The national HTA organisation should be evaluating according to local epidemiological data	79.6%	14.3%	6.1%
The national HTA organisation should be able to make decisions independently from the EU HTA organisation	66.6%	25.5%	7.9%

From the results above, it can be deduced that the respondents were in favour of an HTA organisation that would be part of a wider European network which would encourage the exchange of information of evaluations between HTA bodies. From the results that had the highest numbers of respondents disagreeing, it appears that there were a few concerns regarding both the main evaluation taking place by a HTA organisation in Europe but also in the possibility of the national HTA to be able to make decisions independently from the EU HTA organisation.

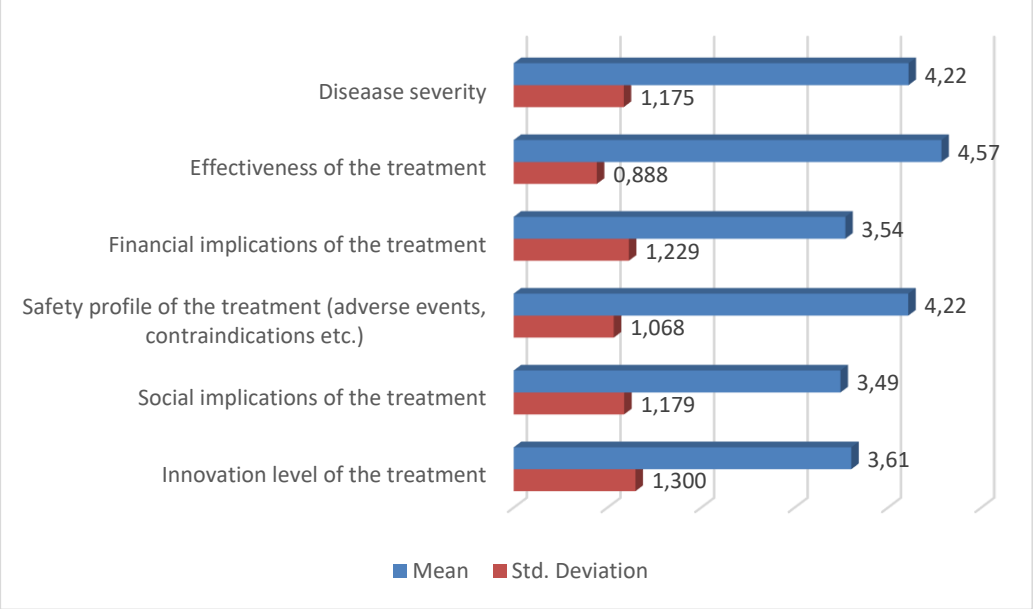
Evaluation criteria

With respect to the evaluation criteria examined in the questionnaire, the first question was relating to a number of criteria that could be taken into account during a Health Technology Assessment. The respondents were requested to grade the importance of these criteria on a 1-5 Likert scale (Likert, 1932), with 1 graded as Not important and 5 as extremely important. The criteria selected were the main criteria proposed by the Advance Value Tree, with the exception that the socioeconomic impact was divided to social impact and economic impact, in order to be better understood by the respondents (Angelis & Kanavos, 2017). The mean values and corresponding standard deviation were calculated and the results are summarised below (Table 4.6; Figure 4.3).

Table 4.6: Responses to the question "For the evaluation of a new treatment *versus* the existing ones, how important do you consider the below criteria?"

Replies	Mean	Std. Deviation
Disease severity	4.22	1.175
Effectiveness of the treatment	4.57	0.888
Financial implications of the treatment	3.54	1.229
Safety profile of the treatment (adverse events, contraindications etc.)	4.22	1.068
Social implications of the treatment	3.49	1.179
Innovation level of the treatment	3.61	1.300

Figure 4.3: Responses to the question "For the evaluation of a new treatment *versus* the existing ones, how important do you consider the below criteria?"



As it can be seen, effectiveness of the treatment, followed by the safety profile of the treatment and disease severity, with mean values of 4.57, 4.22 and 4.22 respectively, scored much better than innovation level of the treatment, financial implications and social implications, with mean values of 3.61, 3.54 and 3.49, respectively. It can therefore be deduced that the respondents put more value to the criteria relating to the treatment itself (safety-efficacy) and the seriousness of the disease rather than socioeconomic criteria.

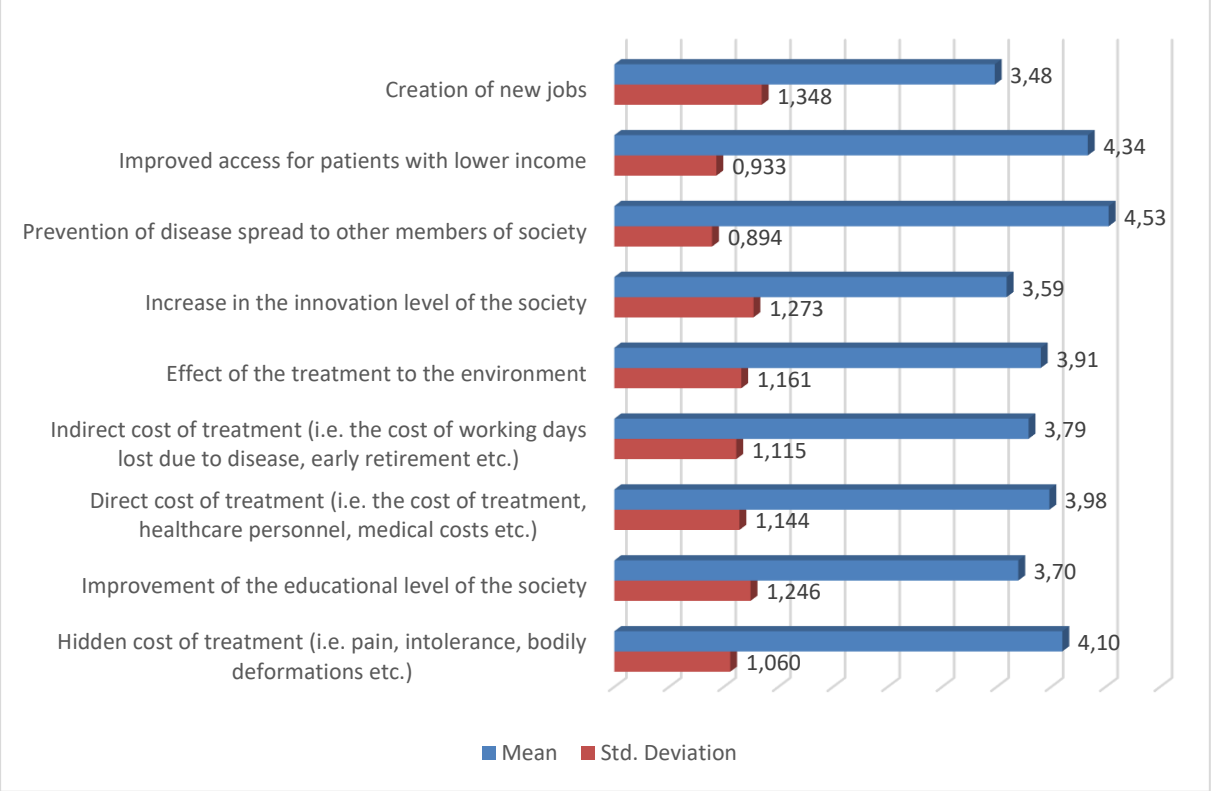
Similarly, a number of socioeconomic criteria were evaluated on the subsequent question, in particular the five criteria correlating to the Europe 2020 targets (employment, poverty, innovation, environment/climate change and education), the 3 sub-criteria of the socioeconomic group of the Advance Value Tree (direct costs, indirect costs, public health) and the hidden costs. The same Likert scale was employed as in the previous question, the mean values and corresponding standard deviation were calculated and the results are summarised below (Table 4.7).

Table 4.7: Responses to the question "For the evaluation of the socioeconomic criteria of a new treatment, how important do you consider the below criteria?"

Replies	Mean	Std. Deviation
Creation of new jobs	3.48	1.348
Improved access for patients with lower income	4.34	0.933
Prevention of disease spread to other members of society	4.53	0.894
Increase in the innovation level of the society	3.59	1.273
Effect of the treatment to the environment	3.91	1.161
Indirect cost of treatment (i.e. the cost of working days lost due to disease, early retirement etc.)	3.79	1.115
Direct cost of treatment (i.e. the cost of treatment, healthcare personnel, medical costs etc.)	3.98	1.144
Improvement of the educational level of the society	3.70	1.246
Hidden cost of treatment (i.e. pain, intolerance, bodily deformations etc.)	4.10	1.060

From these responses, highest score was obtained for the prevention of disease spread to other members of society (4.53) followed by improved access for patients with lower income (4.34) and hidden cost of treatment (4.10). These were followed by the direct cost of treatment (3.98), the effect of the treatment to the environment (3.91), the indirect cost of treatment (3.79), the improvement of the educational level of the society (3.70) and, lastly, the creation of new jobs (3.48).

Figure 4.4: Responses to the question "For the evaluation of the socioeconomic criteria of a new treatment, how important do you consider the below criteria?"



In the next group of questions, the WTP of the respondents for local production of pharmaceuticals was evaluated. In the first question, a scenario was given where they had to choose between two identical drugs, one imported and one produced locally, with their choice being differentiated by the relative cost of the locally manufactured drug compared to the imported one.

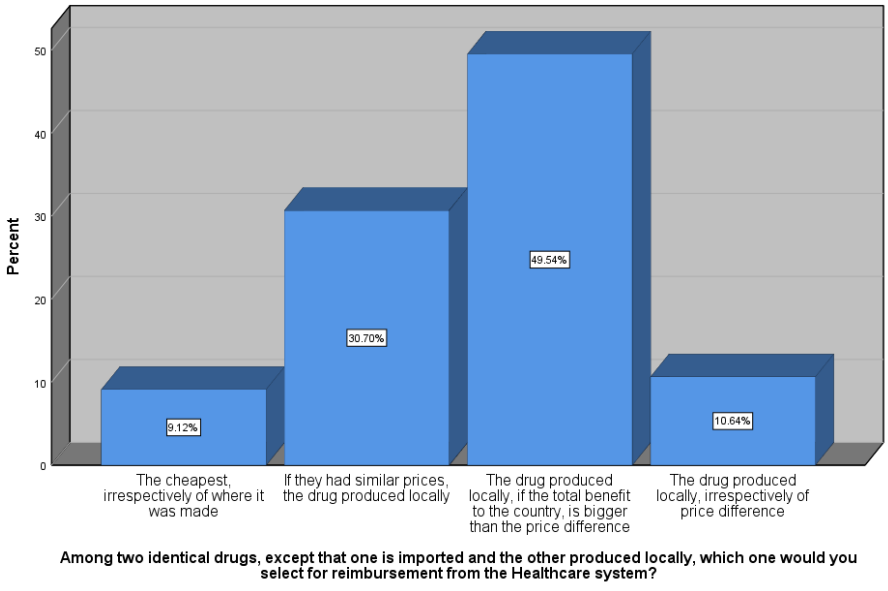
A significant preference towards local production was observed, as more than 90% of respondents were in favour of the locally produced pharmaceuticals, however, only 10.6% of respondents were in favour of local production irrespectively of its cost. On the other hand, only 9.1% of respondents were in favour of the cheapest drug, irrespectively of where it was made.

The results are summarised below (Table 4.8; Figure 4.5).

Table 4.8: Responses to the question "Among two identical drugs, except that one is imported and the other produced locally, which one would you select for reimbursement from the Healthcare system?"

Replies	Frequency	Valid Percent	Cumulative Percent
The cheapest, irrespectively of where it was made	30	9.1	9.1
If they had similar prices, the drug produced locally	101	30.7	39.8
The drug produced locally, if the total benefit to the country, is bigger than the price difference	163	49.5	89.4
The drug produced locally, irrespectively of price difference	35	10.6	100.0
Total	**329**	**100.0**	

Figure 4.5: Responses to the question "Among two identical drugs, except that one is imported and the other produced locally, which one would you select for reimbursement from the Healthcare system?"

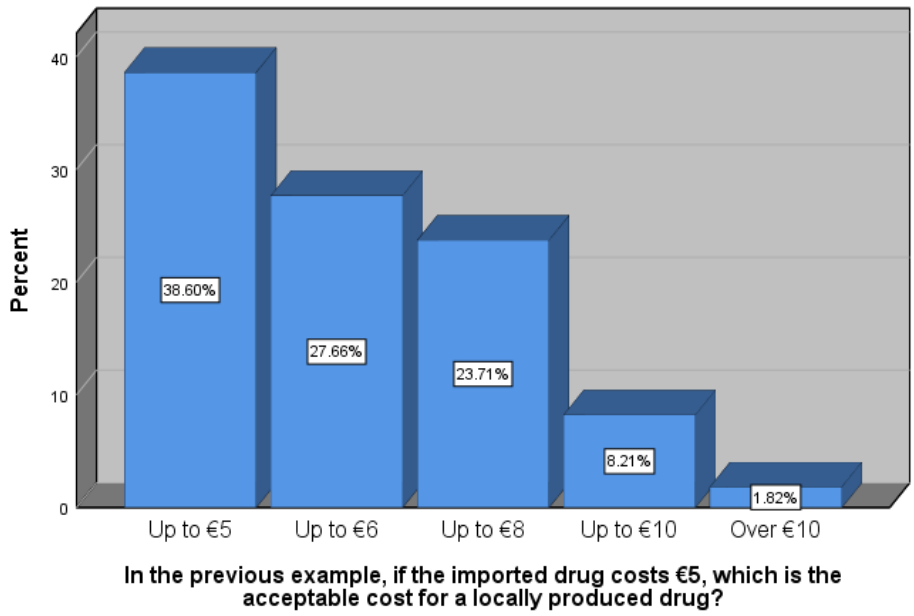


For the next question, the above-mentioned scenario continued by giving a set price for the imported drug (€5) and asked the respondents what they would be willing to pay for the same drug if it was locally produced. The obtained results are summarised below (Table 4.9, Figure 4.6).

Table 4.9: Responses to the question "In the previous example, if the imported drug costs €5, which is the acceptable cost for a locally produced drug?"

Replies	Frequency	Valid Percent	Cumulative Percent
Up to €5	127	38.6	38.6
Up to €6	91	27.7	66.3
Up to €8	78	23.7	90.0
Up to €10	27	8.2	98.2
Over €10	6	1.8	100.0
Total	**329**	**100.0**	

Figure 4.6: Responses to the question "In the previous example, if the imported drug costs €5, which is the acceptable cost for a locally produced drug?"



Those willing the locally produced drug to have maximum the same price as the imported one (up to €5) formed the highest percentage group (38.6%). However, this also indicated that 62.4% of respondents were willing to pay more for a locally produced pharmaceutical. The next two groups (up to €6 and €8) also had high acceptance (27.7% and 23.7% respectively), while the two more expensive groups (up to €10 and over €10) had lower acceptance (8.2% and 1.8% respectively).

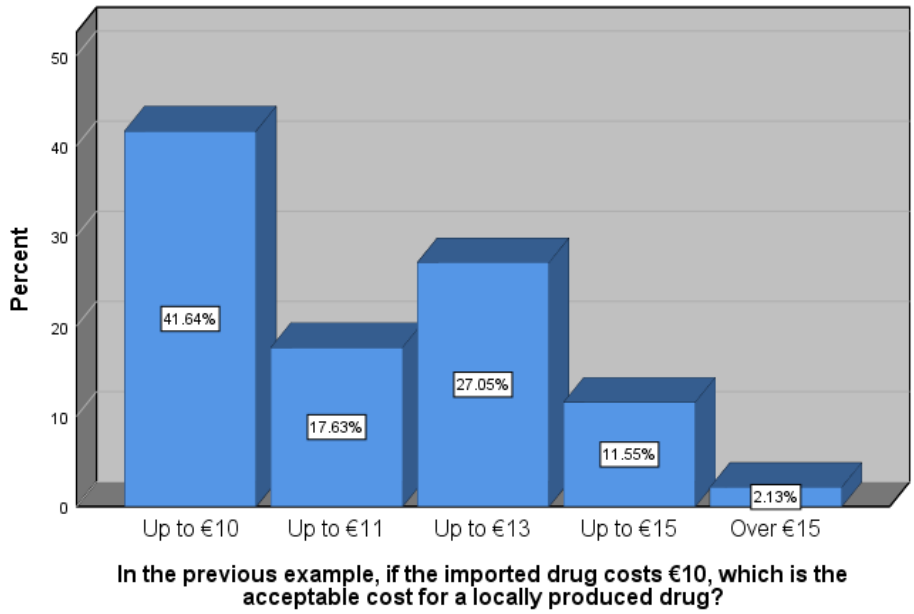
For the next question, the same dilemma was repeated, only this time the price of the imported pharmaceutical was €10. The obtained results can be seen below (Table 4.10).

Table 4.10: Responses to the question "In the previous example, if the imported drug costs €10, which is the acceptable cost for a locally produced drug?"

Replies	Frequency	Valid Percent	Cumulative Percent
Up to €10	137	41.6	41,6
Up to €11	58	17.6	59.2
Up to €13	89	27.1	86.3
Up to €15	38	11.6	97.9
Over €15	7	2.1	100.0
Total	**329**	**100.0**	

The same pattern as above is observed, with those willing the locally produced drug to have maximum the same price as the imported one (up to €10) formed the highest percentage group and this time it was also slightly increased (41.6%). This meant that the number of respondents willing to pay more for a locally produced pharmaceutical dropped to 58.4%. On the other hand, the next two groups (up to €11 and €13) were still the second largest, but with a 10.1% drop for the first one and with the latter actually increasing to 27.1%. Finally, the two more expensive groups (up to €15 and over €15) still scored low, however, their numbers were also increased compared to the previous question (11.6% and 2.1% respectively). This shift becomes more obvious in the graphic representation that follows (Figure 4.7).

Figure 4.7: Responses to the question "In the previous example, if the imported drug costs €10, which is the acceptable cost for a locally produced drug?"

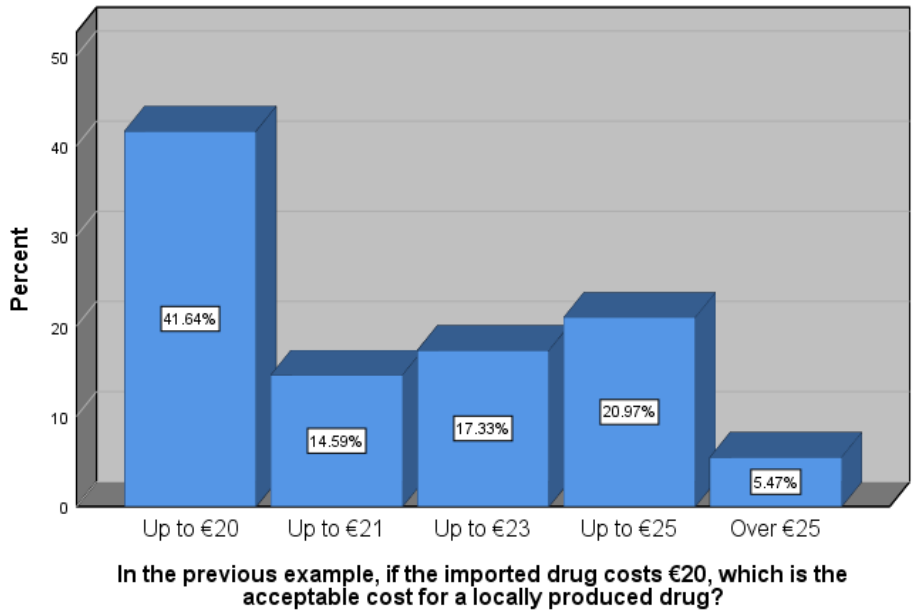


For the final question of this section, the same dilemma was repeated, only this time the price of the imported pharmaceutical was €20. The obtained results can be seen below (Table 4.11, Figure 4.8).

Table 4.11: Responses to the question "In the previous example, if the imported drug costs €20, which is the acceptable cost for a locally produced drug?"

Replies	Frequency	Valid Percent	Cumulative Percent
Up to €20	137	41.6	41.6
Up to €21	48	14.6	56.2
Up to €23	57	17.3	73.5
Up to €25	69	21.0	94.5
Over €25	18	5.5	100.0
Total	**329**	**100.0**	

Figure 4.8: Responses to the question "In the previous example, if the imported drug costs €20, which is the acceptable cost for a locally produced drug?"



The same pattern as before is generally observed. Those willing to pay up to €20 remained the highest percentage group at 41.6% However, this time the second highest group was willing to pay up to €25 (21.0%). The other two groups (willing to pay up to €21 and €23) saw their numbers reduced to 14.6% and 17.3%, respectively, while the over €25 group slightly increased to 5.5%, compared to the previous question.

From the above it can be deduced that the majority of respondents are willing to pay more for a locally produced pharmaceutical (compared to an identical imported pharmaceutical), while some patterns are observed with are further analysed in the discussion chapter that follows.

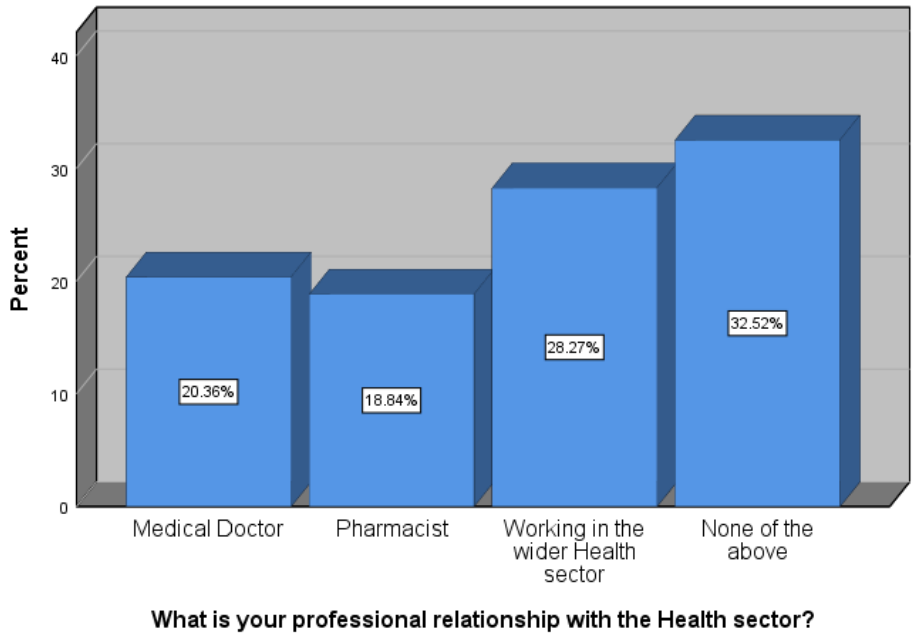
Demographics

The first question regarding demographics was actually the first question in the questionnaire and not part of the demographics section. It was about the professional relationship of the respondent with the Health sector and the replies can be seen below (Table 4.12, Figure 4.9).

Table 4.12: Responses to the question "What is your professional relationship with the Health sector?"

Replies	Frequency	Valid Percent	Cumulative Percent
I am a doctor	67	20,4	81,2
I am a pharmacist	62	18,8	100,0
I am working in the wider Health Sector (nursing, pharmaceutical companies etc.)	93	28,3	60,8
None of the above	107	32,5	32,5
Total	**329**	**100.0**	

Figure 4.9: Responses to the question "What is your professional relationship with the Health sector?"

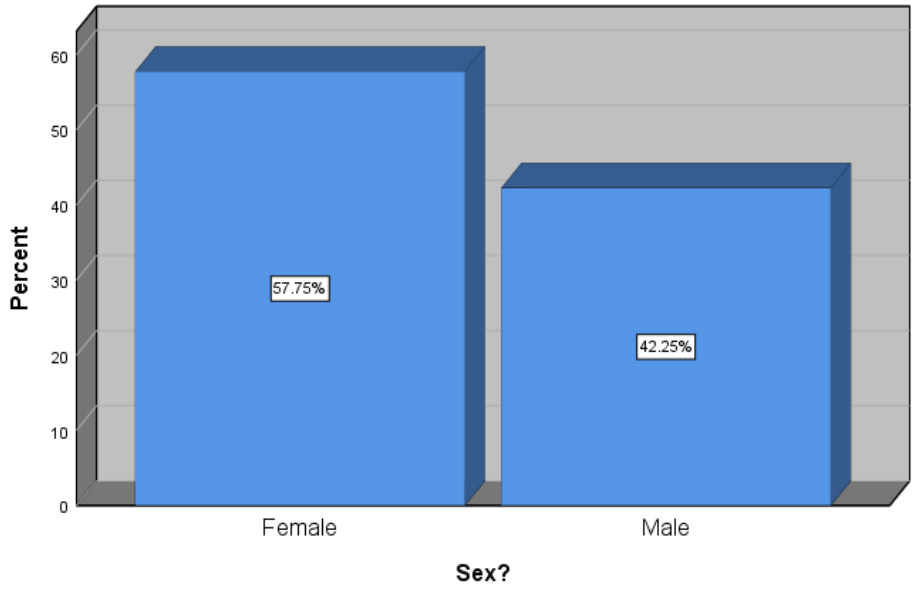


Similarly, with regards to the sex of the respondents the below results were obtained (Table 4.13, Figure 4.10). It can be observed that the majority of respondents were female (57.8% *versus* 42.2%).

Table 4.13: Responses to the question relating to the sex of the respondents

Replies	Frequency	Valid Percent	Cumulative Percent
Female	190	57.8	57.8
Male	139	42.2	100.0
Total	**329**	**100.0**	

Figure 4.10: Responses to the question relating to the sex of the respondents

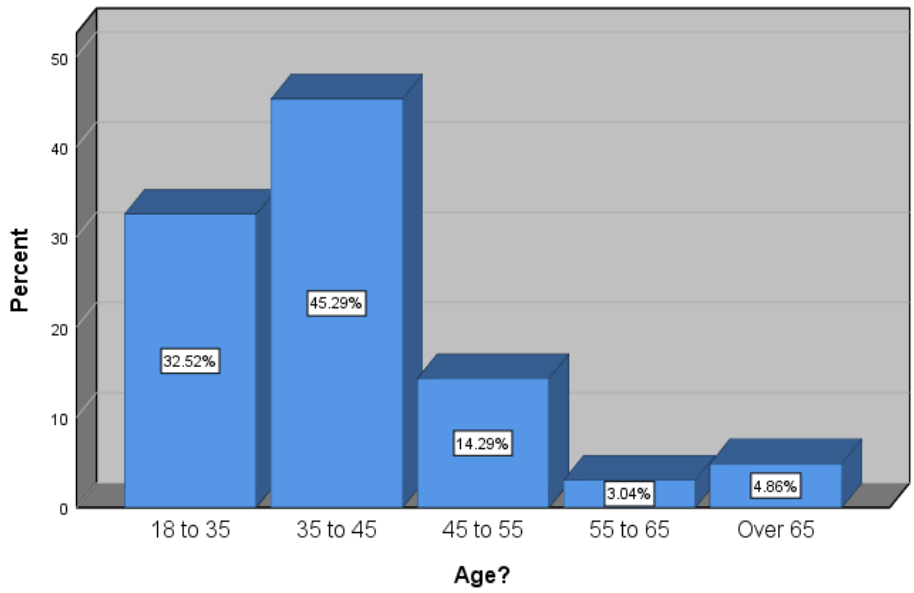


Similarly, the next question was for the determination of the age group of the respondents where the below results were obtained (Table 4.14, Figure 4.11). The first two age groups make up for 77.8% of the respondents, with the last two age groups constituting only 7.9% of the respondent population, which means that this is a relatively young respondent population.

Table 4.14: Responses to the question relating to the age of the respondents

Replies	Frequency	Valid Percent	Cumulative Percent
18 to 35	107	32.5	32.5
35 to 45	149	45.3	77.8
45 to 55	47	14.3	92.1
55 to 65	10	3.0	95.1
65+	16	4.9	100.0
Total	**329**	**100.0**	

Figure 4.11: Responses to the question relating to the age of the respondents

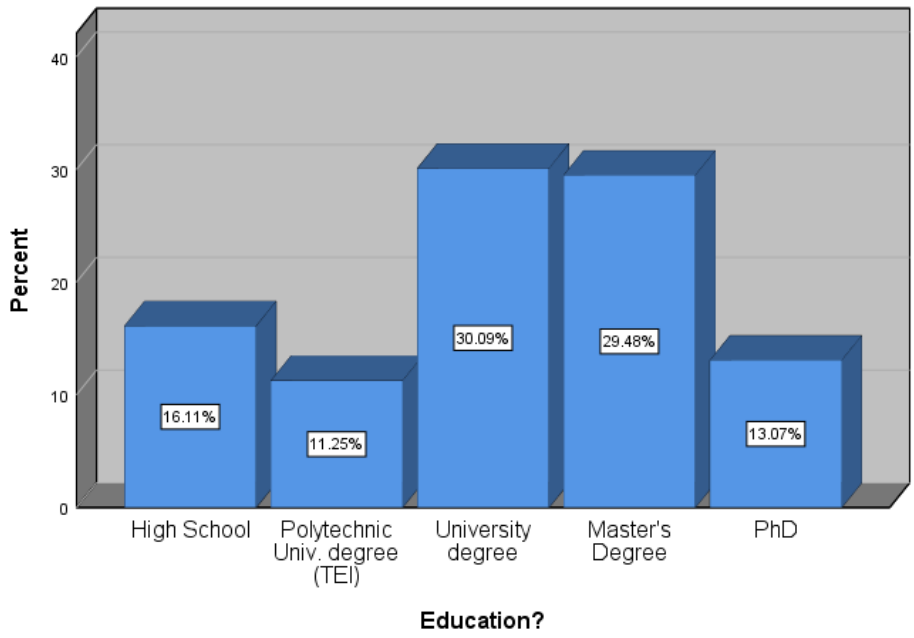


With regards to the educational level of the respondents the results are summarised below (Table 4.15, Figure 4.12). The biggest group is the respondents having a University degree (30.9%), closely followed by a Master's Degree (29.5%), High-school education (16.1%), PhD (13.1%) and finally a Polytechnic University Degree (TEI, 11.3%).

Table 4.15: Responses to the question relating to the education of the respondents

Replies	Frequency	Valid Percent	Cumulative Percent
High School	53	16.1	16.1
Polytechnic University Degree (TEI)	37	11.2	27.3
University degree	99	30.1	57.4
Master's Degree	97	29.5	86.9
PhD	43	13.1	100.0
Total	**329**	**100.0**	

Figure 4.12: Responses to the question relating to the education of the respondents

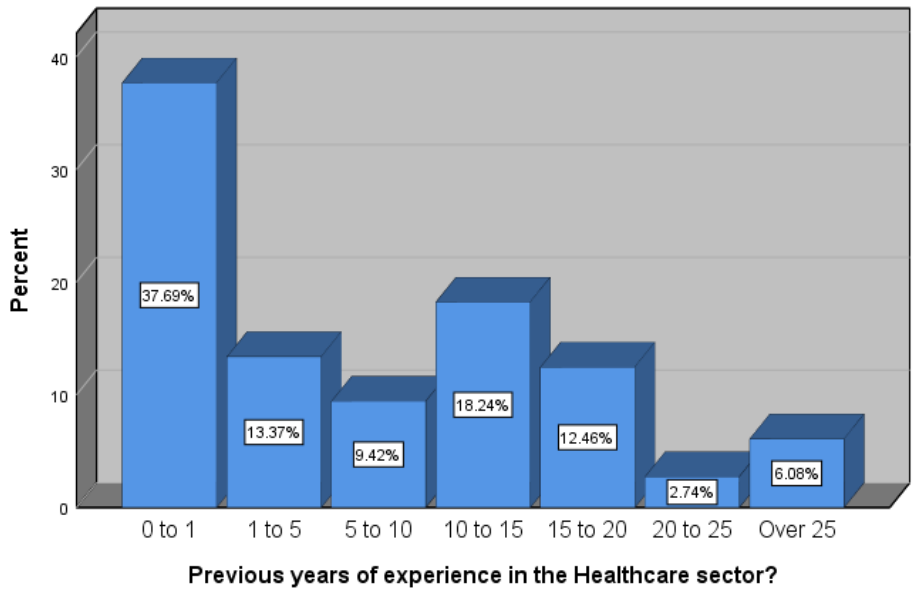


The next question was relating to the previous years of experience in the Healthcare sector, the results of which are summarised below (Table 4.16, Figure 4.13). The largest group, consisting of 37.69% of the respondents indicate 0 – 1 years of experience in the Healthcare sector, followed by 18.2% for 10 – 15, 13.4% for 1 – 5 years, 12.5% for 15 – 20 years, 9.4% for 5 – 10 years, 6.1% for over 25 years and 2.74% for 20 – 25 years of experience.

Table 4.16: Responses to the question relating to previous years of experience in the Healthcare sector

Replies	Frequency	Valid Percent	Cumulative Percent
0 – 1	124	37.7	37.7
1 – 5	44	13.4	51.1
5 – 10	31	9.4	60.5
10 – 15	60	18.2	78.7
15 – 20	41	12.5	91.2
20 – 25	9	2.7	93.9
25+	20	6.1	100.0
Total	**329**	**100.0**	

Figure 4.13: Responses to the question relating to previous years of experience in the Healthcare sector



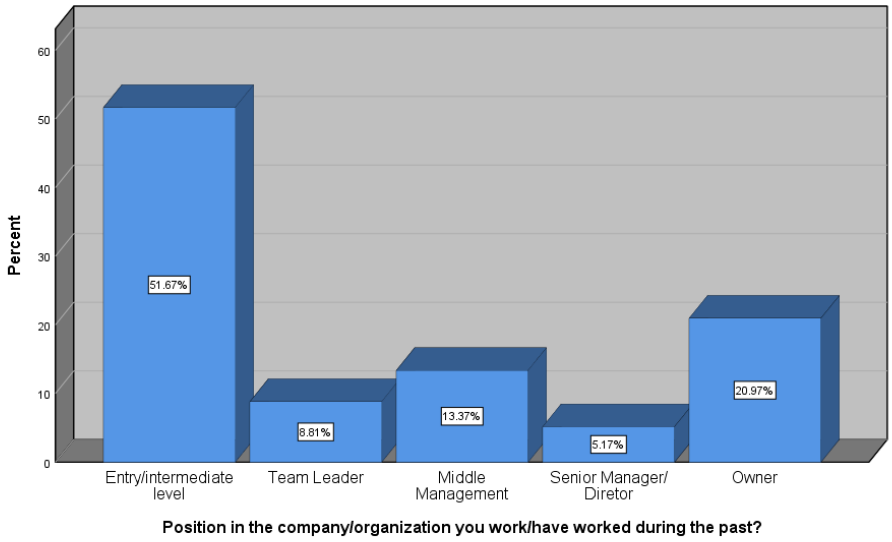
The final question related to the position of the respondent in the company/organisation they work/ have worked in the past. This question was also a means to deduce the income group, indirectly, since each position should relate to a corresponding salary level. The results obtained are summarised and graphically represented below (Table 4.17, Figure 4.14). The largest respondent group with 51.7% has an entry/intermediate level position, which should be expected due to the overrepresentation of the first

two age groups, followed by owners with 21.0%, the size of which can probably be explained from the increased representation of pharmacists who are one of the focus groups in this questionnaire. Middle management is the third group with 13.4%, followed by Team Leaders (8.8%) and Senior Managers/ Directors (5.2%).

Table 4.17: Responses to the question "What is the position in the company/ organisation you work/ have worked in the past?"

Replies	Frequency	Valid Percent	Cumulative Percent
Entry/ Intermediate level	170	51.7	51.7
Team Leader	29	8.8	60.5
Middle Management	44	13.4	73.9
Senior Manager/ Director	17	5.2	79.0
Owner	69	21.0	100.0
Total	**329**	**100.0**	

Figure 4.14: Responses to the question "What is the position in the company/ organisation you work/ have worked in the past?"



DISCUSSION

The present discussion is divided in three parts. The first describes issues identified in relation to HTA processes and methodologies, suggesting potential solutions with straightforward application, at least for most cases. In the second part, questionnaire findings are considered, with respect to the conclusions that can be drawn from the replies. Finally, issues and solutions are discussed particularly for the case of HTA in Greece, in an attempt to address the particularities of the country.

Issues with HTA processes and methodologies

There are several issues that can be identified with the current approaches of HTA bodies. In spite of the ability of HTA to evaluate the efficacy of the provided healthcare interventions, many of the issues observed in healthcare (Υφαντόπουλος, 2006) can also be observed in HTA methodologies.

First of all, information asymmetry exists between the company which submits the application based on years of research and the authors of the report (which, in the case of NICE, needs to be prepared within 8 weeks). Although it may be possible to have external consultants with experience in similar molecules (provided the intervention is not first-in-class treatment), no consultant would have any experience with the particular molecule. If he did, which could happen with a new molecule only if he had worked for the company in that project, he would anyway be bound by very strict confidentiality clauses, which is a standard process for companies to protect their intellectual property. To address this, an approach would be to have external auditors going through the information for a minimum of 6 months before the company can submit an application, in order to be able to observe and validate the collection of data but also to have significantly more time to create the corresponding report. However, as this is impractical and expensive, a more straightforward approach would be to make companies responsible for all uncertainties and assumptions (so that they would have to compensate for any claim that did not materialise as expected), in order for the risk for unpleasant surprises or overoptimistic assumptions to be minimised.

Another issue observed in both Healthcare and HTA is Moral Hazard. The appraisal committee, based on the report created by another body (in the case of NICE the ERG), decides if spending healthcare providers' (i.e. taxpayers') money is justified for a particular intervention. The implications from their recommendations are dealt with after their decision, during the cost-impact analysis. On the other hand, this could be readily addressed during the evaluation phase by including stakeholders who would have vested interests to see the proposal rejected, in the same way as the company making the application

and the patients' organisations have vested interests to see the intervention approved. Such a dynamic equilibrium could make for a more stable system. Similarly, experts from insurance and Healthcare providers could be included which would aim to reject such proposals unless they see real value for their organisations.

HTA also does nothing to address presence of monopolies; a new effective treatment will be approved and will enjoy a monopolistic status for as long as the company which submitted the application can protect its intellectual property. Unfortunately, this cannot be readily addressed under the current legislative system since intellectual property is protected by international agreements (WTO, 2019) and therefore any changes will have to be agreed upon in advance with several countries and organisations.

Apart from the above, there are certain issues inherent within the evaluation methodology. One of the areas that HTA could significantly improve outcomes is preventive and health promotion interventions; however such interventions, particularly preventive activities taking place outside the health care system, are under-represented (Banta, et al., 2002). Once companies are ready to obtain a Marketing Authorisation, there is significant pressure to get the product reimbursed in order for the company to take maximum advantage of its intellectual property protection period. Preventive and health promotion interventions on the other hand, do not have the same financial incentives behind them; therefore, pressure for evaluating them is significantly lower. Lack of financial incentives is also resulting to a lack of clinical data since such studies are expensive and lack of financial incentive also means dearth of available funds. This could be addressed by setting up a process for financing such evaluations, for example there could be research grants awarded to the proposals with the highest potential. The studies could then be run by university institutions or Clinical Research Organisations (CROs) participating in such grant applications.

Another issue encountered relates to the cost-utility analysis performed during HTA. CUA relies on QALYs, which is good on one hand since all pharmaceutical/therapeutic interventions can be directly comparable. We see, however, that it is not always followed through. For example NICE has included several amendments discussed before, where there is a move away from the essence of QALYs as a means to judge all interventions (Paulden, O'Mahony, Culyer, & McCabe, 2014). Consequently, there are inconsistencies regarding the opportunity cost of such interventions. On the other hand, some of these amendments such as the "end of life" have some basis, since QALYs do not adjust for shadow cost. It should be expected that the WTP for a QALY for someone in their final year of life is higher than the WTP for a QALY for someone in their prime. This information cannot be captured by QALY, where a single value throughout all years, patients and interventions is the cornerstone of its utility at evaluations. The universality of QALYs is compromised by having HTA bodies "bending the rules" and there is an increasing need for developing an equally universal platform that would also be able to compensate at least for age.

Another serious issue has to do with the "rule of rescue", the impulse to rescue an identifiable person whose life is in danger, no matter how much this may cost (NICE, 2008). NICE recognises that when making its decisions it should also consider the anonymous people who do not necessarily have people to argue their case on their behalf; however, there is no specific guidance to protect against rule of rescue. On the other hand, patient groups at the committee meetings have been known to affect the outcome leading to treatments above the threshold being recommended due to their input (Rawlins, Barnett, & Stevens, 2010). It can be argued that presence of patient groups and their advocates in such evaluation meetings puts some unnecessary pressure to the committee, by definition is flawed due to the "rule of rescue" and is unjust against other stakeholders who are not present in the meeting, such as patients of other conditions and the taxpayers who deserve an optimal use of their contributions.

The optimal use can only be achieved by ensuring interventions funded are the ones that offer maximum return to the society as a whole. This will have to be shown in a comprehensive way, with minimum subjectivity, which is anyway inherent in complex decisions. It is therefore suggested that a new evaluation methodology is required, which will be better suited to cover these requirements. The new methodology should be better at evaluating the societal perspective in HTA, which is where most of the discrepancies are observed.

Taking this further, it can be argued that the two-perspective approach for HTA seems to be the dominant trend in EU, as shown in the EUnetHTA Core model (EUnetHTA, 2016). The strict healthcare perspective is represented by the four "Healthcare Domains" where a CUA could be reliably implemented for the evaluation of the intervention. For the other five "Socioeconomic Domains" CBA is likely better suited for their evaluation, however, these domains should be expanded to include the interests of all stakeholders necessary to deliver the intervention. This can be achieved by including evaluation criteria such as those discussed above for assessing the contribution of major investment projects towards the achievement of Europe 2020 targets. If necessary, there could even be independent evaluations for different domains or groups of evaluation criteria. In the end, the results from all different evaluations could be incorporated into a MCDA format with each weighed according to the strategic priorities of policymakers, allowing for the final decision to be made in a transparent, systematic and inclusive manner.

There is no point in developing a tool that will not be suitable to those who want to use it – even if it is used initially, it will be replaced the moment a more suitable tool appears, as is the case with all human tools throughout history. It is now a well-known fact and probably the one thing that appears in most papers on HTA, that fiscal pressure in modern societies is pushing governments around the world to implement HTA as a means to control the increasing expenditure in Healthcare. It therefore makes sense to develop a tool that directly addresses such costs, rather than a tool that can potentially justify expenditure in certain interventions, likely increasing such costs.

Questionnaire

With regards to the organisation and role of a Greek HTA body, the respondents indicated that they preferred such an organisation to be part of a European body than of the MoH, which may reflect a belief that such evaluations can better be performed at a European level. It should be noted that the respondents were divided even more regarding the possibility of such an organisation being independent, trusting the organisation to govern itself even less than belonging to the MoH, which may be a reflection of distrust of the public to such self-governed independent organisations. There was more than 90% acceptance in such an organisation evaluating all therapeutic interventions, with only exception being preventive medicine which scored slightly lower (but still above 80%).

The respondents also showed high acceptance to the collaboration between HTA bodies and to the integration of a Greek HTA organisation in a European network. They were less inclined (but still 62.3% agreed) for the main evaluation to take place by a HTA organisation of the EU, but also on the national HTA organisation to be able to make decisions independently from the EU HTA organisation (but still 66.6% believe it should be able to do so).

It should be noted in the question on the socioeconomic criteria the hidden costs of treatment have been added as a potential socioeconomic criterion to be evaluated, although they are not included in the Advance Value Tree model or in the Europe 2020 targets. In fact, many of the hidden costs resulting from the treatment should be reported as adverse drug events. By definition, any untoward medical occurrence (pain, intolerance etc.) constitutes an adverse event and needs to be reported as such (European Medicines Agency and Heads of Medicines Agencies, 2017). As a consequence, these already exist under the safety profile group of criteria and adding them in another group would result in double-counting, which should be avoided in MCDA. It should be also noted, however, that hidden costs scored higher than direct or indirect costs (4.10, 3.98 and 3.79, respectively), in close relation to the score obtained for the safety profile of the treatment (4.22), evaluated as a criterion in the previous question.

Furthermore, the creation of new jobs as a socioeconomic criterion scored lower than any other criterion examined in both corresponding questions (3.48). This is in direct contrast to the replies of the respondents in the immediately subsequent questions, where preference was shown to local production of pharmaceuticals (which results in job creation). It is likely that the average respondent did not make this connection; it is not possible that he believes that there is no value in job creation as this is one of the main demands of the society, rather he did not see that this could happen through the evaluation of therapeutic interventions.

Another possible reason is the fact that this was the first sub-question in the question for the socioeconomic criteria and many respondents may have instinctively believed that this criterion automatically meant higher expenses for pharmaceuticals with no actual value apart from some vague "socioeconomic" value. Once they moved to the next two questions (improved access for patients with lower income & prevention of disease spread to other members of society) they began to see some real value and turned to a more positive attitude (these two questions received the highest score) hence other criteria were subsequently viewed more favourably. It not possible to check this hypothesis, however, unless the questionnaire is repeated with different order of the corresponding sub-questions.

With regards to the WTP for a locally produced pharmaceutical compared to an identical imported one, it was observed that in general the respondents were willing to pay more for having their pharmaceuticals produced locally. However, the biggest group of respondents was the one not willing to pay more. This group was in the range of 40% of all respondents and had a positive trend (from 38.6% to 41.6%) as the price of pharmaceuticals increased. A more significant shift was observed on the second biggest group at each time, when the imported drug cost €5, the second biggest group with 27.6% was willing to pay up to €6; with cost of €10 the second biggest group with 27.1% was willing to pay up to €13; finally, with cost of €20 the second biggest group with 21.0% was willing to pay up to €25. This indicates that there may be a percentage association to the cost of the pharmaceutical regarding the WTP for local production, for some of the respondents.

With regards to the demographics of the respondents, from the question relating to their age it can be deduced that more than three quarters of the respondents belong to the first two age groups, i.e. they are below 45 years old and that the respondent population is not representative of the overall population. The higher participation of the younger groups can be due to several reasons, the particular groups may be more willing to participate in such surveys and they are more familiar with technology therefore can easier access and complete an online questionnaire. Similarly, regarding the work position of the respondents, the majority of the respondents are in entry/ intermediate level (51.7%), which can be explained from the fact of the majority of the respondents also belong to the first two age groups.

Other questionnaire issues

Despite the potential for great numbers of respondents, social networks and professional associations resulted in a fairly small overall contribution to the number of respondents. Regarding social networks, this is attributed to the fact that the potential respondents had less than a month to reply and that during that time they did not have much interest in replying with the majority of them being on holidays. Regarding professional organisations and associations, they were even less helpful either ignoring the request to forward the questionnaire to their members or refusing it, citing the newly imposed General

Data Protection Regulation (GDPR) as responsible for not being able to utilise their mailing lists for such purposes (Council of the European Union , European Parliament, 2016).

Although the questionnaire was timed during pre-testing and was found to be fairly quick (the test subjects were able to complete it within 6 – 8 minutes with the questionnaire description mentioning that it required 10 minutes) there were still a few complaints received about the length of time required, claiming that they needed "some good 15 minutes" for completion. This can be attributed to the fact that the colleagues employed as pre-test subjects have greater familiarity with the subject and such questionnaires, in comparison with some of the respondents. However, the majority of respondents were happy with the size of the questionnaire when enquired about it and since such complaints were relatively few, it could also mean that the questionnaire was appropriately timed and that the particular persons were just slower than the average respondent.

Similarly, there were a few complains that the first page of the questionnaire was difficult to complete, which may have discouraged some people from completing it (particularly seeing that there were more pages to follow). It can be argued that putting simpler questions such as demographic information at the beginning would make for an easier start of the questionnaire. However, due to the nature of HTA, the main questions were bound to be unfamiliar for the majority of the respondents and would have to face them sooner or later. It was so decided that it was better to face these in the first couple of pages, after a few "introductory" questions regarding which group of professionals they belong to and their familiarity with HTA.

Another issue that was encountered was that many pharmacists who owned a pharmacy would also forward the questionnaire to their assistants which often would have similar opinions, being in the same environment and facing the same issues as the pharmacist. However, the assistants were usually not pharmacists and would therefore be grouped together with the other professionals working in the Healthcare sector. This inevitably resulted in the risk of pharmacists' opinions being overrepresented in the other professionals working in the Healthcare sector group and there was an opinion that maybe they should have been grouped together with the pharmacists. On the other hand, by extrapolating this argument nurses should be grouped together with doctors as they would lead to similar overrepresentation. Perhaps a better alternative would have been to create groups according to their place of work, e.g. hospital staff to be grouped together with doctors working in hospitals, another group would be professionals working in private pharmacies, another for pharmaceutical companies etc. In this way it is likely that there could be better correlation between differing views among Healthcare professionals.

The case of Greece

Creation of a dedicated HTA body in Greece is without a doubt a step in the right direction. It is still quite limited in scope and resources; however, one can remain hopeful that expansion will follow when corresponding staff acquires adequate experiences and the organisation begins to mature. Once it reaches that stage it could benefit from the interventions discussed previously which unfortunately are currently more relevant for other HTA bodies. On the contrary, the embryonic nature of the related legislation results in certain issues specific to the Greek HTA.

The issue discussed above, regarding preventive and health promotion interventions is even more pronounced in the Greek HTA committee, since by law evaluations can only be initiated for interventions once the company that has obtained the MA files the corresponding application (ΦΕΚ Α'/5/17.01.2018). Therefore, even if a company had some vested interest to initiate a HTA in Greece for a health promotion intervention, unless the current law is modified it should not be allowed since it does not have a corresponding Marketing Authorisation. The limited resources and scope of the Greek HTA body do not permit it to perform such evaluations on top of its current duties, even if these would only have a positive impact on the Healthcare budget.

This also stands true for the type of interventions that can be evaluated. Currently, the Greek HTA committee can only perform evaluation on pharmaceuticals. The role of the Negotiations committee is a bit more extended, as apart from pharmaceuticals it can also negotiate prices for Medical Devices (ΦΕΚ Α'/5/17.01.2018). Again, given the limited scope and resources of the HTA body, it should only be expected to perform its main role, which is advisory capacity for controlling budget impact of new treatments. In both cases, however, it should be prudent to at least have the available legislation in place so that at least some evaluation of some significant interventions could be performed if needed to.

The only other role that the Greek HTA committee should be able to perform to some extent is disinvestment, since the Positive Reimbursement List has to be re-evaluated every three years. All pharmaceuticals under IP protection that have entered the list since the last evaluation and all pharmaceuticals therapeutically equivalent to those that have applied to be included in the list have to be evaluated, with the ones failing to obtain a positive recommendation being removed from the list. However, there is no other way for the HTA committee to perform any other kind of disinvestment evaluation, while with the current law it will have to wait until the next periodic evaluation to remove a pharmaceutical from the Positive Reimbursement List, which can take up to three years.

In general, though, it can be said that not much can be performed or asked of the Greek HTA organisation, at least at its current state. Any changes or optimisations should not be expected to have significant impact to the *modus operandi* of the organisation. However, what could indeed have some

significant impact was implementing an evaluation methodology as the one described above, with emphasis on the

With regards to incorporating in HTA the criteria applied in other investments, this approach could have significant benefits for the crisis-struck Greece. Health expenditure is a significant part of government spending. Particularly in the case of Greece, expenditure in the Ministry of Health for 2019 is budgeted at €3,884m, while at the same time government contribution in public investment budget for 2019 amounts to €1,000m (Υπουργείο Οικονομικών, 2018). Even if all contributions are taken into account, such as EU funding, the total budget for public investment projects is €6,750m for 2019 (Υπουργείο Οικονομικών, 2018). It can be argued therefore that any HTA including investment criteria as part of its evaluation has the potential to generate significant value to the society that is paying for it, apart from the obvious health benefits resulting from such intervention. Besides, it has been calculated that every €1000 spent in pharmaceuticals produced in Greece there is an increase in GDP amounting to €3,420 (Γκόλνα, Παρατσιώκας, & Βεντούρης, 2013), which means that any such investment would have a cumulative effect on GDP. Greece, in particular, should no longer afford the luxury of utilising such large amounts as "expenditure for the people" and its potential as an investment tool should at least be under serious consideration.

CONCLUSION

It can be argued that Health Technology Assessment, in spite of the significant improvements of the methodological models, the more systematic approaches and the steps towards consolidation has still some distance to cover before reaching maturity. The fragmented nature of its origins but also inefficiencies from different stakeholders having conflicting interests in the system have resulted in certain areas being systematically overlooked in favour of other evaluation criteria.

There are certain methodological issues that have been identified, which if addressed should lead to an optimisation of HTA. This in turn would result in increased utility for the same funds and better overall efficiency. Certain suggestions such as the evaluation of the wider socioeconomic impact may not necessarily lead to approval of the interventions with the highest utility for Healthcare; however, it will lead to choices with the highest utility for all society, which will positively affect Healthcare in the long term.

The above could be of more value to economies with limited resources, such as that of Greece where the austerity measures have resulted in a significant reduction in available funds. Apart from the better allocation of these funds, looking at investments in Healthcare as other investments will enable the country to utilise its limited funds in an optimal distribution of stimulating growth and achieving value in Healthcare. However, HTA in Greece needs to grow before it will be able to fully utilise most of these suggestions. Furthermore, although implementing some of these observations can be fairly straightforward, many would first need extensive work before they could be applied in HTA with any chance of success.

With regards to future work, the evaluation criteria that should be included will have to be refined and adapted to HTA requirements, while they need to cover the interests of all stakeholders. At a minimum, criteria that would treat the investment of these large sums as an actual investment to society, such as the ones in line with Europe 2020 targets, would have to be seriously considered.

In such an approach, feedback will be required from all stakeholders and in particular from people well-versed in HTA, probably by contacting HTA bodies. Another questionnaire would have to be developed based on the outcome of the first, to capture the different stakeholders' interests.

A new model will then have to be developed, probably an adaptation of the EUnetHTA Core model with CUA and CBA analyses with elements from MCDA and in particular the Advance Value Tree, allowing local policymakers to both have a more systematic picture of the impact of each intervention and better effect its evaluation based on strategic targets.

By extrapolation, it would certainly be worth having a more generalised model, to be applied to all major government spending which should have to undergo a similar evaluation (or Technology Assessment) before being approved. The CBA regarding the socioeconomic impact of each intervention should be more-or-less the same for all interventions across fields, since it should be anyway designed to capture the interests of all stakeholder groups across society. For the equivalent of the Relative Effectiveness Assessment, new tools would have to be developed for fields where such systematic evaluation is unavailable, since CUA would not be that useful in interventions outside Healthcare. Such a tool would allow for more efficient allocation of resources for much of the government's budget, significantly increasing the value of most interventions.

It may also be of interest to evaluate an approach to CUA where the ICER value will not be a fixed amount per QALY but would rather correlate with the age that each QALY refers to (or the years left before the end of life). This could address the discrepancies encountered during the evaluation of interventions targeting children or the "end of life" amendment, enabling HTA bodies to have a more universally acceptable threshold range.

Overall, Health Technology Assessment has the potential to be a powerful tool in the hands of societies. It can enable them to utilise the significant funds spent in Healthcare annually in a more productive manner, improving the welfare of both its healthy and ailing members. This may sound counterintuitive at first, as these are funds budgeted for Healthcare; however, since every sale is also a purchase, economics can perform just that.

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ANNEX I: HTA PROCESS EMPLOYED BY NICE

A description of the typical steps followed during a Single or Multiple Technology Appraisal by NICE can be seen below (NICE, 2018)**:**

Single Technology Appraisal (STA)

Assesses a single drug or treatment. Takes min 30, max 43 weeks (if there are no appeals):

Week 0:

Start of Development – Invitation to stakeholders to take part in the appraisal, as non-company consultees to submit a statement on the potential clinical and cost effectiveness of a treatment

Request for evidence – ask company to produce corresponding report of all relevant published and unpublished evidence in 8 weeks

Key information added to NICE website (remit, scope and list of consultees and commentators)

Week 2:

Request for clinical, commissioning and patience experts (nominated by consultees/commentators)

Week 9:

Initiation of evidence report review – Evidence Report Group (Independent academic centre) prepares the ERG report by evaluating the company's evidence submission report. The report is to be submitted to NICE within 8 weeks (by week 17).

Week 10:

Selected clinical, commissioning and patient experts are invited to attend the appraisal committee (in week 21) and to submit a statement on the technology and how it should be used in the NHS in England, be submitted to NICE within 8 weeks (by week 18).

Week 12:

Request for clarification to the company, if the ERG deems the evidence submission to be incomplete. Letter of clarification sent to the company, which must respond within 10 days.

Week 18:

ERG report sent to company for fact checking

Week 19:

Key documents sent to the appraisal committee:

- The ERG report and any comments
- The company submission
- The written submission from non-company consultees
- Personal statements from patient, clinical and commissioning experts
- A pre-meeting briefing written by NICE's technical lead for the appraisal
- The final scope of the appraisal and the list of consultees and commentators

The appraisal committee is open to public, however, any members of the public who have registered to attend the meeting do not receive the above papers

Week 21:

Appraisal committee meet to consider the evidence – based on the result of this meeting a document is produced:

- Either an appraisal consultation document (ACD), if the use of the technology is not recommended, or its use is limited beyond the specifications in the marketing authorisation
- Or a final appraisal determination document (FAD), if an ACD is not needed.

Week 24:

Appraisal consultation document (ACD) and supporting documents are sent out for comment, where consultees and commentators have 20 working days to submit their comments on the draft recommendations

Week 25:

The ACD and supporting documents are published on the website for public consultation, which is open for 15 working days (by week 28).

Week 26:

Final appraisal document (FAD) is sent out to consultees and commentators (if no ACD was produced), on which consultees have 15 days to appeal.

Week 27:

Final appraisal document (FAD) published in website (if no ACD was produced)

Week 29:

Appraisal committee meet to develop the Final Appraisal Document (FAD) by considering the comments made during the public consultation and makes the final recommendation on how the technology should be used in the NHS in England.

Week 30:

Guidance issued (if no ACD was produced and no appeals have been received)

Week 34:

FAD and supporting documents sent to consultees and commentators, who have 15 days to appeal against the final recommendations of the FAD (by week 37).

Week 35:

FAD and supporting documents are published on the NICE website

Week 37:

If no appeals have been received the guidance is prepared for publication. If appeals have been received, the appeals process is followed.

Week 43:

Publication of the technology appraisal on the NICE website and incorporated into NICE pathways (if no appeals have been received). Registered stakeholders are notified by email. A review date for the guideline is issued (where it will be checked with relevant organisations if the guideline will need updating).

Multiple Technology Appraisal (MTA)

It is a process that assesses several drugs or treatments used for one condition. Similar process to the above, with the below exceptions:

- The relevant information is not requested from a company but from the consultees, who have 14 weeks for a submission (instead of 8 weeks for a statement),
- There is a potential Stakeholder Information Meeting (SIM) on week 8 for consultees and commentators
- If no ACD is produced, guidance is issued on week 47, if an ACD is produced (and no appeals have been received) the guidance is issued on week 60.

ANNEX II: NICE's Technology Appraisal Decision Factors

Source: (de Folter, Trusheim, Jonsson, & Garner, 2018):

DOMAINS	FACTORS/ SUB-FACTORS
Clinical Effectiveness	Treatment effectiveness
	Relative effectiveness/ comparisons
	Sub-group effectiveness
	Sub-group comparison
	Application in current practice
	Relevance to clinical practice
	Evidence/ New evidence
	Evidence reliability
	Evidence availability
	Evidence suitability
	Evidence Validity
	Population generalisability
	Effect on QoL
	HRQoL
	HRQoL measurement
	Analysis method
	Additional analysis
	Post hoc efficacy analysis
	Post hoc subgroup analysis
	Manufacturer's post hoc analysis
	ERG's exploratory analyses
	Sensitivity analysis
	Scenario analysis
	Relevance Comparison
	Long-term effects
	Adverse effects
	Risk of recurrence/ relapse
	Patient-reported outcomes/ PROM
	Health utility/ Estimation of utility

Cost effectiveness	Cost effectiveness analysis
	Manufacturer's economic analyses
	Validity
	ICER
	Estimated ICER(s)
	Most appropriate/ plausible ICER
	Additional analysis
	Manufacturer's sensitivity analysis
	Manufacturer's new cost effectiveness estimates
	ERG amendments
	Impact
	Treatment length in practice
	Treatment application in practice
	Economic model
	Key drivers
	Model validity
	Model limitations
	Model relevance
	Model suitability
	Model structure
	Model time horizon
	Model input
	HRQoL
	Treatment in current practice
	Treatment duration
	Sub-group effectiveness
	Treatment effectiveness
	Long-term treatment effects
	Health utility
	Adverse events
	Changes in model input
	Model outcome
	Sensitivity to model input
	Long-term outcome prediction
	Effect on QoL
	Model corrections

	Comparison scenario
	Most appropriate comparison scenario
	Representation of current scenario
	Limitations
Condition	Condition management
	Effect on QoL
	Patient
	Carer
	Family
	Psychological aspects
Current practice	Current available treatments
	Current treatment pathway
	Variation in current practice
	Clinical management
	Treatment impact
	Treatment in current practice
	Level of success in current treatment
	Stigma of expert treatment
	Treatment service
	Treatment duration
	Uptake
Clinical need	Clinical need for treatment
	Clinical need for additional treatment
	Clinical need for better practice
	Improved monitoring
	Improved dosing
	Clinical need of particular sub-group
New treatment	Treatment safety
	Adverse events
	Treatment duration
	Long-term treatment effects
	Treatment effectiveness
	New patient access scheme
	Comparator treatment/ comparator validity
	Clinical treatment pathway
	Addition to treatment pathway

	Prescription setting
	Adherence issues
	Adjuvant treatment
Studies	Study relevance
	Study method
	Study quality
	Statistical significance
	Population group
	Population generalisability
	Generalisability to current practice
Other factors	Innovation
	Rare condition
	Children
	Lack of recent advances in field treatment
	Equality issues/ Protected characteristics
	Stigmatisation of condition
	Impact on family
	Uncaptured benefits
	Health benefits
	HRQoL
	Patient
	Family
	Benefits to particular population groups
	Displacement of other treatments
	End of Life considerations

ANNEX III: QUESTIONNAIRE

Αξιολόγηση Τεχνολογιών Υγείας (ΑΤΥ) και κοινωνικο-οικονομικές επιπτώσεις

Σκοπός του ερωτηματολογίου είναι η απόκτηση πολύτιμων πληροφοριών σχετικά με την Αξιολόγηση Τεχνολογιών Υγείας (ΑΤΥ) και τις πιθανές επιπτώσεις των κοινωνικο-οικονομικών κριτηρίων στην αξιολόγηση αυτή. Ο χρόνος συμπλήρωσης του ερωτηματολογίου είναι 10 λεπτά.

* Required

1) Ποια είναι η επαγγελματικής σας σχέση με τον τομέα της Υγείας; *

- ○ Είμαι ιατρός
- ○ Είμαι φαρμακοποιός
- ○ Εργάζομαι στον ευρύτερο τομέα (νοσηλευτικό προσωπικό, φαρμακευτικές εταιρείες κτλ.)
- ○ Κανένα από τα παραπάνω

2) Ποια είναι η γνώση σας για την Αξιολόγηση Τεχνολογιών Υγείας (Health Technology Assessment); *

- ◯ Δε γνωρίζω τι είναι
- ◯ Έχω μια μικρή γνώση του αντικειμένου
- ◯ Έχω βασική γνώση του αντικειμένου
- ◯ Έχω καλή γνώση του αντικειμένου
- ◯ Έχω πολύ καλή γνώση του αντικειμένου

3) Ένας Οργανισμός που καθορίζει την προστιθέμενη αξία μιας θεραπείας σε σύγκριση με τις υπάρχουσες, ώστε να παρέχει τεκμηριωμένη πληροφόρηση στους υπεύθυνους χάραξης πολιτικής για την υγεία, θα πρέπει: *

	Συμφωνώ	Διαφωνώ	Δεν έχω άποψη
Να υπάγεται στο Υπουργείο Υγείας	○	○	○
Να υπάγεται σε έναν αντίστοιχο κεντρικό ευρωπαϊκό οργανισμό	○	○	○
Να είναι ανεξάρτητος, με δική του δομή και διοίκηση	○	○	○
Να είναι Νομικό Πρόσωπο Δημοσίου Δικαίου	○	○	○
Να είναι Νομικό Πρόσωπο Ιδιωτικού Δικαίου	○	○	○
Να αξιολογεί φαρμακευτικά προϊόντα	○	○	○
Να αξιολογεί ιατροτεχνολογικά προϊόντα	○	○	○
Να αξιολογεί διαγνωστικά προϊόντα	○	○	○
Να αξιολογεί θεραπευτικές/ νοσοκομειακές παρεμβάσεις	○	○	○
Να αξιολογεί παρεμβάσεις προληπτικής ιατρικής	○	○	○

4) Κατά τη διάρκεια της αξιολόγησης μιας θεραπείας, ο οργάνισμός θα πρέπει να προσκαλεί για διαβούλευση: *

	Συμφωνώ	Διαφωνώ	Δεν έχω άποψη
Τις ομάδες ασθενών	○	○	○
Τους οργανισμούς Επαγγελματιών Υγείας	○	○	○
Τις εταιρείες των οποίων τα προϊόντα σχετίζονται με τη θεραπεία	○	○	○
Τις εταιρείες των οποίων τα προϊόντα σχετίζονται με ανταγωνιστικές θεραπείες	○	○	○
Τις ασφαλιστικές εταιρείες	○	○	○
Τους παρόχους υγείας (π.χ. ΕΟΠΥΥ)	○	○	○

5) Υπάρχει οργανισμός στην Ελλάδα επιφορτισμένος με την Αξιολόγηση Τεχνολογιών Υγείας; *

○ Ναι

○ Όχι

○ Δε γνωρίζω

6) Ποια θα πρέπει να είναι η σχέση μεταξύ ενός εθνικού οργανισμού Αξιολόγησης Τεχνολογιών Υγείας και ενός αντίστοιχου οργανισμού της ΕΕ; *

	Συμφωνώ	Διαφωνώ	Δε γνωρίζω
Η κύρια αξιολόγηση θα πρέπει να γίνεται από έναν οργανισμό ΑΤΥ της ΕΕ	○	○	○
Ο εθνικός οργανισμός ΑΤΥ θα πρέπει να υπάγεται άμεσα στον οργανισμό ΑΤΥ της ΕΕ	○	○	○
Η αξιολόγηση από κάθε εθνικό οργανισμό ΑΤΥ θα πρέπει να είναι διαθέσιμη και στους υπόλοιπους	○	○	○
Ο εθνικός οργανισμός ΑΤΥ θα πρέπει να αξιολογεί κυρίως με βάση τα εγχώρια επιδημιολογικά δεδομένα	○	○	○
Ο εθνικός οργανισμός ΑΤΥ θα πρέπει να μπορεί να παίρνει αποφάσεις ανεξάρτητα από τον οργανισμό ΑΤΥ της ΕΕ	○	○	○

7) Για την αξιολόγηση μιας νέας θεραπείας σε σχέση με τις υπάρχουσες, πόσο σημαντικά θεωρείτε τα παρακάτω κριτήρια; *

	1 (Λιγότερο σημαντικό)	2	3	4	5 (Περισσότερο σημαντικό)
Σοβαρότητα της ασθένειας	○	○	○	○	○
Αποτελεσματικότητα της θεραπείας	○	○	○	○	○
Οικονομικές επιπτώσεις της θεραπείας	○	○	○	○	○
Προφίλ ασφαλείας της θεραπείας (παρενέργειες, αντενδείξεις κτλ.)	○	○	○	○	○
Κοινωνικές επιπτώσεις της θεραπείας	○	○	○	○	○
Επίπεδο καινοτομίας της θεραπείας	○	○	○	○	○

8) Αντίστοιχα, για την αξιολόγηση των κοινωνικο-οικονομικών επιπτώσεων μιας νέας θεραπείας, πόσο σημαντικά θεωρείτε τα παρακάτω κριτήρια; *

	1 (Λιγότερο σημαντικό)	2	3	4	5 (Περισσότερο σημαντικό)
Δημιουργία νέων θέσεων εργασίας	○	○	○	○	○
Βελτίωση της προσβάσης σε ασθενείς χαμηλότερων εισοδημάτων	○	○	○	○	○
Αποτροπή της μετάδοσης της ασθένειας σε άλλα άτομα στην κοινωνία	○	○	○	○	○
Αύξηση επιπέδου καινοτομίας της κοινωνίας	○	○	○	○	○
Επιπτώσεις της θεραπείας στο περιβάλλον	○	○	○	○	○
Έμμεσο κόστος της θεραπείας (δηλ. το κόστος των ημερών εργασίας που χάνεται λόγω ασθένειας, ανάγκη για φροντίδα κατ' οίκον, πρόωρη συνταξιοδότηση κτλ.)	○	○	○	○	○

Άμεσο κόστος της θεραπείας (δηλ. το κόστος της θεραπείας, νοσοκομειακής περίθαλψης, ιατρικό κόστος κτλ.)	○	○	○	○	○
Βελτίωση του μορφωτικού επιπέδου της κοινωνίας	○	○	○	○	○
Κρυφό κόστος της θεραπείας (π.χ. πόνος, δυσανεξία, σωματική παραμόρφωση κτλ.)	○	○	○	○	○

9) Μεταξύ δύο πανομοιότυπων φαρμάκων, με μόνη διαφορά το ένα παράγεται εγχώρια ενώ το άλλο εισάγεται από το εξωτερικό, ποιο θα επιλέγατε για αποζημίωση από το σύστημα υγείας; *

- ○ Το φθηνότερο, ανεξαρτήτως χώρας παραγωγής, η χώρα παραγωγής δε θα πρέπει να αποτελεί κριτήριο αξιολόγησης
- ○ Εάν είχαν παρόμοιες τιμές, το φάρμακο που παράγεται εγχώρια
- ○ Το φάρμακο που παράγεται εγχώρια, αν το αναλογούν συνολικό οικονομικό όφελος για τη χώρα (από φόρους, θέσεις εργασίας κτλ.) είναι μεγαλύτερο από τη διαφορά στην τιμή
- ○ Το φάρμακο που παράγεται εγχώρια, ασχέτως διαφοράς τιμής

10) Αν στο παράδειγμα της προηγούμενης ερώτησης, το εισαγόμενο φάρμακο κοστίζει €5, πόσο είναι το αποδεκτό κόστος για ένα εγχώρια παραγόμενο φάρμακο; *

- ○ Μέχρι €5
- ○ Μέχρι €6
- ○ Μέχρι €8
- ○ Μέχρι €10
- ○ Πάνω από €10

11) Αν στο παράδειγμα της προηγούμενης ερώτησης, το εισαγόμενο φάρμακο κοστίζει €10, πόσο είναι το αποδεκτό κόστος για ένα εγχώρια παραγόμενο φάρμακο; *

- ○ Μέχρι €10
- ○ Μέχρι €11
- ○ Μέχρι €13
- ○ Μέχρι €15
- ○ Πάνω από €15

12) Αν στο παράδειγμα της προηγούμενης ερώτησης, το εισαγόμενο φάρμακο κοστίζει €20, πόσο είναι το αποδεκτό κόστος για ένα εγχώρια παραγόμενο φάρμακο; *

- ◯ Μέχρι €20
- ◯ Μέχρι €21
- ◯ Μέχρι €23
- ◯ Μέχρι €25
- ◯ Πάνω από €25

Δημογραφικά

13) Φύλλο; *

- ◯ Άνδρας
- ◯ Γυναίκα

14) Ηλικία; *

- ◯ 18 – 35
- ◯ 35 – 45
- ◯ 45 – 55
- ◯ 55 – 65
- ◯ 65+

15) Εκπαίδευση; *

- ◯ Λύκειο
- ◯ ΤΕΙ
- ◯ ΑΕΙ
- ◯ Μεταπτυχιακό
- ◯ Διδακτορικό

16) Έτη προϋπηρεσίας στον τομέα της Υγείας; *

- ◯ 0 – 1
- ◯ 1 – 5
- ◯ 5 – 10
- ◯ 10 – 15
- ◯ 15 – 20
- ◯ 20 – 25
- ◯ 25+

17) Θέση μέσα στην επιχείρηση/οργανισμό που εργάζεσθε/ εργαζόσαστε κατά το παρελθόν; *

- ◯ Στέλεχος (Entry/Intermediate level)
- ◯ Προϊστάμενος Ομάδας (Team Leader)
- ◯ Υπεύθυνος Τμήματος (Middle Management)
- ◯ Διευθυντής/Γενικός Διευθυντής (Senior Management/Director)
- ◯ Ιδιοκτήτης

Σας ευχαριστώ για το χρόνο σας!

Σε περίπτωση που επιθυμείτε να σας αποσταλεί μια περίληψη των αποτελεσμάτων μόλις ολοκληρωθεί η συλλογή των απαντήσεων παρακαλώ αφήστε το email σας εδώ: