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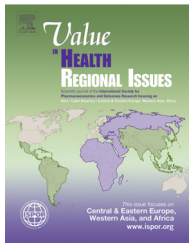

A Framework for Applying Health Technology Assessment in Cyprus: Thoughts, Success Stories, and Recommendations

Panagiotis Petrou, MBA, PhD, PhDc, Michalis A. Talias, PhD*

Healthcare Management Programme, Open University of Cyprus, Nicosia, Cyprus

ABSTRACT

Objectives: Health care decision making, assessment, and procurement of medicines is a complex, human resource–demanding, and time-consuming process. A thorough evaluation of all factors involved is necessary to optimize the process. The objective of this study was to describe and analyze the current stage of health technology assessment (HTA) in Cyprus. **Methods:** Literature research and private communication with all involved parties and competent authority. Moreover, data, decisions, and recommendations of the Drug's Committee were used. **Results:** Cyprus is a latecomer in this field. HTA has entered a growing phase after the 2007 reform. It has not reached its full potential, and the current state is applicable only to the public sector, because of the nonexistence of a national health system. Therefore, this poses both a great challenge and a great barrier considering maximization of the value of money spent and health access equity. **Conclusions:** There is definitely enough space and clear necessity for further dissemination, and early successes indicate that steps should be taken toward the introduction of an HTA procedure that will cover both private and public sectors. The introduction of a national health system will further enhance the uptake of HTA, optimize the process, and use the common knowledge strategy for evidence-based decision making.

Keywords: Drug's Committee, evaluation, HTA, pharmaceuticals, private sector, public sector.

Health Care Sector in Cyprus

Currently in Cyprus, two fragmented systems run in a parallel, overlapping, and competitive manner with clear disparities among them: public sector and private sector. This situation is caused by the absence of a national health system. The Ministry of Health (MOH) is the provider, regulator, and payer of public sector beneficiaries. Public health care is highly centralized, and the policymaking process takes place at the macro (ministerial) level. There are five major categories of beneficiaries [1] according to income and employment status. It is essential to underline that 85% of the total population is entitled to free public medical care, without any direct or indirect contribution. As a result, moral hazard [2] has been prominent and was expressed by overuse and misuse of medicines in the pharmaceutical sector. In contrast, private sector's patients pay the full amount out of pocket, unless they are covered by an optional private insurance.

Health care costs in Cyprus account for 6% of gross domestic product [3], which pushes Cyprus to the European low segment. The rate of increase in costs in the health care sector outpaces almost all other European Union (EU) countries [4] primarily because of the following reasons [5]:

1. An aging population that has an increasing life expectancy, with concurrent increased morbidity.
2. Lack of prescribing control due to the nonexistence of an interface management system. The system was launched in 2010, but it is still not fully operational.
3. No direct contribution of beneficiaries—Exploitation of moral hazard.
4. Policy susceptible to colloquial evidence especially regarding new expensive products.
5. Pharmaceuticals in the private sector are regulated only at the price level.
6. There is a duplication of high-cost hospital services in Cyprus, which have high running cost but are not fully utilized.
7. The above remark is augmented by the low value of the public sector perceived by beneficiaries. This was an undisputable finding of a recent study [6] that examined the value for money regarding beneficiaries of the public sector. Under the hypothesis that all health care systems want to gain more health for the same amount of money, the perceived value of the health system was assessed. The most important finding is presented in Fig. 1.
8. Preventive programs are underfunded. Preventive programs apply usually to beneficiaries, while the financial burden of many diseases is entirely shifted to the MOH.
9. There are no quality indicators. As a result, the MOH cannot assess any health policy, and consequently arbitrary decisions are taken regarding abortion or carryover of them.

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* *Address correspondence to:* Panagiotis Petrou, Healthcare Management Programme, Open University of Cyprus, P.O. BOX 12794, 2252. Latsia, Nicosia Cyprus.

E-mail: panayiotis.petrou@st.ouc.ac.cy.

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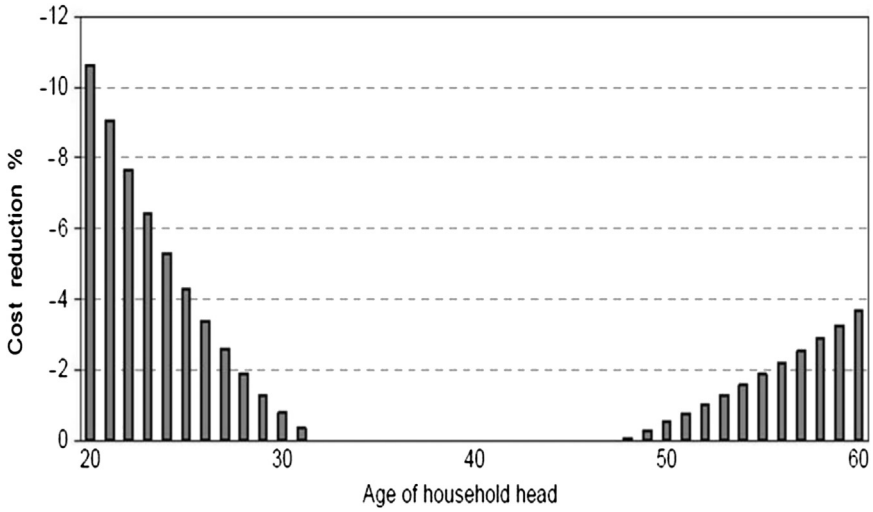

Fig. 1 – Estimated savings from free public health care by age per household member (as percentage of household income). For beneficiaries to free public health care of the age group 30 to 50 years, "no perceptible benefit is realized from access to free of charge public medical care." This partly explains the fact that although 85% of the total population is a beneficiary of free medical care, Cyprus has one of the highest out-of-pocket contributions in the European Union, along with the higher prices of the private sector.

The pharmaceutical market has some unique and inherent traits that make it quite hard to interpret and definitely tell it apart from other products with regard to their market analysis. The pharmaceutical market posseses an unrivalled demand and supply feature. There is a three-tier demand structure in which the recipient (patients) of the products consumes but has little, if any at all, involvement in the decision-making process. Moreover, the prescriber of the product is perceived as the customer, but does not consume the product. Another feature is that the cost does not represent the production cost. This is quite illustrative in generic products that have, in certain cases such as in Italy, half of the original product's price, and they are still profitable. The price of the product is set to offset the research and development expenses and in certain cases, such as in France, is set at a premium to reward innovation.

Governments worldwide and health agencies have applied specific and strict legislation to the pharmaceutical market to ensure that

1. Life-saving products are available; health systems should not be exploited by industry.
2. Good manufacturing processes are safeguarded along the way.
3. The unique demand and supply does not hinder the control role of health agencies regarding product availability [7].

HTA in Cyprus

Many authors have described HTA in a detailed manner [8]. In Cyprus, HTA appeared as a term of reference of the Drug's Committee in early 2000 as a tool to address uncontrolled increase in expenditure through rationalization of the decision-making process [9]. Terms of reference were updated and enriched in 2007, allowing further flexibility and introduction of more complex and legally demanding schemes. HTA is performed through the Drug's Committee, which falls under the MOH (Pharmaceutical Services). We must highlight the participation of Health Insurance Organization in the Stakeholder Forum and the participation of Pharmaceuticals Services at the Joint Action 2 of European Network of Health Technology Assessment .

The successful use of tendering, however, led to significantly low prices for the public sector, which distorted the need for a sustaining and rational decision-making process (Fig. 2).

Goals of HTA in Cyprus

According to the terms of reference, HTA should reach the following goals [9,10]:

1. Constantly upgrade, change, and improve clinical guidelines. Currently, guidelines exist in the majority of therapeutic areas.
2. Define performance indicators and assess effectiveness of medicines.
3. Limit the use of newly launched technologies to therapeutic areas for which there is sufficient documentation of efficacy and safety.
4. Reevaluate high expenditure monopoly medicines that contribute disproportionately to the overall cost.
5. Categorize evidence deficit in areas in which certain technologies are destined and ways to fill this.
6. Disinvestment.

Criteria for Inclusion of a Medicine in the Formulary

The Drug's Committee decides on the reimbursement (or not) of a product. It assesses drug request on the basis of five main pillars:

1. Prevalence and epidemiology of the disease (prioritization of resource allocation).
2. Comparative effectiveness according to common practice.
3. Economic evaluation, primarily budget impact analysis and to a lesser degree substantial cost-effectiveness studies (no inclusion of indirect data).

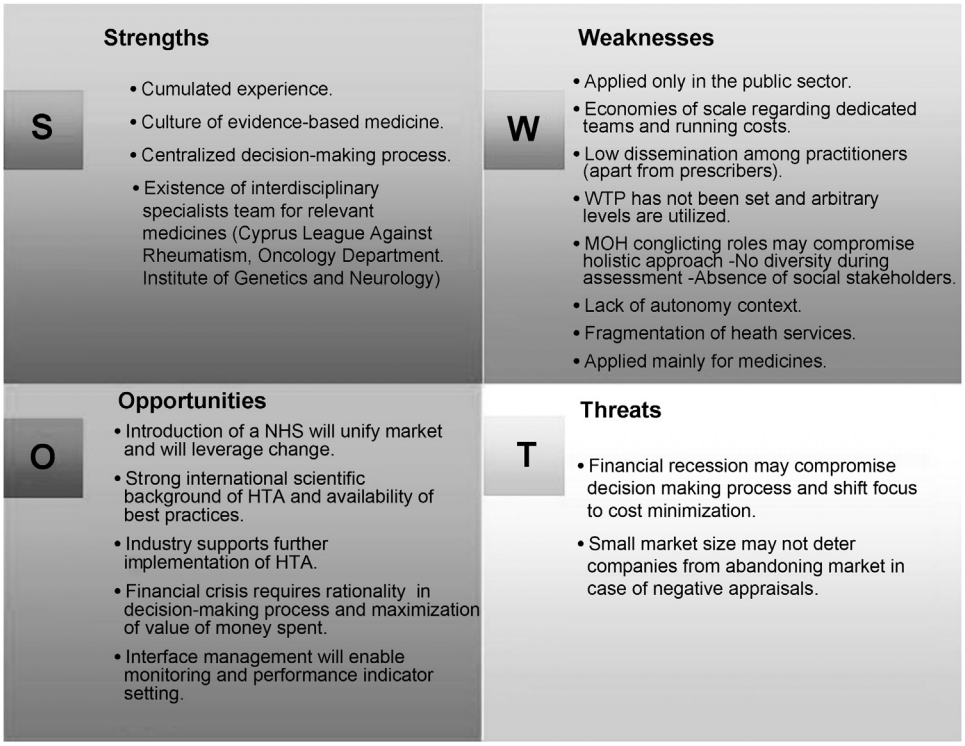

Fig. 2 – SWOT analysis of health technology assessment in Cyprus. Source: Authors approach. HTA, health technology assessment; MOH, Ministry of Health; NHS, National Health System; SWOT, strength, weakness, opportunities, and threat; WTP, willingness to pay.

4. Appraisal of medicine by other HTA agencies such as the National Institute of Clinical Excellence.
5. Existing competitive medicines in the formulary.

The breadth and quality of data are assessed. As in other small countries, the goal is to foster best practices instead of developing ones. Because assessment is a context-free and context-sensitive issue [11], transferability of data may be flawed because of

1. Demographic heterogeneity.
2. Costs. Difference in pricing, reimbursement rates, and between the negotiating power of health prices will lead to cost divergence between countries.
3. Health care practices/different efficiency factor between health systems.
4. Cultural differences and social values between different populations [12].

The Committee assesses medicines on the basis of several criteria (Table 1) [13]:

Health outcomes measures include cost per quality-adjusted life-years, life-years gained, progression-free and overall survival, and disease-specific measures such as Psoriasis Approach Severity Index and American College of Rheumatology Index. The number needed to treat approach was implemented in the assessment of smoking cessation products. This was also implemented for competitive medicines that have a significant price difference (e.g., different Anatomic Therapeutic Chemical 3 categories) in order to enhance competition in the tendering process.

In 2007, the ministerial decision [13] enabled the formation of a therapeutic algorithm based on the outcome of the tender. Therapeutically equal products competed and instead of eliminating the losers, these were designated as second- and third-line therapy, respectively. This occurred in certain therapeutic categories for which there is enough documentation that tolerance to relevant medicines is limited and therefore, there is strong possibility that patients may need to switch treatment. The case of the anti–tumor necrosis factor agents was a landmark because the contribution of all stakeholders (MOH, physicians, and patients) to the HTA process has led to a mutually beneficial outcome, and as a result every year the list for anti–tumor necrosis factor agents has still available slots.

Major therapeutic categories that got into this scheme include aromatase inhibitors, adjuvant immunosuppressive treatment, such as mycophenolic acid, antidepressants, antiepileptic agents, and erythropoetins. Before the assessment, companies are allowed to provide further supporting materials regarding the efficacy and estimated cost of their products, which adds to the transparency of the process.

Another concern of the Drug's Committee is the possible off-label use of expensive products, due to the overuse of medicines in Cyprus as addressed earlier. This may lead to a reduction in health benefits associated with the use of a product, due to the uncertainty associated with its off-label use. Therefore, the risk of off-label use is counterbalanced by the requirement of preapproval. This was the primary reason for the rejection of ranibizumab, despite recommendations by the National Institute for Health and Clinical Excellence [14].

HTA implementation has not always been very successful in broadening the scope and in certain cases overlooked one intrinsic factor, interrelation to health policy [15]. The MOH implemented a public campaign to create awareness among the public for the prevention of cervix cancer; however, the Drug's Committee did not approve the only available vaccine. Moreover, as the complexity factor of the therapeutic regimen increases, such as in immunosuppressive ones, assessment can be complicated and lengthy. A prominent example was assessment of the mammalian target of rapamycin inhibitors whose dosage is highly personalized and budget impact of each product is

Table 1 – Criteria for assessment.

Criteria	Importance	Comments
Disease prevalence	Major	Easy to assess
Guidelines of the National Institute for Health and Clinical Excellence	Major	Transferability of data has to be checked for major divergences
Efficacy data	Major	Clinical effectiveness must be assessed
Budget impact analysis	Dominant	May conflict with cost-effectiveness approach
Off-label use	Medium (unless specific trend documented)	Difficult to assess, may compromise actual medical need. Interface management will address this issue
Cost-effectiveness	Major (difficult to apply for each medicine a country-specific study)	A basic economic analysis is performed
Impact on spending for other medical interventions	Medium	Incorporation of nonpharmaceutical interventions. Interface management may enable control. Difficult to assess

Source: Terms of Reference, Drug's Committee.

determined by other factors, such as adjuvant immunosuppressive treatment.

Prescription Guidelines and Preapprovals

The Drug's Committee has successfully implemented controlled prescription of certain medicines. The majority of guidelines specify treatment line, exceptions, patient profile, further requirements such as serum marker levels, expected duration of treatment, and indication of failure. Statins were one of the most successful examples. The introduction of prescription guidelines for statins (including preapproval for high-potency statins) concomitantly with the introduction of generic simvastatin was successful in avoiding the "reallocation of demand," as observed in Belgium (2007–2011: Daily defined dose consumption increased by 52%, cost decreased by 48%).

Similar guidelines were elaborated for the prescription of all oncology medicines, insulin glargine, rosiglitazone, cinacalcet, and darbeopetin alpha. For the majority of these products, a preapproval is also necessary, usually with the obligation for the submission of relevant laboratory documentation. The details of the patients are filed.

Indication-based guidelines were elaborated for angiotensin II receptor blockers. Different protocols were compiled for hypertension, congestive heart failure, and diabetic nephropathy.

In oncology medicines with significant uncertainty and high cost, due to the lack of effectiveness data, the Drug's Committee has made exceptions for the compassionate use of cancer drugs in a small target group population in which benefits may not be sufficiently captured. Criteria are as follows:

1. Patient's life expectancy is less than 24 months.
2. There is sufficient data that the treatment will extend life for at least an additional 3 months compared with current treatment.
3. There is no alternative treatment with equal effectiveness available.
4. The target group is a small patient population [16].

Managed Entry Agreements in Cyprus

Risk sharing [17] has not been implemented and price volume agreement has been applied only scarcely, mainly due because of human resources required for monitoring. Pemetrexed gained another indication of malignant pleural mesothelioma, in addition to the one existing for non–small cell lung cancer. Because of comparative effectiveness among all available treatments for non–small cell lung cancer, an approach was set up that consisted of three scenarios. The prices incorporated expected efficacy of the product and net benefit for the company.

The addition of a new indication of deferasirox and the increase in the daily dose to 40 mg/kg led to the managed entry agreement of dose capping agreement between Novartis and the MOH. On the basis of this agreement, the MOH reimburses daily doses up to 30 mg/kg (average 2160 mg daily per patient) while additional dosage burdens the company. The company is obliged to provide free goods to the MOH, based on dose agreements. Currently, 38 patients are registered in this scheme, which will last for 3 years, and data will be revised every 6 months to check for deviations.

Further Potential for HTA in the New Financial Era

Cyprus has recently signed a memorandum of understanding with Troica (term used to define the committee consisting of the International Monetary Fund, the European Union, and the European Central Bank) to secure a life-sustaining bailout of 10 billion euros. As Troica's primary target is to enhance the efficiency of governance, one important prerequisite for the health sector is the implementation of HTA for the 10 costlier pharmaceutical and medical equipment. This provision will further leverage shift toward an integrated HTA system, and several approaches are currently being considered, such as the introduction of two HTA formats, according to the estimated budget impact (light and full version), an approach currently implemented in many countries such as The Netherlands [18].

Challenges for HTA in Cyprus

The current product mix of these two fragmented markets does not allow dissemination of policies in the private sector, negatively affecting health equity. Moreover, the Drug's Committee should be authorized to act proactively regarding the assessment of new medicines.

An important limitation is the lack of an official willingness-to-pay threshold in Cyprus [19] regarding economic evaluation.

Finally, the conflicting role of the MOH, which in the case of HTA, it assesses, appraises, and procures as well, is a

major negative aspect of the system, compromising objective appraisal.

Discussion

HTA should be incorporated in the context of a general health policy because health policy defines the optimum use of a medicine to deliver superior results. Health policy should cover both sectors because ultimately all chronic patients will be beneficiary of the public sector and prevention of discrimination must be pursued.

Incorporation of other stakeholders (university, patient associations) may enrich the decision-making process and lead to a context for more informative outcomes, diverting the conflicting role of the MOH.

A detailed cost-effectiveness analysis must be implemented, at least for the cost driver categories, which also needs to be regulated with regard to technical parameters, such as time horizon, modeling methods, discounting, and type of economic evaluation (budget impact, cost-effectiveness analysis). This was also recommended by the Internal Audit department of Cyprus [20].

Uncertainty needs to be addressed in the context of HTA in all its expressions because it affects the impact of the decision and sensitivity analysis must cover a range of assumptions.

Because of the variety of statistical approaches such as metanalysis or mixed treatment comparison, an accepted format should be elaborated taking into consideration particularities of certain therapeutic categories. Moreover, the rating of evidence is crucial and we suggest that GRADE classification should be adapted because it provides an excellent grading of evidence [21].

The scope of the assessment should be broad and must be able to compare interdisciplinary interventions (i.e., medical vs. pharmaceutical interventions) [22,23].

The existing coverage system does not make provision for different levels of reimbursement, because all diseases are considered to have the same utility. Consequently, the reimbursement levels are the same for all diseases. A classification of strength of evidence will enable better forecasting, resource allocation, and demand control.

We observed that reduction in the pharmaceutical growth rate seems to have coincided with the introduction of HTA methods; however, this has to be verified. The normalization of the annual pharmaceutical growth rate to less than 3% is a good first sign and at least partially is attributed to HTA implementation, which is gaining ground in Cyprus [24], as seen in Table 2.

We must however interpret this reduction in the increase rate with caution because Cyprus's economy entered a prolonged recession period in 2008 [25]; therefore, this reduction can be attributed to a tighter control of expenditures, rather than to the ability to control expenses as such.

Table 2 – Output of Drug's Committee.

Year	Number of HTAs performed	Total number of appraisals (including resubmissions)
2010	11	116
2009	24	116
2008	8	165

HTAs, health technology assessments.
Source: Annual Report of Ministry Of Health, 2010.

The Drug's committee evaluates each product only at request. We believe that this leads to lack of symmetry of the system. More importantly, this does not allow comparison among treatments and does not elaborate an overall approach to a disease, which could be achieved by assessing other intervention methods. Several therapeutic interventions run in parallel and comparative effectiveness has not been documented. Periodical assessment of guidelines and disease management should be established and also assessment of medicines by the Drug's Committee would minimize reactions from the industry and subsequent exerted pressures.

Finally, newer approaches must be incorporated taking into account clinical uncertainty. The introduction of risk-sharing methods, price volume agreements, and managed entry agreement will further optimize the HTA context in Cyprus. HTA is emerging in Cyprus's health care sector. There is an imperative need, and the current financial era does support further dissemination. The small size of the country and market fragmentation hinders its full uptake.

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REFERENCES

[1] Golna C, Pashardes P, Allin S, et al. Health Care Systems in Transition: Cyprus. Copenhagen: WHO Regional Office for Europe on behalf of the European Observatory on Health Systems and Policies, 2004.
[2] Sachs JD. Macroeconomics and Health: Investing in Health for Economic Development. World Health Organization WHO Library Catalogue-in-Publication Data World Health Organization. Geneva, Switzerland: World Health Organization, 2001.
[3] Eurostat [online]. Health care statistics, 2009. Available from: http://epp.eurostat.ec.europa.eu/statistics_explained/index.php/Healthcare_statistics. [Accessed September 17, 2011].
[4] Sammoutis G, Paschalides C. Will the sun shine over Cyprus's national health system? Lancet 2011;377:29.
[5] Antoniadou M. Can Cyprus overcome its health care challenges? Lancet 2005;365:1017–20.
[6] Andreou M, Pashardes P, Pashourtidou N. Cost and value of health care in Cyprus. Policy paper. Nicosia: University of Cyprus, 2010. Available from: http://www.ucy.ac.cy/data/ecorece/DOP02-10. [Accessed August 18, 2011].
[7] Kanavos P, Vandegrift M. Health policy versus industrial policy in the pharmaceutical sector: the case of Canada. Health Policy 1997;41:241–60.
[8] Battista RN, Hodge NJ. The development of health care technology assessment: an international perspective. Int J Technnol Assess Health Care 1995;11:287–300.
[9] Petrou P. PHIS Hospital Pharma Report; 2009. Available from: http://phis.goeg.at/downloads/hospitalPharma/PHIS%20Hospital%20Pharma%20Report%202009%20Cyprus.pdf. [Accessed September 6, 2011].
[10] Ministry of Health. Pharmaceutical reform in Cyprus. 2006. Available from: http://www.cyprus.gov.cy/moi/pio/pio.nsf/All/BEFF3C4943A9C696C2257127003D66A8?OpenDocument&print. [Accessed September 11, 2011].
[11] Velasco Garrido M, Gerhardus A, Røttingen JA, Busse R. Developing health technology assessment to address health care system needs. Health Policy 2010;94:196–202.
[12] Goeree R, He J, O'Reilly D, et al. Transferability of health technology assessments and economic evaluations: a systematic review of approaches for assessment and application. Clinicoecon Outcomes Res 2011;3:89–104.
[13] Drug's Committee, Ministry of Health. Terms of reference drug's committee. Available from: http://www.moh.gov.cy/moh/phs/phs.nsf/dmlphcomm_gr/dmlphcomm_gr?OpenDocument. [Accessed June 10, 2013].
[14] Appraisal of macular degeneration (age-related)—ranibizumab and pegaptanib (TA155). 2008. Available from: http://www.nice.org.uk/TA155. [Accessed December 17, 2011].
[15] Drummond M, Kanavos P, Sorenson C. Ensuring Value for Money in Health Care: The Role of Health Technology Assessment in the European Union. Denmark: World Health Organization on behalf of the European Observatory on Health Systems and Policies, 2008.
[16] National Institute for Health and Clinical Excellence. Appraising end of life medicines. 2008. Available from: http://www.nice.org.uk/media/26E/43/Endoflifemedicines.pdf. [Accessed December 17, 2011].

[17] Espín J, Rovira J, García L. Experiences and Impact of European Risk Sharing Schemes Focusing on Oncology Medicines. Grenada, Spain: Andalusian School of Public Health, 2011.
[18] Stolk AE, de Bont A, van Halteren AR, et al. Role of health technology assessment in shaping the benefits package in The Netherlands. Expert Rev Pharmacoecon Outcomes Res 2009;9:85–94.
[19] Dorte Gyrd-Hansen. Willingness to pay for a QALY. Health Econ 2003;12:1049–60.
[20] General audit recommendations for rational medicines procurement. 2011. Available from: http://pdf.politis-news.com/pdf/pdf?-A=257761,pdfview.html&-V=pdfarchivefullpaper. [Accessed November 17, 2011].
[21] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.
[22] Culyer AJ, Lomas J. Deliberative processes and evidence-informed decision making in healthcare: do they work and how might we know? Evidence Policy 2006;2:357–71.
[23] Garrido VM, Kristensen FB, Nielsen CP, et al. Health Technology Assessment and Health Policy Making in Europe: Current Status, Challenges and Potentials. Denmark: World Health Organization, 2008.
[24] Cyprus Ministry of Health. Annual health report, Nicosia; 2010. Available from: http://www.moh.gov.cy/moh/moh.nsf/page09_gr/page09_gr?OpenDocument. [Accessed June 10, 2013].
[25] Statistical Service of the Republic of Cyprus. Latest figures: GDP growth rate, 1st quarter 2010. Available from: http://www.cystat.gov.cy/mof/cystat/statistics.nsf/All/ADAE80767589A7B9C22579AE0029E929. [Accessed June 8, 2012].