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**ORGANISATIONAL ISSUES FOR BUILDING HEALTH-TECHNOLOGY
ASSESSMENT (HTA) CAPACITY IN CYPRUS**

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EXECUTIVE SUMMARY

The main characteristics of HTA systems around Europe are presented as background before a model for HTA in Cyprus is proposed. A range of issues around implementation, human resources, data sources and technical facilities, stakeholder involvement, the development of process and methods guides are identified. The report concludes with the following recommendations:

- (1) A particular HTA model is recommended for Cyprus, which has two different pathways depending on whether or not an assessment is to be made of clinical effectiveness and cost-effectiveness.
- (2) A small dedicated committee will review all proposals and determine which pathway is appropriate.
- (3) Potential criteria by which pathway decisions can be made are the therapeutic area, likely budget impact, degree of innovation and anticipated added value.
- (4) Those medicines selected for clinical and economic evaluation will be handled by an HTA unit within PS.
- (5) The competencies required by the HTA unit include: searching for evidence, understanding of design of clinical studies, evidence synthesis, health economic modelling, and interpretation of clinical and economic evidence.
- (6) A programme of training is required in order to ensure that not only the HTA unit has the full set of competencies required, but a wider group within PS have these competencies so that the HTA unit can respond flexibly to peaks in HTA workload.
- (7) It is recommended that the new system be introduced at a particular future date rather than having two systems running in parallel for a period.
- (8) A number of drugs, which are already provided in Cyprus, should be assessed by the HTA unit as if they were new submissions in order to provide valuable training opportunities prior to the introduction of the new system.
- (9) Consideration should be given to running pilot appraisals with members of the TCRM and stakeholders.
- (10) An evaluation of all aspects of the new system should be undertaken one year after its introduction.
- (11) A conflict of interest policy should be designed for both Ministry of Health employees and the stakeholders in order to provide greater transparency.
- (12) Explicit consideration needs to be given to what relationship between health benefits and costs represents good or poor value for money.

1. INTRODUCTION

As agreed in the Memorandum of Understanding on Specific Economic Policy Conditionality (MoU), the Cypriot authorities are required to adopt a number of measures to strengthen the sustainability of the funding structure and the efficiency of public healthcare provision. A specific engagement of the Cypriot authorities is to continue to establish the system for health technology assessment (HTA).

As part of this agreement and together with the Support Group for Cyprus (SGCY), the purpose of this consultancy work is to provide support to the Cypriot authorities in their efforts towards successfully establishing HTA capacity, through technical expertise with regard to the organisational set up of the national HTA capacity.

The principal aim of this report is to give support regarding organisational issues for building health-technology assessment (HTA) capacity in the Pharmaceutical Services (PS). The main points that were requested are outlined below:

- 1) Appropriate institutional arrangements that should be established in order to develop a dynamic HTA model.
- 2) Description of how the HTA system will be implemented.
- 3) Human resources needed according to the HTA model (skills, training, number of experts)
- 4) Development of technical facilities and data sources.
- 5) Standard Operation Procedures: process and methods.

2. HEALTH TECHNOLOGY ASSESSMENT IN EUROPE

Health Technology Assessment (HTA) has been a concept in the field of health care since the 1970s. The concept arose as a result of rapid growth of new medical technologies and limited health budgets. In order to overcome this issue, health care systems had to make choices regarding products and services that could be covered by public resources. HTA is a multi-scientific and interdisciplinary activity, which provides input to the system in order to help set priorities and take decisions in the health sector (Sigmund et al, 2007).

The definition of HTA comprises the analysis and assessment of health technologies that have implications for the National Health System (NHS) budget. Health technology is usually defined broadly to include diagnostics, treatment, procedures and methods of prevention, care and rehabilitation, equipment and medical drugs. HTA can be mainly divided into four areas that usually overlap: the technology, the patient, the organisation and the economy. The production and review of evidence is an important part of the assessment and together with an economic analysis, provides the information needed for a final decision.

In Europe, HTA started in the 70s with formal and informal initiatives in different countries. Sweden started a programme on evaluation of medical technology. Other countries like the United Kingdom, France and the Netherlands were already using “scientific standards” to decide on the provision of health technologies. Moreover, the Netherlands wrote down a policy-oriented analysis. However, the first formal initiative was the creation of national agencies that were in charge of this assessment. The first agency was established in Sweden in 1987, called the Swedish Council on Technology Assessment in Health Care (SUB). France and Catalonia (Spain) followed Sweden and also created formal agencies. During the last two decades many EU countries have established their own agencies (such as, Denmark, Finland, Germany, Austria, UK, Hungary, Ireland, Belgium, Latvia, Poland, and Italy).

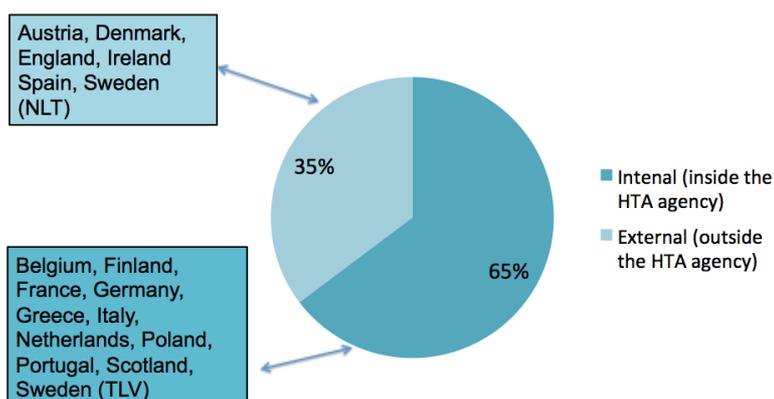
Several of the early European agencies were founding members in 1993 of the International Network of Agencies for Health Technology Assessment (INAHTA). This international network was created to provide a forum for the identification of common interests to HTA agencies. In particular, it was projected to motivate the collaboration among agencies, to promote information sharing and to prevent unnecessary duplication of analysis. Apart from the International Network, in 2004, the European Commission (EC) targeted as a priority the creation of a European Network (EUNETHTA), with the aim of supporting collaboration among the European HTA bodies.

Even if the European countries have common objectives for HTA systems, the process is not homogenous. The operative processes and the organisations work differently across the European countries. The HTA procedure has attracted attention from several authors, due to the different HTA systems that exist. Various comparative analyses have been published recently (Sorenson et al., 2008; Le Polain et al., 2010; Wilsdon and Serota, 2011; Paris and Belloni, 2013; Barneih et al, 2014) describing the different national models in the world. Due to these differences, depending on the drug-indication and the country assessing it, the final reimbursement decision can differ across countries (for review see Wilsdon and Serota, 2011; Fischer, 2012).

In order to define the different HTA systems that exist across Europe, we have designed a taxonomy defining the main characteristics of these models. This classification has been created considering the Hutton Framework (Hutton et al., 2006) and the information collected in a country-based analysis. Out of this research, we can classify the variables that characterise each procedure into two main groups, the system-level variables (organisational, process and method) and product-specific variables. These variables show the main differences across HTA systems and, at the same time, the complexity of each model. In other words, we can observe countries with a more in-depth HTA system (e.g. England, Scotland,) than others (Spain, Greece).

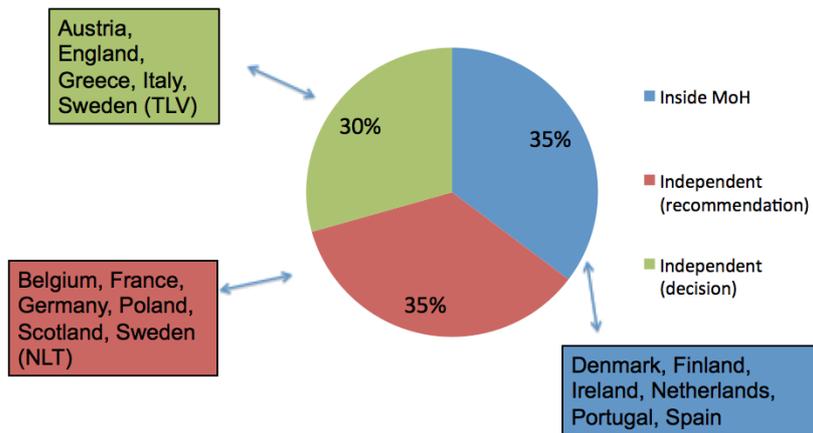
The following graphs show the outcome of each of the variables of our taxonomy by country. We have plotted the outcome of 15 European Union (EU) countries. These EU countries have been selected because they each have a well-defined HTA process. Figure 2 shows that in most of the EU countries evidence is produced and reviewed inside the HTA. A few countries, like Austria, Denmark, England, Ireland, Spain and Sweden (NLT), go outside of the agency for this part of the process.

Figure 1. Production and review of evidence (internal or external)



The body in charge of HTA in each country can be part of the Ministry of Health or an independent scientific body. In the last case, the body can either make recommendations or take a final decision. In some countries, this body only undertakes the assessment, while in others it does both the assessment and the appraisal. We can see from Figure 3 that there are differences across the HTA bodies in the EU countries.

Figure 3. HTA Body independence



The following variable shows the level (regional or national) of the recommendation and the final decision. In the EU countries, most of the recommendations and decisions are made at the national, however, there is also the possibility to take the decision at the regional level (Scotland and Sweden) or that the regions have some freedom of implementation (Italy and Spain, Miners et al (2014)) (Figure 4).

Figure 4. Decision level

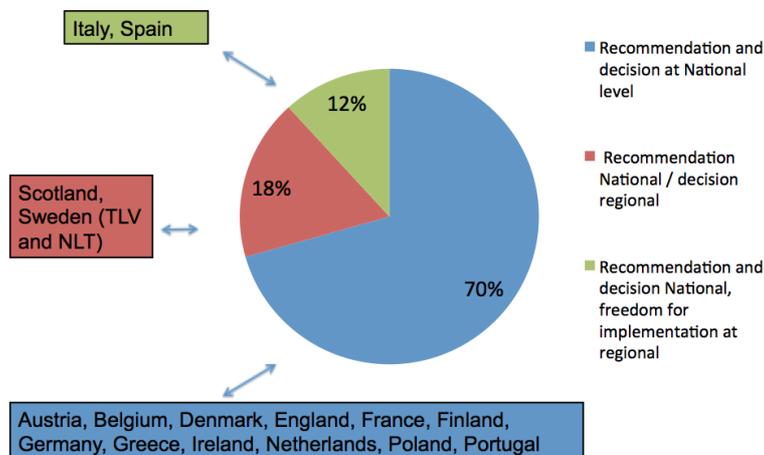
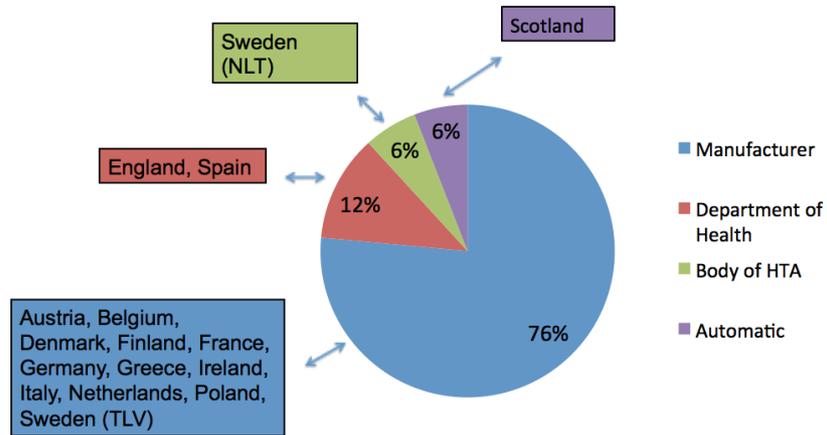


Figure 5 identifies the initiator of the HTA process in each of the studied countries. In most of

the EU countries, the initiator is the manufacturer, however, we also find cases where the process is automatic (Scotland), the Department of Health is the initiator (England and Spain) or the body in charge of the HTA starts it (Sweden and NLT).

Figure 5. Initiator



Figures 6 and 7 indicate the transparency of the approach used in each country. More stakeholders involved in the process and more documentation publicly available makes the decision making process more transparent. For the EU studied countries, most of them have the stakeholders fully or moderately involve in the process and they tend to make available a considerable number of documents. Most of the EU countries have an established appeal process by which a manufacturer can challenge the final decision (Figure 8).

Figure 6. Stakeholders' involvement

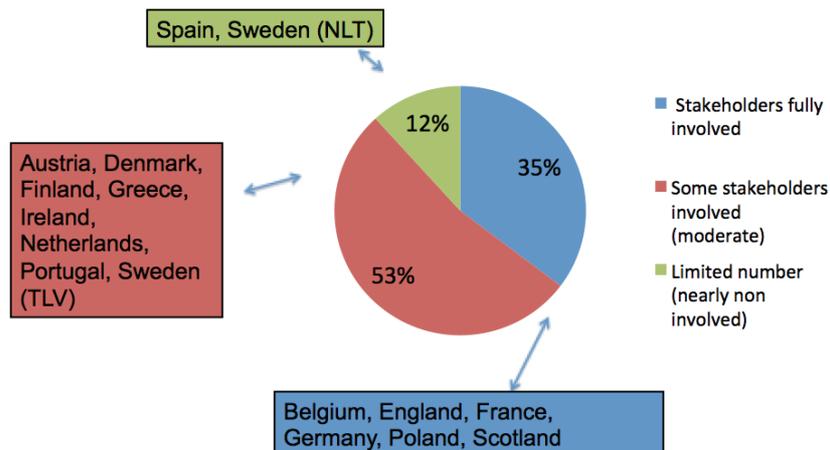


Figure 7. Publicly available documents

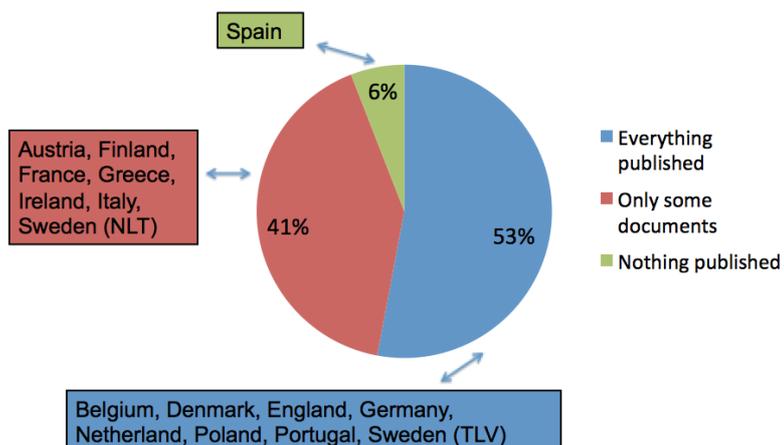


Figure 8. Appeal process

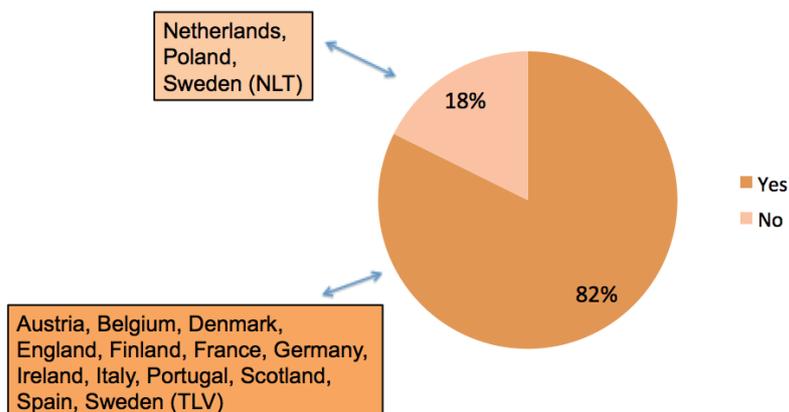
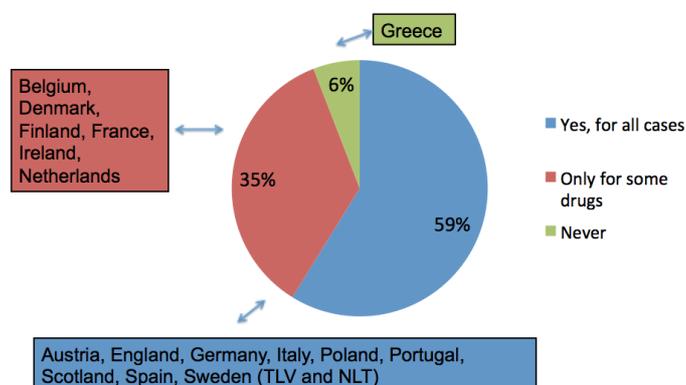


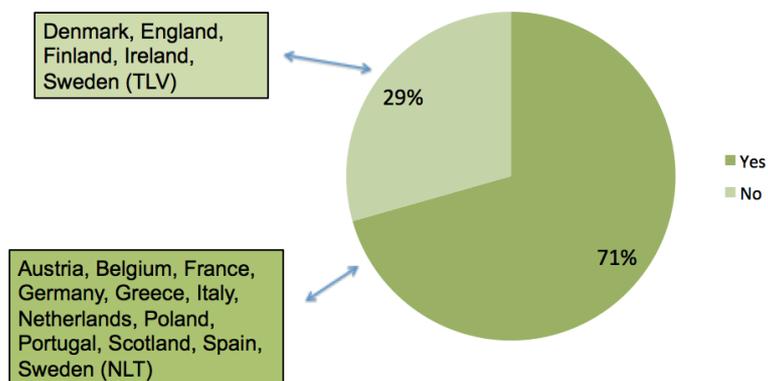
Figure 9 indicates whether or not economic evaluation is required for the final decision. We can see that for most of the EU countries an economic evaluation is a requirement for the HTA decision to take place. However, some countries, like France and Belgium, classify their drugs and they only request an economic evaluation when they are adding therapeutic benefit.

Figure 9. Economic Evaluation required for the decision



The variable plotted in Figure 10 is quite similar to the previous variable as it answers if a budget impact analysis is a condition for the final decision. In this case, a budget impact assessment is required in most of the studied EU countries.

Figure 10. Budget impact



3. MODEL FOR CYPRUS

In this section, we propose an HTA model for Cyprus. We detail a structure for the HTA process and describe the main characteristics of the model in terms of evidence, economic evaluation analysis, and pricing decisions.

It is important that Cyprus develops an HTA system which while recognising the potential value of HTA to informing decisions is not too demanding in terms of scarce manpower within the Ministry of Health and, in particular, the PS. Ultimately the small population of Cyprus sets an upper limit to the potential benefits an HTA system can deliver and thus the resources it is appropriate to devote to HTA. As a result, we try to define a suitable model, which allows for an appropriate HTA analysis but, at the same time, is designed according to the country limitations. As a result, the principal aims of the model are the following:

- Define a structure for the whole procedure.
- Determine which drugs the HTA unit will assess (criteria)
- Resolve the issue of producing evidence itself or reviewing evidence from other HTA agencies/manufacturer submission.
- Justify the importance of an economic evaluation.
- Design a model that allows for the fulfilment of the Council Directive 89/105/EEC.
- Address the pricing decision.

3.1. Model Structure

The structure of the process for the Inclusion of New Medicines into the Positive List of Pharmaceutical Products (PLPP) is detailed in this section and it is presented in a flowchart at the end. All aspects of the assessment and appraisal process will be based inside the PS. The main advantage of managing the process in the PS is that the current process is in this unit; so, they already have expertise in these matters. Moreover, the Registration unit, in charge of granting the marketing authorisation, is also located in the PS. So, the units involved in the process will be able to access the data used by the Registration Unit.

The process starts with a submission by the Marketing Authorisation Holder (MAH). This market authorisation can be granted either by the European Medicine Agency (EMA) or the National Drug Council (Cyprus). The Registrar of the Council for the Reimbursement of Medicines (CRM), who will be the Director of PS, will receive the MAH application. This submission will follow a template provided by the PS on their website. It will collect the main

information needed in order to proceed with the assessment of the new drug or medical device (submission detailed at 7.4. Manufacturer dossier).

An Administrative Committee formed by a member of the HTA Team, a member of TCRM, a member of the Managed Entry Agreement (MEA) team and a member of the Pricing department will apply criteria that will determine the assessment path for the submission, whether the application will initially be sent to the HTA unit or to the Technical Committee for the Reimbursement of Medicines (TCRM). This determination will be based on factors such as, the budget impact, the degree of innovation, the added value and the therapeutic area of the technology taking into account the capacity and the workload of the HTA unit (extended explanation at 3.4. Potential criteria for selecting the assessment pathway).

The application of such criteria by the Committee will enable it to control the flow of work to the HTA unit (which is potentially important in order to fulfil the Council Directive 89/105/EEC, commonly referred as the Transparency Directive). This Committee will meet at least once a month, however, we suggest a virtual weekly meeting might be useful to avoid delays.

The nature of the subsequent assessment will depend on whether the application is initially reviewed by the HTA unit or the TCRM.

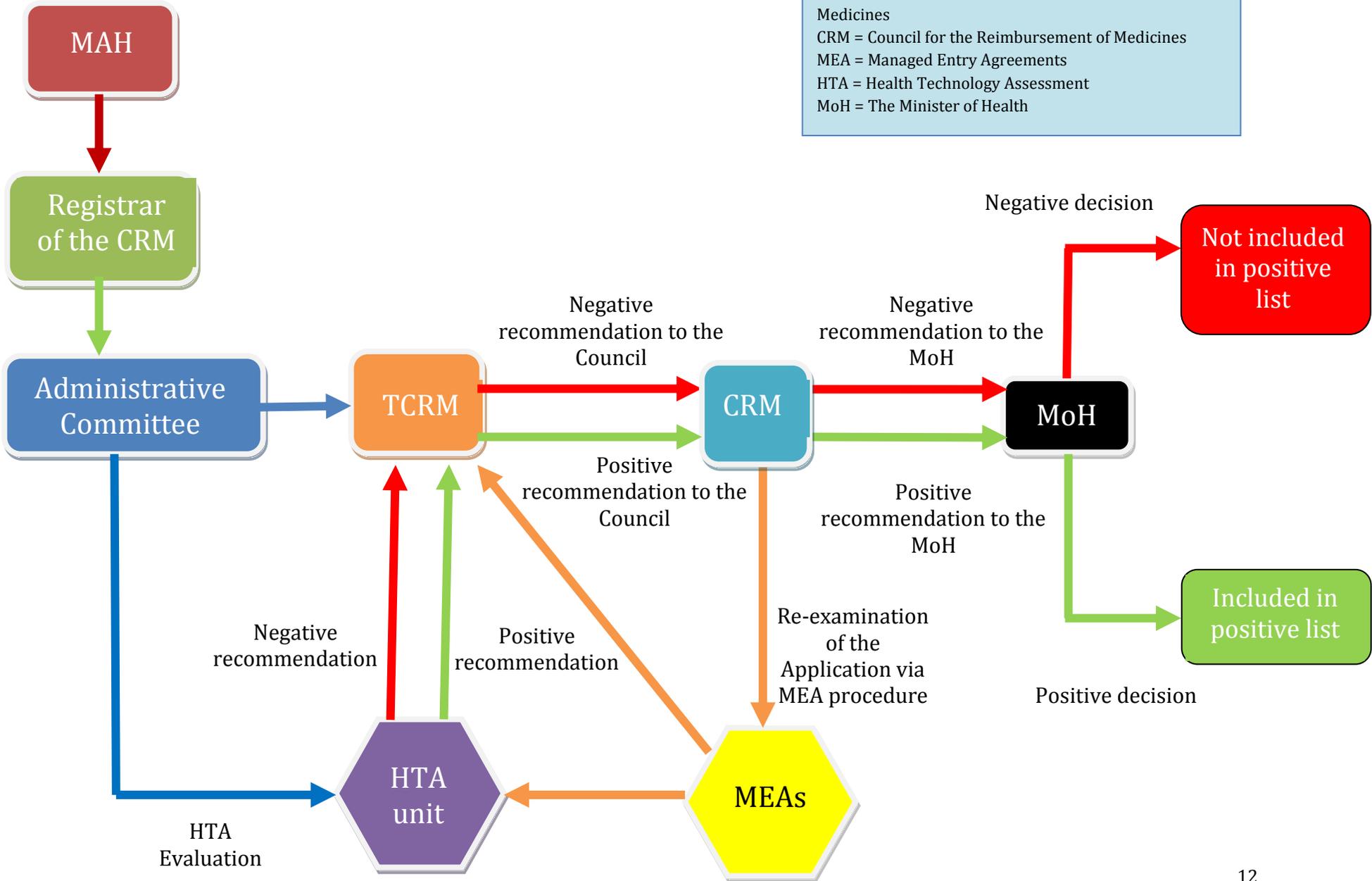
1) HTA unit assessment. A process of consultation with the main stakeholders will begin when an application goes to the HTA unit. The MAH, the clinicians, the patients groups and other specific experts will be invited to give comments on the assessed technology. Moreover, the MAH will be asked to submit an extended version of their application, including an economic analysis. The HTA unit based on the evidence collected during the assessment procedure (clinical effectiveness and economic analysis) will make a positive or negative recommendation to the TCRM. Once this recommendation has been made, the stakeholders will be given the opportunity to comment on it and the TCRM will have these comments and the report of the HTA unit to assist them in reaching a decision. The TCRM will make a positive or negative recommendation that will go to the CRM. There will be a clock stop in the timeline every time the stakeholders are being consulted.

2) TCRM assessment. It is anticipated that applications sent directly to the TCRM, will receive a lighter evaluation, mainly based on comparative effectiveness. To aid transparency the TCRM will invite the MAH, and other stakeholders such as patient representatives, to participate in the meeting. Following this meeting the TCRM will make a positive or negative recommendation to the CRM.

The CRM will be comprised of senior public employees such as, the Permanent Secretary of the Ministry of Health, the Permanent Secretary of the Ministry of Finance, the Permanent Secretary of the Ministry of Labour Welfare and Social Insurance, the Permanent Secretary of the Ministry of Energy, Commerce, Industry and Tourism, the General Executive Director of the Health Insurance Organisation, the Director of the Department of the National Health System (Ministry of Health) and the Director of the PS (Ministry of Health).

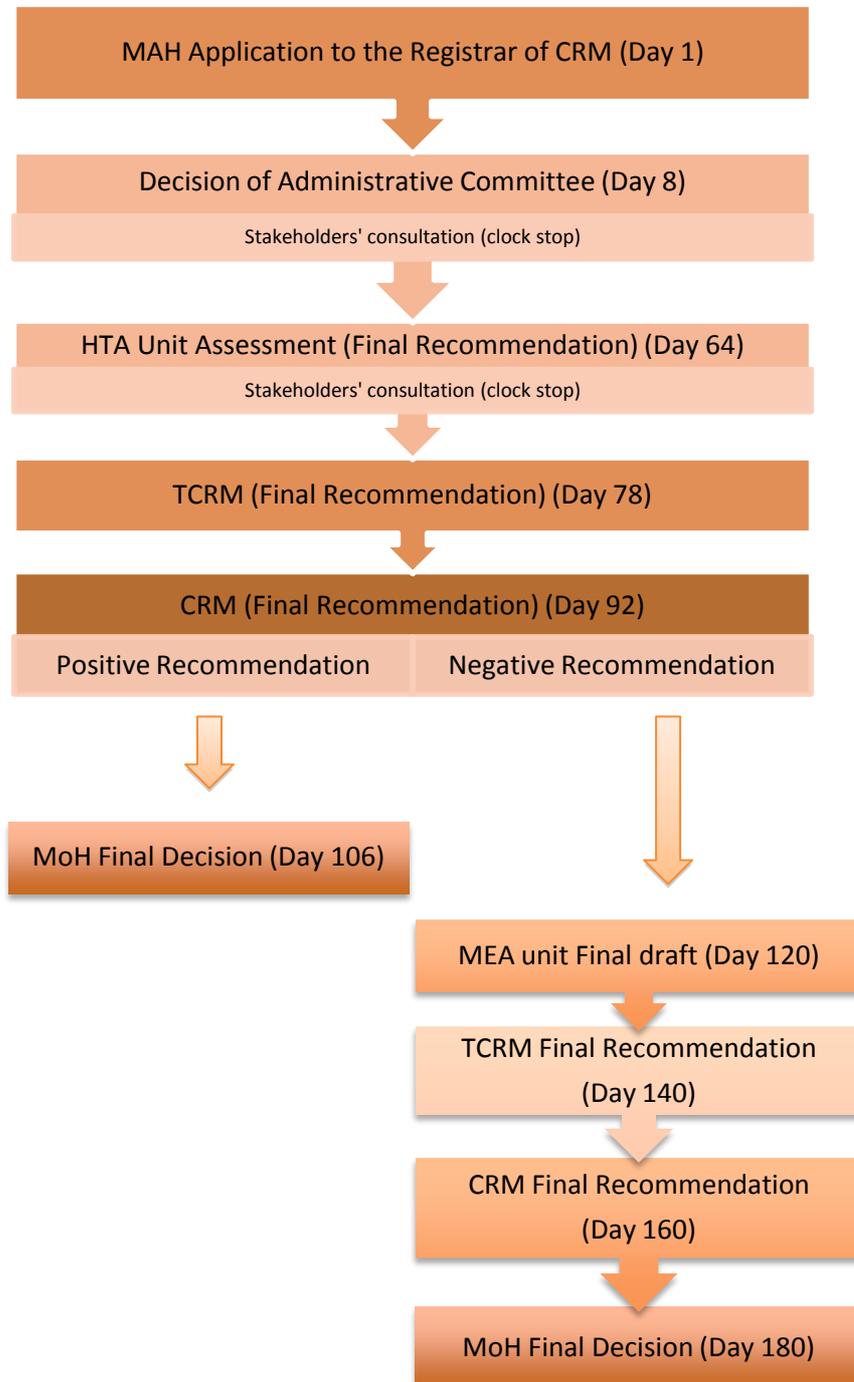
The CRM will review the recommendations of the TCRM and will make a recommendation to the Minister of Health (MoH) taking into account the budget impact and budget availability. In addition, the CRM will have the opportunity to request that the MEA team should approach the MAH with a view to agreeing an MEA. This might happen, for example, when the recommendation based on the MAH's initial price is negative. While it will be more feasible to determine whether a particular MEA is worthwhile when a product has been assessed by the HTA unit, in principle an MEA could also be sought for products assessed by the TCRM. Once any MEA has been agreed, the CRM makes a final recommendation to the MoH, who is responsible for the final decision. The outcome determined by the MoH can be positive or negative. A positive decision will imply the inclusion of the new drug in the positive list of pharmaceutical products.

MAH = Marketing Authorization Holder
 TCRM = Technical Committee for the Reimbursement of Medicines
 CRM = Council for the Reimbursement of Medicines
 MEA = Managed Entry Agreements
 HTA = Health Technology Assessment
 MoH = The Minister of Health

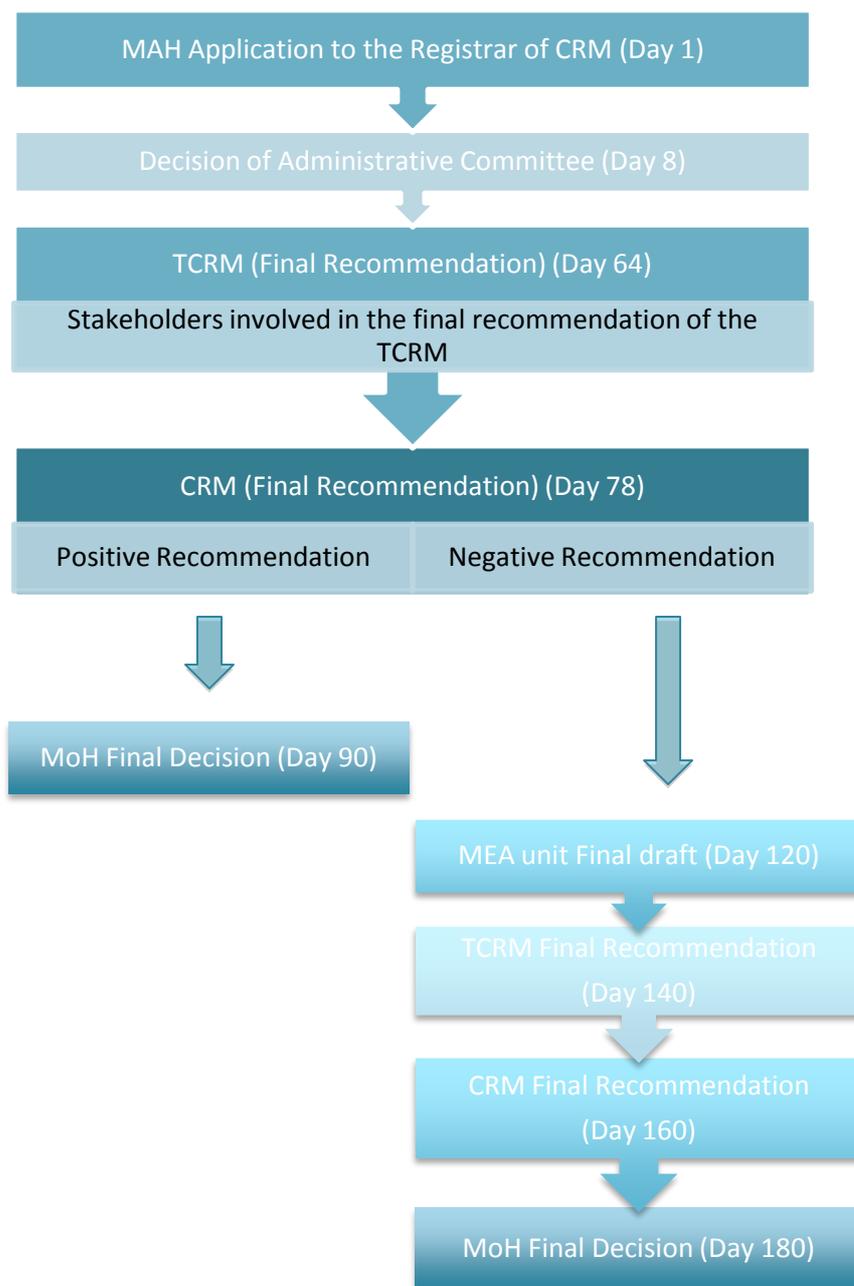


3.2. Suggested timelines

The following graphs describe the timeline procedure according to the model defined in the previous section. The first one describes the process when the **HTA Unit** undertakes the assessment.



The second graph describes the timeline when the **TCRM does the assessment**.



These suggested timelines could be modified after the Pilot exercise that it is proposed is undertaken before the implementation. This Pilot exercise will establish the feasibility of the timing and it will help to develop the Standard Operating Procedures.

3.3. Review of Evidence

As is evident from the review of EU practice with respect to HTA there are many different ways in which to introduce HTA into the decision making process around the introduction of

pharmaceuticals and medical devices. A key choice is whether to base a decision on a review of evidence produced elsewhere (such as by HTA agencies in other countries or by the manufacturer) or whether evidence is to be produced and reviewed. This is one of the main choices that must be made regarding the assessment by the HTA unit, which will clearly impact on the overall timeline.

This is best exemplified with respect to assessing cost-effectiveness. The Scottish Medicines Consortium does not independently review evidence on clinical effectiveness or undertake economic evaluations but rather reviews the evidence synthesis presented to it by the manufacturer. This is also true of NICE in the case of *Single Technology Appraisals*, where the Evidence Review Group critiques the case made by the MAH. This review may involve exploring alternative assumptions using the manufacturer's model. But there is insufficient time and resource for the ERG to go beyond critiquing the manufacturer's submission. In contrast, the Assessment Group in the case of a *Multiple Technology Appraisal* performs an independent review of clinical effectiveness and undertakes a de novo economic evaluation. In the latter case, however, NICE is not producing the evidence itself but is sub-contracting the activity to independent (predominantly university-based) teams.

HTA to some extent can be viewed as having the attributes of a public good, namely being non-rival and non-excludable. In other words once an HTA has been undertaken one agency's use of the information doesn't mean that there is less information available for others to use, and (if the HTA is reported) it is not possible to prevent others from enjoying the benefits arising from their use of the HTA to inform decision-making. Note it is not the decisions based on HTAs that have the public good properties but rather the evidence (particularly on clinical effectiveness) and the exploration of the implications of this evidence for decision-making that is non-rival and non-excludable. Consequently, one suitable option would be for Cyprus to use HTAs undertaken by other agencies (or the manufacturer) as an input to decision-making, that is, not to undertake any HTA itself.

The distinction between using information collected and analysed by others as an input to decision-making and undertaking the collection and analysis of data (the HTA) then used to reach a decision is an important one. The big advantage of the former approach is that it would require less staff time and possibly would require a narrower range of competencies. There are, however, several disadvantages: an HTA performed by another agency possibly to inform a particular decision may not always be directly applicable to the decision to be made in Cyprus, sometimes HTAs may be available from more than one agency and they may not

agree, restricting roles to the review of others' HTAs will lead to fewer opportunities for staff to develop their skills, and it might possibly lead to a delay in decision making. Moreover, were such "free-riding" behaviour to arise across several agencies the overall volume of HTA might be sub-optimal.

In order to justify that a review of evidence would be feasible in Cyprus, as opposed to a full HTA being undertaken by the HTA unit, we have investigated whether there could be a considerable potential for delay. In other words, we need to demonstrate that other HTA agencies will have already produced evidence before Cyprus starts looking at it.

In order to investigate this potential delay we considered the 33 drugs examined in Cyprus during the period from December 2012 to October 2013, and for each identified the date at which decisions were published for a range of European countries (Belgium, England, Scotland and Sweden). Decisions had been made elsewhere for two thirds of the drugs by the date at which the Cypriot decision was made. Moreover, it is not the decision in other countries *per se* which is of primary interest but rather the information upon which the decision was based. This information will often be available at a much earlier date than that when the decision was announced. For example, the bulk of the data upon which a decision is made is available on the NICE website when a decision goes out for consultation. Taking boceprevir, telaprevir, exenatide, abiraterone, everolimus and panitumumab, for example, this was on average 16 weeks before the announcement of the final decision. In table 1, we show a comparison by date of decision between HTA agencies (England, Scotland, Sweden, Belgium, Canada and Australia) only for cancer drugs. The main result is that for all cancer drug-indications (except for Brentuximab Vedotin), there was already evidence from other HTA agencies when Cyprus took the final decision. In Annex 1, we have described the steps in order to find this evidence in selected HTA agencies websites and a brief explanation of what can be found in each of them.

Table 1. Cancer drug-indications appraised in Cyprus 2012/2013 compared other HTA agencies

Product	CYPRUS Date of decision	England Date of decision	Scotland Date of decision	Sweden Date of decision	Belgium Date of decision	Canada Date of decision	Australia Date of decision
Panitumumab (Vectibix)	8/2/2012*	25/1/2012	13/2/2012	Non-assessed	21/8/2012	Non-assessed	3/2013
Abiraterone	20/6/2012*	27/06/2012	13/8/2012	19/9/2012	20/7/2012	Non-assessed	11/2011
Cetuximab+ chemotherapy	20/6/2012*	24/6/2009	9/03/2009 Non-submission	Non-assessed	21/10/2010	Non-assessed	3/2007
cabazitaxel	20/6/2012*	11/05/2012	7/11/2011	18/12/2013	20/04/2012	Non-assessed	7/2011 (not accepted)
Everolimus	21/9/2012*	Non-assessed	14/5/2012	Non-assessed	21/8/2012	Non-assessed	11/2012
Everolimus	21/9/2012*	28/08/2013	8/7/2013	Non-assessed	18/2/2010	Non-assessed	3/2013
Trastuzumab	21/9/2012*	24/11/2010	7/02/2011	Non-assessed	1/5/2002	Non-assessed	7/2011 (not accepted)
Gefitinib	21/9/2012*	28/7/2010	13/12/2010	4/3/2010	18/6/2010	26/6/2004	7/2004
Erlotinib	21/9/2012*	27/6/2012	16/1/2012	Non-assessed	1/7/2006	7/12/2005	3/2006 (but not accepted until 8/2008)
Pemetrexed	20/2/2013*	2/12/2010	8/2/2010	Non-assessed	6/4/2009	Non-assessed	3/2009
Pazopanib	24/4/2013*	23/2/2011	7/03/2011	4/1/2011	18/2/2011	Non-assessed	7/2010
Brentuximab vedotin	2/8/2013	Non-assessed	14/1/2013 Non-submission	17/10/2013	30/10/2013	Non-assessed	3/2014
Vandetanib	10/10/2013*	Non-assessed	11/6/2012	Non-assessed	1/5/2013	Non-assessed	Non-assessed

* When Cyprus took the decision there was already evidence from another HTA agency.

This previous case study supports our suggestion of reviewing evidence from other HTA agencies. Moreover, as specified in the model structure, the HTA unit can complement this review with the submission of the manufacturer that can be required to contain an analysis of both clinical effectiveness and cost-effectiveness.

It is possible that new drugs will be considered for introduction in Cyprus at an earlier stage than was the case in the past. Thus, it may not always be the case that an assessment is available from another agency. This highlights the importance of the HTA unit developing its ability to provide robust assessments of the case made by the MAH. These assessments will be of particular importance when there is a negative recommendation and the prospect of discussions taking place regarding the introduction of an MEA.

3.4. Economic evaluation

An important decision is whether or not to consider cost-effectiveness information in every instance or just in some cases (for example, where there are likely to be important implications for overall spending). The advantage of not requiring an economic evaluation in all cases is that it reduces the evidence to be examined before a decision is made, thereby facilitating more rapid decision-making. The disadvantage is, of course, that only clinical effectiveness will be assessed and not cost-effectiveness, and of course it is not uncommon for an intervention to be effective but not to be cost-effective (and the budget impact cannot help identify these cases). Moreover, another important drawback of not assessing cost-effectiveness is the lack of a basis upon which to judge any proposed Managed Entry Agreement. A cost-effectiveness analysis might assist negotiations over price.

The structure of the model defines a full HTA process (clinical effectiveness and an economic analysis) only for those drugs assessed by the HTA unit. In other words, given resource constraints the model identifies a subset of medical devices or pharmaceuticals for which an HTA would be undertaken, while other decisions would be subject to a rapid review (done by the TCRM) focussing on comparative effectiveness and their cost-effectiveness would not be assessed.

3.5. Potential criteria for selecting the assessment pathway

In the structure of the model section we have already suggested criteria that might be used to decide which drugs will be assessed by the HTA unit. In this section we discuss each criterion further. The main reason for having these criteria is to ensure that the Transparency Directive is fulfilled while allowing more detailed investigation of the worth of a number of particularly important drugs. The Directive requires the reimbursement and pricing process should take no more than 180 days (90 days for each part). In order to achieve this goal, and recognising the necessarily limited capacity of the HTA unit, it is important that its workload can be appropriately managed.

Criteria:

- 1) **Budget impact analysis (BIA):** its main objective is to estimate the financial effects of the introduction of a new health-care technology when resources are constrained. In other words, a BIA predicts the spending impact of a new technology on a specific health condition. This analysis is very important when the budget is limited and it helps on the reimbursement decision. In the Cyprus context, a BIA will be expected to form

part of the MAH application. A high budget impact, compared to the total budget, will require an assessment by the HTA unit.

2) **Degree of innovation.** The definition of innovative technology is not unanimous across the different participants of the health sector (AIFA, 2007). There are different conditions that can be considered in order to determine whether or not a technology is innovative.

- It is a new technology.
- Availability of existing treatments (AIFA, 2007). A) Disease currently without adequate treatment, B) Technologies for subgroups of patient resistant or non-respondent to the first-line treatment, C) New technologies with an existing treatment (more effective or safer, with a pharmacological innovation or with a technological innovation).
- Extent of the therapeutic effect (AIFA, 2007). A) Greater benefits on clinical end-points, B) Partial benefit or limited evidence on the disease, C) Minor or temporary benefit on the disease.

3) **Added therapeutic benefit.** This condition answers the following question: does the drug bring some clinical progress over existing therapies? It is mainly based on clinical effectiveness. France and Germany are examples of countries that use this criterion to rank new technologies in terms of the extent of additional benefit.

4) **Therapeutic area.** If the technology falls under a particular therapeutic area, considered of high importance in the Cypriot health sector, for instance: Cancer, Multiple sclerosis, Rheumatoid Arthritis, rare disease, blood disease, infectious disease, Diabetes or cardiovascular diseases

The Administrative Committee will need to have some degree of flexibility when applying these criteria. Thus, how many of these criteria must be fulfilled in order for an application to be sent to the HTA unit for assessment should be determined in the light of the capacity of the HTA unit and the flow of applications.

The primary objective in applying these criteria is to avoid overloading the HTA unit, particularly initially when procedures are being refined and competencies strengthened. It will be necessary for a strict timetable to be met if the Transparency Directive is to be fulfilled. Consequently, the workload of the HTA unit must recognise the capacity of the unit (particularly initially). While it may be feasible in due course to augment the capacity of the unit in response to workload peaks, we suggest that flexible application of the selection

criteria can play an important role in ensuring an appropriate workload.

While it is possible, and probably worthwhile, to undertake horizon scanning in order to establish the drugs that might ask for reimbursement in Cyprus the following year, this process could be time consuming and there will always be uncertainty regarding any forecasts. The forward plans of agencies in other countries might facilitate prediction regarding which drugs will require decisions in the future. Also effort might be focussed on a limited number of clinical areas where spending is already high, such as cancer or Multiple Sclerosis. Horizon scanning will have implications for human resources and technical facilities required.

3.6. Pricing

Another important subject to consider is how the price of the new drugs applying for reimbursement will be determined. In Europe, there exist different options. England, Scotland, Netherlands, Poland and Sweden (TLV) takes the price set by the manufacturer. However, other countries like Austria, Belgium, Denmark, Finland, France, Greece, Ireland, Portugal, and Spain use Reference Pricing, in other words, they base the price on prices in other EU countries. Both of these options allow for the possibility of Managed Entry Agreements. Another option is to determine price by negotiation between the Ministry of Health and the manufacturer, as is done in Germany, Italy, and Sweden (NLT). Pricing is an important issue in the drug reimbursement process; so, it is crucial to decide the way it is determined.

In the new model for Cyprus, pricing will be following the pattern of England and Scotland and the appraisal will take the price set by the manufacturer. This price will be used in the economic analysis presented by the MAH. However, it might also be interesting, when reviewing the evidence (other HTA agencies and the manufacturer submission), to use the reference price for that particular technology and re-run the economic model with it. This complementary analysis will allow for interesting comparisons. However, the price used in the assessment will be the one set initially by the manufacturer. If at this price the technology does not appear to be cost-effective, then the cost-effectiveness of the technology can be re-examined by the MEA team (with assistance from the HTA unit) in the light of any proposed MEA.

3.7. Determining cost-effectiveness

There are three broad approaches to determining cost-effectiveness. In each a judgement is being made as to whether the expected health benefits from adopting the health technology are sufficiently large to justify any increase in the costs following adoption. The key challenge

is to re-express the health benefits (possibly expressed in terms of QALYs) in monetary terms.

The three ways to do this are:

- (1) Set a cost-effectiveness threshold (or threshold range)
- (2) Establish a societal willingness-to-pay for additional health benefits
- (3) Determine what health benefits are likely to be displaced by increased spending on the new health technology.

These are not entirely independent of each other in that it might not be unreasonable to set a threshold taking into account how highly the population values health gains and also the health benefits displaced elsewhere. In some jurisdictions the cost-effectiveness threshold has been set with respect to GNP per capita. NICE have a threshold range from £20,000 to £30,000 per QALY gained which the evidence suggests lies somewhere between the willingness-to-pay for a QALY and the ability of the NHS to turn money into health benefits (an indicator of the health benefits displaced).

The CRM will need to form a view as to whether a particular cost per QALY represents acceptable or unacceptable value for money in Cyprus. One way forward might be to establish a threshold range – when the estimated cost per QALY gained is below the lower end this could be agreed to represent good value for money, and when it lies above the upper end it could be regarded as poor value for money. When the cost per QALY falls within the range a judgement might be made on a case by case basis taking into account the particular features of the health technology.

4. HTA MODEL IMPLEMENTATION

In principle, the new HTA system could be introduced in the form of a “Big-Bang” or in a phased approach. While the “Big-Bang” method involves a direct implementation of the new methodology, the phased approach defines a series of steps to be followed in order to reach the final model. Both approaches have their advantages and disadvantages but a combination of both will be suggested in this case.

We are aware of the challenges of switching wholly over to a new system at a particular date; however, we suspect that the challenges of having a transition period with two different systems operating are greater. For this reason, we suggest a “Big-Bang” method in order to change to new system. Nevertheless, we propose a feasible option to facilitate this direct implementation by making use of the phased approach before the fully implementation.

A “Big-Bang” can be achievable if before the implementation the HTA team has gained enough expertise and the process is clearly defined. We suggest the introduction of a pilot exercise during the months before the day of implementation. This pilot exercise will involve the HTA unit considering some drugs that are already in the positive list of Cyprus. The drugs that will be analysed will correspond with the drugs with higher budget impact. Once the drugs have been chosen, the HTA unit will contact the manufacturers and ask them to collaborate in the pilot exercise. The MAH should send a submission for the specific drug. The HTA unit will treat this as if it is a new submission, and following review of the MAH’s submission and evidence from other HTA agencies will make a recommendation. The primary purpose of this retrospective review is to assist the HTA unit in getting ready for the launch of the new HTA model. But of course it might be that the review of the evidence suggests the current price is too high and a decision would then need to be made whether to explore opportunities for an MEA.

This pilot exercise makes the “Big-Bang” approach more feasible, as it allows for a period of adaptation. Such a phased “Big-Bang” will avoid the inherent confusion and duplication attendant on running two different systems for a transitional period. After this adaptation period, the full implementation of the model must occur. We strongly recommend an evaluation of all aspects of the HTA system a year after its introduction. We believe that this evaluation is very important to confirm the full implementation of the model and that everything is running as planned.

5. HUMAN RESOURCES

This section is written based on the model defined above. We are going to define the human resources needed in the HTA unit in order to reach a proper assessment. First of all, it is assumed that the human resources needed to fulfil the process will all be in-house. In other words, all the work will be done inside the PS and it will not be outsourced. The only external linkage will be the consultation with the stakeholders.

As noted above, it is difficult to know how many drugs will be sent to the HTA unit every year. Knowledge of this number is central to determining the number of people needed in the team. An analysis of new drugs registered in Cyprus during recent years suggested that about 10 drugs per year might merit assessment by the HTA unit. Another unknown is the extent to which the members of the HTA unit will have other duties to perform beyond the evaluation of new health technologies.

Apart from the number of new drugs, it is also important to recognise that new applications will not necessarily arrive at a steady pace but rather from time to time there is likely to be bunching of applications. While this is to some extent under the control of the committee selecting the pathway for particular drugs to follow, it is likely that sometimes the HTA unit will need to assess two drugs at the same time. Thus, in order to complete the appraisals in a timely fashion, we suggest having a flexible HTA team. In particular, a core group formed of six or seven people and other staff who have appropriate competencies who can be brought in when required. The core team should be formed by professionals with the following skills: two with health economics background, two with clinical pharmacy skills, one with specialised medical knowledge and one or two with critical review and statistical skills. The medical doctor might be different for each assessment, as the relevant knowledge required will vary by therapeutic area. This medical doctor need not be employed in the PS, but is likely to come from the Medical Services. So, the main advice is to have a core team but to be able to expand it when the workload requires it. These extra staff will require appropriate training. Another benefit of having a wider pool of individuals is that it would enable rotation of staff.

As with the suggested timeline, the human resources required can be modified in the light of experience with the pilot exercise. The pilot exercise will provide information on the number of people needed and the real capacity of the team.

6. DATA SOURCES AND TECHNICAL FACILITIES

In this section of the report, we define the needs related to data sources and technical facilities in order to develop the HTA.

6.1. Linkages with HTA agencies

The first item that we consider of great importance is that the HTA team need to have a very good link with other HTA bodies. This linkage will facilitate the collaboration among agencies and the exchange of information. Moreover, it will be essential for the rapid review process. Annex 1 summarises the main steps in order to find evidence in each of the selected HTA agencies websites.

6.2. Access to Databases

All the HTA staff will need access to the main databases:

- **The Cochrane database**¹. This collection of databases contains different types of high-quality, independent evidence to inform healthcare decision-making, for instance: Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, NHS Economic Evaluation Database and The Cochrane Collaboration. This resource can be provided nationally, however, this is not the case for Cyprus. The source has an Institutional license can be purchased but there is also a pay per view option (\$35 plus VAT).
- **PubMed**². This contains over 24 million citations from the biomedical literature from MEDLINE, life science journals and online books. It is a free resource.
- **Econlit**³. This is the electronic bibliography of The American Economic Association and it indexes over 120 years of economics literature from around the world. It contain index of journal articles, books, book reviews, collective volume articles, working papers and dissertations. Econlit is only provided in libraries and universities.

These databases will be crucial in order to look for information on the health technologies (i.e. clinical effectiveness, trials, economic evaluation) and to facilitate systematic review of the evidence. PubMed only provides the abstract of the paper and access to the full text must be purchased. Given the cost of journal licenses payment per paper is likely to be more efficient.

¹ <http://www.thecochranelibrary.com>

² <http://www.ncbi.nlm.nih.gov/pubmed>

³ <https://www.aeaweb.org/econlit/>

A dedicated budget for journal articles needs to be established and usage carefully monitored. In order to use Econlit, an option would be to collaborate with the University of Cyprus or a library in order to subscribe to the database.

6.3. Internal platform

Good co-ordination among those involved in HTA decision-making will be crucial. This can be facilitated by the introduction of an internal platform to share information to which all those involved in HTA have access. The documentation for each HTA will be uploaded to the platform and a follow up process can be defined for each HTA assessment. This platform will have two main objectives: coordination among the HTA bodies and monitoring of the HTA process. It will improve the efficiency of the whole process.

6.4. Website

A dedicated website is essential for maintaining the transparency of the HTA system. This website will be maintained within the PS' website. There are important decisions to be made regarding just how much information should be made available on the HTA website, for example, with respect to the work schedule, outcomes of the HTA process and the evidence used to inform decisions.

Among the most important documents that should be uploaded to the website are the Process and Methods Guide. Both documents are the ones defining the whole HTA procedure in terms of timings and methodology. Other documents that might be included on the website are: the schedule of the work programme of the HTA unit, the final recommendations of the HTA unit, the HTA's summary of the evidence, the final decision of the MOH, and the minutes of the Committees, meetings. The provision of such online information will be an important means of encouraging stakeholder engagement and facilitating transparent decision-making.

7. PROCESS

In this section, we suggest a design for the HTA process based on a combination of the different HTA systems in Europe, mainly focusing on England (NICE) and Scotland (SMC). The information from each system is selected to address the needs for the situation in Cyprus and determine the suitable HTA model.

Both a “Process Guide” and a “Methods Guide” should be produced for the new HTA system. These guides will cover the main steps involved in the HTA process and the preferred methodology to be used in the production of evidence. It is essential that all those involved in the HTA system – those reviewing evidence and those making decisions and the stakeholders (such as, the manufacturers, doctors and patients) have a common understanding of the process and methods to be used. This detailed information is crucial to meet the Transparency Directive and to facilitate the building of good working relationships with the various stakeholders.

7.1. Stakeholders involvement

A very important decision concerns the involvement of stakeholders, such as, manufacturers, patient groups and clinicians. The different stakeholders often have relevant knowledge and experience such that they can be important sources of evidence, they can assist understanding of the clinical condition and interpretation of the evidence, and they can contribute usefully to the discussion of the advantages and disadvantages of different treatments. Their potential contribution can be further enhanced by having a consultation process prior to a final decision. The advantages arising from active stakeholder involvement are in terms of increased transparency of the decision making process, permitting a wider range of expertise to be drawn upon, and increasing the acceptability of decisions. However, this has implications for the HTA process – it requires fuller reporting of decisions and, in particular, of the reasons why particular decisions were made. An important consequence is the need to build sufficient time into the overall process to permit meaningful consultation.

The HTA model designed for Cyprus anticipates the invitation of comments from the different stakeholders in both cases, when the assessment is done by the HTA unit or when it is done by the TCRM. When the HTA unit is responsible for the assessment, the first step of the process will be to contact the MAH, the clinicians, the patients groups and the specific experts relevant for each decision. The HTA team will invite them to give comments on the assessed technology. Moreover, the stakeholders will be consulted again when the HTA unit complete

their report. Then, the TCRM will make their recommendation given the report of the HTA unit and the comments from the stakeholders. On the other hand, when the TCRM undertakes the assessment, the stakeholders will be invited to give comments in the final discussion.

7.2. Process Guide

The main points to be included in the Process Guide are the phases of the procedure (NICE, 2014). A Process Guide is essential in order to facilitate appropriate engagement from stakeholders. It needs to indicate clearly the opportunities for stakeholders to be involved and the timetable to be followed by all parties.

First of all, the MAH makes a submission to the PS and the Committee decides which body will take charge of the assessment. This submission should follow a specific template that will be provided in the PS' website. The HTA team will follow the below procedure when the assessments falls under their responsibility:

- 1) First, there must be a detailed definition of the *initiation of the procedure* with a description of the health technology, a development of the scope, identification of the interested parties in the HTA, and a decision on the round of comments by the stakeholders.
- 2) The second phase involves requesting a detailed submission of evidence from the MAH, which will include the economic analysis. What information is to be provided and in what form will be defined by the MAH submission template. The MAH will also provide an electronic version of the economic model to the HTA team, so that they can check the manufacturer's results and, where appropriate, explore the impact of alternative assumptions.
- 3) The HTA team will review the evidence submitted by the manufacturer. If this submission is incomplete (poor quality or/and some required information missing), there should be the possibility to ask the manufacturer to improve it. Moreover, the HTA team will review evidence from other HTA agencies and undertake a brief literature review.
- 4) The last phase is the appraisal where a recommendation is made by the HTA team on the basis of the evidence. The outcome of this decision will be a positive or negative recommendation that will go to the TCRM supported by summaries of the relevant evidence.

7.3. Methods Guide

This guide will cover the methodology to be used in the assessments (NICE, 2013). This guide is not independent of the “Process Guide” as both guides need to be used together. A Methods Guide is important in order to facilitate consistent decision-making and to assist manufacturers in the preparation of their submissions. The main points of this guide in relation to the phases defined above are as follows.

- 1) In the first phase, when defining the scope of the technology, there are different components to be taken into account: background information on the disease or health condition, the technology, the population eligible, the comparators, the evidence base, the measures of health outcome and the measures of cost, among other issues that could impact on the technology appraisal.
- 2) It is important that the evidence and the analysis are of highest standard and are transparent. If the submission meets the standards set down in the Methods Guide it is likely to be appropriate and robust. Related to the evaluation of effectiveness, a quantification of the effect of the technology and of the relevant comparators on survival, disease progression and health-related quality of life are required. Moreover, in terms of costs, it is necessary to quantify the effect of the technology on resources used and valuing these effects in monetary terms.

The submission should also specify the nature of the evidence base, for instance, randomised control trials (RCT) or non-randomised control trials (non-RCT), systematic reviews, or qualitative research.

- 3) In the appraisal phase, the evidence presented by the HTA team will cover different aspects: defining the decision problem, comparators, perspectives on outcomes, perspective on cost, type of economic evaluation (cost-effectiveness, cost-utility, cost-benefit), time horizon, evidence on health effects, measuring and valuing health effects, data measuring HRQoL, equity considerations, evidence on resource use and cost, discounting, budget impact.

7.4. Manufacturer dossier

We base this section on the SMC Guidance to Manufacturers for Completion of New Product Assessment Form (NPAF) (April 2014). This guidance is appropriate because the SMC does not produce evidence itself, but rather relies on the manufacturers to provide it. The SMC

manufacturer dossier is a good place from which to start when designing a template for submissions to be made in Cyprus. Consideration should be given to whether the situation in Cyprus suggests that any additional information is required or whether some of the proposed information is unnecessary.

The manufacturer dossier should include the following parts:

i) Drug (generic and trade name), Company name and contact details.

ii) Patient Groups and Voluntary Organisations

1) Registration details

- a. Indication(s) for the product, which are detailed in the submission.
- b. Positioning (e.g. subpopulation of the licensed indication, only part of the licensed indication).
- c. Other indication(s) for the product.
- d. Licence status of the product for the indication(s) detailed in the submission, including dates of granted or expected marketing approval.
- e. Is the product an end of life treatment (medicine for a condition that leads to death within 3 years with currently available treatments), designated as orphan drug by EMA (equivalent size of population <5 per 10,000) or medicine use to treat a condition with a prevalence of <1 in 50,000 people i.e. ultra-orphan?
- f. Has the product been designated as a biosimilar medicine for the indication(s) detailed in the submission?
- g. Does the product require a companion diagnostic test in order to identify patients eligible for treatment?
- h. Details on estimated or actual launch date for the product in the indication(s) detailed in the submission.
- i. Details of the formulation(s) of the product that are or will be licensed for the indication(s) detailed in the submission and their actual or anticipated list price(s).
- j. Details of any relevant active comparator(s) for the product in the indication(s) detailed in the submission.
- k. Is the product or any of the relevant active comparator(s) scheduled for or are currently subject to any other form of health technology assessment?

2) Overview or Positioning. Context within which the submission is being made and if the product is an end of life medicine or a medicine that will be used to treat an orphan or ultra-orphan condition.

3) Comparative efficacy.

- a. Details of studies, which provide evidence of the clinical benefits with the medicine in the indication(s) under review relative to active comparator(s) used in clinical practice.
- b. If the clinical and / or economic case is based on only part of the marketing authorisation (selective by indication). The clinical evidence base to support the use of the product in that population should be described.
- c. Details of ongoing studies or updated analyses of studies described previously, which would provide additional evidence within the next 6 to 12 months for the medicine in the indication(s) under review

4) Comparative safety.

- a. Details of studies, which provide evidence of the clinical adverse effects with the medicine in the indication(s) under review relative to active comparator(s) used in clinical practice.
- b. Details of any additional safety issues for the medicine in the indication(s) under review compared to relevant active comparator(s), which were not identified in the studies described previously.

5) Clinical effectiveness.

- a. Relative to relevant active comparator(s).
- b. Relevance of the outcomes assessed in clinical studies to clinical benefits and adverse effects expected in practice.
- c. Describe any factors that may influence the applicability of study results to patients in routine clinical practice in Cyprus.
- d. Details of the main alternative treatments used for the indication(s) under review within clinical practice in Cyprus.
- e. Relevant guidelines and protocols relating to the medicine for the indication(s) under review.
- f. Details of any advantages or disadvantages compared to usual clinical practice with the relevant active comparator(s). These would include differences in terms of: (a) tests or investigations for selection or monitoring of patients; (b) routes or schedules of administration; and (c) service changes.

- g. State if data on the clinical benefits and adverse effects with the medicine in the indication(s) under review relative to relevant comparator(s) were available from active-controlled studies.
- h. If results from indirect or mixed treatment comparisons have been used in the economic model to define clinical benefits and adverse effects.
- i. Details of the search strategies and rationale for identification of data sources.
- j. Details of any relevant differences between the data sources providing evidence of clinical benefits and adverse effects.
- k. Provide results (hazard ratios and 95% confidence or credible intervals) and where appropriate include ranking of treatments, a measure of heterogeneity or sensitivity analysis to account for heterogeneity, description of evidence consistency, use of random or fixed effects or other relevant information.
- l. Provide a conclusion detailing any limitations in terms of the evidence synthesis or extrapolation to the Cyprus population.

6) Pharmaco-economic Evaluation (this will only be relevant for those submissions which are to be reviewed by the HTA unit). The analysis should include the following elements. It is tremendously helpful if the manufacturer indicates where each piece of information is to be found.

The design of the evaluation		Paragraph
1.	The alternatives compared are clearly described.	
2.	The rationale for choosing the alternative programmes or interventions compared is stated.	
3.	The patient group(s) considered in the economic evaluation is (are) clearly stated and justified.	
4.	The viewpoint of the analysis is clearly stated and justified.	
5.	The time horizon over which costs and benefits were calculated is stated and justified.	
6.	The primary outcome measure(s) for the economic evaluation is clearly stated and justified.	
7.	Evidence is provided linking proxy or disease-specific outcomes to final health outcomes.	
Data collection		
8.	The source(s) of effectiveness estimates used is (are) stated and cross-referenced to the clinical section of the submission.	
9.	Methods to value health states and other benefits are stated and details of the subjects from whom valuations were obtained are given.	

10.	Quantities of resources are reported separately from their unit costs.	
11.	Methods for the estimation of quantities and unit costs are described.	
12.	If a model is used, the choice of approach is justified.	
Analysis and interpretation of results		
13.	The approach to sensitivity analysis is stated.	
14.	The choice of variables for sensitivity analysis and the ranges over which the variables are varied is stated and justified.	
15.	Major outcomes are presented in a disaggregated as well as aggregated form.	
16.	The relevance (generalisability) of the analysis to Cyprus is discussed.	
17.	Any equity implications of the analysis are discussed.	

7) Resource implications. Budget impact analysis.

8) References.

7.5. Clinical Guidelines

Decisions with respect to the nature and extent of clinical guideline development activity will need to be considered. HTA can clearly assist decision making over the development of clinical guidelines. In clinical guideline development it is not uncommon to focus on reviews of clinical effectiveness and have economic evaluation play a much smaller role. This is not because consideration of cost-effectiveness is not relevant or important but rather is based on the recognition that it is not feasible or appropriated to consider the cost-effectiveness of all of the different options at every step in the clinical pathway.

8. RECOMMENDATIONS

- (1) A particular HTA model is recommended for Cyprus, which has two different pathways depending on whether or not an assessment is to be made of clinical effectiveness and cost-effectiveness.**
- (2) A small dedicated committee will review all proposals and determine which pathway is appropriate.**
- (3) Potential criteria by which pathway decisions can be made are the therapeutic area, likely budget impact, degree of innovation and anticipated added value.**
- (4) Those medicines selected for clinical and economic evaluation will be handled by an HTA unit within PS.**
- (5) The competencies required by the HTA unit include: searching for evidence, understanding of design of clinical studies, evidence synthesis, health economic modelling, and interpretation of clinical and economic evidence.**
- (6) A programme of training is required in order to ensure that not only the HTA unit has the full set of competencies required, but a wider group within PS have these competencies so that the HTA unit can respond flexibly to peaks in HTA workload.**
- (7) It is recommended that the new system be introduced at a particular future date rather than having two systems running in parallel for a period.**
- (8) A number of drugs, which are already provided in Cyprus, should be assessed by the HTA unit as if they were new submissions in order to provide valuable training opportunities prior to the introduction of the new system.**
- (9) Consideration should be given to running pilot appraisals with members of the TCRM and stakeholders.**
- (10) An evaluation of all aspects of the new system should be undertaken one year after its introduction.**
- (11) A conflict of interest policy should be designed for both Ministry of Health employees and the stakeholders in order to provide greater transparency.**
- (12) Explicit consideration needs to be given to what relationship between health benefits and costs represents good or poor value for money.**

9. REFERENCES

- AIFA (2007), “Criteria for ranking therapeutic innovation of new drugs and elements for supplementing the dossier for admission to the reimbursement system”, Working Group on Innovative Drugs.
- Barnieh, L., Manns, B., Harris, A., Blom, M., Donaldson, C., Klarenbach, S., HuserEAU, D., Lorenzetti, D. and Clement, F. (2014) “ A synthesis of Drug Reimbursement Decision-Making Processes in Organisation for Economic Co-operation and Development countries”, *Value in Health*, 17, 98-108.
- Council Directive 89/105/EEC (1989), harmonised provisions to ensure the transparency of national provisions regulating the pricing and reimbursement of medicinal products.
- Fischer, K. (2012) ‘A systematic review of coverage decision-making on health technologies—Evidence from the real world’, *Health Policy*, 107, 218-230.
- Franken, M., Le Polain, M., Koopmanschap, M. and Cleemput, I. (2012) ‘Similarities and differences between five European drug reimbursement systems’ *International Journal of Technology Assessment in Health Care*, 28:4, 349–357.
- Hutton, J., McGrath, C., Frybourg, JM., Tremblay, M., Bramley-Harker, E., Henshall, C. (2006) ‘Framework for describing and classifying decision-making systems using technology assessment to determine the reimbursement of health technologies (fourth hurdle systems)’. *International Journal of Technology Assessment in Health Care*; 22(1):10-8.
- Le Polain, M., Franken, M., Koopmanschap, M. and Cleemput, I. (2010) ‘Drug reimbursement system: international comparison and policy recommendation’, *Belgian Health Care Knowledge Centre, KCE reports 147C*.
- Miners, A., Maynou, L. and Ruiz, F. (2014) ‘The UK’s National Institute for Health and Care Excellence (NICE) and the application of evidence-based policy making.’ *Asociación de Economía de la Salud, Boletín Informativo no. 80*, from:
<http://www.aes.es/boletines/news.php?idB=21&idN=1311>.
- NICE (2014) Guide to the processes of technology appraisal. 2014.
- NICE (2013) Guide to the methods of technology appraisal. 2013.
- Paris, V. and Belloni, A. (2013), ‘Value in Pharmaceutical Pricing’, *OECD Health Working Papers*, No. 63, OECD Publishing.

- Sigmund, H., Kristensen, FB. And Bonnevie, B. (2007) “HTA- clarifications and planning”, *Health Technology Assessment Handbook, DACEHTA*.
- Sorenson, C., M. Drummond and P. Kanavos (2008) ‘Ensuring value for money in health care: the role of health technology assessment in the European Union’, *European Observatory on Health Systems and Policies*, Copenhagen.
- SMC Guidance to Manufacturers for Completion of New Product Assessment Form (NPAF) (April 2014).
- Theodorou, M., Charalambous, C., Petrou, C. and Cylus, J. (2012) “Cyprus: Health System Review”, *Health Systems in Transition*, 14(6):1–128.
- Wilsdon, T. and A. Serota (2011) ‘A comparative role and impact of health technology assessment’, *Charles River Associates*, London.

ANNEX 1. HTA AGENCIES' WEBSITES

In this annex, we analyse the dissemination of different HTA bodies. In particular, we describe the path that needs to be followed inside the websites, in order to find the main documents related to the HTA procedure. NICE is the agency with more documents publicly available on its website. The other agencies analysed in this annex, only upload the final decision/recommendation.

ENGLAND AND WALES: NICE

www.nice.org.uk

- 1) Inside "Guidance" --- "Conditions and disease" --- e.g. "Cancer" (or other categories).

<http://www.nice.org.uk/GuidanceMenu/Conditions-and-diseases>

Inside each category you can find technology appraisals, guidelines, guidance in development, quality standards, NICE advice, NICE diagnostics guidance and NICE interventional procedures guidance.

- 2) For the HTA process, you can look inside each technology appraisal where you can read the whole guidance (very detailed) and also a Pathway for the condition.
- 3) Once you are inside the technology appraisal, on the left hand side, you have information on how this guidance was made.
 - a. Resources: audit support, costing template, Multiple guidance audit tool, Uptake databases and Guidance into practice.
 - b. History: timeline of the guidance and documents. In the documents section there is a lot of information: background information, final appraisal determination, appraisal consultation document and evidence considered.
- 4) Inside the technology appraisal, there is another section called "Information for the public" where you can find a pdf document with the information on how to understand the guidance.

SCOTLAND: SMC

<https://www.scottishmedicines.org.uk/Home>

Inside “SMC Advice” you can look for all the drugs that have been assessed. You will find a pdf document for each decision with an analysis, but it is not very exhaustive. This agency is only providing the final decision.

BELGIUM: INAMI

<http://www.inami.fgov.be/homefr.htm>

- 1) Inside “Médicaments et autres fournitures pharmaceutiques” --- “Médicaments” ---- Décisions du Ministre et rapports d'évaluation par la CRM ---- “Décisions du Ministre” - --- “moteur de recherche”.

http://www.inami.fgov.be/inami_prd/ssp/cns2/pages/SpecialityCns.asp

- 2) In “moteur de recherche” you enter into a database where you can get the decision of each drug by selecting the name. Inside the decision you can see a summary of the analysis.

For this agency, you can only find the final recommendation uploaded and the following submissions (e.g. when there is a new indication for an already assessed drug). The recommendations are in French and Dutch.

SWEDEN: TLV

<http://www.tlv.se/In-English/in-english/>

<http://www.tlv.se/beslut/>

- 1) Inside “Sök an database” you can type the drug and find out if it is reimbursed. Once you know the type of reimbursement of that specific drug, you can go on “Beslut läkemedel” and look for the decision in “Generell subvention” or “Begränsad subvention” or “Avslag och utslutningar” (general subvention, restricted subvention and non-subvention).
- 2) When you find the link for the specific drug, you can enter into it and look at the decision. The analysis (clinical and economic) is very detailed. The only problem is that it is in Swedish. For this agency, you can only find the final recommendation uploaded.

SWEDEN: NLT (hospital drugs)

<http://www.skl.se>

http://www.skl.se/vi_arbetar_med/halsoochvard/lakemedel/nya-lakemedel/nlt/rek

In the last link, you can find the NLT recommendations. The analysis inside the recommendation is done by the TLV and it is very detailed. These recommendations are not binding, but the final decision has, in most of the cases, the same outcome.

CANADA: CADTH

<http://www.cadth.ca/en>

Inside “Products” --- “Health Technology Assessment” --- “Common Drug Review”. You find a database for the drugs assessed. For each drug you can find: date of submission, date of recommendation, the indication, the status of the recommendation and two documents, the submission status report and the final recommendations and reasons. This last report is only there when the recommendation is completed, but it is not very detailed.

AUSTRALIA: PBAC

<http://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings>

The PBAC meets every three months and makes recommendations for a number of drugs. You can find a brief summary of the recommendation for all the drugs recommended on that meeting (PBAC outcomes), but also a detailed analysis for each drug (Public Summary Documents). It is not straightforward to find the analysis, as there is not a search place that leads you to the individual decision. However, the Public Summary for each drug is quite complete. For this agency, you can only find the final recommendation uploaded.