Advance HTA

Rethinking the future of Health Technology Assessment

D7.1: A horizontal and vertical exposé of lessons learned and policy recommendations

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SEVENTH FRAMEWORK PROGRAMME

Advance HTA

List of Abbreviations

EASP	Escuela Andaluza de Salud Publica (Andalusian School of Public Health)
EBC	European Brain Council
EC	European Commission
EFTA	European Free Trade Association
EMA	European Medicines Agency
EU	European Union
EUnetHTA	European Network for Heath Technology Assessment
GDP	Gross Domestic Product
HAS	Haute Autorite de Sante (High Authority for Health)
MCDA	Multiple Criteria Decision Analysis
NICE	National Institute for Health and Care Excellence
OECD	Organisation for Economic Co-operation and Development
PPRI	Pharmaceutical Pricing and Reimbursement Information
QALY	Quality-Adjusted Life-Years
TLV	Tandvårds- och läkemedelsförmånsverket (Dental and Pharmaceutical Benefits Board)
VBA	Value-Based Assessment
WHO	World Health Organisation
WP	Work Package

Abstract

This final deliverable of Advance-HTA (D7.1) aims to contribute to the debate on future developments in Health Technology Assessment, the advances in a number of aspects of HTA implementation, the policy implications these are having and their contribution to the debate of efficiency in resource allocation in health care systems and the related health system sustainability.

The specific objectives of this report are threefold:

First, to provide a concrete analysis of the policy implications of the research results for HTA in the domains researched upon (part I of the report);

Second, to identify how the research results can be incorporated in the decision-making process and implemented at national, supra-national and international level and what implications are there for specific stakeholders (part I of the report);

Based on the above objectives, the key findings per work package are summarized in a number of sections notably:

- Objectives
- Methods deployed
- Key findings
- Policy implications
- Recommendations to stakeholders
    - Regional government level
    - National government level
    - Supra-national & international level
    - Patient level
    - Health care professional level
    - Procurers of medical technologies
- Contribution to the debate of efficiency in resource allocation in health care systems
- Future development: application in the real world

Third, in synthesizing the results of this project, part II of this report explores the wider conceptual/theoretical, economic, social, political, R&D, and policy implications for HTA and the relevance of the findings of Advance-HTA in this context.

Contents

Background

The London School of Economics and Political Science – LSE Health (LSE) together with 12 other academic and institutional partners have been awarded this grant by the European Commission under DG Research's 7th Framework Programme. The consortium combines geographical and disciplinary diversity with academic rigour and policy relevance emphasized by the members' experience in linking research to policy and comprises the following institutions: 1) The London School of Economics and Political Science – LSE Health (LSE), UK; 2) The London School of Hygiene and Tropical Medicine (LSHTM), UK; 3) Istituto Superiore di Sanità (ISS), Italy; 4) University of Castilla-La Mancha, Spain; 5) The Institute for Economic Research, Slovenia; 6) Technische Universität Berlin, Germany; 7) The Andalusian School of Public Health, Spain; 8) Pan American Health Organisation (PAHO), USA; 9) The European Brain Council (EBC), Belgium; 10) University Paris-Est Créteil, France; 11) National Institute for Health and Clinical Excellence (NICE) - International, UK; 12) Agency for Health Technology Assessment (AOTM), Poland; 13) The Dental and Pharmaceutical Benefits Agency (TLV), Sweden.

ADVANCE-HTA aims to contribute to advances in the methods and practices for HTA in European and other settings by involving the wider stakeholder community in areas actively and heavily debated given their implications for decision-making and resource allocation. ADVANCE-HTA aims to make a number of contributions in six distinct areas, which carry significant policy implications for resource allocation (see Figures 1 and 2). These are:

- First, the *issue around value for money* and the different approaches surrounding current thresholds for resource allocation, where ADVANCE-HTA will systematically explore alternative means of assessing value for money and trace the implications for the conduct of HTA and the use of cost-effectiveness data to inform decision-making.

- Second, the *concept of value assessment*, and the factors that need to be considered and incorporated beyond cost effectiveness, such as burden of disease, disease severity, quality of the data and evidence produced and the implications these are having on the continuous assessment of new health technologies and relative effectiveness. ADVANCE-HTA will aim to explore new tools and methodologies in this domain, for example Multi-Criteria Decision Analysis, and investigate their adoption and implementation.

- Third, to improve the quality of the evidence required for and the *methods associated with the assessment of rare diseases* by relying on new data providing a more realistic understanding of the socio-economic benefits of orphan drugs. In this context, ADVANCE-HTA it will develop and validate a framework to support decision-making relating to orphan drugs for rare diseases, by means of a Multi-Criteria-Decision framework.

- Fourth, to improve the robustness of the evidence on the *elicitation of preferences* by deriving these in more realistic settings, by drawing on the wider EU citizenship and from within the patient community. ADVANCE-HTA will create new data that will incorporate

patient-relevant values into widely used tools of quality of life measurement, such as the EQ-5D.

- Fifth, to advance the debate on the suitability of current HTA tools across *different categories of medical devices*, including diagnostics, ADVANCE-HTA will consolidate the current methods for assessing HTA in medical devices in different settings, address their suitability to appraise different types of medical devices, including diagnostics and propose how current tools can be modified or adapted in order to arrive at more robust methods of assessment.

- Sixth, to improve the *implementation and capacity building of HTA*, also incorporating improvements as outlined above in settings outside Europe, where HTA is beginning to be considered explicitly in decision-making. ADVANCE-HTA will create a framework for HTAs at different levels (national, hospital [mini-HTAs]) by benchmarking with evidence from countries that have developed such frameworks.

Additional activities within ADVANCE-HTA contribute to furthering the debate on future developments in HTA by bringing together the research being conducted across the Consortium. Further, extensive dissemination of the results has been carried out by effectively linking policy makers, stakeholders and patient networks to the research evidence on HTA.

ADVANCE-HTA impacts a range of stakeholders and activities. The methodological advances in HTA are likely to influence developments in areas such as value-based pricing of medical technologies, or other areas of HTA (e.g. mini-HTAs). Capacity building activities in Latin America and Eastern Europe have transferred the accumulated expertise to countries that are new to HTA, while involving experts from other settings on the debate surrounding HTA and the health care resource allocation debate.

Overall, ADVANCE-HTA aims to broaden the spectrum, complement and address areas of intense methodological debate in the application, use and implementation of HTA. It also aims to improve HTA methods, which can be taken further by competent authorities nationally whilst supplementing the work of supra-national bodies (e.g. EUnetHTA) towards a common understanding of choices in health care decision-making.

This final deliverable of Advance-HTA (D7.1) contributes to the debate on future developments in Health Technology Assessment, the advances in a number of aspects of HTA implementation, the policy implications these are having and their contribution to the debate of efficiency in resource allocation in health care systems and the related health system sustainability.

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    - Procurers of medical technologies
- Contribution to the debate of efficiency in resource allocation in health care systems
- Future development: application in the real world

Third, in synthesizing the results of this project, part II of this report explores the wider conceptual/theoretical, economic, social, political, R&D, and policy implications for HTA and the relevance of the findings of Advance-HTA in this context.

Figure 1: An outline of Advance-HTA and its work packages

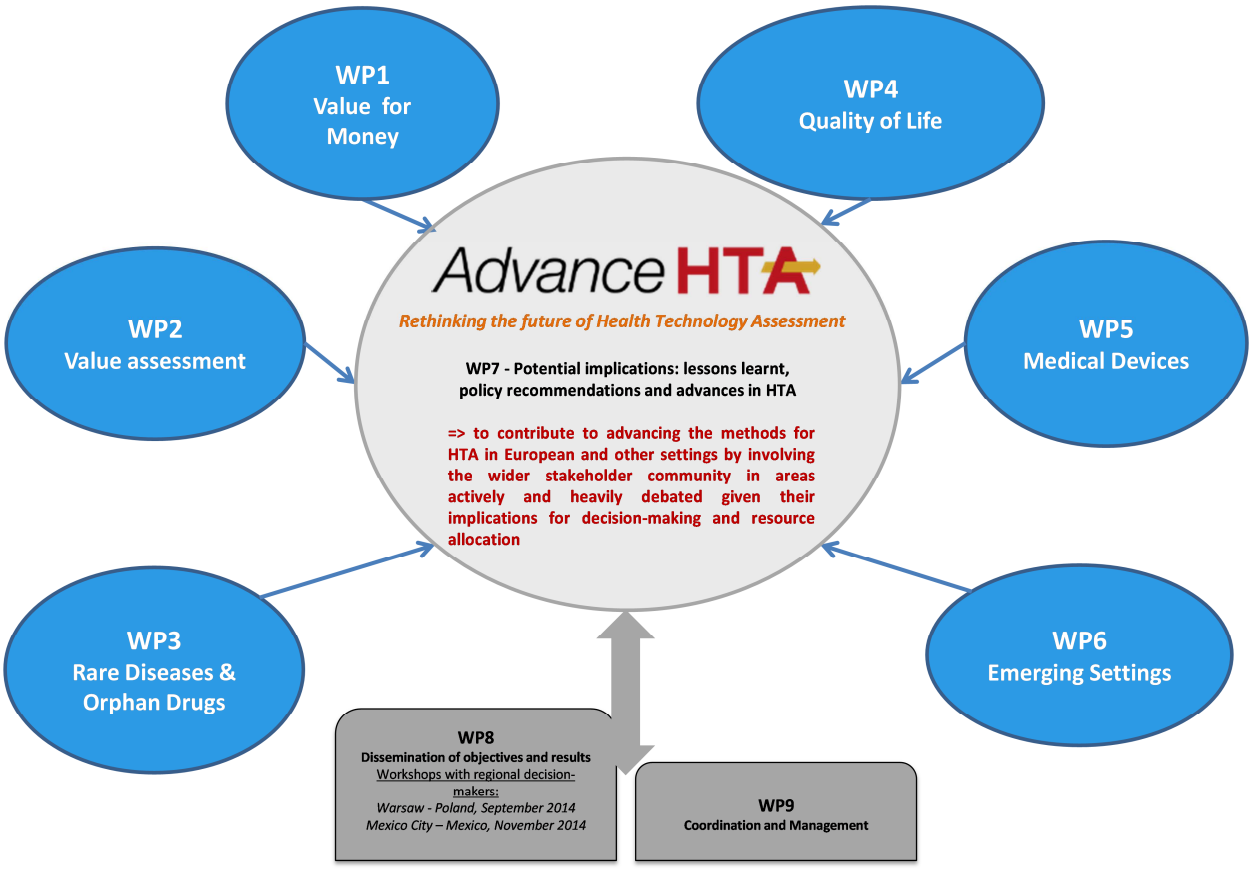
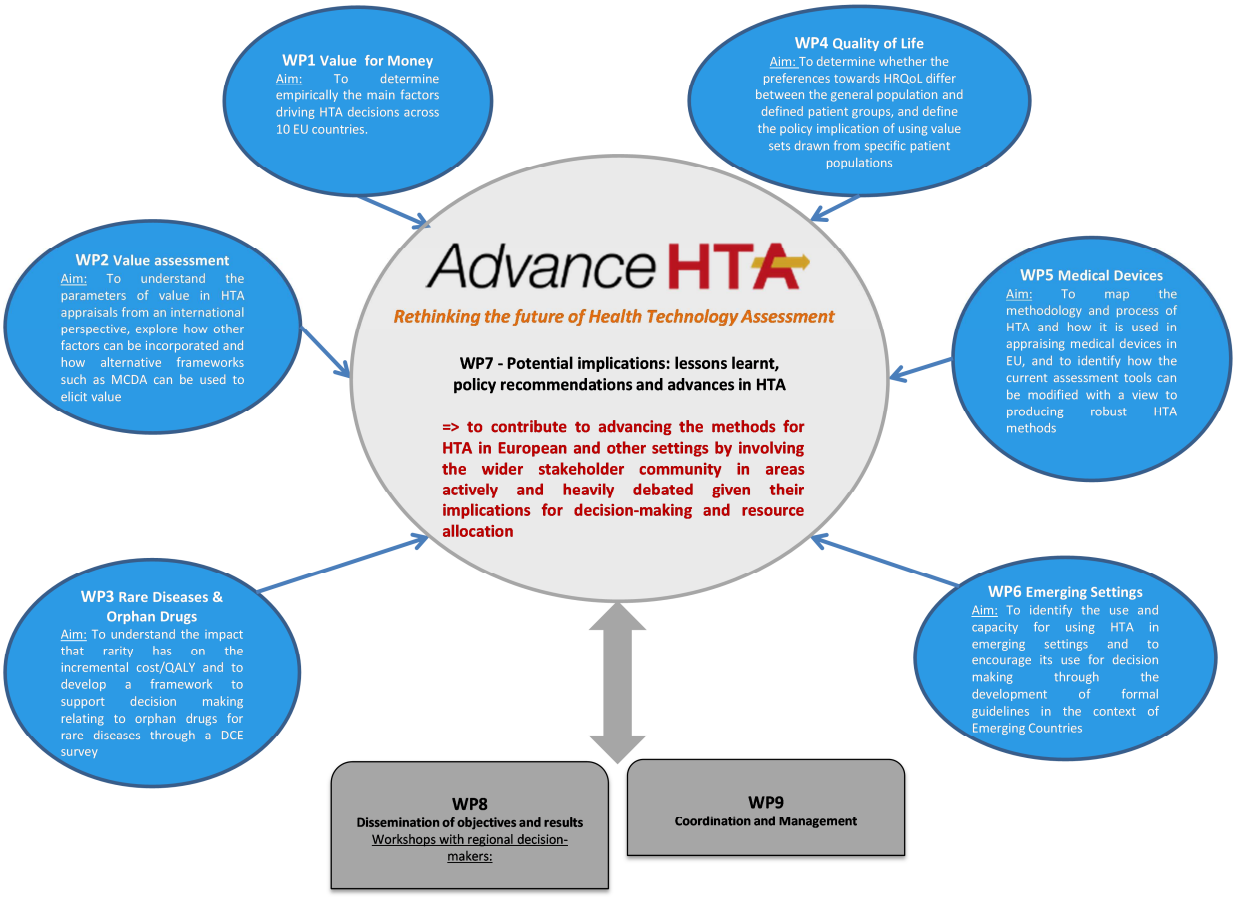


Figure 2: A presentation of key Work Package features of Advance-HTA



Part I: Horizontal analysis of results achieved – A Comparative presentation and scenario development based on the research findings and implementation

1. Work Package 1: Value for money

1.1. Work package Objectives

- To expand knowledge and understanding of the advantages and disadvantages of the different approaches to assess cost-effectiveness and the main factors defining HTA decision-making and to construct a database of HTA decisions of different European countries;
- To consolidate the lessons from existing research, and to identify what new research would be of greatest value to improve HTA decision-making processes; and
- To advance the methodology in HTA by systematically exploring alternative means of assessing value for money and tracing the implications for the conduct of HTA and the use of cost-effectiveness data to inform decision-making regarding which health technologies to adopt, by empirically identifying the main factors driving HTA decision-making across countries

1.2. Methods

Key methods deployed: (a) Systematic review; (b) Tool development

The methodology applied to this work package involved developing a taxonomy characterizing the system-wide, the product-specific and the socioeconomic conditions. Key informants of the HTA system were analysed and interviewed from ten selected European countries - Belgium, France, Germany, Netherlands, Poland, Portugal, Spain, Sweden and United Kingdom. England and Scotland were analysed separately, due to the differences between the two systems.

Data was collected then regarding HTA decisions in respect to Cancer, Multiple Sclerosis and Rheumatoid Arthritis drugs for the selected 10 countries. This included the decision outcome, date of decision and taxonomy. The data was taken from the national websites or from internal databases.

An econometric analysis was applied using the data collected and the taxonomy variables.

1.3. Key findings

Through the application of an econometric model, we were able to identification the key features (similarities and differences) across the HTA systems.

This included (a) the classification of the HTA systems in terms of the taxonomy variables;

(b) Identification of a country specific pathway in order to find the HTA decisions in the website or internal database and (c) the identification of the differences across countries in terms of transparency and accessibility to the decisions.

The two key findings were being able to empirically identify the main factors (Table I) driving HTA decisions across countries and differences across country and time which were captured in the econometric model.

Table I. Decision outcome by therapeutic area

Decisions	CANCER	MULTIPLE SCLEROSIS	RHEUMATOID ARTHRITIS	TOTAL
Non-Favourable	122 (14.3%)	7 (7.6%)	6 (4.5%)	**135 (12.5%)**
Restricted	190 (22.3%)	32 (34.8%)	56 (42.4%)	**278 (25.8%)**
Favourable	541 (63.4%)	53 (57.6%)	70 (53.1%)	**664 (61.7%)**
Total	853 (100%)	92 (100%)	132 (100%)	**1077 (100%)**

1.4. Policy implications

In order to understand why HTA decisions may differ across countries, there is a need to know the differences between the health care systems. These differences relate to the system-wide variables.

During the data collection process there was difficulty in finding factors impacting on HTA decisions. Therefore, we believe there is scope for greater transparency and accessibility in the decision making process, across countries and within the HTA community.

By policy-makers being aware of the factors that drive the HTA decisions, a new or reformed HTA process can help defining the procedure.

1.5. Recommendations to stakeholders

Having highlighted the key features of the HTA system of each country, we would recommend that stakeholders use the taxonomy in order to understand differences across countries.

The patients groups and the health care professionals in particular would be interested in having these decisions available to encourage the improvement of access to the system and influencing final choices.

Through the analysis undertaken and data collected, stakeholders will have greater awareness of the determinants of drug reimbursement decisions, therefore empowering them to shape the process.

Regional government level/National government level /Supra-national & international level

For the National and Supra-national governments, in order to understand why HTA decisions may differ across countries, they need to know the differences between the systems.

Both, the documentary analysis of the HTA systems and the taxonomy are essential for understanding the differences across systems. The advantage of the taxonomy is that it is easy to interpret.

There are examples of good practice of countries with good accessibility and transparency, which other countries may want to follow.

Patient level/Health care professional level

For the patients and health care professionals, the documentary analysis of the HTA systems and the taxonomy defining each system, is very important to understand the differences in decisions across countries. The advantage of the taxonomy is that it is easy to interpret;

Patients and Health Professionals would be interested on having these decisions available. They should encourage the improvement of access to the system;

Relevant information of the important factors driving HTA decision-making. The patients and health professionals will have a better knowledge of how to influence decisions.

Procurers of medical technologies

It is useful for the procurer to be aware of decisions from other countries and the general framework in which such decisions are taking place as well as the system-level variables that may influence decision-making processes.

1.6. Contribution to the debate of efficiency in resource allocation in health care systems

By analysing the drug reimbursement decisions across countries, this work package examines and explains how HTA decision-making works. In other words, it helps understanding whether or not a drug is accepted in the positive list of a country. This research contributes to this debate, as the final decision has an impact on resource allocation as not all drugs can be reimbursed due to budget limitations.

The main factors determining the final decisions and the differences across countries have been the main aim of this research.

Moreover, the contribution of our findings to other work packages is mainly the in-depth understanding of HTA decision-making. Our research will help patients, health professionals and decision-makers to better understand drug reimbursement decisions. Under WP2 (Value Assessment), our results complement the micro level analysis undertaken and has potentially great interest for the model they are presenting.

In WP3 (HTA and Rare Diseases: Assessing the Societal Value of Orphan Drugs) and WP4 (HTA and Quality of Life Measurement) we carried out surveys with patients and the general population. Findings and analysis from WP1 can be conveyed and applied to the surveys, providing a more in depth cross-analysis. WP5 designed a taxonomy for medical devices, which complements our taxonomy of drug reimbursement systems.

Finally, WP6 can complement its tool for HTA implementation with relevant findings from WP1 research.

1.7. Future development: application in the real world

The findings of our WP1 have a straightforward application to the real word. The HTA community (decision-makers, patients, health care professional) can, first of all, benefit from our taxonomy of drug reimbursement systems. Secondly, the factors associated with a higher or lower probability of reimbursement can be used to better understand the final decisions. Finally, all this information can be used when a new HTA system is implemented or it is reformed.

The future steps of WP1 are the following:

- Include more countries and more therapeutic areas into the analysis, in order, to improve the econometric inference.
- Determine new assumptions for the database. For example, consider rejection for French decisions when ASMR is 5 and for Germany when the drug is non-adding value.

- Analysis of the effect of the crisis in cancer drug reimbursement procedures across countries.
- Analyse the effect of different drug reimbursement decisions across countries on health outcomes (country based).

2. Work Package 2: Value Assessment in HTA

2.1. Work package Objectives

- To understand the parameters of value in HTA appraisals from an international perspective;
- To explore how factors such as disease severity, burden of disease, distinguishing between levels of innovation, and the quality of the available evidence can be incorporated more explicitly – and in a quantifiable way, in the HTA process;
- To explore how alternative analytical frameworks, such as Decision Analysis, can be used to elicit value;
- To conduct case studies in specific disease areas by using alternative analytical tools and by explicitly incorporating all identified parameters of value.

2.2. Methods

Key methods deployed: (a) systematic review; (b) development of 2 tools, one for *retrospective* analysis of HTAs, based on a detailed study of HTA recommendations and the factors influencing them and one for *prospective* analysis of value drivers, based on multiple criteria decision analysis (MCDA) principles.

Conceptual and theoretical foundations of MCDA were explored, which led to the development of an MCDA methodological framework and a generic value tree for assessing the value of new medical technologies.

The development of the Advance Value Tree © was undertaken through an experimental application using two real world case studies; one with multiple stakeholders (UK) and one with an HTA agency (TLV Sweden).

2.3. Key findings

Overall, all countries assess similar types of evidence, however the specific endpoints used, their level of provision and requirement, the way they are incorporated (e.g. explicitly vs. implicitly) and their relative importance varies across countries. The main evidence assessed could be divided into four clusters of evidence: (a) burden of disease; (b) therapeutic impact; (c) innovation level; and (d) socioeconomic impact.

We have proposed a methodological process outlining the use of MCDA in the context of HTA based on Multi Attribute Value Theory methods and the respective phases and stages of such a process. We are suggesting using the MACEBTH technique for scoring the alternative options through the elicitation of value functions, the assignment of weights through a swing weighting technique, and the aggregation of scores and weights through a linear additive model. We have developed a generic value tree consisting of the following five clusters: (a) burden of disease; (b) therapeutic impact; (c) safety profile; (d) innovation level; and (e) socioeconomic impact.

The methodological framework and value tree we developed were applied and adapted accordingly to assess the value of the alternative drugs considered under the scope of the exercises. The drugs were ranked based on their overall value by producing explicit index scores. Finally a cost per value metric was derived to reflect their value for money.

2.4. Policy implications

The main policy implications found through exploring value assessment in health technologies are: (a) the absence of an explicit value for money definition; (b) the inadequacy and subjectivity in a significant part of the evaluation criteria used and (c) the heterogeneity over HTA recommendations across settings, partly as a result of the above.

Although a variety of MCDA techniques exist, it is likely that the most important stages that act as the foundations to the analysis are the establishment of objectives and the definition of criteria and attributes.

MCDA has the potential to generate a more holistic metric of value.

The incorporation of costs can produce a metric of efficiency, involving incremental cost per incremental MCDA value unit - which can be used for reimbursement and coverage decisions.

Overall, the MCDA approach provides improved comprehensiveness, flexibility, and transparency.

2.5. Recommendations to stakeholders

Decision-makers as well as other stakeholders need clear, comprehensive and transparent ways of assessing clinical and economic benefit and the impact those new treatments have from a wider socio-economic perspective in order to make rational decisions about priority setting. By not having such methods creates a conceptual, methodological and policy gap.

We have focused on best practice requirements, as reflected through the appropriate properties needed for criteria and attribute selection, all of which feed into the model-building phase.

We would recommend attention is paid on the theoretical foundations of decision analysis so that the results are meaningful and decision recommendations provided are robust.

Regional government level/ National government level/ Supra-national & international level

Any efforts of MCDA implementation should start by building a research team with the appropriate technical expertise as part of an educational phase.

A number of hypothetical pilot studies could be carried out in a testing phase acting as testing exercises, in order to gain a first-hand experience on the technical aspects of the MCDA process.

Actual case studies could be conducted as part of a transition phase, using actual evidence from past health technology appraisals.

Finally, the MCDA approach could become fully operational as part of an execution phase, running in parallel with any existing formal appraisals taking place. The MCDA approach could start as a supplementary source of information, acting as a decision making tool on top of standard appraisals, and then following the decision making needs and vision of the Agency it could eventually become the sole approach implemented.

Patient level/Health care professional level

At a Patient and Healthcare professional level, we would recommend that these stakeholders can be involved in the model building phase so that their value concerns are included. Their participation in the model assessment and mode appraisal phase can ensure that their preferences are incorporated.

Procurers of medical technologies

It is very useful for procurers of medical technologies to understand – whether prospectively or retrospectively – how value is assessed in different settings, what criteria are used in different circumstances and whether social value judgements do make a difference in reaching a decision. Additionally, the MCDA tool (Advance Value Framework) developed through the project, provides a structured approach to decision-making and has applications across different stages of the HTA process, including regulatory decisions and R&D decisions, among others.

2.6. Contribution to the debate of efficiency in resource allocation in health care systems

The findings of WP2 exert important contributions to the debate of efficiency in resource allocation by offering an alternative approach for assessing and appraising the value of new medical technologies. Through the explicit incorporation of multiple criteria and the elicitation

of their relative importance for the particular decision context through the assignment of quantitative weights, it offers a more holistic and accurate way of identifying and quantifying the benefit component of new therapies.

The distinct but interconnected stages of value judgements' establishment and preferences' elicitation, accompanied by the transparency of the methodological framework across all its stages, makes this as an ideal tool that could be used to facilitate the overall process of decision making in the context of Health Technology Assessment. Incorporation of the purchasing costs of the alternative options at the end can give rise to a metric of efficiency, taking the form of cost per unit of MCDA value.

Assuming that the benefit component arising are robust and that they can capture more comprehensively the different value dimensions of the alternative options under consideration, then any improvements in the efficiency of resource allocation realised, possibly through the application of portfolio optimisation methods, could overall enhance health outcomes in the society.

2.7. Future development: application in the real world

This is a newly emerging research area that is still in its infancy stage. Testing in practice any forthcoming future developments through real world applications will prove vital for the validation of such approaches, a prerequisite for their implementation in routine policy making. These applications should be scientifically robust, respecting all the necessary theoretical foundations, but on the same time they should be conducted in collaboration with the actual decision makers and any key stakeholders which they aim to serve in order to maximise the insights that they can offer.

Following up with a series of similar case studies that adopt the same scope of exercise and decision context as the ones conducted already, but with the involvement of decision makers across different countries, would be the immediate application in the short term which could highlight any differences in their value judgements and preferences. Application of the methodology for other sets of alternative treatments, both within the same disease indication but also across disease indications could be the next round of applications in the medium term, in tandem with additional research around the way of prioritising the allocation of resources involving portfolio optimisation methods for the case of definite budgets or the exploration of "efficiency" thresholds establishment.

Finally, the methodology could be investigated and applied in a range of different health care related decision contexts, including shared clinician-patient decision making at the prescribing stage, the licencing approval of new technologies at the marketing authorisation stage, and the pipeline optimisation of new medicines at the development stage.

3. Work Package 3: HTA and Rare Diseases - Assessing the Societal Value of Orphan Drugs

3.1. Work package Objectives

Horizontal and vertical coordination of WP3: In order to generate a more robust basis to the assessment of orphan drugs, there is need to understand the current criteria based on which value assessments are being made;

Current criteria of value assessment for orphan drugs: To understand in what way(s) does rarity impact in assessing the cost effectiveness of orphan drugs compared with drugs for more common diseases and whether rarity impacts mainly on the incremental costs or on the incremental QALYs;

- Impact of rarity in assessing the clinical cost effectiveness of orphan drugs compared to common drugs (QALY threshold criterion)

As part of WP3, a small number of case studies were conducted to test empirically the effectiveness and societal value of orphan treatments and the above approach, by using registry data. A specific Questionnaire was also developed to collect information from patient groups on the societal value of orphan drugs.

3.2. Methods

Key methods deployed: (a) Systematic literature review; (b) Tool development (discrete choice experiment) and application.

Based on results from the systematic comparison of HTA decision processes for 10 orphan drugs in four European countries, we explored the differences across countries through semi-structured interviews with HTA body representatives. Qualitative thematic data analysis was applied to the interview transcripts using the Framework Approach.

A comparison of 31 drug-indication pairs within 3 therapy areas (cancer, orphan and central nervous system treatments), and across four countries (England, Scotland, Sweden, France) was performed.

Qualitative thematic data analysis was applied to the interview transcripts using the Framework Approach. This identified systematically the criteria considered during the decision processes. A quantitative analysis of these criteria enabled us to measure cross-country agreement in accounting for these criteria as well as agency-specific risk and value preferences.

The development of the tool enabled us to obtain the potential attributes considered important in terms of evaluating rare disease by general public, decision makers and patients. It also gave us a chance to develop a DCE survey online in five countries (England, Germany, France, Italy and Spain) to obtain decision makers preferences with rare diseases on funding decisions for health technologies. The development a pilot questionnaire outlined preferences with rare diseases on funding decisions for health technologies, while the DCE survey online in Italy provided details on patients' preferences with cystic fibrosis and haemophilia from Registries.

3.3. Key findings

The application of the framework allowed us to capture the full taxonomy of criteria considered, at each stage of the decision process, together with how the criteria were provided and how they influenced the final decision. The criteria were decomposed across the decision process in order to render these complex processes in a comparable manner.

Quantitative analysis of these criteria enabled to measure cross-national agreement in handling uncertainty, and risk and value preferences influencing these decision processes.

Cross-national differences at each stage of the decision process were identified, and differentiated according to whether they were a consequence of context-specific considerations from those that were a consequence of the application of HTA and potential methodological limitations.

Focusing on those issues relating specifically to rare diseases (e.g. small patient populations) enabled us to understand how the different countries dealt with these issues, facilitating cross-country learning.

This systematic review identified relevant attributes to study patients, decision makers and general public preferences around health technologies on rare disease. The attributes found were improvement in health, cost of treatment, side effects, waiting time, severity of disease, availability of other treatments and value for money and should be considered to better capture and describe the preferences of the society on HTA.

The data obtained from the DCE survey in the five countries by decisions makers was used to estimate the weights associated with each criteria by means of regression models.

The five country models (each probit and logit), show preferences for some attributes over others. "Cost of the treatment" (Spain, France, England and Italy), "improvement in health" (Germany, France, England and Italy), "value for money" (England, Germany and France), "availability of other treatment" (England and France), "waiting times" (Germany, Spain and Italy), "side effects" (Italy) and "beginning of life" (Germany) are the attributes receiving greatest attention, while less important are "important of the disease" (France, England and

Germany), “value for money” (Spain), “availability of other treatment” (Italy and Spain), “waiting times” (France and England) “beginning of life” (Italy) and “side effects” (France and Spain).

The data obtained from the DCE survey from the registries of patients with cystic fibrosis and hemophilia in Italy was used to estimate the weights associated with each criteria by means of regression models. The findings presented in this document provide evidence about how patients with cystic fibrosis and haemophilia think that decision should be made in Italy when considering which health technology scenarios are more appropriate to receive funding. “Improvements in health”, “the cost of treatment” and “value for money” are the attributes receiving greatest attention from patients with rare diseases, while less important for patients with rare diseases are “importance of the diseases” and available of other treatment”.

The DCEs conducted in this study provided valuable insights regarding benefit valuation and are therefore useful as additional information to complement QALYs when assessing health care interventions.

3.4. Policy implications

There were five key policy implications identified from the study.

(i) The extent of cross-national differences in the HTA recommendations further emphasise that they matter (for patients and for society);

(ii) Raising awareness about the different ways of conducting HTA provides a way forward to highlighting those cases when they are a consequence of limitations in the application of HTA methods, and learn from how these were dealt with across countries (cross-country learning). This can be useful for initiatives focusing on improving European collaboration (EUnetHTA);

(iii) It also allows us to focus on those cases dealing with issues relating to rarity and how they were dealt with across settings; and

(iv) Retrospectively identifying the social value judgments made throughout the deliberative process provides a way forward to (a) identify areas where societal preferences may need further elicitation, (b) improve their accountability for reasonableness, and (c) improve the consistency in their use.

Through these findings, a general algorithm could be developed to facilitate making uniform decisions over rarity impact in assessing the cost effectiveness of orphan drugs.

In its current form, the preference data may be used in a number of ways; together with other relevant information and to inform the difficult priority-setting dilemmas faced by health policy decision makers.

Changed allocation decisions and priority setting due to differences in attributes utilities attached to the DCE survey.

The results are useful and indicative of what may be possible in future, more comprehensive research initiatives of this type.

3.5. Recommendations to stakeholders

Our key recommendations to applying this framework across drugs and countries are:

- (i) Raise awareness of the different ways of applying HTA, including differences across therapy areas, drugs and countries;
- (ii) The extent of value judgments made, and on that basis whether accountability for reasonableness, and consistency of these judgments can be improved;
- (iii) Support different stakeholder groups dealing with HTA, to learn their input was received and dealt with retrospectively, and account for this prospectively;
- (iv) The taxonomy of criteria including what mattered in these decisions, identified with the framework, provides a way forward to for innovative models such as MCDA or continuous assessment (including highlighting those patient-relevant outcomes); and
- (v) Learning from the application of HTA to rare diseases provides a good basis for discussion on how to tackle these and beyond, given that we are shifting towards a model of personalized medicines.

Further to this we believe that stakeholders should to continue explore preferences about which health technologies patients would like to fund in health systems. It still stands; raising awareness of the different ways of applying attributes and levels for patients with rare in different countries for decision makers is necessary. It highlights for stakeholders the key attributes for decision makers of each country. We recommend to the stakeholders the preferences of the decision makers in order to understand differences across countries.

The level of involvement of stakeholders in the system, have an influence on the final decision. If stakeholders are interested on positive decisions, with the DCE survey they will be aware of the circumstances that may make it feasible.

Regional government level/ National government level/ Supra-national & international level

At a national level, the application of this framework allows governmental bodies to retrospectively analyse their decisions in order to:

a) identify the criteria accounted for in the decisions, and account for these prospectively to improve their accountability for reasonableness and consistency in their use; b) whether different therapy areas were assessed differently, and understand whether methods or preferences should be further adapted or elicited; and c) identify how issues relating to rarity were dealt with within their own setting and in other settings, to further the debate around how to tackle these particular cases.

Our findings favour the use the DCE approach for the elicitation of patients and decision makers preferences over different priority settings scenarios for health care provision.

The application of this framework at a supra-national level allows the identification of cross-country differences, contributing to cross-country learning. This is useful for European collaboration initiatives, such as EUnetHTA, highlighting scenarios and discussion points to further the debate about European collaboration.

Patient level/Health care professional level

The application of this framework allows identifying the type of patient input and how it influenced the decision (e.g. information about living with the disease and taking the treatment, plausibility of an uncertainty). This contributes to understand the type of information meaningful for patients to generate.

To use DCE approach for the elicitation of patient and decision-maker preferences over different priority settings scenarios for health care provision can be extremely useful for decisions taking place at societal level and can be used in order to elicit weights relating to the importance of different variables driving decisions.

Procurers of medical technologies

Same as for government level

3.6. Contribution to the debate of efficiency in resource allocation in health care systems

This study contributed to showing the reasons why current systems, and the HTA methodological approaches being used, are not sufficiently suitable to tackle the issues that

relate to rarity, as highlighted not only be the magnitude of and conflicting differences in the HTA recommendations made, but also be the contrasts seen in the various ways of dealing with these issues emerging from the rare nature of the diseases they treat. This is all the more urgent as our pharmaceutical environment is shifting towards niche and targeted therapies.

This study contributed to determine in what way(s) current processes for assessing drugs need to be adapted to make them suitable for orphan drugs, and whether all elements of societal value can be adequately reflected in existing decision-making procedures.

Moreover, this study contributed to showing the reasons why current systems, and the HTA methodological approaches being used, are not sufficiently suitable to tackle the issues that relate to rarity, as highlighted not only be the magnitude of and conflicting differences in the HTA recommendations made, but also be the contrasts seen in the various ways of dealing with these issues emerging from the rare nature of the diseases they treat. Our research will help patients, health professionals and decision-makers to better understand orphan drug reimbursement decisions;

This study adds to the sparse literature informing on the use of DCE methods to explore preferences about funds in health systems. In addition, DCE data can be used to consider the strength of preference over alternative scenarios in a priority-setting context.

3.7. Future development: application in the real world

Future developments would be to further apply the methodological framework to systematically compare HTA decision processes to additional drugs, therapy areas and countries. A greater sample will allow for further quantitative analysis (factor analysis) to identify the factors most contributing to these decisions. It will also allow us to compare how different therapy areas are being appraised within and across countries. Of immediate interest are the following comparisons: cancer versus central nervous system versus orphan drugs; orphan versus non-orphan cancer. The framework can also be used by specific stakeholders (e.g. patient, clinicians), to help understand how their input has been useful in previous decisions. Finally, the taxonomy of criteria identified can feed into more innovative models, such as MCDA which aim identify a broader range of criteria and their weights in these decision processes.

The findings of WP3 have a straightforward application to the real word. Future developments will be to further apply the methodological framework to systematically compare HTA decision processes to orphan drugs for rare diseases in different countries by decision makers and patients.

The DCEs conducted in this study provided valuable insights regarding benefit valuation and are therefore useful as additional information to complement QALYs when assessing health care interventions.

The DCE approach is an instrument that allows us to measure the preferences of decision makers and patients about all kinds of health care interventions. It can also be used by decision makers and patients to help understand how their input has been useful in previous decisions. We also assert the approach aims to identify a broader range of criteria and their weights in these decision processes.

The future steps of WP3 are the following:

- Include more countries and general population into the analysis.
- Analyse the effect of different orphan drug reimbursement decisions across countries.
- To address many of the limitations highlighted, for example, using qualitative methods to investigate the interpretation of attributes, terminology used, and the considerations when respondents make their choices.
- To define the place of DCEs versus other preference elicitation methods in health care.
- To generate DCEs which are as easy as possible for respondents, but still provide adequate answers to the research question.

4. Work Package 4: HTA and Quality of Life Measurement

4.1. Work package Objectives

- To determine whether the preferences towards health related quality of life differ between the general population and defined patient groups, including those benefitting from personalised treatments;
- To examine the causes of the established differences between general population and patient group preferences;
- To define advantages and disadvantages of the value sets drawn from the general population and patient populations respectively of cost-effectiveness.

4.2. Methods

Key methods deployed: (a) systematic literature review; (b) primary data collection through survey tool and analysis; (c) primary data collection through face to face interviews via deployment of Euroqol EQ-5D-5L.

4.3. Key findings

Differences between general population and patient population exist. The patients consistently valued high end health states higher and low end health states lower;

Adaptation is not the cause of the differences. Patients are able to more accurately imagine non tangible dimensions of health states (anxiety or depression, pain or discomfort). Patients consider problems related to mobility less problematic and problems related to anxiety or depression and pain or discomfort as more problematic;

First-hand experience; theoretical explanation and justification.

4.4. Policy implications

Changed priority setting decisions;

Changed allocation decisions due to differences in values attached to health states;

Use of general population preferences is not appropriate as their veil of ignorance is too thick. Adaptation with patients is trivial.

4.5. Recommendations to stakeholders

Prepare and use patient-based value sets, rather than population-based value sets;

Use of data sets, based on patients' preferences instead of general population preferences;

Suggestion to put patient in the centre of the health care system, use patients to determine values of health states in order to define priorities.

4.6. Contribution to the debate of efficiency in resource allocation in health care systems

One critical finding was that resource allocation is biased. Further research's focus needs to be shifted from adaptation issues into experience that enables proper valuation of health states. The ignorance veil for general population is too thick and using their preferences for priority setting is wasting resources in research and, more importantly, in health care due to wrong priority.

All arguments against using patient preferences (not enough patients, non-comparability across diseases, adaptation issues) are not valid. Patients, regardless of the disease, have similar preferences; their cause is not adaptation issue.

4.7. Future development: application in the real world

There needs to be better preparation and use patient based value sets. Patients value sets are to be determined for more diseases and in more countries; possibilities of mapping are to be explored; inclusion of patient into priority setting process need to be redefined. Using patients preferences means that treatment of conditions that affect mobility would thus receive fewer funds and treatment of conditions that affect pain/discomfort and anxiety/depression would receive more funds.

5. Work Package 5: HTA and Medical devices

5.1. Work package Objectives

- Develop a Taxonomy of Medical Devices (MDs) based on existing classifications and nomenclatures and test its plausibility and usefulness;
- Identify and compare current HTA methodologies, processes and practices across EU Member States;
- Clarify and supplement earlier findings, and to trace methodological and procedural challenges and trends.

5.2. Methods

Key methods deployed: (a) systematic review; (b) tool development

Exiting classification schemes of MDs were identified and analyzed in combination to create a normative taxonomic model. Testing of the taxonomy: 1) Plausibility: based on a broad sample of European HTA reports, 2) Usefulness: based on interviews with 16 European institutions.

A Systematic Review of literature was conducted to search on HTA institutions website, and analysis of report samples across different taxonomic positions (covering 55 reports from 2004-2014). We also conducted telephone interviews using a semi-structured guide with 16 HTA institutions (e.g. NICE, HAS) from 14 European countries.

5.3. Key findings

A matrix in table format was created based on relevant aspects from the existing classification schemes, incorporating elements of risk (as described in EU-Directives 90/385/EEC, 93/42/EEC, 98/79/EC) and role/functionality (as described in OECD Classification of Health Care Functions) of device types (Figure 3). Active implantable devices as well as in-vitro diagnostics were assigned separate rows. The matrix further incorporates a distinction between the diagnostic or therapeutic nature of devices, which can be crucial for HTA purposes;

Classification criteria of EU-Directives according to risk aspects:		Classification according to the relevance of product & service and reimbursement characteristics (includes OECD Classification of Health Care Functions) + HTA logic					
		Diagnostic Technologies 318			Therapeutic Technologies 760		
		Assistive technology devices (directly used by patients) A1	Artificial body parts (implanted by medical procedure) B1	Medical devices for the assistance of medical professional C1	Assistive technology devices (directly used by patients) A2	Artificial body parts (implanted by medical procedure) B2	Medical devices for the assistance of medical professional C2
		Example *No.*	*Example* *No.*	*Example* *No.*	*Example* *No.*	*Example* *No.*	*Example* *No.*
93/42/EEC	I	0		Ophtalmo-scopy 1	Wrist splint; Insoles 22		Debridement pad 5
	IIa	Continuous glucose monit. 6		Capsule endoscopy 70	Hearing aids 19	Grommets; Dentures 11	TENS device 83
	IIb			PET, PET/CT; MRI 131	Insulin pumps 6	Intraocular lenses; BAHA 72	Endovenous laser therapy 253
	III		Pulmonary Artery Press. Monitor 1	OCT using catheter 1	0	Stents; TAVI 108	Intracoronar Brachyther. 115
90/385/EEC	IV		ICD: heart monitor unit 6			ICD: defibrill. unit 66	
98/79/EC	V	Glucose strip; Pregnancy test 15		HPV test; Genetic tests 87			

Figure 3: Taxonomy for medical devices and number of technologies identified during the plausibility testing including actual examples from the report pool

The relevance of different device categories in regard to HTA was considered quite variable and was color-coded in the matrix, including high ('green'), intermediate ('yellow') and low ('red'). 'Grey' fields were those where no MDs and assessments would be expected.

There were 942 reports addressing 1,064 technologies produced by 31 European institutions were assigned taxonomic positions on the matrix. Their distribution generally confirms that the taxonomy is plausible. The majority of reports in the sample addressed technologies from the green fields, considered of high relevance.

Relatively few reports were available for the red fields considered of low relevance. Only one report was identified for one grey field where no HTAs were expected. Many of the interviewees stated that the taxonomy is useful, although not necessarily for the institution themselves.

The prioritization support aspect was seen as the most helpful but also the most limiting. Suggestions for refinement were given (e.g. separate row for prognostics). However, there is insufficient information on MD assessment as it is not publicly available for all HTA institutions in Europe. Only a few methodological tools have been developed by institutions specifically for MDs. Two key findings from in-depth analysis of reports: There was a lack of high quality

evidence in many cases and a dearth of economic evidence was frequently raised by analysed reports.

There were several challenges encountered, mainly resulting from weak regulation at the European level. Methodological challenges were cited the most: weak evidence base and rapid pace of innovation. There was agreement on the usefulness of considering particularities of MDs in methodological documents. One general document with additional parts or specific aspects to take into account was considered sufficient and more user-friendly than a separate document only for MDs.

Most interviewees wished for a change in EU regulation on the licensing process of MDs especially regarding evidence requirements. The need for a common understanding on terminology, methodological requirements and specific tools (e.g. GRADE for prognostic studies) was raised.

5.4. Policy implications

The taxonomy could be useful for HTA institutions and decision makers (e.g. MoH, insurers) alike;

The above hypothesis was confirmed by the testing;

1) Given that European regulation is currently being revised, there is an opportunity for insights from our work, which among others incorporates the opinions of 16 HTA institutions, to contribute to the discussions both at national and international level and hopefully help ameliorate the current situation.

2) 'Pointers' addressing certain methodological aspects that may be applicable to different device types (and therefore taxonomic cells) and could/should be considered along with the regular methodological approach adopted by each institution are being developed.

5.5. Recommendations to stakeholders

The taxonomic model can serve as a support tool to:

1) select topics for assessment and

2) identify certain aspects/particularities that require tailored (methodological) approaches.

Regional government level

There should be consideration of the remit of institutions responsible for evidence based evaluations guiding coverage decisions and the extent to which different device types are included. To reconsider distribution of responsibility among institutions regarding the evaluation of different device types would be advised. If governments are directly involved in setting methodological requirements, consider differentiation for MDs (and potentially for different device types). Competent authorities, be it at national or regional level, should take these findings into account when considering licensing and reimbursement regulation. If governments are directly involved in setting methodological requirements, consider and/or disseminate 'Pointers' from this WP.

National government level /Supra-national & international level

There are four aspects that stood out at the national, supra-national and international levels

- Potentially reconsider distribution of responsibility among institutions in different countries regarding the evaluation of different device types (e.g. REDETSA).
- International networks (e.g. EUnetHTA) could disseminate or promote taxonomic model.
- Reconsider regulatory prerequisites for MD licensing at European level. Bringing awareness to the findings of this WP maybe fruitful in this respect;
- International networks (e.g. EUnetHTA) could disseminate or promote relevant pointers.

Patient level

The impact of the implementation would be indirect: a) through a more explicit consideration of user skills for relevant device types; b) by endorsing patient participation in evaluations particularly for certain device types. Indirectly: potential changes will have influence on patient safety and health.

Health care professional level

An awareness raising among healthcare professionals regrading methodological particularities when conducting clinical trials would be highly recommended. Further support on behalf of scientific or professional associations regarding regulatory changes would also be beneficial.

Procurers of medical technologies

If hospitals are involved in or conduct HTA, regrading methodological particularities and support on behalf of scientific or professional associations regarding regulatory changes would need to be also applied and seriously considered. We would also highlight that relevant associations could promote idea of hospital base HTA of MDs.

5.5. Contribution to the debate of efficiency in resource allocation in health care systems

The results of work package 5 could contribute mainly in three ways. The developed and tested taxonomy could form the basis for a better prioritization approach for HTA of medical devices (MDs) and assist in deciding which MDs actually need an (full-fledged) assessment to determine reimbursement. The collective opinion of 16 European HTA institutions on MD evaluation could provide impulses to ameliorate the current regulatory situation and start broader, more in-depth methodological discussions around the issue. Finally, methodological insights on specific device types can help HTA-doers refine and focus their work.

5.6. Future development: application in the real world

Insights on methodological approaches for MD evaluation adopted by European HTA institutions show that further work, mostly on detailed methodological recommendations for different types of devices, is needed. Relevant research steps have been planned accordingly: the case studies based on HTA reports for different taxonomic positions will be expanded (further case samples, update of report pool, indication focus), also taking the international perspective into account (e.g. by including relevant reports from Australia and Canada). In this context, a more direct comparison to HTA of drugs is also conceivable.

Furthermore, impulses gained during this work which went beyond the scope of the project, such as suggestions for the refinement of the taxonomic model made by interviewed HTA institutions or the creation of an interactive database for HTA reports of MDs will be explored further and relevant results will be disseminated.

6. Work Package 6: HTA in Emerging Settings

6.1. Work package Objectives

- To identify the use and capacity for using HTA in emerging settings (Eastern Europe, Region of the Americas) including not only decision making bodies, but also some other institutions (universities, private companies, etc.). This includes the identification of HTA mechanisms and techniques apply in different emerging countries/regions;
- To encourage the use HTA for decision making through the development of formal guidelines for HTA methodologies in the context of Emerging Countries (South-) Eastern Europe, Region of the Americas, etc.) that make more transparent the use of these tools; and;
- To enable and facilitate an effective exchange of economic evaluations and evidence, reducing duplication of effort, between countries in Eastern Europe/Latin America and EU countries that have strong HTA tradition.

6.2. Methods

Key methods deployed: (a) systematic review; (b) tool development; (c) direct dissemination

A literature review was conducted using key terms and free words in the databases MedLine, Embase and Google. It also was used to identify if there was a Toolbox already present. The review was enriched with cross references and papers sent by experts.

A Cross-sectional study was performed in CEE and LAC countries. The questionnaires were sent to Ministries of Health and HTA organizations. The focus was to develop a toolbox outlining best practice and including recommendations. It was to provide a selection of the health technologies and countries with different development in their HTA systems and provide benchmarking HTA across countries and health technologies selected. A Toolbox was developed for HTA implementation.

Direct dissemination took place in Latin America (2014 and 2015) and Eastern Europe (2014 and 2015).

6.3. Key findings

The main result of the literature review is the lack of information about the capacity or decision making process of HTA in the Central and Eastern European (CEE) and Latin America and the Caribbean (LAC) countries. The most mentioned barriers faced by those whom perform HTA in

CEE countries were skills training and sources of funding, while in LAC countries were skills training and institutional support.

Some CEE countries have created formal decision-making processes for which HTA is used, mostly for medicines. However there is much heterogeneity related to the degree of development of such structures. We investigated and identified other Toolbox or Toolkit were, which are used to complete our Toolbox.

The Toolkit developed consisted of 6 chapters with adapted recommendations for the emerging countries. It was not possible to achieve the objective of comparing three countries/three technologies in CEE countries (it was in LAC) but the information obtained have made possible to make a comparative analysis. The lack of transparency, jointly with the language barriers, has been the main difficulties faced to made a more complete case studies analysis.

6.4. Policy implications

So far, HTA capacities have been evaluated and the decision-making process have been reviewed and evaluated. The toolbox is being disseminated to HTA communities worldwide.

6.5. Recommendations to stakeholders

The following key recommendations were identified for stakeholders:

- Increase capacities in HTA;
- Increase link between HTA and decision;
- Increase transparency in the decision-making process;
- Produce and disseminate HTA guidelines;
- Improve the transparency in the decision-making process;
- Support HTA networks and exchange of coverage decisions.

Regional government level/National government level

Findings indicated that there was a lack of information reinforces the need of research and development on these countries, therefore the skills capacities in HTA must be improved.

We would wish to see a follow up guidelines in order to give legitimacy to the decisions and the link coverage decision with HTA evidences. There is a need of more transparency in the use of HTA was denoted, in order to can compare the different coverage decisions.

Supra-national & international level

At a supra-national and international level an increase funds and support for HTA capacities is required. It is necessary to perform Guidelines/ methodologies/standard procedures.

We would also encourage the implementation of WHO resolution (WHA67.23). The harmonization and coordination in this field is important in order to avoid duplication and overlapping (or even contradictions) in the decisions based on the same evidence.

6.6. Contribution to the debate of efficiency in resource allocation in health care systems

WP6 focuses on two important emerging regions in the use of HTA, namely Central, Eastern and South Eastern Europe (CESEE) and Latin America and the Caribbean (LAC). First, the WP contributes to the debate of efficiency in resource allocation by providing a mapping of capacity to perform HTA and current HTA processes in these emerging settings.

The findings provide insights into the level of HTA capacity of organizations in the region. The most common barriers faced by those performing HTA were skills training and sources of funding in CESEE, while skills training and institutional support were the most cited in LAC. With respect to barriers to conducting HTA encountered by institutions not engaged in the practice, the most cited limitations are of political nature. Results also highlight the heterogeneity in the use of HTA.

Some elements of HTA are in place in these countries; however, in general no comprehensive and transparent system exists in most of them. In some countries there is not a defined structure that assumes the assessment or legislation establishing supporting HTA. Generally, countries with lower GDP per capita have more limited budgets and human resources for conducting HTA.

This limitation leads policymakers and payers to consider foreign HTAs in their decisions. This requires transparent decision criteria, including assessment of cost effectiveness. On the other hand, relevant local databases and clinical guidelines are often incomplete or unavailable. This decreases accuracy of HTAs, increases bias in evaluations of medical practice, and makes adaptation of economic model to local reality difficult or almost impossible. As a consequence, the findings can assist both national policymakers and/or international donors in the analysis of needs and the planning of actions to be taken to strengthen regional HTA capacity and systems.

Moreover, existing HTA networks can benefit from these findings by using it for advocacy to local policymakers and to provide technical assistance. Second, parties interested in the advancement of HTA may gain additional insights from the multi-country case studies on the adoption of particular technologies. Lessons learnt from the cases can further support advocacy

efforts and decision-making as they offer real-world recommendations for best practice. Lastly, the HTA Toolbox for Emerging Settings can be helpful to promote the use of HTA, to serve as a guide for countries to develop HTA (methods/process) guidelines and as a basis for training, and to improve decision-making processes based on HTA.

6.7. Future development: application in the real world

The HTA mapping is a valuable resource for knowing where CESEE and LAC countries currently are in the use of HTA, and help these countries plan the steps that they can follow in order to improve. There is no a single or common direction; each country has to follow each own route according with their development stage and the characteristics of their health care systems.

There are also some lessons drawn from the case studies. Overall, there is a need for more transparency in the use of HTA. Improving transparency in the decision process based on HTA needs to be encouraged, taking into account the necessity of balance between transparency and confidentiality. A transparent process would also support the legitimacy of the decisions made. Taken together, the HTA Toolbox for Emerging Settings stands out as a useful tool to increase capacity and guide the strengthening and implementation of HTA.

In line with the above, real efforts –including political will and donor commitment–would need to be made if advances in the implementation of HTA are to be made.

First, an increase in resources for HTA capacity building is needed, including financial, technical and training resources. Second, it is important to improve methods and processes, so that HTA products are taken into account for decision-making (e.g., reimbursement, guidelines development) and decisions based on HTA are acceptable for all stakeholders (thereby reducing phenomena such as judicialization). Third, collaboration among countries, including harmonization of HTAs and exploring the possibility of transferability of foreign data, is crucial for strengthening and implementing HTA in emerging settings.

Part II: Vertical analysis of Advance-HTA results and what they mean for health policy and its objectives

7. Advance-HTA: the Wider Policy Implications

7.1. Background

The Advance-HTA Project was based on a collaboration between 13 partner agencies and funded by the European Commission's Research Framework Programme (FP7) during the three year period 2013-15. Advance-HTA explored the different processes and varying criteria used for assessing clinical cost-effectiveness across Europe, and how frameworks such as Multi-Criteria Decision Analysis (MCDA) might be used to further enhance the value and acceptability to all stakeholders of current 'mainstream' approaches to cost-effectiveness evaluation as the central element in modern Health Technology Assessment.

The Project, in addition, sought to determine the extent to which disease rarity impacts on assessments of the incremental cost per QALY ratios (the ICERs) for orphan drugs, and the ways in which preferences relating to health related quality-of-life differ between the general population and patients who have actual experience of given conditions. Two further work streams were designed to cast light on the degree to which, and ways in which, HTA is used in appraising the value of medical devices, and the establishment of both governmental and private sector HTA capacity in 'emerging' economic settings like those of Eastern Europe and the Americas, excluding the US.

Finally, this LSE-led initiative sought to identify and promote public consideration of the wider policy implications of the research findings generated via the above sets of research activity. This brief paper is intended to contribute to this last objective.

8. Theoretical and conceptual considerations addressed by Advance-HTA

It would be outside the scope of the analysis in this section to attempt to offer a detailed summary of all the Advance-HTA work stream conclusions – this was done in Part I of this report. But an introductory point worth special note is that they in general show that differences in the evaluation criteria underlying how products such as innovative medicines are assessed can (over and above issues such as variations in national per capita GDPs) consistently and significantly influence whether or not a treatment is judged cost-effective in one country as opposed to another.

This does not mean that the work undertaken by health economists and others involved in HTA leads to arbitrary decisions. But it does mean that if more or less value is ascribed to, say, the scientific originality of a therapeutic innovation (and so, implicitly, the unknowable but potentially important long term returns to communities from publicly or privately funded biomedical research investment) relative to the immediately demonstrable benefits generated

for individual patients, then differing purchasing and treatment supply decisions will result. Similar points apply to the use or non-use of 'adjusting' factors such as disease severity and rarity or 'end of life' care applications.

From a pan-European policy perspective this raises social equity concerns and a number of wider economic and industrial policy questions, alongside more immediate health sector resource allocation issues. One important challenge for the future relates to ensuring a better balance between achieving short-term equity in health care areas where there is already evidence available relating to the promotion of allocative efficiency and the inevitably more uncertain task of defending public interests in long-term innovation, and the eventual achievement of fundamentally improved technologies for preventing and treating conditions such as cancers and neurodegenerative disorders. These are different goals, which in some circumstances conflict.

Similar questions and possible consequences arise in fields ranging from how affordability criteria are set in relation to '*cost per QALY*' and allied utility measures in different nations and/or contrasting spheres of social and economic activity in a single country, through to – not least in the rare disease and cancer care contexts – whether or not rationing choices should be made on the basis of Benthamite utilitarianism as opposed to Rawlsian concepts of social justice. The latter are more likely to ascribe premium values to treatments that benefit minority populations than the former.

The topic of utilitarianism 'versus' the value of social solidarity and the defence of unusually disadvantaged group interests is returned to again later in this analysis. But a key introductory point to emphasis here is that, as with all issues relating to fundamental technical innovations, it too has temporal dimensions linked to the essential unknowability of the future.

For example, a new drug that is still under patent protection and is of known value to just a few thousand people world-wide will almost certainly appear non-cost effective in conventional terms. Yet in fact the main costs incurred in its development and potential future supply could have been incurred before its limited immediate marketability was understood. In these circumstances humanity as a whole will not necessarily 'save' by leaving such advances unused. Further, their long term 'supply affordability' will increase after the development costs have been written-off, their IPRs have expired and the cumulative number of potential beneficiaries rises over time[1].

[1] Also, previously unknown applications of the biological action involved may emerge, changing the initial 'cost effectiveness' calculations.

Other important Advance-HTA findings range from new observations showing that patients tend to ascribe higher relative values to physical pain and mental distress reduction than observers who have not experienced relevant disease states directly, through to revealing the limited extent to which HTA techniques have to date been applied to the evaluation, pricing and purchasing of medical devices as compared to that of medicines and vaccines. Given the fact that the proportion of the average EU Member State's GDP spent on medical devices is now reportedly approaching half that spent on pharmaceuticals (ie 0.7% of GDP as opposed to about 1.5%) this imbalance should be seen as a matter of significant policy interest.

Its existence stems from the relative lack of centrally accessible data on medical devices use and the outcomes attributable to them, and the fact that their employment is often intimately associated with other forms of hospital spending. The special focus of HTA on drug evaluations is also linked to the (in some ways questionable) Western pharmacological tradition of evaluating medicines as discrete molecular entities, as opposed to items that act in combination with not only additional drug treatments but many other medical, surgical, nursing, psychological and wider social inputs.

Advance-HTA's findings indicate that further investment needs to be made in developing Health Technology Assessment tools for use in areas outside the narrowly defined pharmaceutical sector, in order to further increase the productivity of health care as a whole. They may also need to be adapted to accommodate the reality that drugs do not normally act alone to achieve the best possible outcomes, albeit the discovery of optimum combinations and administration strategies can – as experience in spheres such as the treatment of child leukaemias has shown – be a long drawn-out process.

However, from a practical perspective it is presently the case that HTA is centrally concerned with a relatively narrow form of medicinal product evaluation, pricing, purchasing and use. This paper reflects this fact. It initially offers an outline of the origins of health economic evaluation in Europe and the United States, and highlights some basic economic aspects of pharmaceutical research, development, manufacturing and supply. It then explores from a public policy perspective a spectrum of topics arising from the Advance-HTA research. These centre on issues like the value of further involving patients and their representatives in determining whether or not treatments are affordable, and the need for well-balanced national and international policies aimed at incentivising public interest focused private investment in pharmaceutical research and development.

9. Health economics and the financial dynamics of pharmaceutical research, manufacture and supply

In the late 1940s, when the first pharmaceutical revolution was in its infancy, recorded spending on health care stood at little more than 3-4 per cent of GDP in the most economically advanced

nations. Notwithstanding the difficulties of evaluating informal sector activities in 'less developed' settings, it was probably less in poorer societies. Total spending on pharmaceuticals in the richer nations was at that time approaching 0.5 per cent of GDP.

Today the European average figures for health spending as a whole and pharmaceuticals specifically are about 10 per cent of GDP (net of health related social care) and 1.5 per cent respectively. The equivalent US figures are 17-18 per cent of GDP and about 2 per cent. Rising publicly (including obligatory insurance) resourced health and social care costs, coupled with the growing complexity of a pharmaceutical market in which innovators with legally recognised intellectual property rights are typically supplying near-monopsonist purchasers and/or third party funded prescribers, has helped drive the emergence of health economics.

From around the 1980s onwards of HTA as applied to the pharmaceutical sector has, as already noted, assumed particular importance. Key steps forward have included:

- in the US, the publication of an article entitled '*Uncertainty and the Welfare Economics of Medical Care'* by the American economist Kenneth Arrow in 1963, and in 1972 the establishment of the Congressional Office of Technology Assessment (the OTA). Arrow's early work is widely regarded as serving as an intellectual cornerstone for the subsequent development of health economics as an academic sub-discipline. The OTA produced a series of in-depth economic and wider analyses of health and other science-based topics aimed at informing decision making processes in an economically and socially informed manner. Yet after sustained political criticism it was closed in 1995, during the Clinton Presidency;
- in the UK, the formation (in the shadow of the Thalidomide tragedy) of the pharmaceutical industry funded Office of Health Economics in 1962, and from the early 1980s onwards the practical development of the QALY (a term first used by the American academic Richard Zeckhauser in 1976) as a unit of health care utility by Alan Williams and colleagues in the University of York. This led on over the course of some twenty years to the establishment of NICE in 1999, early on in the first Blair administration; and
- in Europe more widely, the work of agencies such as the Paris based OECD and the later establishment and work of HTA agencies such as the Swedish SBU; HAS in France; AHTAPOL in Poland; IQWIG and the DIMDI in Germany; and the CVZ in the Netherlands. Today these and other agencies are participants in EUnetHTA, the European Network for Health Technology Assessment

Much useful work has been achieved. However, it may be argued that since the start of this century concentrating health economics effort on 'cost per QALY' pharmaceutical sector and related HTA work has resulted in a narrowing of its scope. This has on some occasions threatened to over-simplify complex policy decision making relating not only to patient access to high cost therapies in fields like, for example, oncology, but also to industrial and research

development strategies. At worst, current approaches to HTA can be accused as being rigidly formalised in ways that require increasingly costly investments in quantifying the fine details of the impacts of therapeutic interventions on patients, but fail to reflect the dynamic nature of incremental clinical care improvement or its wider societal and – more importantly – its long term value to people, families and communities.

There is an obvious danger that ill-informed attempts to avoid risk and maximise the current politically demonstrable value of taxation-raised money outlays will undermine the exercise professional judgement in inherently uncertain circumstances. They may also reduce market-led investments in areas that should ultimately lead to highly desirable future ends such as (for example) being able to cure breast cancers or stop the development of Alzheimer's Disease.

As an illustration of this point, the British social researcher Richard Titmuss was strongly supportive of the NHS. He described its creation as one of the '*least sordid acts of British social policy in the twentieth century*'. But despite his concern for effective health policy making and the appropriate use of NHS resources, Titmuss also mocked health economists for statements that he believed implied they had *'a direct line to God'*. Some of the patient contributions to the Advance-HTA research programme reflected similar concerns about a perceived tendency towards reductionism, and even intellectual arrogance.

9.1. Valuing affordability and innovation

There is ongoing debate about topics such as the costs of pharmaceutical research and development, the premiums legitimately required for securing 'risk capital' outlays, and the medicine and allied product price levels necessary for not only assuring continuing private (and linked public) investment in ongoing biopharmaceutical research but also the consistent, high quality, supply of 'true generic' (post Intellectual Property Right – IPR – expiry) medicines. There are, for instance, disputes relating to how the costs of failed research programmes should be accounted for, and the extent of the clinical trials needed before new products can initially be offered for sale to patients.

There are also uncertainties as to the degree to which the prices of large molecule biopharmaceutical products should in future be expected to fall, as and when 'bio-similar' products become available. However, at a more general level of analysis most medicines and allied products have low marginal costs of production as compared to the fixed costs of their development, including their safety and clinical effectiveness testing and licensing. Put in a summarised manner, this means that products like new medicines are not normally valuable in the sense that materials like gold are prized highly because of their inherent scarcity.

New treatments that in the long term can be supplied at a relatively low cost are instead temporarily of high value because of their intellectual content, and the resources used in their

development and initial manufacture. This key observation has a number of important implications and raises a variety of policy related questions linked to the funding and practice of HTA. They include:

- '*can existing national and international price discrepancies between patented or otherwise protected products and generic medicines and allied products be satisfactorily justified from a public interest/HTA standpoint, and if they can are the reasons underlying such variations communicable at the political and electoral levels*?'
- '*should cost per QALY calculations relate only to the periods during which products like innovative medicines are in receipt of patent or regulatory data protection, or ought they to include projections relating to their ongoing value to consumers during their whole life cycles?*' and
- *'if the development costs of 'new medicinal entity' based treatments for rare and ultra-rare diseases are broadly the same the same as those for NME's for common indications but their unit sales are orders of magnitude less, would this justify either adjusting 'cost per QALY' calculations for rarity or might it be more appropriate to adjust affordability thresholds for 'orphan' drugs by corresponding orders of magnitude, at least during periods of exclusive supply?*'

As discussed below, the Advance-HTA Project generated data relevant to the above questions and many more besides. But a final point to make here is that the purpose of State interventions in the working of manifestly imperfect markets for products such as innovative research based pharmaceuticals is not simply to minimise public (or indeed private) spending on such items. If this were a central policy objective it could more simply be achieved by removing intellectual property rights on goods like new medicines, albeit that (saving the existence of alternative protections such as resorting to secrecy based strategies) this would either shift responsibility for funding research and development more directly to tax payers, or dramatically cut future investment in innovation.

The key policy objective of HTA based pricing and purchasing of products and services is – it is suggested here – rather to balance public interests in affordable access to currently available technologies, and so present levels of wellbeing, with those that individuals and communities have in continuing innovation and enhanced future welfare. From a trade and *per capita* income perspective, citizens of the EU have – along with future generations of humanity world-wide – important interests in ensuring that 'enough' is spent on products like new biomedical treatments, as well as in preventing inappropriate profit taking and curbing the use of ineffective therapies.

10. HTA methodologies and the appropriate application of HTA findings

Failures to understand the importance of concerns such as achieving a robust balance between short term welfare maximisation as against investing in uncertain but nonetheless important future gains could have serious unwanted consequences. There is an arguable need either to incorporate more appropriate provisions for such factors into HTA evaluation techniques, or to accept that higher level policy makers will (overtly or covertly) always need to moderate the *'real world'* application of HTA based research findings to prevent their causing damage to public interests.

The Advance-HTA research on both the use of Multi-Criteria Decision Analysis (MCDA) and the ways HTA linked findings are currently being used by government agencies and political leaders in Europe highlights a number of points relevant to this area. For instance, may be taken to indicate that the value of innovation *per se* could be better assessed than at present, and that costs like those associated with side-effect risks need fuller evaluation than they presently receive in conventional HTA analysis.

However, there remain important unanswered questions as to the precise ways in which MCDA based evaluations should be conducted, and the extent to which the use of such methods would in practice impact on HTA evaluation outcomes[2]. There are also many other methodological topics that could usefully be explored in greater depth.

For example, from the perspectives of both investors in pharmaceutical innovation and patients with currently inadequately treatable conditions they include fears that – as touched on above – failures to take a 'whole life cycle' approach to valuing NME based medicines are creating unduly high barriers to initial market entry that could undesirably distort access to treatment. It may also be that using minimal cost 'generic' (that is, commodity cost) comparators in HTA analyses can have similarly detrimental effects. European policy makers should, for instance, be

[2] There is a danger that a great deal of extra work may yield disappointing results in terms of increasing the sensitivity of HTA findings via the application of MCDA. Alternative ways forward might be either to simplify the categorisation of innovations/therapeutic advances, or to explore further areas such as the possibility that some states of distress should be attributed comparatively high negative values. If this interpretation of the available evidence (which may in part reflect some of the Advance-HTA's observations on patient experiences) were accepted, it could significantly change the balance of HTA based findings as they relate to treating severe non-fatal conditions. So too could adjustments to HTA calculations designed to reflect the long term impacts of premature deaths caused by conditions like cancers on surviving family members.

aware that in Japan evaluations of new products are required to use alternative treatments that are still covered by IPRs as comparators in order to avoid the ICER cost exaggerations that would otherwise occur.

Other concerns and opportunities relate to topics such as the extent to which HTA evaluation methodologies could be standardised between EU nations or within wider regions, and the degree to which there could and should be internationally agreed mechanisms for adjusting affordability thresholds to take into account GDP variations and local variations in the incidence and prevalence of given diseases. Such measures could generate substantive benefits throughout the EU. Yet in the short to medium term practical progress will almost certainly prove difficult to achieve.

Seen from this angle one of the most important wider policy linked findings Advance-HTA offers is that presently HTA generated results are not always – regardless of evaluation criteria variations – implemented consistently. National interests with regard to – for instance – fostering local generic medicines manufacturing and substituting imports with home produced items, or alternatively attracting research investment, may underlie observed inconsistencies.

To some HTA practitioners it may seem unethical or otherwise undesirable that bureaucrats and politicians are over-ruling their recommendations. However, economists and other analysts cannot realistically expect to control the actions of democratically elected (or other) governments and their appointed officials, especially when their calculations can reasonably be seen as failing to include legitimate financial and/or social concerns. More appropriately, they can either seek to build in additional criteria into the models they use in order to bring their findings more into line with decision maker and electoral priorities, or as constructively as possible promote informed public debate in areas of disagreement.

In instances where HTA based recommendations clash with the views of clinicians and those of either individual patients or patient group representatives such problems can arise because individual needs and responses are highly variable. By contrast, HTA analyses often reflect averaged preferences and aggregated outcome data. On other occasions conflicts may be associated with the fact that HTA recommendations are based on static rather than dynamic models, and on established evidence that necessarily lags behind ‘cutting edge’ clinical practice and knowledge.

To a degree, such difficulties are to be expected and have to be accommodated as best as possible in any setting where efforts are being made to optimise value for money at scale. However, the policy implication drawn here is that wherever possible HTA based guidelines and controls should be flexible enough to accommodate variations in patients’ personal needs and in well informed clinical judgement. Rhetorically, this may already be the case, but in practice HTA implementation approaches can be relatively harsh. In sophisticated environments one way of avoiding this danger might be via careful systems of retrospective audit. These can allow unjustifiable practices to be stopped over time in ways that minimise the risks of health services

users being exposed to traumatic denials of access to what they see as life-saving or life-changing treatments.

Additional ways forward include introducing conditional forms of treatment authorisation based on '*coverage with continued evidence gathering*' strategies, and budget capping approaches which limit the total amount that health care providers and funders pay for medicines and related products. The latter approaches seek in part to exploit the '*high fixed cost of development and supply, low marginal cost of production*' realities of pharmaceutical supply referred to above. However, they can be seen as threatening not only by some pharmaceutical industry interests but also by HTA study 'vendors' whose activities are based on producing 'product-by-product' assessments of individual level health gain, instead of community wide benefit evaluations of more broadly defined innovative processes.

11. The importance of appropriate service user involvement in HTA evaluations

From a public policy perspective some of the strongest findings of the Advance-HTA research discussed here stem from observations made in relation to preference elicitation, and in the rare disease treatment context. These include the discovery that people who have experienced conditions such as physical pain or depression (and perhaps other psychiatric states such as, for example, severe anxiety disorders) are likely to value their alleviation more highly than those without such direct experiences. At the same time reductions made in the degree of QoL los recorded via instruments like the Euroqual-5D-5L in the context of problems that can more readily be accommodated, such as being unable to conduct self-care tasks autonomously, are likely to be less highly valued by patients with relevant experiences than they are by 'naïve' observers.

Although the likely impact of such variations on quality of life estimations should again not be over-stated, such variations are potentially significant with regard to the ways that HTA research might best be conducted. This is particularly so when they are combined with findings that demonstrate that in areas such as rare disease research it is often the case that patients and their family members have deeper and more accurate insight into their conditions than many clinicians, let alone academic or directly State employed economists.

Given this, the key policy related conclusions drawn here are not only that there are opportunities for technical improvements in the ways in which the quality of life related impacts of health care interventions are measured, but also that closer patient involvement in the governance and direction of HTA and other forms of health care research and evaluation remains an important priority. At worst, patient involvement can be little more than a form of 'box ticking'. But done well it is likely to add significantly to the quality of HTA findings, and the ways in which they are understood and implemented.

There is further work to be done in defining how best to translate this promise into reality. But progress in this area should, amongst other things, increase the credibility and acceptance of HTA based decisions. It might also help counter fears relating to the narrowing and so-called 'commoditisation' of not only HTA research and its products, but health economics more widely. The enhanced depth of understanding offered by constructive patient involvement in economic assessments should increase their relevance to clinical decision making, partly via generating more detailed and reliable insights into the burdens imposed by differing types of disease and disability.

12. Rare disease/orphan medicine treatments and the value of HTA in industrial policy formation

As outlined earlier, Advance-HTA's findings with regard to rare disease treatment and the affordability and access to orphan medicines highlight the fact that if evaluations include criteria which relate to their low prevalence and variables such as the severity of distress and other exceptional burdens that inheritable monogenic disorders can impose on not only individuals but entire families and occasions on specific ethnic/racial minorities, then they are more likely to be judged affordable than if more general assessment methodologies are used.

In linked areas like some areas of cancer care (and probably in future some forms of dementia treatment) patient access is also likely to be affected by the existence or otherwise of additional HTA evaluation modifying factors. These could relate to not only the value of demonstrating social solidarity in situations where only relatively small numbers of people are involved, but also the social fact that at given points in history some disease may be popularly seen as deserving greater investment than others. Such prioritisation judgement may be driven by subjectively perceived fears or objectively based beliefs that some sorts of innovation are more likely to prove viable than others, despite having equal potential 'worth'.

Two main sets of policy related ideas are worth discussion here. First, the European Union, like nations such as the US and Japan, has in recent decades recognised the important health equity and industrially funded research challenges associated with developing better treatments for rare indications. Special incentives have been put in place to promote relevant activities. The EU has also encouraged Member States to develop rare disease strategies, which they have done at varying speeds and with differing degrees of excellence. But there is in the short term at least little point in bringing new treatments for rare disorders to market if they are not subsequently made available to those who could benefit from them.

Some commentators may take this to imply that in the European context more effort should now be made to facilitate the timely production of orphan medicine assessments produced to an agreed Union-wide standard and implemented in a manner consistent with the spirit of the existing European legislation on rare diseases. Whether or not this will be achievable is

uncertain. But Advance-HTA clearly identifies this as a question that will demand increasing attention during 2016 and beyond.

Following on from the above, present-day orphan drug supply issues can also be seen as indicative of the limitations of approaches to HTA that fail to take into realistic account industrial policy issues. These range from, for example, current and future EU wide balance of trade and employment concerns to the impacts that major variations in the levels of volume demand for innovative products such as new medicines have on the economics of their development and their sustainable supply at what are perceived to be affordable unit prices.

Some experts may argue that such factors cannot properly be taken into account when calculating ICERs and should not be considered when interpreting their product pricing and purchasing implications. But if this is the case it severely limits the practical utility of HTA findings. There is a strong policy case for arguing that even if '*cost per marginal QALY'* figures should continue to be calculated in much the same way as they are at present, affordability thresholds could and should be systematically adjusted to permit better quality future decision making. If this is agreed, then more effort needs to be put into the 'science and art' of determining affordability thresholds across Europe, and more widely[3].

Concerns like these can be linked back the 'utilitarianism versus Rawlsian social justice' debate noted in the introduction to this brief paper. Benthamite thinking may, rightly or wrongly, taken to imply that minority interests should be sacrificed if greater overall welfare gains can be made by pursuing alternative social goals. But John Rawls' theory of justice indicates that in some circumstances the (apparent) sacrifice of majority welfare optimisation interests in favour of meeting the needs of the least advantaged in a community can offer a more desirable path towards achieving what is generally accepted as being the fairest possible society-wide distribution of goods and the welfare derived from them

Whether or not there is a genuinely irreconcilable divide at the heart of this apparent dilemma is disputable. But for the purposes of this analysis it can be said that the Advance-HTA

[3] In countries such as the UK there is, despite high level political interest in increasing both R&D investment levels and access to medicines, bureaucratic pressure for lowering the ICER based affordability threshold for pharmaceuticals to a postulated NHS mean of about €20,000 per QALY. There is a limited academic case in support of such an intervention, albeit it fails to take into account variables such as the fact that while medicines and allied products fall in price markedly after IPRs expire this is not the case with labour intensive innovations. The WHO recommended (DALY) ICER threshold for medical and allied interventions is up to three times the local per capita GDP, which in the UK context would be well over €100,000 per 'marginal' QALY.

programme's outcomes point to the dangers of failing to understand the significant of such philosophical issues in the context of the '*cost per QALY*' calculations currently central to the cost-effectiveness assessments undertaken by European HTA agencies. At worst, 'simplistic' utilitarianism could lead to an undermining of social solidarity and the intent of European policies aimed at ends like encouraging rare disease research.

13. Global health and health care development

Advance-HTA also revealed marked variations in the numbers of qualified health economists and other HTA practitioners in emergent as opposed to more mature economies, and in the ways in which HTA based findings are used to determine policies and decision making. The world-wide picture is to a degree complicated by the position of the United States. There both industrial and allied research investment arguments, together with policy questions relating to the acceptability of using quality of life related calculations to determine care access, have had a significant influence on the evolution of HTA and attendant disciplines like comparative efficacy studies.

The US, with an economy equivalent to about a fifth of Gross World Product, is presently funding approaching half of the world's biomedical/biopharmaceutical research. At the same time the extent to which until recently it can be said to have instituted universal health care (UHC) for its citizens is debateable, despite high health sector expenditures.

However, in broad policy terms the emergence of health economics and within it the field HTA can be taken to be related to the processes of global demographic and epidemiological transition. These seem in their later stages to be normally attended by increased public (including compulsory insurance supported) spending on UHC provision. As health outlays increase, so do concerns for equity, efficiency and service excellence. So too do investments in aspects of quality management and value-for-money improvement.

However, it should not be uncritically assumed that these are always appropriate or in themselves cost effective. It is debateable, for instance, as to whether or not individual emerging economies should currently be seeking to increase their indigenous HTA capacity, as opposed to drawing on evaluative work conducted elsewhere and concentrating attention on further building their clinical workforces and generic health sector management capacities. Nevertheless, they will either way benefit from becoming more able to use health care resources to optimal effect. This includes promoting cost effective use of medicines as well as in

other areas of care, albeit drugs and allied items are now unlikely to account for more than 20-25 per cent of gross care costs in any setting[4].

Even in poor countries, paying appropriate prices for IPR protected products be taken to include making fair and proportionate contributions to the world research effort. Europe – along with the US – has significant interests in supporting efforts to define the latter in intellectually coherent and socially equitable ways, as well as in defining terms such as 'essential drugs' and assuring world wide access to such treatments.

With regard to the latter, Advance-HTA studies undertaken in the Americas identified an increasing tendency for local courts to require public health care systems to supply medicines to individuals seeking better health care. In other parts of the world judicial actions appear to have been aimed more at improving treatment access by limiting intellectual property rights.

It would not be appropriate here to make judgements on the desirability or otherwise of such interventions. However, their existence underlines the importance of being able to price and supply products such innovative medical devices and medicinal drugs in ways that are consistent with individual human rights and collective interests in achieving better care standards and ongoing global efforts to improve the effectiveness of treatments.

14. Conclusion

Since the end of the 1940s global life expectancy at birth has increased by some twenty years. New medicines, vaccines and related products have probably accounted for about half of this progress, and similarly important gains achieved in areas such as reducing age specific disability rates. At the same time the overall cost of pharmaceuticals has – relative to world-wide wealth – kept relatively stable in recent decades, at between 1 and 1.5 per cent of GWP.

For some observers, such macro-level data may give rise to questions as to the value of recent attempts to use HTA based cost-effectiveness evaluations to determine the individual prices and permitted uses of innovative treatments purchased in that they imply that other overall expenditure control mechanisms have long been in place. But the view taken here is that in today's social, political and economic environment HTA assessments have, when well conducted and appropriately applied, a useful role to play. This exists both in respect of keeping treatment costs within what are commonly seen as fair and affordable parameters and in helping to raise

[4] The relevant European mean is around 15 per cent, with the northern European Union proportion (at least until very recently) typically being markedly lower than that recorded in southern settings like Greece, Portugal, Spain and Italy.

the effectiveness and efficiency of treatment uses, as well as in ensuring continuing research investments into better therapies for the future.

It may be argued that HTA should principally be concerned with creating appropriate incentives for developing the next generation of improved treatments, rather than 'fairly' rewarding past discoveries. Yet if this view is accepted its policy implications are not as straightforward as may be assumed. On occasions, for example, it might be judged to be as important to reward investors for supporting failed research as it is to enable successful innovators to enjoy high 'winner takes most' levels of profitability. On others the societal value of medicines that alleviate low incidence conditions might be seen as a being as great as those which achieve similar levels of individual health gain in larger numbers of people, not least because – as already noted – of the collective value of maintaining high levels of visibly expressed social solidarity within the EU.

The Advance-HTA project's findings offer European decision makers a wide range of useful insights into how in future cost effectiveness evaluations of not only medicines but products such as medical devices (and perhaps in time interventions such as surgical operations) could be better conducted. They also raise important questions as to the extent to which in contexts like promoting enhanced outcomes in areas of cancer care and the treatment of rare monogenic diseases the criteria used for evaluating the 'worth' of therapeutic innovations might be standardised across the European Union, and how regionally or globally consistent approaches to adjusting for factors like GDP and disease prevalence variations could be instituted.

Technically, Advance-HTA's results raise questions about how the affordability thresholds used in assessments can best be set, and the degree to which the extended use of MCDA techniques would materially enhance the validity and acceptability of currently established evaluation methods. They also highlight as yet unresolved uncertainties about the extent to which national policy decisions or individual treatment choices could ever be determined on the basis of HTA findings alone.

It is of course rational to try to make policy making, market regulation and personal care decisions as 'evidence based' as possible. But in the final analysis individuals' needs for and responses to treatments vary widely, while the future value of investing in fields like bio-pharmaceutical research cannot be predicted with any degree of certainty. It is also apparent that many people are not purely concerned with improving their own health and wellbeing as opposed to that of successor generations, even if political policy makers sometimes appear to be at risk of encouraging over-spending on consumption today at the expense of improving health and other forms of welfare tomorrow.

The productive development and application of HTA techniques demands the honest and flexible recognition of such difficult truths. It also requires constant awareness of cautions such as the fact that although that which is measured and quantified often guides what is done, that which is most important to individuals and the communities in which they live is not always

measurable or quantifiable in numerical terms. At the end of the day, complex ethical and social choices cannot be reduced to simple economic calculations.

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