



Value Added Medicines

Time to Adjust the HTA Decision
Frameworks

July 2017

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Acknowledgements

The authors would like to thank the following experts for their support and for providing valuable inputs and comments to develop this white paper (listed in alphabetical order):

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Funding

This white paper has been funded by Medicines for Europe. Medicines for Europe is the voice of the generic, biosimilar and value added medicines industries.

Medicines for Europe began over 20 years ago as the European Generics Medicines Association (EGA) with the goal of representing the emerging generic industry, and later growing to include biosimilar medicines to its portfolio, and more recently value added medicines.

1. Executive Summary

Value added medicines are defined as “*medicines based on known molecules that address healthcare needs and deliver relevant improvements for patients, healthcare professionals and/or payers*”¹. They represent an opportunity for increasing the cost-effectiveness of treatments or services that may bring substantial value to individual patients and society (including citizens, healthcare professionals, payers, etc).

The added value may be achieved through:

- Medicine repositioning (to extend medicine indication)
- Medicine reformulation
- Medicine combination (medicine/medicine or medicine/device or medicine/service)

Value for patients:

- Better efficacy, safety and/or tolerability profile
- Optimised route of administration and/or convenience of use
- Access to new therapeutic uses of already existing products covering unmet needs

These improvements may enhance adherence/persistence, health outcomes or quality of life, work productivity and match patients’ and/or caregivers’ preferences.

Value for society:

- Addressing a number of medicine-related healthcare inefficiencies
- Enhancing healthcare system efficiency by improving healthcare provision and organisation
- Contributing to sustainability of healthcare systems through economic advantages

However, current European health technology assessment (HTA) decision frameworks, depending on the country, represent various challenges for full value recognition of value added medicines.

We call for HTA policy changes and robust research support to ensure population of the European Union (EU) may benefit from the potential value of value added medicines.

Several initiatives undertaken at European level and involving HTA bodies, regulators, academics, research organisations and pharmaceutical industry may contribute to ensuring that the society captures all the potential benefits associated with value added medicines.

Key recommendations

On the research front, complementary HTA methods should be promoted.

- 1. There is a need to support the development of a robust and reliable methodology to implement multiple criteria decision analysis techniques (MCDA) in HTA decision frameworks.**

MCDA methods appear to be the most appropriate for integrating multiple attributes, but they require additional research and shared guidelines for appropriate use to become actionable.

The benefits of value added medicines on value dimensions such as patient preferences, socio-economic impact (e.g. productivity loss impact, re-allocation of freed healthcare resources) are not clearly integrated into HTA decision frameworks. MCDA methods may ensure that these attributes are considered with the relevant weights.

- 2. There is a need to support research on constraint optimisation modelling (with associated research on disease burden) to be used in HTA decision frameworks.**

Constraint optimisation modelling uses mathematical programming techniques to maximise population and society health gain while adhering to a predefined budget and other recognised constraints. This should be recognised by HTA bodies as a relevant method that could be used when a product may create a shift in the interventions mix within one specific therapeutic area and for a defined patient population, when it is possible to document the associated budget. This method may be valuable for supporting payer decisions for value added medicines and should be considered by HTA bodies as a useful alternative to cost-effectiveness analysis in some circumstances (i.e. when the budget constraint can be estimated in the disease considered and when multiple interventions exist, to allow identification of the mix of interventions that will optimise the health gain with no budget impact).

On the policy front, we call policy-makers to consider 8 aspects of HTA decision frameworks that should be adjusted.

- 1. Whenever requested, all medicines should be eligible for HTA.**

There should be no legislative or regulatory barriers preventing companies from pursuing HTA for value added medicines in order to demonstrate relevant improvements for patients, healthcare professionals and/or payers.

A dedicated HTA programme may be considered for value added medicines where the manufacturer would not have to provide a full HTA submission (abbreviated HTA) but would only provide evidence on the benefits of value added medicines.

- 2. Whenever requested, all medicines should be eligible for early HTA dialogue at national or European level (multi-HTA advice or parallel scientific advice – EMA/multi-HTA advice).**

All medicines claiming added value should be eligible for multi-HTA early dialogue and parallel scientific advice (EMA-Multi-HTA early dialogue), in order to better shape their clinical development plan.

3. HTA decision frameworks should encompass all attributes recommended by the EUnetHTA Core Model®, under the following nine domains:

1. Health Problem and Current Use of the Technology
2. Description and technical characteristics of technology
3. Safety
4. Clinical Effectiveness
5. Costs and economic evaluation
6. Ethical analysis
7. Organisational aspects
8. Patients and Social aspects
9. Legal aspects

These attributes should be integrated in a standardised and explicit way through a transparent and reproducible deliberative process, i.e.:

- With explicit metrics
- Reported in HTA reports

For attributes recommended by the EUnetHTA Core Model® which are not yet included in HTA decision frameworks or informally included, it is suggested to include these attributes as modifiers of the existing HTA frameworks (i.e. as modifiers of incremental cost-effectiveness ratio [ICER] threshold or as modifiers of added clinical benefit assessment scoring).

Such changes in HTA decision frameworks may ensure that all benefits of value added medicine are appropriately captured.

4. HTA decision frameworks should be patient-centric and consider the patient perspective, including patient-reported outcomes, patient-centered outcomes, and patient preferences.

- There is a need to promote the development of validated PROs instruments, compliant with HTA requirements.
- There is a need to promote research to identify the outcomes that are patient-centric, so that HTA agencies can value them appropriately.
- Patient preferences, when adequately elicited, should be clearly considered in HTA decision frameworks.

Value added medicines bring key benefits for patients, which are not currently well captured by HTA decision frameworks and will benefit from a patient-centric assessment.

5. Beyond randomised clinical trials (RCTs), HTA decision frameworks should consider alternative study designs (e.g. pragmatic design, adaptive design, observational studies), when more appropriate to address the research question.

RCTs are generally regarded as the “gold standard” study design with respect to minimising the risk of bias for evidence generation. However, if RCTs are designed to maximise internal validity, they may have some limitations regarding external validity (e.g. restriction in patient population due to strict eligibility criteria) and may not be the most appropriate study design for answering all the

evidence questions potentially relevant to HTA bodies. For instance, improvement in patient's preference, adherence, and convenience of use brought by value added medicines may be difficult to demonstrate through RCTs.

- 6. HTA organisations should encourage the use of coverage with evidence development, to allow some benefits that may be complex to demonstrate during development to be captured post launch.**

Real-world evidence might be more appropriate to demonstrate some benefits of value added medicines.

- 7. HTA decision frameworks should adopt a broader perspective in order to better reflect patients' and society's views of healthcare.**

In Europe, when cost-effectiveness is requested by HTA bodies, there is a variety of perspectives that are considered:

- Societal perspective (e.g., in Sweden)
- National health insurance perspective (e.g., in the UK)
- Mixed perspective (e.g., in France)

Due to the potentially substantial impact of productivity costs on cost-effectiveness outcomes, they should be considered in HTA decision frameworks. This may enhance the efficiency related to usage of medicines (including value added medicines) to improve overall society performance.

- 8. A broad range of stakeholders, including patients, healthcare professionals, society representatives (citizens), and hospital administrators, should be voting members of HTA committees in order to integrate a broad perspective into the final recommendation.**

Due to the importance of their perspective in medicine assessment (including for value added medicines), patient representatives, citizen representatives, but also healthcare provider representatives and hospital administrators, should be represented, and have full voting rights, in HTA organisations.

2. Context

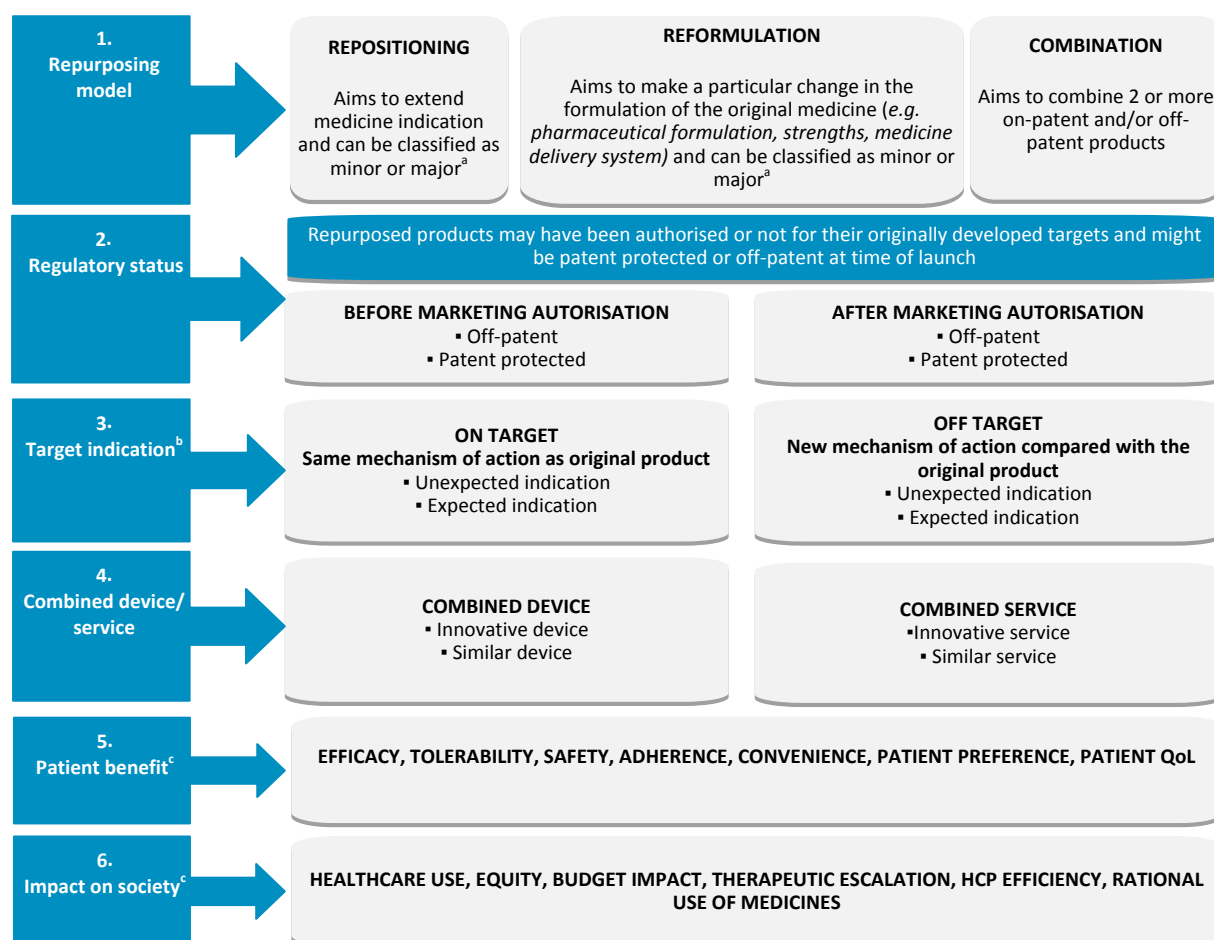
2.1 Definition and typology of value added medicines

Value added medicines are defined as *"medicines based on known molecules that address healthcare needs and deliver relevant improvements for patients, healthcare professionals and/or payers"*².

Due to the broad concept of value added medicines, a typology has been developed to standardise it, including two separate but interconnected algorithms³:

- The first algorithm relates to the typology of value added medicines itself, including 6 dimensions as described in **Figure 1**.

Figure 1. Typology of value added medicines



QoL: quality of life; HCP: healthcare professionals

^a In terms of risk for the company to develop such a new indication/reformulation (return on investment)

^b Target indication:

- Repurposed products may act via the same mechanism of action as the original product, i.e., same target (on target), or may act via a new mechanism of action, i.e., new target (off target)
- The targeted indication might be expected if this is a known clinical target for the repurposed product (e.g. it is well known that antiepileptic drugs might be effective in bipolar disorders and pain), or unexpected if this is an unknown clinical target for the repurposed product (e.g. antiepileptic drugs which would be effective in Parkinson's disease)

^c Each patient benefit and impact on society category is rated as high or medium or low

- The second algorithm relates to the disease environment, as the general context of the disease and target population cannot be disconnected from the typology when assessing the overall product value. This algorithm includes 4 dimensions:
 1. **Target population** considers any specific patient subgroups with high unmet needs, and vulnerable populations (e.g. paediatric/elderly>80, mentally disabled, rare diseases, end of life, pregnant women).
 2. **Disease burden** (clinical, humanistic and economic) assessed as high, moderate or low.
 3. **Type of disease** categorised as acute or chronic and according to its severity (severe, moderate, or mild).
 4. **Unmet needs** assessed as high, moderate, or low.

2.2 Value delivered by value added medicines

Value delivered to patients

Value added medicines can deliver relevant improvements for patients, including:

- Better efficacy, safety and/or tolerability profile.
E.g. A new formulation of a well-known chemotherapy product helping to reduce serious side effects of the original product used in many chemotherapy regimens.
- Optimised administration and/or better convenience of use for patients.
E.g. A new device used to administer generic products for inhalation in Chronic Obstructive Pulmonary Disease (COPD), with evidence of reducing inhaler errors versus current device(s) used with the same active substances.
- Access to new therapeutic uses of already existing products covering unmet needs (new indication).
E.g. Repositioning of a well-known product in a rare pediatric indication as an alternative to reference treatments not specifically approved in this indication.

These improvements may enhance adherence/persistence, health outcomes or quality of life, work productivity and match patients' and/or caregivers' preferences.

It is important to highlight here that adherence has a substantial impact on patients' health. An overview of adherence to long-term therapies conducted by the World Health Organization (WHO) in 2003 found that the average adherence rate in developed countries was around 50%⁴. Poor adherence has been estimated to cost European governments about €125 billion annually and contribute to the premature deaths of nearly 200,000 Europeans per year⁵. The WHO⁴ highlighted that low-cost interventions improving adherence were demonstrated to be cost-saving and increase effectiveness of health interventions, quoting Haynes R.B. (2001)⁶: "*Increasing the effectiveness of adherence interventions^a may have a far greater impact on the health of the population than any improvement in specific medical treatments*". A study conducted by Roebuck MC. et al (2011)⁷

^a E.g. information, counselling, reminders, self-monitoring, family therapy

showed that improved medication adherence produced substantial medical savings due to reductions in hospitalisation and emergency department use.

Value delivered to society

In addition to the benefits for individual patients, value added medicines can deliver three key relevant improvements for the broader society, as elucidated by the examples given below ²:

- 1. Addressing a number of medicine-related healthcare inefficiencies.**
- 2. Enhancing healthcare system efficiency by improving healthcare provision and organisation.**
- 3. Contributing to sustainability of healthcare systems through economic advantages.**

Value added medicines can address a number of medicine-related healthcare inefficiencies by:

- Improving the rational use of medicines.
 - New medicine formulations or combinations could help improving adherence to already available therapies.
E.g.
 1. A fixed-dose combination of products already available on the market and used as free dose combination in HIV to reduce pill burden in a highly medicated patient population.
 2. An extended-release formulation of a product already available on the market for a neurocognitive disease indication, reducing administration regimen from once-weekly injection to 3-monthly injection.
 - New and appropriate medicine packaging and vial conditioning could contribute to limited medicine wastage.
E.g. Pre-filled syringes with automatic dosing of an already known product (click-based procedure; 1 click=1 dose)
- Making appropriate treatment options available.
 - Value added medicines could contribute to tailored and expanded access to well-known therapies, to suit the needs of particular patient subgroups.
E.g. Reformulation and repositioning of a well-known product to be used in vulnerable populations such as children or elderly patients with co-morbidities.
- Making optimal timely drug monitoring and patient management.
E.g. Electronic-based inhalers in asthma can inform on patient clinical status including alerts when degradation of respiratory function and inform on medication adherence to tailor treatment plans to each patient.

Value added medicines can enhance healthcare system efficiency by improving healthcare provision and organisation.

- Value added medicines could contribute to improve efficacy, and/or safety, and/or efficiency of healthcare professional resources used with or without reduction and re-allocation in healthcare use.
E.g. A ready to use well-known chemotherapy, which may improve medicine handling, reduce errors and save time for healthcare providers (reduce the opportunity costs of time devoted by healthcare professionals).

- Value added medicines could improve equity, for example, by addressing geographical inequity in medicine access.
 - Value added medicines offer an opportunity to create an intermediate step before switching to costly products that require specific settings not widely available across the country, and improving affordability.
 - They also offer the opportunity to provide new medicine formulations for hospital-only medicines which are suitable for use in the outpatient setting, thus improving access in remote rural areas for example.

E.g. A self-injected subcutaneous formulation of a product which was already available on the market in a severe inflammatory disease as an intravenous formulation administered only at hospital under medical monitoring.

Value added medicines can contribute to sustainability of healthcare systems through economic advantages.

Value added medicines may represent an opportunity to limit therapeutic escalation by increasing the number of treatment options, and to reduce budget impact by creating an intermediate step before switching to more costly products.

E.g. New intermediate effective dosage, or a new alternative therapy reducing the need to switch to last resort therapies, which are often very expensive.

2.3 Current challenges to capturing the full value of value added medicines

Current HTA decision frameworks and pricing rules in place in some countries have been reported as the key hurdles preventing the full recognition of value added medicines' benefits, and creating a disincentive for further development ². For example, approaches such as internal reference pricing or tendering processes, involve very little consideration on added value and focus almost solely on cost. More detailed HTA approaches, especially those using cost-effectiveness analyses, may use outcome measures that do not fully capture all the added benefits of improved care, such as greater convenience of use.

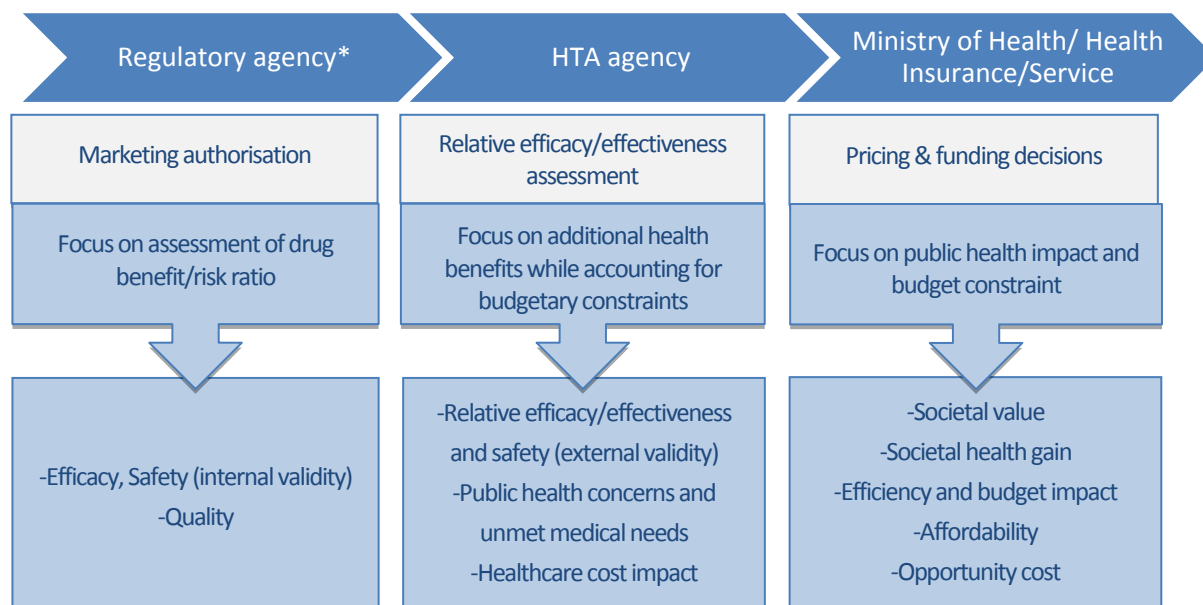
This white paper aims to assess the key challenges in current European HTA decision frameworks for full value recognition of value added medicines. It suggests policy changes which are required to better acknowledge the value of these medicines by European HTA bodies, i.e., what would be the optimal HTA decision framework contributing to better and timely patient access to value added medicines and rewarding development efforts from manufacturers.

3. Current challenges of European Health Technology Assessment (HTA) decision frameworks

3.1 HTA decision framework concept

Following marketing authorisation of new medicines, most European Union (EU) Member States (MS) use HTA decision frameworks to decide if a medicine can be publicly funded by the national healthcare system (**Figure 2**).

Figure 2. From medicine approval to funding^{8,9,10}



Medicine funding and pricing are matters on which decisions are made at the national level, i.e., by each single European country independently of others, following its own methodologies. Across their differently operating health care systems, there is a lack of shared value definitions, no common understanding of the attributes that contribute to value in healthcare, and a lack of joint formal processes to assess therapeutic options and to set health priorities^{11,12}.

The HTA decision frameworks can be presented according to 6 key features^{13,14}, which characteristics differ between European countries.

1. **Methods**
2. **Attributes**
3. **Stakeholders**
4. **Value judgement decisions**
5. **Eligibility criteria**
6. **Perspective**

3.2 HTA methods

HTA agencies currently base their decision either on relative clinical benefit assessment and/or health economic assessments,¹⁴ and may be clustered in three key archetypes of HTA decision frameworks, i.e., clinical model, health economic model, and mixed model.

Clinical model

Some HTA agencies, such as the Institute for Quality and Efficiency in Health Care (IQWiG)¹⁵ / the Federal Joint Committee (G-BA)¹⁶ in Germany, use clinical benefit assessment as a key decision

driver. A cost-benefit assessment is only conducted in case of disagreements during pricing negotiation, following arbitration process.

Until recently, France also solely used the clinical model, but introduced economic assessment in 2013 (see the “mixed model” section).

Health economic model

A number of HTA agencies, including the National Institute for Health and Care Excellence (NICE)¹⁷ and the Scottish Medicines Consortium (SMC)¹⁸ in the United Kingdom, as well as the Dental and Pharmaceutical Benefits Agency (TLV)¹⁹ in Sweden, mainly base their decisions on cost-effectiveness analysis using the incremental cost-effectiveness ratio (ICER).

Mixed model (Clinical/HE)

Some HTA agencies combine both clinical benefit assessment and health economic assessment when making their decisions (cost-effectiveness and budget impact analysis).

In some of these ‘mixed’ HTA frameworks, decisions are mainly driven by budget impact analysis rather than cost-effectiveness analysis. For example, in Italy and Spain, cost-effectiveness analysis and budget impact analysis are not mandatory for national pricing and reimbursement application, but they can be submitted by the manufacturers^{20,21}; however budget impact analysis plays a key role at regional levels (“budget holders”). In Poland, cost-effectiveness analysis is required for products with no equivalent reimbursed product on the market, but the Polish HTA Agency (AOTMiT) recognises that for decision makers, budget impact analysis is often more important because of its greater transparency and simpler way of calculating costs^{22,23}.

In other HTA frameworks, for example in the Netherlands (the National Health Care Institute, ZIN²⁴), cost-effectiveness/cost-utility analysis is an important criterion in decision making.

In France, the HTA model is mixed but dominated by clinical assessment performed by the Transparency Committee of the National Authority for Health (HAS). Health economic assessment was introduced in 2013 and is performed by the Economic and Public Health Assessment Committee (CEESP), another committee part of the HAS, for innovative and high-budget impact medicines, in order to inform payers when setting prices. Cost-effectiveness analysis is required for medicines claiming a major, important, or moderate improvement of the actual benefit (*Amélioration du Service Médical Rendu*, or ASMR-I, II, or III) and medicine with yearly projected revenues of €20 million or more during the second full year of availability on the market; budget impact analysis is optional, except if annual sales revenues are expected to be of €50 million or above²⁵.

Other models under discussion

Inconsistency, variability and lack of predictability are reported in the current HTA value frameworks and, to address these challenges, initiatives such as Multiple Criteria Decision Analysis (MCDA) for healthcare decision making have been frequently debated over the last years^{26,27,28, 29,30}. This method seems conceptually very appropriate for integrating multiple attributes. However, due to technical issues, it is currently mainly used for experimental pilot projects or for academic purposes.

Other methods, such as the ‘replacement approach’ are also under discussion, albeit more from an academic perspective and appear to be unrealistic in practice^{29,31,32}.

An interesting methodology gaining popularity in HTA is the constraint optimisation model^{29,33}. This method uses mathematical programming techniques to maximise population and society health gain, while adhering to a predefined budget and other recognised constraints.

Brief description of these methods is provided in Appendix 1.

3.3 HTA attributes

HTA attributes integrate three dimensions:

1. **Attribute definition**
2. **Relative importance of each attribute**
3. **Evidence collection and hierarchy per attribute**

Attribute definition and weight

The HTA Core Model® (version 3.0)³⁴ of the European network for HTA (EUnetHTA) - *integrating a European vision of the best HTA practice* - defined nine domains of attributes including:

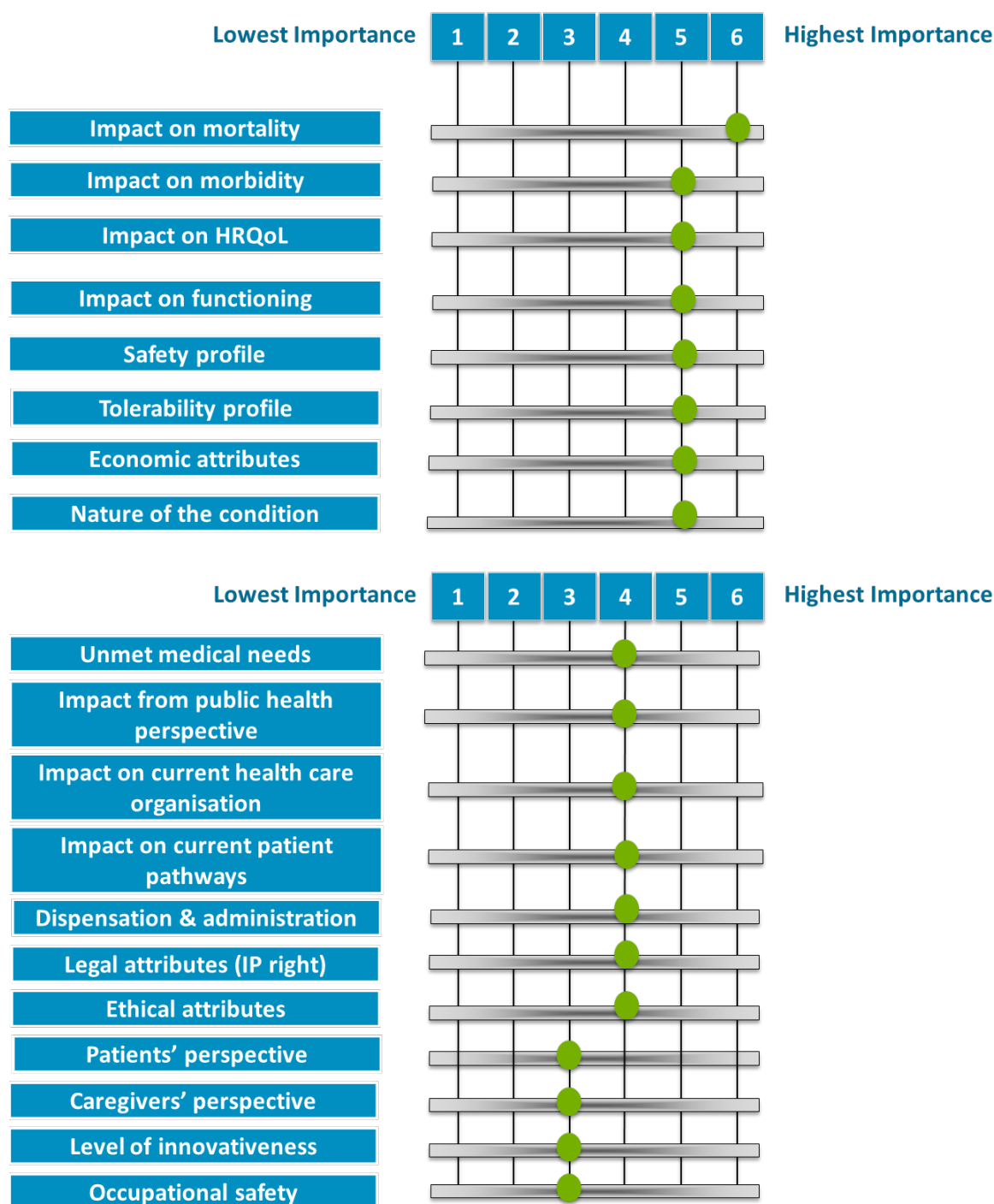
1. **Health Problem and Current Use of the Technology**
2. **Description and technical characteristics of technology**
3. **Safety**
4. **Clinical Effectiveness**
5. **Costs and economic evaluation**
6. **Ethical analysis**
7. **Organisational aspects**
8. **Patients and Social aspects**
9. **Legal aspects**

However, the weight of each attribute is not specified and left to the appreciation of individual HTA bodies. Although all these attributes are considered important for HTA practice, HTA bodies tend to mainly consider clinical efficacy, safety, and - depending on country - economic aspects, as key attributes.

The WHO “2015 Global Survey on Health Technology Assessment by National Authorities”³⁵, assessing the frequency of covering 10 different pre-specified aspects of HTA, showed that more emphasis was put on safety, clinical effectiveness, and economic and budgetary considerations, rather than on other potential components of HTA. Acceptability to healthcare providers and patients, equity issues, ethical issues and feasibility considerations (e.g. availability of budget, human resources, and infrastructure) were rarely considered.

Interviews conducted with 9 European HTA experts (from France, Germany, Italy, the Netherlands, Poland, Spain, Sweden, and the UK) asking to rank attributes in the order of importance from the HTA perspective, provided similar results (**Figure 3**). Details of these interviews per country are provided in Appendix 2.

Figure 3. Importance of HTA attributes from HTA expert perspective (n=9)



A recent study conducted by Angelis A. *et al.* (2017)¹⁴ in the context of the Advance-HTA project^{b,36} in eight EU countries using either clinical, economic or mixed HTA decision framework models

^b EU funded project to advance and strengthen the methodological tools and practices relating to the application and implementation of HTA.

reported that HTA agencies mainly based their “formal” assessment on what the authors called “scientific value judgements” encompassing safety, efficacy and effectiveness; this evidence being potentially assessed in relation to cost. The authors highlighted that “social value judgements” including burden of disease, innovation level and socio-economic impact were also used as attributes, but in an implicit and non-systematic way, with no clarity on their relative weight in decision making¹⁴. They concluded that, even if most HTA bodies are recognising the importance of multiple criteria beyond clinical and economic attributes in decision-making, the different HTA decision frameworks would require a more transparent and structured process to assess health technologies from a wider socio-economic perspective¹⁴.

In particular, patient perspective is an important feature to be considered in HTA decision frameworks. Patient preferences for aspects of their healthcare can make their perspectives on medicine value significantly different from those of physicians or payers. Even though patient-centeredness is increasingly discussed along the medicine development value chain, some efforts remain to be made to develop a patient-centric HTA^{37,38,39,40,41,42}. To appreciate patients’ perspective and integrate it in a decision framework, three different and complementary components need to be considered (definition reported in Appendix 3):

- **Patient-reported outcome (PRO)**
- **Patient-centered outcome (PCO) (or patient-relevant outcome)**
- **Patient preferences**

PROs are generally considered in all HTA decision framework models. However, their results are usually undermined due to methodological issues associated with collecting PRO data, and the lack of appropriate validated instruments. To anticipate HTA bodies’ expectations in terms of PRO tools and methodological requirements, it is important to get engaged in early HTA advice.

Regarding PCOs, HTA attributes based on expert or clinician criteria are likely not patient-centric, because patients and experts or clinicians have a different appreciation of which outcomes are important for them. Previous research showed that outcomes of the greatest importance to patients might not be the ones on which physicians are putting emphasis. For example, in oncology, it has been shown that, in contrast to physicians, patients would value a treatment with positive probability of durable survival more than a therapy with same mean survival but no variability (“*hope of durable survival*”)⁴³; in other words, the surrogate endpoint “disease-free survival” may be preferred to the endpoint “overall survival” in cases where disease progression is associated with bothersome symptoms and/or affects quality of life. Another study explored how various stakeholders valued new cancer treatments through estimated ICER values based on structured interviews; it was found that oncologists valued gains in survival the most, while patients and the general population valued improved quality of life the most. Healthcare policy makers placed a higher value on survival gain, but at a lower willingness to pay⁴⁴.

Finally, patient preferences have currently low weight in HTA decision frameworks. For example, in England, while patient preferences are widely used by the National Health Service (NHS) to determine healthcare organisation policies, the HTA body (The National Institute for Health and Care Excellence-NICE), on the contrary, does not integrate patient preferences in HTA methods guidance. In Germany, there have been some pilot experiences by the HTA body (the Institute for Quality and Efficiency in Healthcare-IQWiG) to integrate patient preference in the field of oncology and

depression; although it was very informative and enlightening, this experience has not been pursued further. Notably, HTA bodies using cost-utility analysis rely on quality-adjusted life years (QALY) for assessing health gain. QALYs are derived from preference elicitation of the overall society. Therefore, the social tariffs used to generate utility from the QoL instrument are based on society and not individual patient preference. Although this makes perfect sense for budget allocation between conditions, it is more questionable for resource allocation within a given condition⁴⁵. Moreover, socio-economic benefits such as increased convenience of use may not be adequately captured by QALY measurements⁴⁶.

Evidence collection and hierarchy per attribute

How the attributes are collected is also an important element of the HTA decision framework. Attributes collected in randomised clinical trials (RCTs) are generally regarded as the “gold standard” study design with respect to minimizing the risk of bias. However, if RCTs are designed to maximise internal validity, they may have some limitations regarding external validity (e.g. restricted patient population due to strict eligibility criteria) and may not be the most appropriate study design for answering all evidence questions of potential relevance to HTA bodies. RCT are often poorly transferable and not broadly generalizable, thus providing little insight on value of interventions in real life, which is the information needed by HTA bodies. A wide range of alternative designs are described in the literature (e.g. pragmatic design, adaptive design, observational longitudinal studies) which might be more appropriate depending on the research question.

Due to limitations associated with the use of RCTs to assess relative effectiveness of medicines (eg. in clinical practice), there is a growing interest in the use of real world data by HTA agencies. A recent research conducted by Makady A. *et al* (2017)⁴⁷ in six EU countries in the context of the EU IMI GetReal project^{c,48} showed that the use of real world data varied depending on the context of assessment (i.e. initial reimbursement discussion, input for pharmaco-economic analyses, conditional reimbursement scheme) and differed between HTA agencies.

Of note, the opportunity for coverage with evidence development does not exist in all countries and can be restricted to specific categories of medicines, for example, expensive hospital-only medicines in the Netherlands⁴⁹, or innovative products in France. This may be a key limitation for medicines which benefits can be demonstrated in real-life practice, such as improved adherence or persistence.

3.4 Stakeholders

Involvement of stakeholders in HTA bodies is heterogeneous between countries⁵⁰. Even if some efforts to better engage the citizens and patients in HTA are ongoing, this process is still in its infancy^{51,52}. The type and level of involvement vary widely between countries, i.e., consultation regarding perspectives, experiences or preferences about health technologies, versus participation in prioritisation, scoping, evidence assessment, and dissemination of HTA findings^{51,52}. When

^c A three-year project launched in 2013, run by the Innovative Medicines Initiative (IMI), a EU public-private consortium consisting of pharmaceutical companies, academia, HTA agencies, regulators, patient organisations and SMEs.

citizens, patients and healthcare providers are represented in HTA organisations, they usually have a consultative role and their perspective is rarely explicitly documented in HTA reports.

3.5 Value judgement decision

The value judgement decision is the step that allows moving from the evidence review and analysis to the final recommendation to reimburse an intervention or not.

Value judgement decision process can be based on:

- Scoring system
- Deliberative process without scoring
- ICER thresholds in HTA decision frameworks considering cost-effectiveness analysis (fixed or flexible, explicit or not)

Key challenges of value judgement decisions in clinical/health economic/mixed HTA models

Regardless of the methodology being used, ultimately, HTA agencies apply a deliberative process, which may be defined as an open discussion between the HTA committee members to address the pros and cons of adopting a new technology based on clinical and economic evidence, as well as other value dimensions such as disease burden and unmet medical needs, level of medicine innovativeness, patient preferences, equity considerations and socio-economic impact (e.g. public health or productivity loss impact) ^{14,53}.

Significant subjectivity in interpretation of evidence, and a lack of transparency on which attributes and which dimensions contribute to the final decision have been reported^{14,53}; therefore, it becomes impossible to appreciate, for example, which important considerations may be overlooked and which ones might be driven by biased perceptions. Especially, appreciation of unmet need, disease burden (clinical, economic, and humanistic), transferability and generalisability of clinical data, desirability for the society and patients, and public health priorities are not standardised in HTA decision framework, i.e., either used informally, or through non-transparent aggregation of different criteria, introducing some varying degrees of arbitrariness. The way questions are framed, the leadership in the deliberative discussion, the potential conflicts of interest, and/or human behavior will definitely take over rationality in an unstructured and non-standardised deliberative process.

For example, the management of uncertainty by HTA bodies is often related to transferability and generalisability of clinical trial outcomes. It is often referred in HTA reports as a critical issue which may downgrade the value judgement decision, but it is never explicit and quantified to appreciate the magnitude of this uncertainty on the overall outcome. Uncertainty may sometimes be addressed in cost-effectiveness analysis through deterministic or probabilistic sensitivity analysis; however how quantitative results influence the value judgement decision remains based on expert intuitive appreciation and experience.

Moreover, the social media and public pressure to gain access to medicines is often unbalanced across conditions and may also impact HTA committee members' recommendations. In the same

way, political pressure from government or parliament, for example, may affect the committee recommendations.

Specific challenges of value judgement decisions in health economic models

While HTA decision frameworks based on cost-effectiveness models may appear more transparent as they use a robust methodology for informing resource allocation decisions by relying on the ICER threshold, the final decision is modulated by a deliberative process that is not explicitly reported in published HTA opinions⁴⁵. This deliberative process includes, on top of uncertainty associated with cost-effectiveness results, other value dimensions. For example, the SMC is applying modifiers in some cases of medicines. These modifiers include criteria such as substantial improvement in life expectancy and/or in quality of life, absence of other therapeutic options of proven benefit. Although these modifiers are explicit, their weight in the final decision is unclear^{18,54}.

It has also been evidenced, that beyond ICER, other factors are addressed in the deliberative process impacting NICE recommendations. NICE – which is considered to be one of the most robust and transparent HTA agencies using cost-effectiveness analysis and ICER threshold for making recommendations – has recommended a broad range of products with ICER above £30 000 per QALY. A study conducted by Dakin H. *et al.* (2014)⁵⁵ assessing drivers of NICE decisions found that the type of disease had a significant impact on NICE decisions; oncology products had three times higher chances to be recommended by NICE than non-oncology products and musculo-skeletal products enjoy more than five times the chances to be recommended by NICE than other products. These results suggest that some conditions may be associated with a non-transparent and potentially unconscious higher willingness to pay per QALY, while the pivotal principal of equity in the UK is that all QALYs are of equal value and “QALY is a QALY is a QALY”⁵⁶. The exemption of ultra-orphan medicines from cost-effectiveness analysis and the development of end-of-life criteria also support that the horizontal equity (“a QALY is a QALY is a QALY”) is not written in stone and that specific undocumented and opaque situations may affect willingness to pay.

Moreover, even if it has been challenged for a long time, recent experience with sofosbuvir in the treatment of hepatitis C has shown the limitation of ICER threshold in addressing budget impact and affordability. Indeed, despite sofosbuvir being considered a cost-effective therapy under most scenarios and subgroup analyses, because of the high disease prevalence, it was estimated that the budget impact of introducing the medicine would threaten the sustainability of health insurance in most EU countries if no additional price discount was considered.

Specific challenges of value judgement decisions in mixed models

Most mixed HTA models operate in two steps. The first step is to appreciate the health gain associated with a therapy, based on clinical information, and then to conduct a cost-effectiveness analysis to identify the price premium that such health gain produced deserves (e.g., this is typically the case in the Netherlands). Some countries, such as Spain, Italy and Hungary, rely more on budget impact analysis rather than cost-effectiveness analysis to support decision making, which is difficult, as no rules are available and no thresholds exist. Budget impact analysis within a pre-defined affordability threshold may be more or less acceptable based on multiple criteria, such as the number of patients, burden of the condition, unmet needs, total health gain, societal desirability of treating the disease, public health priorities, pressure from patient groups and political instructions. However, it is unclear how all these criteria may be objectively integrated to conclude in a robust,

standardised and reproducible way which level of budget impact is acceptable for a given intervention. Other countries, like France, may use a three-step method with clinical assessment to identify potential health gain, cost-effectiveness analysis to inform which premium price is cost-effective and then budget impact analysis to match price with affordability. These countries accumulate the limitations of the individual models.

3.6 HTA eligibility

Depending on countries, not all medicines may be eligible for HTA. For example, in Germany, there is no HTA for new formulations of active ingredients already authorised in the same indication, unless a benefit is claimed over the appropriate comparator therapy, based on RCTs¹⁶. In Poland, HTA applies to medicines for which there are no reimbursed equivalent products on the market²². In England, NICE only review limited new medicines, mainly based on potential budget impact of new molecules¹⁷.

Moreover, in some countries, early HTA advice does not apply to all medicines, especially when the advice is free of charge such as in France. In France, to be eligible, the medicinal product must present a new way of treating a disease, such as a new mode of action²⁵. Currently, multi-HTA early dialogues are available for new medicines, or existing medicines with a new indication; due to the limited number of applications which can be submitted, priority is given to medicines intended to treat severe conditions for which there is no satisfactory therapeutic alternative⁵⁷.

In parallel scientific advice with the EMA, participation of HTA bodies solicited by the manufacturer for the advice will depend on their national policies, i.e. some HTA bodies may refuse to participate if the product is not considered to comply with their eligibility criteria (e.g. level of innovativeness, level of unmet medical needs)⁵⁸.

3.7 HTA perspective

In Europe, when cost-effectiveness is requested by HTA bodies, there is a variety of perspectives that are considered. Some HTA agencies, such as the TLV in Sweden consider the societal perspective, while others consider the national health insurance perspective, like NICE in the UK, or a mixed perspective – for example, the French HAS considers a perspective known as the collective perspective, which includes, beyond health insurance costs, some societal perspective costs such as the time patient/carer spends going for a consultation or undergoing a medical test, and some transfer cost such as sick leave allowances).

One important societal cost is related to work productivity. When included in HTA decision frameworks, definition of these costs and methods of valuation differ between countries⁵⁹. It has been shown that inclusion of productivity costs in cost-effectiveness analysis could have a substantial impact on ICER⁶⁰.

3.8 To capture the full value of value added medicines, HTA decision frameworks and policies should be revisited

The benefits of value added medicines to individual patients and the society are not fully acknowledged by HTA bodies, especially due to value assessment approaches being based on clinical and economic assessment (mainly cost-effectiveness/budget impact). Even if a multi-dimensional

approach of value assessment is considered by HTA bodies, additional value dimensions, such as disease burden and unmet medical needs, level of medicine innovativeness, patient preferences, equity considerations, socio-economic impact (e.g. public health impact, productivity loss impact, re-allocation of freed healthcare resources) are not clearly integrated into HTA decision frameworks.

Value added medicines may address key unmet medical needs such as:

- Improvements in efficacy and safety of current therapies
- Adherence /persistence issues
- Therapies not tailored to specific patient populations
- Medicine wastage
- Geographical inequity in medicine access
- Non optimal timely medicine monitoring and patient management

However, criteria considered by HTA agencies to assess the unmet medical needs, and their relative weight, are not explicitly defined, and value added medicine benefits are often not captured by current HTA decision analysis framework.

Moreover, value added medicines bring key benefits for patients, which may be well captured by patient-centric assessment. While improvements in efficacy, safety, and/or tolerability profile demonstrated in RCTs can be acknowledged through current HTA decision frameworks, other benefits of value added medicines may not be adequately captured. For instance, improvement in patient's preference, adherence, and convenience of use may be difficult to demonstrate. In clinically-driven HTA models, such benefits need to be translated into patient-relevant clinical benefit in terms of impact on efficacy, safety of quality of life. In cost-effectiveness driven HTA models, such benefits are poorly (or not at all) captured by QALY, which is the reference measure of medicine value in several countries. Demonstration of these benefits requires substantial and disproportionate investments to be proven through study designs acceptable to HTA agencies before marketing authorisation is granted. Additionally, real-world evidence might be more appropriate to demonstrate some benefits, such as improvement in patient adherence, but coverage with evidence development is not in place in all countries and may be restricted to specific categories of medicines (usually medicines classified as "innovative").

Finally, value added medicines may not be eligible for HTA in some countries, e.g. they may be categorised as generic medicines, despite having significant additional benefits versus already approved formulations of the same active substance. Moreover, they may not be eligible for early HTA scientific advice, even though these products may highly benefit from HTA bodies' feedback on clinical development plan. As mentioned above, benefits of value added medicines may be difficult to demonstrate, and early HTA scientific advice should ensure the clinical development plan captures their full value and comprehensively addresses the requirements of HTA bodies.

4. Key Recommendations for HTA Decision Frameworks and Policy Implications

4.1 HTA methods

The MCDA^d method appears to be the most appropriate to integrate all EunetHTA Core Model[®] attributes, although it would require additional research and shared guidelines for appropriate use to become actionable. Public research funding and public-private collaborations will be needed to identify how to optimise this methodology and make it applicable to daily HTA practice.

Constraint optimisation modelling^c should be recognised by HTA bodies as a relevant method that could be used when a product may create a shift in the intervention mix within one specific therapeutic area and for a defined patient population, and when it is possible to document the associated budget. Constraint optimisation modelling could be enhanced thanks to research investigating cost of illness, which could be funded either publically or through public-private collaborations.

Introduction of modifiers that may impact the decision (see section 4.4 value judgement decision) appears to be the most appropriate way to integrate, in a transparent and robust way, a multiplicity of attributes only addressed through the deliberative process.

4.2 HTA attributes

All domains of EunetHTA HTA Core Model[®] attributes should be integrated by HTA bodies in their decision frameworks in a transparent way. For each domain, all considered attributes should be explicitly stated, be subject to a dedicated assessment and reported in HTA reports, to ensure all product benefits are fairly considered and properly assessed.

Most of these attributes are either not yet integrated in decision making or are integrated with no clear framework, and they do not benefit from explicit metrics to be measured. Therefore, they are integrated in a non-standardised way and their impact on the final decision is driven by personal judgement and unstructured deliberative discussion. It is recommended that all attributes are systematically scored with appropriate metrics (whether ordinal or cardinal), reproducible and meaningful.

For example, for unmet medical needs, the following criteria may be explicitly considered:

- Number of alternative treatments
- Limitations of current therapies in terms of efficacy, tolerability and safety
- Adherence issues
- Medicine wastage
- Therapies not tailored to specific patient populations

^d Description in appendix 1

For disease burden, clinical, humanistic and economic burden may be explicitly considered:

- Clinical burden
- Humanistic burden (i.e. impact on health-related quality of life, body functions, work ability, return to previous living conditions, activities of daily living)
- Economic burden (i.e. from societal, patient, healthcare provider, and national health insurance perspectives)

This approach may raise questions on independence or redundancy of the dimensions considered within each domain. This should be explicitly addressed in the value decision framework, to ensure that the selected attributes are not redundant and do not lead to double counting.

There is a need for more developed and validated PRO tools that comply with HTA requirements. Incentives for academics to develop such instruments may come from manufacturers, governmental bodies or national research foundations.

It is important to ensure that HTA agencies prioritise patient-centric outcomes, especially when considering arbitration within diseases. This encompasses research aiming to identify and disseminate those outcomes applicable to diseases of interest that are patient-centric, so that HTA agencies may value them appropriately when assessing interventions.

Finally, patient preferences, when adequately elicited, should be clearly considered in HTA frameworks.

4.3 Stakeholders

Due to the importance of their perspective in medicine assessment, patient representatives, citizen representatives, but also healthcare provider representatives and hospital administrators, should be represented, and have full voting rights, in HTA organisations.

Patients should also be involved in value framework discussions, to ensure a patient-centric approach is adopted when reshaping current HTA decision frameworks (e.g. consideration of patient-centric outcomes).

Efforts should also be made to increase the influence of patient and citizen representatives in HTA bodies. For example, they should be given adequate training in HTA in general, and in how they can best fulfil their role in committees.

4.4 Value judgement decision

The deliberative process should be explicit, transparent and reproducible, and the aggregation of individual attributes should be standardised, with explicit criteria and methodology. Baltussen R. *et al.* (2017) recently suggested an “evidence-informed deliberative processes”, integrating multiple explicit criteria (MCDA with a mathematical component) and accountability for reasonableness in view of broad integration of social values⁶¹.

All the attributes of the EUnetHTA Core Model® should be included in HTA decision frameworks; their assessment and weight in the decision should be transparent and standardised.

For attributes recommended by the EUnetHTA Core Model® which are not yet included in HTA decision frameworks – or informally included – it may be beneficial to include these attributes as modifiers of the existing HTA framework, thus preventing major revisions of HTA decision frameworks.

For health economics-driven HTA frameworks, these modifiers could modulate the ICER threshold, as has been established in Scotland by the SMC, so that a product qualifying for modifiers would see the ICER threshold increased by a given percentage. The increase in the ICER threshold would automatically translate into a higher price for the assessed intervention.

In clinically-driven HTA frameworks, modifiers would allow to modulate the additional benefit score, allowing the product to move to a higher class. For example, in Germany, modifiers may allow moving from no additional benefit (score 5) to no quantifiable additional benefit or minor additional benefit (score 4 and 3, respectively). In France, this may change the added clinical benefit assessment of the Transparency Committee, moving from no improvement in actual benefit (ASMR V) to minor improvement (ASMR IV).

The aforementioned modifiers may include, for example:

- How the product positively addresses the current unmet needs, such as issues related to adherence/persistence or medicine wastage
- How the product positively impacts the current healthcare organisation
- How the product positively impacts current patient pathways
- How the product addresses patient preferences, based on patient preference studies
- How the product positively impacts other healthcare resources (as normally included in health economics-driven frameworks)
- How the product addresses health inequities

Each of these modifiers would qualify for a score and a grid would inform how cumulative scores impact either the ICER threshold or the clinical benefit assessment score. Integration of these modifiers in HTA decision frameworks for the assessment of value added medicines is illustrated in **Table 1**. As some benefits might be difficult to demonstrate at the time of product launch (e.g., improvement in patient adherence), coverage with evidence development (time-limited resolution with further evidence generation) might be a good option for all medicines claiming an added value.

Table 1. Illustrative examples of modifiers in HTA decision frameworks for value added medicines

<p>Medicine repositioning model</p>	<p>Repositioning of a well-known product in a rare pediatric indication as an alternative to reference treatments not specifically approved in this indication.</p> <p><u>Two</u> options are possible:</p> <p>Option 1. The treatment was already used in the pediatric population but the formulation was inappropriate for children. In this case, treatment benefit may not be recognised in a traditional HTA decision framework. However, the new formulation addresses an unmet medical need that might be supported by a patient preference study.</p> <p>For example, in HTA decision frameworks driven by clinical evidence, the modifiers “unmet needs” and “patient preferences” may allow the product to be granted a higher score (e.g. in France increasing from “no improvement in actual benefit” to “minor improvement in actual benefit”). In HTA decision frameworks driven by cost-effectiveness analysis, the same modifiers may increase the ICER threshold by a pre-defined percentage (e.g. 5% or 10%), which means the new formulation might achieve a premium price.</p> <p>Option 2. The treatment was not used in the pediatric population. In this case, this product could generate added benefit versus current therapies, based on the magnitude of the benefit. Moreover, the “unmet medical need” modifier might also modulate scoring.</p> <p>For example, in HTA decision frameworks driven by clinical evidence, the new product will bring an additional clinical benefit and the modifier “unmet needs” may allow the product to be granted a higher score (e.g. increasing from “minor improvement in actual benefit” to “moderate improvement in actual benefit” in France). In HTA decision frameworks driven by cost-effectiveness analysis, the new product will bring an additional clinical benefit that will gain a premium price based on the ICER threshold. The modifier “unmet needs” may allow increasing the ICER threshold, which means the product will qualify for an additional premium price.</p>
<p>Medicine reformulation model</p>	<p>A self-injected subcutaneous formulation of a product already available in a severe inflammatory disease as an intravenous formulation administered only at hospital under medical monitoring.</p> <p>In this case, medicine administration-related savings will be captured by traditional HTA decision frameworks and any applicable modifiers will improve the scoring.</p> <p>In HTA decision frameworks driven by cost-effectiveness analysis, the reduced cost of treatment administration will be transferred onto the price of the new formulation. In HTA decision frameworks driven by clinical evidence, the reduction in treatment administration cost will lead to a discussion with payers to determine the proportion of savings that will be allocated to the product.</p>

	<p>A new formulation of a well-known chemotherapy product helping to reduce serious side effects of the original product used in many chemotherapy regimens.</p> <p>In this case, the reduction of serious side effects will be captured by traditional HTA decision frameworks and applicable modifiers will improve the scoring.</p> <p>For example, if the safety issue is very severe and limits the use of the product, the unmet need would be very high, qualifying for a modifier.</p> <p>An extended-release formulation of a product already available in a neurocognitive disease indication, reducing administration frequency from once-weekly to 3-monthly injection.</p> <p>In this case, the benefit may arise from two key outcomes:</p> <ol style="list-style-type: none"> 1. Increased convenience of use that should be captured through patient preference and lead to a modifier being applied. 2. Improved adherence that should permit coverage with evidence development, providing the chance for the manufacturer to enter the market with a reasonable price and develop evidence for improved adherence and related clinical outcomes.
<p>Medicine reformulation model/Medicine-device combination model</p>	<p>A new inhaled device to administer generic products in COPD, with evidence of reducing inhaler errors versus current device used with the same active substances.</p> <p>Three outcomes may contribute to the perceived product benefit:</p> <ol style="list-style-type: none"> 1. Increased convenience of use that should be captured through patient preference and lead to a modifier being applied. 2. Improved adherence that should permit coverage with evidence development, providing the chance for the manufacturer to enter the market with a fair price and develop evidence for improved adherence and related clinical outcomes. 3. Better medicine deposition in the lungs, leading to a higher efficacy being captured by traditional HTA decision frameworks.
<p>Medicine-medicine combination model</p>	<p>A fixed-dose combination of two products already used as a free-dose combination in arterial hypertension, allowing to reduce pill burden and avoid intake errors in a highly medicated patient population.</p> <p>In this case, the benefit may be on two key outcomes:</p> <ol style="list-style-type: none"> 1. Increased convenience of use that should be captured through patient preference and lead to a modifier being applied. 2. Improved adherence that should permit coverage with evidence development, providing the chance for the manufacturer to enter the market with a fair price and develop evidence for improved adherence and related clinical outcomes.
<p>Medicine-device combination model</p>	<p>A therapeutic medicine monitoring device allowing potentiating efficacy while minimising toxicity of a cancer therapy known to exhibit a narrow therapeutic window.</p>

	Safety profile and potentiation of medicine efficacy should be captured in traditional HTA decision frameworks.
Medicine-service combination model	<p>An injectable biological which needs to be kept refrigerated will be provided to patients with cool bags and sharps containers (not provided with the reference product), aiming to facilitate daily administration.</p> <p>In this case, benefit will be captured through patient preferences and may lead to a modifier being applied, depending on the intensity/magnitude of the preference.</p> <p>Such benefit may not be acknowledged when treatment is administered once a day, as the need for transport of the therapy is limited. However, for a treatment that is administered 3 times a day and needs a cool chain, this may have an impact on patient preferences. Nonetheless, the benefit of the product may be considered to arise from improving patient life style rather than health.</p>

4.5 HTA eligibility

There should be no legislative or regulatory barriers preventing companies from pursuing HTA for value added medicines in order to demonstrate relevant improvements for patients, healthcare professionals and/or payers.

A dedicated HTA programme may be considered for value added medicines where the manufacturer would not have to provide a full HTA but would only provide evidence on the benefits of value added medicines such as improved adherence.

All medicines claiming added value should be eligible for multi-HTA early dialogue and parallel scientific advice (EMA-Multi-HTA early dialogue), in order to better shape their clinical development plan and, consequently, demonstrate relevant improvements for patients, healthcare professionals and/or payers that will match HTA organisation expectations/requirements (e.g. it will be crucial to anticipate HTA bodies' expectations in terms of PRO tools and methodological requirements through early HTA advice.)

4.6 HTA perspective

In Europe, healthcare is mostly funded from taxes and insurance contributions; as such, it would make sense to consider healthcare costs as an investment by the society. Therefore, societal perspective would be highly advisable in health economic HTA decision framework models. This is consistent with the fact that the utility elicitation to estimate the social tariff is performed through a general sample of the society, as they are the ones funding healthcare cost through tax payments. Indeed, public national health insurance aims to manage a budget funded from tax payments to achieve optimal benefits for the society.

4.7 EU initiatives

In the EU, a regulatory initiative to support the development of value added medicines is ongoing, with the aim to allow the society capturing all the associated benefits (from outcomes to efficient development).

“Repurposing of established medicines” is currently in discussion at the European Commission level, through the Commission Expert Group on Safe and Timely Access to Medicines for Patients (“STAMP”), recognising the importance of fully investigating different opportunities that such a molecule could bring for patients, with faster development times, and at reduced costs and risk for pharmaceutical companies⁶². Discussions are currently mainly focused on medicine repositioning of off-patent medicines in areas of unmet medical need⁶³. It is interesting to note that market access issues related to medicine repurposing are emerging for further consideration from the “regulatory” STAMP Commission Expert Group⁶³:

- *“What has been the experience of marketing authorization holders in assessments by down-stream decision makers with regard to added value compared to other technologies?”*
- *“Are there any experiences concerning challenges in national pricing and reimbursement discussions, e.g. reference pricing that impact translation of added value into economic value?”*
- *“Was the clinical evidence generated for regulatory decision making adequate for subsequent decision making? Have there been opportunities to discuss and agree such evidence generation plans for repurposing across all relevant decision makers?”*
- *“What is the experience for the healthcare professionals /patients regarding repurposing of medicines?”*
- *“What are opportunities and challenges in bringing different decision makers together for discussion of concrete products for repurposing, e.g. to guide on evidence plans or to facilitate added value discussions?”*

There is currently a gap between increasing regulatory authority interest in capturing value added medicines’ benefits and the resistance of most HTA bodies, which have so far not considered this segment of the pharmaceutical landscape. However, value added medicines may be considered during EUnetHTA Joint Action 3, as they are cited in the public consultation report published in May 2017: *“Medicines for Europe, the association representing the European generic, biosimilars and value added pharmaceutical industries, observed that value added medicines were not eligible to participate in the previous joint actions”*^{64,65}.

Moreover, key collaborations between regulators and HTA bodies discuss features related to value added medicines. In November 2016, the European Commission published a reflection paper on *“synergies between regulatory and HTA issues in pharmaceuticals”*. Among all the areas of cooperation identified, *“the involvement of patients and healthcare professionals understanding patient preferences within a given therapeutic area”* and *“defining which PRO/QoL tools would be valuable for both parties”* were cited⁶⁶.

Further, EU projects involving various stakeholders (including HTA agencies), such as the Advance-HTA³⁶ and IMI GetReal⁴⁸ projects provided key insights on current HTA shortcomings, and recommendations and tools to improve HTA processes. Especially, the need for improvement in HTA transparency is highly acknowledged, e.g.:

- IMI GetReal project: *“Public decision makers, including regulators, HTA bodies and payers should develop and publish policies on their use of RWE. Greater transparency*

and clarity in how these decision makers ultimately use RWE has the potential to spur and influence data infrastructure investments, the collection and utilisation of high quality RWD, data sharing, and the translation of RWD into relevant and actionable RWE that can improve decision making and patient outcomes.”⁶⁷

- Advance-HTA: *“The limitations of the current value assessment methodologies and the identified conceptual and policy gaps suggest that there is a need for methodological approaches that encompass multiple evaluation criteria explicitly, so that value can be an explicit function of a number of dimensions beyond those that are currently explicitly and systematically captured.”¹⁴*

Conclusion

Value added medicines represent an opportunity for increasing the cost-effectiveness of treatments or services that may bring substantial value to individual patients and society (including citizens, healthcare professionals, payers, etc.). Current HTA policies are fraught with various country-specific challenges to capture their full value.

We call for policy changes and robust research support to ensure the EU population may benefit from the potential value of value added medicines.

On the research front, complementary HTA methods should be promoted.

1. There is a need to support the development of a robust and reliable methodology to implement MCDA techniques in HTA decision frameworks.
2. There is a need to support research on constraint optimisation modelling (with associated research on disease burden) to be used in HTA decision frameworks.

On the policy front, we call policy-makers to consider 8 aspects of HTA decision frameworks that should be adjusted.

1. Whenever requested, all medicines should be eligible for HTA.
2. Whenever requested, all medicines should be eligible for early HTA dialogue at national or European level (multi-HTA advice or parallel scientific advice – EMA/multi-HTA advice).
3. HTA decision frameworks should encompass all attributes recommended by the EUnetHTA Core Model® and be integrated in a standardised and explicit way through a transparent and reproducible deliberative process.

For attributes recommended by the EUnetHTA Core Model® which are not yet included in HTA decision frameworks, or informally included, it is suggested to include these attributes as modifiers of the existing HTA frameworks (*i.e. as modifiers of ICER threshold or of added clinical benefit assessment scoring*).

4. HTA decision frameworks should be patient-centric and consider the patient perspective, including patient-reported outcomes, patient-centered outcomes, and patient preferences.

- 5. Beyond RCTs, HTA decision frameworks should consider alternative study designs (e.g. pragmatic design, adaptive design, observational studies), when more appropriate to address the research question.**
- 6. HTA organisations should encourage the use of coverage with evidence development, to allow some benefits that may be complex to demonstrate during development, to be captured post-launch.**
- 7. HTA decision frameworks should adopt a broader perspective in order to better reflect patients' and society's views of healthcare.**
- 8. A broad range of stakeholders, including patients, healthcare professionals, society representatives (citizens), and hospital administrators, should be voting members of HTA committees, in order to integrate a broad perspective into the final recommendation.**

Ultimately, the need to acknowledge benefits of value added medicines happen to be of high consideration by the EU authorities and multiple ongoing initiatives may contribute to ensure the EU society is capturing all the potential benefits associated with value added medicines.

Appendix 1

Multiple Criteria Decision Analysis, Replacement Approach and Constraint Optimisation Model: a Brief Description

MCDA^{26,27,28,29,30}

MCDA is based on three key features:

- Relevant decision-making criteria and their relative importance to be elicited from appropriate stakeholders.
- Aggregation of scores on different criteria to calculate the overall performance of a medicine.
- Resource allocation based on the ranking of medicines according to their performance scores, until the budget is exhausted.

Technical issues associated with MCDA implementation include:

- The complexity of generating weights, even if this is not the most critical challenge.
- The lack of integration of budget constraints and efficiency.
- The complexity of identifying the threshold for adopting or rejecting an intervention.
- The lack of a clear method for making investment choices.

Replacement approach^{29,31,32}

Replacement approach identifies an existing medicine X which, if cancelled, would generate at least enough resources to fund the incremental costs of new medicine Y and, consequently, increase total health at the same or lower cost. Program budgeting and marginal analysis (PBMA) is similar to the replacement approach. Within the constraints of a program budget, an expert panel is asked to identify potential programs for service expansion, the costs of which are paid by reducing other programs. If this process increases population health, resources are switched from current programs to programs identified for service expansion. While this approach allows a perfect control of the budget constraint at neutral or lower cost, in reality, it is difficult to discontinue or reduce medicines/programs from an ethical perspective.

Constraint optimisation model^{29,33}

In such a model, all possible solutions are considered and the best solution is selected, in contrast to traditional health economic models, which assume unconstrained resources and are limited to evaluating “what-if” scenarios one-by-one. Therefore, it addresses directly the issue encountered by payers that is managing budgetary constraints. However, the limitations of this method are that: 1) it considers only one disease and does not take into account budget shifts between diseases; 2) the budget constraint for the selected disease must be defined. This method may be valuable for supporting payer decisions and should be considered by HTA bodies as a useful alternative to cost-effectiveness analysis in some circumstances (i.e. when the budget constraint can be estimated in

the disease considered and when multiple interventions exist, to allow identification of the mix of interventions that will optimise the health gain with no budget impact).

Appendix 2

The Importance of Attributes for HTA Frameworks- Results from EU HTA Expert Consultation

In 2017, Creativ-Ceutical conducted interviews with nine EU HTA experts from France (n=1), Germany (n=1), Italy (n=1), Netherlands (n=1), Poland (n=1), Spain (n=1), Sweden (n=1) and the UK (n=2). Experts were affiliated with academic or research institutions working in the HTA field, and /or ex-members/advisors for HTA agencies, and/or deeply involved in HTA dossier filing and early HTA dialogues.

There were provided with a table listing selected HTA attributes ([Table 2](#)) and , requested to rate the importance of each attribute from a HTA body perspective, on a scale from 1 to 6 (1 representing the lowest importance and 6 the highest). Results per expert are presented in [Figure 4](#).

Table 2. Selected HTA attributes tested with EU HTA experts

Attribute	Details of each attribute
Nature of the condition	<ul style="list-style-type: none"> ○ Rarity ○ Severity ○ Acute or chronic ○ Risk factors ○ Age of onset ○ Natural course of the disease when untreated (extent to which the disease is life-threatening, including median survival from the absence of the intervention, or chronically debilitating)
Unmet medical need	<ul style="list-style-type: none"> ○ Number of alternative treatments ○ Issues related to efficacy and safety of current therapies ○ Partial responders/non-responders/treatment resistance ○ Adherence/compliance/persistence issues ○ Off-label use ○ Medicine wastage ○ Therapies not tailored to specific patient populations
Level of innovativeness	<ul style="list-style-type: none"> ○ Novelty (e.g. new MoA) versus modification of an existing technology (e.g. medicine-medicine combination, new delivery system, reformulation) or established technology used in a different way, e.g. in a new indication
Dispensation & administration	<ul style="list-style-type: none"> ○ Dose & frequency of administration ○ Treatment duration (e.g. max. number of cycles); starting & stopping rules ○ Route of administration and who administers the treatment (patient, caregiver, healthcare provider) ○ Treatment monitoring
Impact on morbidity	-
Impact on mortality	-
Impact on functioning (mental, physical, social)	<ul style="list-style-type: none"> ○ Body functions ○ Work ability ○ Return to previous living conditions ○ Activities of daily living

Impact on HRQoL	-
Safety profile compared to current therapeutic strategy	<ul style="list-style-type: none"> ○ Category and frequency of AEs and SAEs ○ Severity Grade of AEs ○ Acute versus irreversible or long-lasting toxicity ○ Interference with activities of daily living ○ Number of hospitalisations for toxicity ○ Drug-drug interactions ○ Discontinuations for safety issues
Tolerability profile compared to current therapeutic strategy	<ul style="list-style-type: none"> ○ Degree to which adverse effects can be tolerated by the patient ○ Discontinuations due to tolerability issues
Occupational safety vs current therapeutic strategy	<ul style="list-style-type: none"> ○ Harm to professionals applying the technology: working positions, radiation or infection risks, etc.
Economic attributes	<ul style="list-style-type: none"> ○ Budget impact, cost-effectiveness analysis (ICER)
Impact on current health-care organisation	<ul style="list-style-type: none"> ○ Change in current healthcare-related activities ○ A shift towards a different setting (e.g. community care or inpatient care) ○ Specific education/training required
Impact on current patient pathways	<ul style="list-style-type: none"> ○ Location of treatment and frequency of patient visits ○ Any specific treatment preparation/monitoring ○ A shift towards a different settings (e.g. community care or inpatient care) ○ Specific education/training required ○ Changes for caregivers
Patient perspective on their disease and the new technology	<ul style="list-style-type: none"> ○ Patient preferences regarding outcomes and treatment characteristics, including communication aspects, shared decision making and financial stress ○ Impact on patient acceptability, compliance and persistence
Perspectives of caregivers on disease burden and the new technology	<ul style="list-style-type: none"> ○ Perspective of people supporting the patients (e.g. parents, children, friends, colleagues)
Impact from the public health perspective	<ul style="list-style-type: none"> ○ Impact on distribution of healthcare resources, (i.e. re-allocation of human resources, funding and training) ○ Impact on reduction of health inequalities (e.g. treatment outcomes that reduce disparities across various patient groups) <ul style="list-style-type: none"> ○ Expanding patient access to therapy
Ethical attributes	<ul style="list-style-type: none"> ○ Estimated benefits and harms to patients, caregivers, and society when implementing or not implementing the technology (consequences of the formal intended use, but also of unintended and extended use) ○ Any ethical obstacles for evidence generation regarding the benefits and harms of the intervention (e.g. when ethically unacceptable to conduct a study in which the comparative group would be denied the procedure, case of a vulnerable group of subjects who are difficult to study) ○ Provision of equal access to technology for all citizens, which must protect the vulnerable and be non-discriminatory
Legal attributes	<ul style="list-style-type: none"> ○ Intellectual property rights

Figure 4. Ranking of attributes by a sample of EU HTA experts (n=9)



*Answer given at EU level:
In countries where cost-effectiveness analysis is systematically done: 6
In other countries: 4-5

Appendix 3

Definitions of Patient-Reported Outcome, Patient-Centered Outcome and Patient Preferences

- **Patient-reported outcome (PRO):** In the EMA guideline related to the use of PRO measures in oncology studies, a PRO is defined as *“any outcome evaluated directly by the patient himself or herself and is based on patient’s perception of a disease and its treatment(s). PRO is an umbrella term covering both single dimension and multi-dimension measures of symptoms, HRQL, health status, adherence to treatment and satisfaction with treatment”⁶⁸*. If PROs are considered as *“a unique means of capturing the personal and social context of the disease and treatment experience”⁶⁸* in clinical research, it is important to note that PROs are built to capture subjective perception on domains and concepts that have been pre-determined by experts (even though patients have been involved in elicitation of the items that represent the domains or concepts in question best).
- **Patient-centered outcome (PCO):** The Patient-Reported Outcomes PCORnet Task Force considers PCO as *“outcomes that matter to patients”⁶⁹*.
- **Patient preferences:** patient preferences are defined as *“statements made by patients regarding the relative desirability of a range of health experiences, treatment options, and health states”⁷⁰*. Patient preferences allow to elicit – usually through a discrete choice experiment – the preference of patients for different attributes and to provide a preference weight per attribute.

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