Description of the use of Multicriteria to Support Pricing and Reimbursement Decisions by European Health Technology Assessment Bodies.

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Abstract

Background

Heterogeneity in drug access throughout Europe may be influenced by differences in drug-assessment strategies. The EUnetHTA's assessment core model (EUnetHTA-core) and the EVIDEM's multicriteria framework are reference methodologies in this context, the latter including a wider compromise between non-contextual and contextual criteria. Compliance of 37 European Health Technology Assessment bodies (HTAb) with EUnetHTA-core has been reported, but the use of EVIDEM by this HTAb is still unknown.

Objective

To describe the uptake and use of multicriteria approaches to evaluate drug value by European HTAb using EVIDEM as reference framework.

Methods

Multicriteria framework was obtained based on EVIDEM model. The criteria used for drug appraisal by HTAb was extracted from the EUnetHTA report, and completed through search of websites, publications and HTAb reports. Use of EVIDEM assessment model in 37 European HTAb has been described semi-quantitatively and summarized using an alignment heatmap.

Results

Aligned, medium or misaligned profiles were seen for 24,3%, 51,4% and 24,3% of HTAb when matching to EVIDEM dimensions and criteria was considered. HTAb with explicit responsibilities in providing specific advice on reimbursement showed more aligned profiles on contextual and non-contextual dimensions.

Conclusions

Most of the 37 European HTAb have room to broaden their contextual assessment tools, especially when social and medical perception of need requires to be explicit to support payer's decision on reimbursement.

1 Introduction

One of the major cost drivers in the European healthcare systems is the pharmaceutical 'innovation'; even considered more relevant than demographics []. At the same time, it is also recognized as one of the main contributors to the improvement of the population health status [].

According to the most recent study from the Organization for Economic Co-operation and Development (OECD) [], pharmaceutical expenditure accounts for a percentage that range between 11.4% (UK) and 19.1% (Spain) of total healthcare expenditure across the five largest European drug markets (France,

Germany, Italy, Spain, and the UK). Specifically, the oncological and hematological drugs are leading the budget impact related to pharmaceutical innovation. The impact is driven by the expansion of multiple new indications normally based on a molecular definition that restricts the population to be treated and the drug ends up being designated as orphan-like medicines []. As estimated by a recent study [-], the healthcare expenditures on cancer in the European Union member states represented roughly 6% of total healthcare expenditures. The steady increase of oncology costs is aligned with the disease increasing incidence, the progressive reduction of mortality as well as high prices, in contrast with the less robust evidence data on outcomes [].

A recent study [] estimated that 40% of the new orphan drugs authorized in Europe are related to rare neoplastic disorders, and compare to non-oncologic indications, the authorization is received at more advance stages of the clinical development and recognizing a higher potential clinical benefit. From 2009 to 2013, only 35% the 68 oncology indications approved by the EMA showed a significant prolongation of survival and only 10% showed an improvement in quality of life at the time of market approval. The magnitude of the benefit on overall survival ranged from 1.0 to 5.8 months (median 2.7 months). In the subsequent post marketing period (3,3 years later) there was evidence for extension of life in 7% of the previous authorizations and reported benefit on quality of life in 11% of the cases [].

Occasionally, when the drug can cover clinical unmet needs with poor prognosis, the regulators trend to accept less and poorer evidence and include especial approvals, such as conditional approval related to further of adequate risk benefit rate in real world, after commercialization, or approval under exceptional circumstances when this may not be achieved, in order to ensure an earlier access to market. As described recently [] the potential benefit of patients' early access to new medicines in areas of high unmet medical need, and based on initial data only, have relevant implications in terms of medical and economic costs (opportunity costs of using alternative more efficient treatments available for patients). Several initiatives have been developed in Europe to address these challenges of funding premium priced products related to clear medical unmet needs but with limited evidence []. New access management models of these drugs have been promoted across Europe recently, especially for advance therapies, orphan drugs and medicines for cancer, and including innovative access schemes as value-based pricing, conditional reimbursement schemes or risk sharing approaches []. Despite the smooth increase of these new access schemes, the number of outcome-based solutions is still very limited being the lack of a systematic and harmonized value assessment methodology one of the main limitations [].

Beyond the general awareness among healthcare authorities to ensure "value for money", or the link between price and social or clinical value of the pharmaceutical innovation [], the reimbursement process and value assessment of drugs is still an open debate in Europe []. Several methods have been developed to assess the value of drugs and set meaningful prices affordable to health-care systems []. These methods are normally based on the clinical benefits of the drugs and partially on value-based pricing (e.g. cost-effectiveness analysis). However, there is neither a consensus nor a European harmonization related to drug-pricing systems and, based on a comparative international policy analysis, value-based approaches to determine the prices of innovative products are diverse []: including the implicit clinical

value of the QALYS (mainly used in UK, Sweden or Australia) or the value classification based on innovation scales (used in France, Italy, Germany, Austria, Canada or Japan) []. Normally new drugs classified as an innovative medicine are reimbursed at a higher price than the current therapeutic alternatives; although the amount, type and methodology to set the premium is normally veiled by the healthcare authorities [].

In Europe, the HTA Network was set up in 2013 and includes all EU Member States to provide strategic guidance and policy orientation on the assessment of health technologies (including drugs), by developing policy papers and discussing areas of potential collaboration. During the last decade the network has focused the efforts on the development of common methodologies, piloting and producing joint early dialogues and HTA joint assessment reports, as well as developing and maintaining common tools []. One of the most relevant tools developed by the network is the HTA Core Model for Rapid Relative Effectiveness Assessment (REA) []. The Model is a methodological framework for the collaborative production and sharing of HTA information that defines the content elements to be considered in an HTA and it enables standardized assessment reporting across Europe. Because of the objective of the framework is to share commonly required elements of information, only information that is considered both important and transferable is collected. The model brings a standardized framework that allows a common comparison of the drivers that lead pricing and reimbursement decisions among different European authorities.

HTA Network approach is focused on technical aspects of the evaluation, so that the methods rarely integrate the diversity of non technical components of decisions, such as those related to societal values, ethical values, reasoning or opportunity aspects, as formal parts of appraisal []. In many countries, healthcare authorities are including a broader approach to assess the pharmaceutical products (especially in therapeutic areas like oncology and rare diseases) []. EVIDEM [] was developed based on an analysis of the foundations of healthcare systems, the reasoning underlying decisions and fair processes, and has become a reference for multicriteria decision approaches in this setting. It includes the concept of reflective multicriteria assuming decision-makers are guided by a generic interpretative frame rooted in the baseline values of the healthcare systems, drawing on several domains of knowledge including healthcare ethics, evidenced-based medicine, health economics or health technology assessment approaches. A multicriteria analysis provides an effective approach to increase the legitimacy of decisions. Beyond a tool, reflective multicriteria pioneered by EVIDEM is geared to transform the vision of the value of healthcare interventions and how they might contribute to relevant, equitable and sustainable healthcare systems. EVIDEM criteria overlap with EUnetHTA-core except for 4 non-contextual and 3 social criteria, which are absent or partially included in the EUnetHTA framework. Inversely, 2 EUnetHTA criteria are absent in the EVIDEM framework [Table 1].

Table 1
EVIDEM and EUnetHTA criteria correspondence

EVIDEM DIMENSION	EVIDEM CRITERIA	EUnetHTA CRITERIA
NON-CONTEXTUAL CRITERIA		
Disease severity	• Effect of disease on life-expectancy • Effect of disease on morbidity (includes disability and function) • Effect of disease on patients' quality of life • Effect of disease on caregivers' quality of life	Methodology requirements for the clinical assessment compared to the HTA Core Model for REA - SEVERITY DEFINITION
		Assessments include a description of the health problem and current use of technology
Size of affected population	• Prevalence • Incidence	Methodology requirements for the clinical assessment compared to the HTA Core Model for REA - POPULATION
		Assessments include a description of the health problem and current use of technology
Unmet needs	• Unmet needs in efficacy • Unmet needs in safety • Unmet needs in patient reported outcomes • Patient demand	Assessments include a description of the health problem and current use of technology
		Evidence where systematic search strategies are applied (HEALTH PROBLEM - CURRENT TECHNOLOGY USE)
Comparative effectiveness	• Magnitude of health gain • Percentage of the target population expected to achieve the anticipated health gain • Onset and duration of health gain • Sub-criteria for the measure of efficacy specific to the therapeutic area	The comparator is supported by evidence on its efficacy profile for the respective clinical indication/population
		Assessments analyze clinical effectiveness / efficacy (added therapeutic value)
		Evidence where systematic search strategies are applied (EFFICACY-EFFECTIVENESS)
Comparative	• Adverse events	The comparator is supported by evidence on

EVIDEM DIMENSION	EVIDEM CRITERIA	EUnetHTA CRITERIA
safety/tolerability	• Serious adverse events • Fatal adverse events • Short-term safety • Long-term safety • Tolerability	its safety profile for the respective clinical indication/population Assessments analyze safety Evidence where systematic search strategies are applied (SAFETY)
Comparative patient-perceived health	• Improvement in health-related quality of life • Impact on autonomy • Impact on dignity • Convenience / ease of use / mode & setting of administration	QALYs applied Assessments analyze patient aspects Assessments include a separate ethical analysis Evidence where systematic search strategies are applied (PATIENT ASPECTS)
Type of preventive benefit	• Eradication, prevention, reduction in disease transmission, reduction in the prevalence of risk factors). Public health perspective.	Not available
Type of therapeutic benefit	• Symptom relief, prolonging life, cure	Assessments include a description of the health problem and current use of technology
Comparative cost consequences – cost of intervention	• Net cost of intervention • Acquisition cost • Implementation/ maintenance cost	Assessments analyze cost, budget impact or include economic evaluation
Comparative cost consequences – other medical costs	• Impact on primary care expenditures • Impact on hospital care expenditures • Impact on long-term care expenditures	Assessments analyze cost, budget impact or include economic evaluation
Comparative cost	• Impact on	Assessments analyze social aspects

EVIDEM DIMENSION	EVIDEM CRITERIA	EUnetHTA CRITERIA
consequences – non-medical costs	productivity • Financial impact on patients • Financial impact on caregivers • Costs to the wider social care system	
Quality of evidence	• Validity (study design, agreement among studies) • Relevance (population, disease stage, outcomes) • Completeness of reporting (uncertainty, conflicting results across studies, limited number of studies) • Type of evidence	Sources of evidence included as relevant clinical evidence for the clinical assessment (1- randomized controlled; 2- Nonrandomized prospective; 3- Other observational; 4- Expert Opinion).
		Methodology requirements for the clinical assessment compared to the HTA Core Model for REA
		Formal tools or algorithms for evidence grading applied
		The GRADE approach in routine use
		Plan for how evidence will be synthesized (e.g. evidence tables, meta-analysis, qualitative synthesis)
		Standard forms or tables available for evidence analysis and synthesis
		Evidence analysis include surrogate endpoints, composite endpoints, PROs, HRQoL measures, indirect comparisons, meta-analysis, relevant group sub-population, key deficiencies in available data, transferability issues, summary of findings
		Sources of evidence on the technology: A. scientific journal publications, B. grey literature (e.g. published reports), C. unpublished data, D. register data, E. administrative data, F. manufacturer data
		Confidential data from manufacturers accepted
Expert consensus/clinical practice guidelines	Current consensus of experts on what constitutes state-of-the-art practices (guidelines	Not available

CONTEXTUAL CRITERIA

EVIDEM DIMENSION	EVIDEM CRITERIA	EUnetHTA CRITERIA
Mandate and scope of the healthcare system	Alignment with healthcare plans/systems	Circumstances where HTA reports are provided
Population priorities and access	• Current priorities of health system (e.g. low socioeconomic status; specific age groups) • Special populations (e.g. ethnicity) • Remote communities • Rare diseases • Specific therapeutic areas	Assessments analyze social aspects
Common goal and specific interests	• Stakeholder pressures • Stakeholders barriers • Conflict of interest	Assessments analyze social aspects
Environmental impact	• Environmental impact of production • Environmental impact of use • Environmental impact of implementation • Environmental impact of production • Environmental impact of use • Environmental impact of implementation	Not available
System capacity and appropriate use of intervention	• Organizational requirements (e.g., process, premises, equipment) • Skill requirements • Legislative requirements	Assessments include a separate ethical analysis Assessments analyze legal aspects

EVIDEM DIMENSION	EVIDEM CRITERIA	EUnetHTA CRITERIA
	requirements • Surveillance requirements • Risk of inappropriate use • Institutional limitations to uptake	Assessments analyze organizational aspects
Political/historical/cultural context	• Political priorities and context • Cultural acceptability • Precedence (congruence with previous and future decisions) • Impact on innovation & research • Impact on partnership & collaboration among healthcare stakeholders	Assessments include a separate ethical analysis

Although multicriteria EVIDEM approach is now applied by several healthcare authorities [], especially when the social and medical perception of need requires a more holistic assessment framework to support the payer's decision, a formal and systematic comparison of EUnetHTA's and EVIDEM's methodological frameworks and whether European health technology assessment bodies (HTAb) are aligned with the EVIDEM methodology standards is lacking []. Since EUnetHTA and EVIDEM frameworks differ in a substantial number of criteria, it is of interest to know the extent of compliance with EVIDEM framework of HTAs as an additional way to explore potential reasons of assessment discrepancies. Despite the compliance of 37 European Health Technology Assessment bodies (HTAb) with using the supportive criteria for decision making proposed in the EUnetHTA-core framework has been previously reported [20], whether these HTAb do also comply with the wider EVIDEM multicriteria is unknown.

Thus, the main aim of this study is to describe the uptake and use of multicriteria approaches to appraise drug value by 37 European HTAb, using EUnetHTA and EVIDEM as reference frameworks.

2 Methods

A quantitative validation of the degree of alignment with the EUnetHTA's standard framework of 37 European HTAb from 28 countries was done, based on a previous qualitative analysis conducted by the European Commission [20] and an additional thorough search of websites, publications and reports of HTAb. The criteria used for appraisal by the different HTAb were identified and classified, and the

matching with the criteria described in the EVIDEM methodological framework were described semi-quantitatively using a heatmap of alignment.

The items reported included those criteria in the HTA Core Model, namely: Relative Effectiveness Assessment (REA) of pharmaceuticals, EUnetHTA methodological guidelines [] and procedure descriptions [-]. Also, criteria related to the types of technologies assessed, the administrative level (national, regional, institutional) and the formal background (legislation, formal agreement, internal guideline) of certain methodological requirements were also used.

An updated version of EVIDEM framework (v.10) was analyzed in order to assess how the dimensions and criteria included in the EUnetHTA methodological framework fitted within the EVIDEM's methodological framework.

The EVIDEM framework includes 13 non-contextual dimensions and 6 contextual dimensions [Table 1].

An HTAb heatmap was developed, where heatmap categories were generated for each EVIDEM's dimension using as a source the mentioned criteria in the EUnetHTA's report [20], webs and reports available from the different HTAb analyzed. The contribution (weight) of each mentioned criterion to the final heatmap's score by dimension was equal and proportioned to the number of criteria by dimension. Only when the mentioned criteria were not fully aligned with the EVIDEM's criteria, the mention was weighted by 50% of contribution:

*Heat Score = [(∑ # criteria mentioned by dimension)/ (∑ # total criteria by dimension)] *100*

Descriptive statistics (mean, standard deviation, percentiles) were used to summarize the data and 95% confidence interval for each dimension and HTAb, and conditional formatting was used to automatically color code each cell using Microsoft Excel (Windows Office 365) so that graded colors were used with green coding for highest alignement (100) and red for lowest alignement (0). HTAbs with and average heat score above the 75th percentile were considered "Aligned" with the EVIDEM model, and those below 25th percentile were considered "Misaligned". The rest were classified as "Medium" in terms of EVIDEM model's alignment.

3 Results

Most of the non-contextual criteria of EVIDEM are overlapped with the core model of EUnetHTA, except for the type of prevention benefits, non-medical comparative cost consequences, systematic use of expert consensus and use of clinical guidelines to define state-of-the-art, which are not or partially included on the EUnetHTA's framework [Table 2]. Regarding contextual criteria, the assessment of the system capacity and appropriate use of intervention is the most aligned criteria between both frameworks, followed by the political/historical/cultural context assessment, the mandate and scope of the healthcare system, the special population priorities and equity on access criteria. Other social criteria (stakeholders management, conflict of interest assessment or environmental impact assessment) are not reflected in

the EUnetHTA's framework. A systematic general description of the assessed technology and the request of clarification of the assessment process (guidelines and legislation) are key aspects considered by the EUnetHTA analysis that are not explicitly included in the EVIDEM framework.

Table 2: HTAb heatmap of coincidence with EVIDEM framework

COUNTRY	Agency	Disease severity	Size of affected population	Unmet needs	Comparative effectiveness	Comparative safety/tolerability	Comparative patient-perceived health / PRO	Type of preventive benefit	Type of therapeutic benefit	Comparative cost consequences – cost of intervention	Comparative cost consequences – other medical costs	Comparative cost consequences – non-medical costs	Quality of evidence	Expert consensus/clinical practice guidelines	Mandate and scope of the healthcare system	Population priorities and access	Common goal and specific interests	Environmental impact	System capacity and appropriate use of intervention	Political/historical/cultural context
Austria	HVB	100	100	100	100	100	25	0	100	50	50	0	100	0	60	30	0	0	13	0
	LBI	75	75	100	100	100	13	0	100	50	50	10	44	0	60	30	10	0	13	30
Belgium	KCE	100	100	100	100	100	50	0	100	50	50	10	89	0	60	30	10	0	40	30
	INAMI	100	75	100	100	83	50	0	100	50	50	10	100	0	60	30	10	0	27	30
Bulgary	NCPHA	100	100	100	100	83	63	0	100	100	100	10	22	0	60	30	10	0	40	30
Croatia	AAZ	100	100	100	100	100	38	0	100	50	50	10	78	0	30	30	10	0	40	30
Czech R.	SUKL	100	100	100	100	100	50	0	100	50	50	0	56	0	60	0	0	0	0	0
Estonia	UoT	100	100	100	100	100	38	0	100	100	100	0	44	0	60	0	0	0	13	0
Finland	FIMEA	75	75	100	100	100	50	0	100	100	100	10	50	0	30	30	10	0	40	30
France	HAS	100	100	100	100	100	50	0	100	50	50	10	56	0	60	30	10	0	40	30
Germany	G-BA	50	50	75	100	100	25	0	50	0	0	0	83	0	60	0	0	0	0	30
	IQWiG	75	75	100	100	100	63	0	100	100	100	0	67	0	60	0	0	0	40	0
Hungary	OGYEI	100	100	100	100	100	63	0	100	100	100	10	89	0	60	30	10	0	27	30
Ireland	HIQA	100	100	100	100	100	63	0	100	50	50	10	89	0	30	30	10	0	40	30
	NCPE	75	75	100	100	100	50	0	100	100	100	0	33	0	60	0	0	0	0	0
Italy	AIFA	75	75	100	100	100	38	0	100	100	100	0	33	0	60	0	0	0	13	0
	RER	100	100	100	100	100	25	0	100	0	0	0	56	0	30	0	0	0	13	0
	UCSC	100	100	100	100	100	50	0	100	100	100	10	67	0	30	30	10	0	40	30
Latvia	NVD	75	100	50	100	83	13	0	50	100	100	0	44	0	60	30	20	0	13	0
Malta	MOH	100	100	100	100	83	75	0	100	100	100	10	33	0	30	30	10	0	40	30
NL	ZIN	100	100	75	100	100	88	0	100	50	50	10	44	0	60	30	10	0	40	30
Poland	AOTMiT	100	100	100	100	100	38	0	100	50	50	10	67	0	60	30	10	0	27	0
Portugal	INFARMED	50	75	50	83	67	50	0	50	100	100	10	100	0	60	30	10	0	40	30
Slovakia	MOH	75	100	100	100	100	25	0	100	0	0	0	28	0	60	0	0	0	0	0
	UHIF	75	75	100	100	100	75	0	100	100	100	10	89	0	30	30	10	0	53	30
Slovenia	JAZMP	50	50	100	100	50	25	0	100	100	100	10	33	0	60	30	10	0	13	30
Spain	AEMPS	50	50	100	100	100	75	0	100	100	100	20	44	0	60	60	20	0	40	30
	AETSA	100	100	100	100	100	63	0	100	50	50	10	44	0	60	30	20	0	40	30
	SESCS	100	100	100	100	100	88	0	100	100	100	10	100	0	60	30	10	0	53	60
	AQUAS	75	75	100	100	100	75	0	100	100	100	0	67	0	60	30	0	0	13	30
Sweden	SBU	100	100	100	100	100	100	0	100	50	50	10	67	0	30	30	10	0	53	60
	TLV	100	100	100	100	50	25	0	100	100	100	0	67	0	60	0	0	0	27	0
UK	NICE	75	75	100	100	100	38	0	100	100	100	10	72	0	60	30	10	0	13	0
	SMC	100	100	100	100	100	75	0	100	100	100	10	50	0	60	30	10	0	13	0
	AWTTC	100	100	100	100	67	63	0	100	100	100	10	89	0	30	30	10	0	13	0
Norway	NIPH	75	75	100	100	100	50	0	50	50	50	0	83	0	30	30	10	0	13	30
	NOMA	100	100	100	100	67	75	0	100	100	100	10	89	0	30	30	10	0	13	0

Table 3
EVIDEM heat score by dimension

Criteria	Mean	Standard Deviation	Low 95% CL Mean	Upper 95% CL Mean	25th Percentile	75th Percentile
Disease severity	87.2	17.3	50.0	100.0	75.0	100.0
Size of affected population	88.5	16.2	50.0	100.0	75.0	100.0
Unmet needs	95.9	12.5	50.0	100.0	100.0	100.0
Comparative effectiveness	99.5	2.7	83.3	100.0	100.0	100.0
Comparative safety/tolerability	92.8	14.5	50.0	100.0	100.0	100.0
Comparative patient-perceived health / PRO	51.7	21.9	12.5	100.0	37.5	62.5
Type of preventive benefit	0.0	0.0	0.0	0.0	0.0	0.0
Type of therapeutic benefit	94.6	15.7	50.0	100.0	100.0	100.0
Comparative– cost of intervention	74.3	32.5	0.0	100.0	50.0	100.0
Comparative – other medical costs	74.3	32.5	0.0	100.0	50.0	100.0
Comparative – non-medical costs	6.8	5.3	0.0	20.0	0.0	10.0
Quality of evidence	64.0	23.4	22.2	100.0	44.4	83.3
Expert consensus/clinical practice guidelines	0.0	0.0	0.0	0.0	0.0	0.0
Contextual criteria	0.0	0.0	0.0	0.0	0.0	0.0
Mandate and scope of the healthcare system	51.1	13.9	30.0	60.0	30.0	60.0
Population priorities and access	23.5	14.4	0.0	60.0	30.0	30.0
Common goal and specific interests	7.8	5.8	0.0	20.0	0.0	10.0
Environmental impact	0.0	0.0	0.0	0.0	0.0	0.0
System capacity & appropriate use of intervention	25.9	16.3	0.0	53.3	13.3	40.0
Political/historical/cultural context	19.5	17.6	0.0	60.0	0.0	30.0

Criteria	Mean	Standard Deviation	Low 95% CL Mean	Upper 95% CL Mean	25th Percentile	75th Percentile
GLOBAL	47.9	5.8	31.2	60.5	44.7	51.25

Most of the non-contextual dimensions (such as disease severity, size of affected population, unmet needs, comparative effectiveness, comparative safety/tolerability or type of therapeutic benefit) show consistently high rates among the HTAb (mean above 85% and standard deviation below 16%); other non-contextual dimensions (type of preventive benefit, comparative non-medical costs, expert consensus) and relevant contextual dimensions (such as population priorities, common goal, environmental impact, system capacity or political/historical/cultural context) are systematically rated low.

All HTAb address consistently the health problem and current use of technology, technical characteristics, clinical effectiveness and safety criteria, which are included in the EUnetHTA core model. Choices on comparator, methodology of comparison, endpoints and methods of evidence search and synthesis, are consistently aligned. On the contrary, non-clinical domains, assessment approaches, methodology, modelling algorithms and data are consistently dis-aligned.

None of the local HTAb had high heat scores with regards to the use of contextual criteria [Table 2]. Considering alignment to EVIDEM-driven assessment framework, three patterns of HTAs emerged: “Aligned”, “Medium” and “Misaligned” [Table 4].

Table 4
EVIDEM heat score by HTAb

HTAb	Mean	Standard Deviation	Low 95% CL Mean	Upper 95% CL Mean	Degree of Alignment with EVIDEM model
HVB	46.4	44.3	26.5	66.3	Medium
LBI	43.0	37.8	26.0	60.0	Misaligned
KCE	50.9	40.2	32.9	69.0	Medium
INAMI	48.8	39.0	31.2	66.3	Medium
NCPHA	52.4	42.1	33.5	71.3	Aligned
AAZ	48.3	40.0	30.3	66.2	Medium
SUKL	43.3	44.0	23.5	63.0	Misaligned
UoT	47.8	46.8	26.7	68.8	Medium
FIMEA	50.0	40.2	31.9	68.1	Medium
HAS	49.3	39.2	31.6	66.9	Medium
G-BA	31.2	36.8	14.6	47.7	Misaligned
IQWIG	49.0	44.0	29.2	68.8	Medium
OGYEI	55.9	43.3	36.4	75.4	Aligned
HIQA	50.1	40.5	31.9	68.3	Medium
NCPE	44.7	45.0	24.4	64.9	Misaligned
AIFA	44.7	44.5	24.7	64.7	Medium
RER	36.2	45.1	15.9	56.5	Misaligned
UCSC	53.3	42.6	34.2	72.5	Aligned
NVD	41.9	39.5	24.2	59.7	Misaligned
MOH	52.1	42.3	33.1	71.1	Misaligned
ZIN	49.3	38.9	31.9	66.8	Medium
AOTMiT	47.0	41.0	28.6	65.5	Medium
INFARMED	45.3	35.0	29.5	61.0	Medium
MOH	34.4	44.1	14.6	54.2	Aligned
UHIF	53.9	41.4	35.3	72.5	Aligned
JAZMP	43.1	38.3	25.9	60.3	Misaligned

HTAb	Mean	Standard Deviation	Low 95% CL Mean	Upper 95% CL Mean	Degree of Alignment with EVIDEM model
AEMPS	52.5	38.4	35.2	69.7	Aligned
AETSA	49.8	38.9	32.4	67.3	Medium
SESCS	60.5	43.2	41.1	80.0	Aligned
AQUAS	51.3	42.5	32.1	70.4	Medium
SBU	53.0	40.9	34.6	71.4	Aligned
TLV	46.4	45.2	26.1	66.7	Medium
NICE	49.2	42.6	30.0	68.3	Medium
SMC	52.4	44.8	32.3	72.5	Aligned
AWTTC	50.6	44.3	30.7	70.5	Medium
NIPH	42.3	36.5	25.9	58.8	Misaligned
NOMA	51.2	44.6	31.2	71.2	Medium
GLOBAL	47.9	5.8	46.0	49.7	Medium

9 agencies in Bulgary, Hungary, Italy, Malta, Slovakia, Spain, Sweden and UK showed an “Aligned” profile (average heat score above the 75th percentile) with a consistent alignment on non-contextual dimensions and significantly high alignment scores on political/historical/cultural context, system capacity and appropriate use of the intervention.

Most HTAb (19/37; 51%) showed a “Medium” alignment profile. Alignment rates for non-contextual criteria were mainly high (e.g. patient perceived health and quality of evidence dimensions) in these HTAb, and also other contextual dimensions (such as the mandate and scope of the healthcare system, system capacity and appropriate use of the intervention) were rated high. On the contrary, population priorities and access dimension systematically rated below 50%, except for AEMPS.

In 9/37 (24%) HTAb the profile was considered “Misaligned”, with low scores on alignment (average score below 25th percentile) in dimensions such as patients perceived health methods, cost-consequence analysis (cost of intervention and other medical costs) and quality of the evidence. Considering the non-contextual perspective, the German G-BA and the NIPH in Norway show high scores focused and limited to the technical comparison of alternatives (effectiveness, safety and quality of evidence assessment). From the contextual perspective, all the HTAb of this group rated low on the mandate and scope of the healthcare system, population priorities on access, system capacity, appropriate use of the interventions and political/historical/cultural context.

HTAb with explicit responsibilities in providing specific advice on pricing and reimbursement (normally regional agencies in countries with more than one HTAb in place, such as Belgian KCE, German IQWIG,

Irish HIQA, Italian UCSC, Portuguese INFARMA, Slovakian UHIF, Spanish SESCS or Swedish SBU) showed higher and similar scores on contextual and non-contextual dimensions.

4 Discussion And Conclusions

There is a high alignment between the EUnetHTA and EVIDEM methodological frameworks, with consistent approach to assessment of domains related to health problem, current use of the technology, technical characteristics, clinical effectiveness and safety. However, there is a structural misalignment between the non-contextual dimensions of the EVIDEM framework and the EUnetHTA core model.

All HTAb address consistently the main criteria included in EUnetHTA core model: health problem and current use of technology, technical characteristics, clinical effectiveness and safety criteria. As previously reported [20] the institutions go only partially beyond these criteria and it is normally dependent on the topic of assessment. Based on the analysis of 37 European HTAb of 28 member states, the reported criteria used to support decisions on price and reimbursement of those HTAb clearly orientated to advice on price and reimbursement final decisions show a more balanced alignment between both methodological frameworks. That conclusion could explain why in many cases, the subnational HTAb in those countries with multiple agencies, are the ones showing a balanced profile among contextual and non-contextual dimensions.

The interpretive framework of EVIDEM includes multiple criteria for decision analysis, and allows structured accounting of separate values into interpretive scores (quantitative criteria), qualitatively impacts (qualitative criteria) and narrative comments (all criteria)[22]. Such design is aimed to counteract the limitations and to facilitate the processes of discussion and decision making, through systematic collection and synthesis of evidence for relevant quantitative or qualitative generic criteria. The methodology ensures validation at each step of the process through weighting, scoring, use of corresponding narratives and by aggregated measuring)[22].

Because the social and medical perception of need requires a more holistic assessment framework to support the payer's decision on prices of certain drugs, such as disruptive innovations or orphan drugs, it seems that there is room and opportunity to broaden the use of EVIDEM-like contextual assessment tools by European HTAb.

Declarations

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Conflicts of interest/Competing interests: DE is a full-time employee of Sanofi. CP and MO are public employees with no other conflicts of interest.

Availability of data and material: not applicable

Code availability: Not applicable

Authors' contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by DE and MO. The first draft of the manuscript was written by DE and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

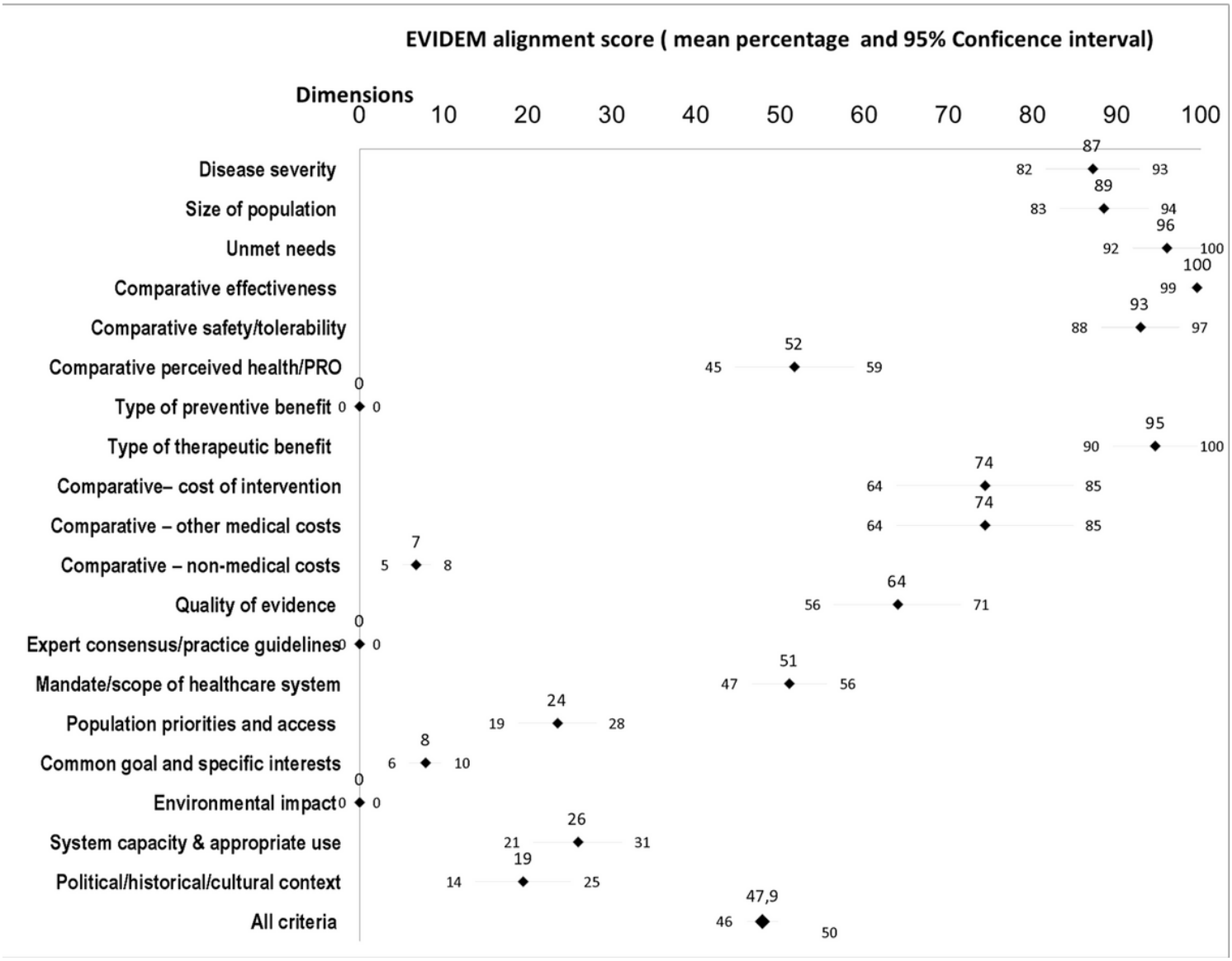

Figure 1

EVIDEM alignment score by dimension

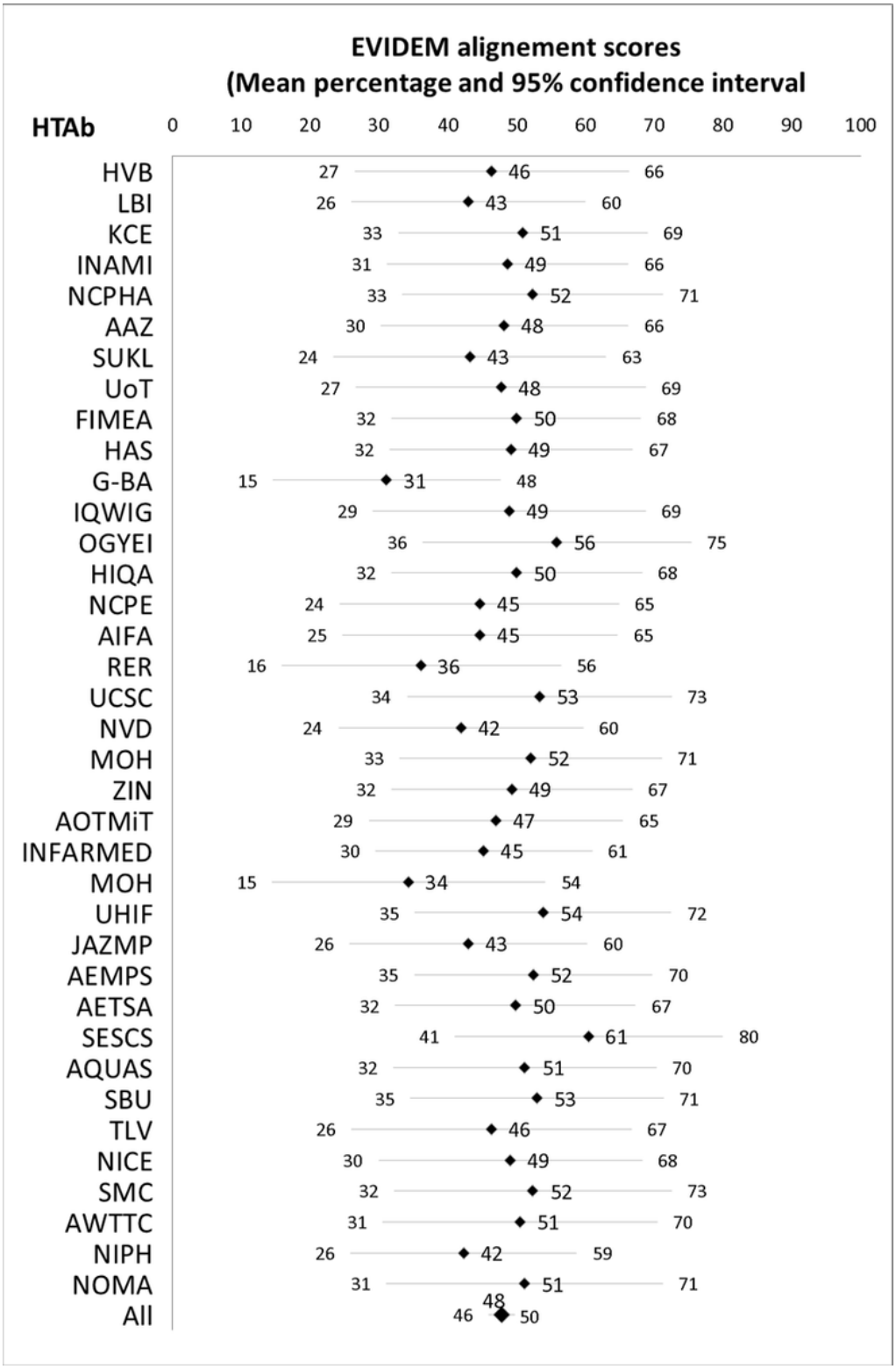

Figure 2

EVIDEM alignment score by HTAb HTAb: Health Technology Assessment body. SESCS: Servicio de Evaluación del Servicio Canario de Salud; SBU: Swedish Agency for Health Technology Assessment and Assessment of Social Services; HVB: Hauptverband der Österreichischen Sozialversicherungsträger; KCE: Belgian Health Care Knowledge Centre; INAMI-RIZIV: National Institute for Health and Disability Insurance ; NCPHA: National Center of Public Health and Analyses; SUKL: State Institute for Drug Control; FIMEA:

Finnish Medicines Agency; HAS: Haute Autorité de Santé; IQWiG: Institute for Quality and Efficiency in Health Care; OGYÉI: National Institute of Pharmacy and Nutrition; HIQA: Health Information and Quality Authority; NCPE: National Centre for Pharmacoeconomics; AIFA: Italian Medicines Agency; UCSC: Università Cattolica del Sacro Cuore; ZIN: Zorginstituut Nederland; AOTMiT: Agencja Oceny Technologii Medycznych i Taryfikacji; INFARMED: National Authority of Medicines and Health Products; UHIF: Union Health Insurance Fund; AEMPS: Agencia Española de Medicamentos y Productos Sanitarios; AETSA: Agencia de Evaluación de Tecnologías Sanitarias de Andalucía; AQUAS: Agència de Qualitat i Avaluació Sanitàries de Catalunya; TLV: Dental and Pharmaceutical Benefits Agency; NICE: National Institute for Health and Care Excellence; SMC: Scottish Medicines Consortium; AWTTC: All Wales Therapeutics and Toxicology Centre; NIPH: Norwegian Institute of Public Health; NoMA: Norwegian Medicines Agency; LBI-HTA: Ludwig Boltzmann Institute of Health Technology Assessment; AAZ: Agency for Quality and Accreditation in Health Care and Social Welfare; UoT: University of Tartu; G-BA: Gemeinsamer Bundesausschuss; RER: Regione Emilia-Romagna; NVD: The National Health Service; MOH: Ministry of Health Malta; MOH: Ministry of Health Slovakia; JAZMP: Agency for Medicinal Products and Medical Devices.