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The value of anticancer drugs — a regulatory view

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Abstract | The high prices of new anticancer drugs and the marginal added benefit perceived by some stakeholders have fuelled a debate on the value of anticancer drugs in the European Union, even though an agreed definition of what constitutes a drug's value does not exist. In this Perspective, we discuss the value of drugs from different viewpoints and objectives of decision makers: for regulators, assessment of the benefit–risk balance of a drug is a cornerstone for approval; payers rely on cost-effectiveness analyses carried out by health technology assessment agencies for reimbursement decisions; for patients, treatment choices are based on personal preferences and attitudes to risk; and clinicians can use several scales (such as the ESMO Magnitude of Clinical Benefit Scale (ESMO–MCBS)) that have been developed as an attempt to measure value objectively. Although a unique definition that fully captures the concept of value is unlikely to emerge, herein we discuss the importance of understanding different perspectives, and how regulators can help to inform different decision makers.

Dedication: We dedicate this paper to Bertil Jonsson, clinical assessor, Medical Products Agency, Sweden, and past vice-chairman of the EMA Scientific Advice Working Party and of the Oncology Working Party.

The regulatory approval of new anticancer drugs is based on the demonstration of efficacy and safety, and the positive balance of benefits and harms. When determining this balance, regulators consider the clinical importance of the observed positive effects — such as improved symptom control and health-related quality of life (HRQOL), prolongation of progression-free survival (PFS) and, most importantly, extended overall survival (OS) — and weigh them against the reported harms — that is, the type, frequency and severity of adverse events (AEs). Benefit–risk evaluations of new anticancer drugs are ideally based on mature and comprehensive data from one or more randomized controlled trials (RCTs) with enough statistical power to detect differences in clinically relevant end points (TABLE 1) relative to the standard-of-care therapy for a particular indication. Medical needs and realities, however, frequently preclude such ideal designs in oncology drug development, and potential long-term AEs are rarely discovered in registration studies. Thus, in practice, regulators often need to manage important uncertainties at the time of approval. Despite these limitations, the benefit–risk balance is analysed and, if judged positive, a marketing authorization is granted together with an agreed risk management plan and any other conditions necessary for the authorization[1].

The high prices of new anticancer drugs and the marginal added value perceived by some stakeholders (patients, payers, regulators and clinicians) have fuelled a debate on the value of these drugs[2]. The uptake of highly priced drugs with a marginal therapeutic value is expected to be low in most markets, raising the further question as to their value from a commercial perspective; however, the high price of 'breakthrough' drugs with substantial clinical value constitutes a major barrier to access and raises doubts over the sustainability of the current drug development and pricing system[3]. The prices of anticancer drugs have increased dramatically in the past decades, and this increase is difficult to justify on the basis of developmental costs needed to satisfy regulatory requirements[4]. Companies might be open to discussion around undisclosed discounts, typically agreed with national and regional competent authorities, although such an approach fails to address the wider issue of rising drug costs[5,6].

An agreed definition of what constitutes value among stakeholders in view of their different objectives does not exist. In this Perspective, we discuss the different views, focusing on how regulators use benefit–risk assessments in their approval decisions. While acknowledging that agreement on a unique definition of value is unlikely to emerge, we discuss the ways in which regulators can help to address the current challenges.

Different stakeholders' views on value

Approaches for determining the value of drugs differ among regulators, payers, patients and clinicians, depending on the importance they each place on the individual perspective and the societal perspective. Distinct definitions require different types of evidence: for example, patients might have personal preferences regarding benefits and risks, clinicians might focus on the added value of a drug over existing treatments, and payers assess 'value for money'. Different approaches might also give more weight to various data sources, such as clinical trials (conducted under ideal conditions) versus pragmatic trials or observational studies (using real-world evidence) (FIG. 1).

For regulators, assessing the benefit–risk balance is the most precise way to define the value of a drug; the balance is positive when beneficial effects are considered to outweigh harmful effects[1]. Typically, regulators assess benefits first and, if a clinically significant benefit exists, they then evaluate whether the toxicity profiles seem acceptable for the patient, irrespective of the margins by which this conclusion is reached[7]. This approach has arguably resulted in regulatory approvals of drugs with a formally positive benefit–risk balance but with marginal therapeutic value for some stakeholders focusing on innovation and economic aspects[8]. These approvals have been criticized for cluttering the market with expensive interventions, fostering misinformation, raising false

Table 1 | **End points commonly used in oncology drug approvals**[66]

End point and common abbreviation	Definition	Comments
Overall survival (OS)	Time from randomization until death from any cause	Generally considered the most clinically relevant and convincing outcome (or 'gold standard') for most oncology drug applications. Duration of survival is considered particularly important in case of good HRQOL. This end point can be measured easily and precisely and does not suffer from the challenges of radiological end points, such as PFS. Similarly to other time-related end points, the effect of treatment on OS is difficult to establish without randomized controlled trials.
Progression-free survival (PFS)	Time from randomization until disease progression or death, whichever occurs first	Similar end points to PFS are disease-free survival (DFS), event-free survival (EFS), recurrence-free survival (RFS) or distant metastasis-free survival (DMFS), among others. These composite end points aim to measure the duration of disease control. Their clinical importance is justified on the basis of the expected unfavourable effects after disease progression, such as expected worsening in quality of life, need for subsequent (probably less efficacious) treatments and additional toxicity. Validation of PFS and the above-mentioned end points as surrogates for OS has generally not been established to regulatory standards. PFS requires careful methodology (for example, blinding) to avoid bias, which can sometimes be challenging given the effects of cancer therapy.
Health-related quality of life (HRQOL)	Ability of an individual to perform the activities of daily life free from pain and mental disturbance, assessed through validated instruments	Together with other patient-reported outcomes, HRQOL is generally considered a relevant end point, especially in the non-curative setting. Similar to PFS, HRQOL requires careful methodology to avoid bias. In practice, HRQOL is often used as a secondary end point. HRQOL is often used as a measure of utility in health technology assessments.
Objective response rate (ORR)	Proportion of patients with either a partial or complete response to therapy according to radiological criteria	ORR is often used as primary end point in single-arm exploratory trials to measure antitumour activity before proceeding to confirmatory trials; a causal association with treatment can generally be established for ORR, even without randomization. Although not considered a clinically relevant end point, conditional or accelerated marketing authorizations (from the EMA and FDA, respectively) have been issued on the basis of outstanding ORRs that are expected to result in clinical benefit in the context of a high unmet medical need; such approvals are justified on the basis of high antitumour activity, and granted with conditions, such as the submission of comprehensive clinical data after approval. ORR is generally interpreted in conjunction with duration of response (DOR), although effects in terms of DOR are difficult to assess outside randomized trials.
Other	Other efficacy end points used in specific situations	In some situations, other primary end points have also been considered appropriate, such as enabling further treatments known to be beneficial (for example, haematopoietic cell transplantation) or avoiding treatments associated with high morbidity or mortality (such as invasive surgery).

hopes, putting unnecessary strains on health-care budgets, providing disincentives to innovation, slowing drug development by depleting precious resources and preventing patients from enrolling in clinical trials of interventions that might be perceived as more valuable[8,9].

In EU (European Union) member states, health technology assessment (HTA) agencies and pricing bodies carry out assessments of effectiveness, in terms of either relative effectiveness or cost-effectiveness (TABLE 2). An often quoted approach to these evaluations is that from the National Institute for Health and Care Excellence (NICE) in England and Wales, which uses the concept of cost per quality adjusted life year (QALY)[10]. This appraisal considers the health state of an individual with the disease, with adjustment of the survival benefit from a particular drug according to HRQOL on a 0–1 scale such that one QALY equals a year of life in perfect health. Whilst this approach has been used for many years, the failure of several anticancer drugs to meet the predefined cost-per-QALY threshold (for example, trastuzumab emtansine (T-DM1) for the treatment of breast cancer) sparked protests from patients and clinicians alike[11]. For T-DM1, the incremental cost-effectiveness ratio (ICER) per QALY gained was calculated at around £160,000 whereas lapatinib plus capecitabine (comparator arm) had a 0% probability of being cost-effective at the £30,000 threshold[12]. This situation led to the implementation of the Cancer Drugs Fund, which was aimed at providing patients with faster access to oncology drugs, but also to drugs not deemed cost-effective by NICE (such as crizotinib for the treatment of previously treated *ALK*-rearranged advanced-stage non-small-cell lung cancer or everolimus for metastatic breast cancer)[13]. Overall, the existence of different approaches to reimbursement has resulted in substantial delays from EMA approval to reimbursement approval across European countries[14,15]. By contrast, from the strictly individual perspective of the patient, treatments that on average offer little

benefit might have large benefits for some individuals[16]. Therefore, unless 'responders' can be prospectively identified, determining the preferred treatment will be a matter of individual circumstances and risk attitudes, even when the probability of benefits is low relative to the likelihood of harms[17]. One example of this approach is the use of ipilimumab in patients with metastatic melanoma, among whom only ~20% typically have durable responses; however, the plateau observed in the survival curve, even years after the treatment is stopped, suggests that some of these patients can be cured[18].

With regard to the perspective of clinicians, European Society for Medical Oncology (ESMO) has developed the Magnitude of Clinical Benefit Scale (ESMO–MCBS), aimed at discriminating drugs associated with a clinically relevant therapeutic benefit from those that only offer marginal improvements over other available treatments[19,20]. Similar frameworks have been developed in the USA, including the American Society of Clinical Oncology (ASCO) Value Framework[21,22], the Memorial Sloan Kettering Cancer Center Drug Abacus[23] and the National Comprehensive Cancer Network framework[24]. All these models were presented as initial, probably imperfect, attempts at rating clinical benefit. Indeed, some aspects of the ESMO–MCBS approach that would limit its application by regulators are worth highlighting. Firstly, the assessment requires direct comparison with other agents used in the same setting, which is not always feasible (for example, for drugs showing dramatic activity in single-arm studies in areas of unmet need). Of note, this limitation was addressed in the ESMO–MCBS version 1.1, launched in 2017, which enables scoring of drugs evaluated in single-arm studies in the case of rare diseases or in situations of high unmet need[20]. Secondly, the evidence used for the assessment comes primarily from pivotal clinical trials. No attempts were made to integrate data from clinical practice and post-approval studies, which are often needed for a more refined understanding of benefits and harms. Thirdly, the MCBS is based on experts' views rather than on systematic evaluation of the patients' preferences, and both might differ in quantitative and qualitative terms (such as the weight given to improvements in patient-reported outcomes). Finally, these scales measure the benefits added by individual treatments relative to existing treatments rather than recognizing small successive incremental benefits, which could eventually add up to large effects versus placebo.

The limitations of the ESMO–MCBS illustrate how a scale that is proposed by clinicians, formally focused on 'living longer' or 'living better', might fit the purpose of quickly flagging drugs with remarkable phase III trial results for rapid HTA, but would be ill-suited for other decision makers using a different perspective. Undoubtedly, stakeholders will continue to perfect their own approach to assessing value, but a unique definition that captures the concept in its entirety is unlikely to emerge. The different definitions will inevitably lead to different conclusions between stakeholders — or even among the same stakeholders.

Value judgements: whose perspective?

According to the current EU legislation, the EMA handles the drug approval process by evaluating the benefit–risk balance on behalf of all EU member states (BOX 1). When balancing benefits versus harms, regulators give primary importance to the perspective of the patient over that of the doctor in clinical decision-making. Thus, the crucial questions for regulators are whether quality, safety and efficacy are established for the drug in the claimed indication and whether the benefit–risk balance of the drug is positive (as estimated by regulators on the basis of available evidence).

An important caveat of the current EU legislation is that the benefit–risk balance is interpreted in absolute terms and not relative to that of other available treatments[25,26]. This somewhat artificial situation of drugs being approved as if in a 'therapeutic vacuum' might lead to the approval of drugs with a potentially inferior therapeutic value. This theoretical scenario is, however, unlikely to occur in practice for anticancer treatments aimed at reducing mortality, delaying tumour progression or addressing other unmet medical needs, such as poor HRQOL. Also, treatments need to be assessed in the relevant context: for example, in 2015 the EMA adopted a negative opinion for dasiprotimut-T, a drug intended for the treatment of follicular lymphoma, because it was not studied in the relevant setting (following standard chemoimmunotherapy combinations including rituximab). Regulators would be wary of introducing such a drug to the market if patients were put at risk of loss of potential curative options and receive a clearly inferior treatment, or in clinical settings that are considered obsolete. Companies would also

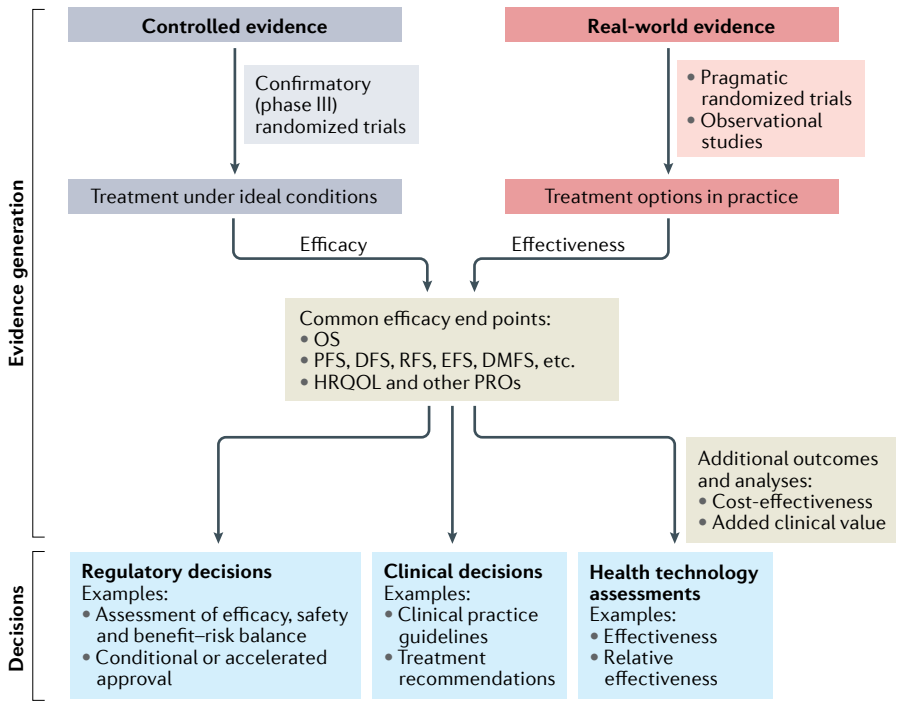

Fig. 1 | **Clinical trials versus real-world evidence.** Clinical trials generate knowledge on the efficacy of a treatment under well-defined conditions. By contrast, outcomes research methods help to assess how this clinical efficacy is translated into clinical practice, thus generating 'real life' population-based effects. DFS, disease-free survival; DMFS, distant metastasis-free survival; EFS, event-dree survival; HRQOL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes; RFS, recurrence-free survival.

Table 2 | **Examples of different health technology assessments of value for EMA-approved anticancer treatments**

Trial	Treatment and disease setting	Comparator arm	mPFS (control arm + increase in experimental arm)	mOS (control arm + increase in experimental arm)	HRQOL favours experimental arm?	Assessment (score and meaning in terms of clinical benefit)		
						GBA benefit[a]	HAS ASMR[b]	ESMO MCBS[c]
LUX-Lung 3 (REF.[67])	Afatinib; NSCLC with *EGFR* mutations, first line, stage III–IV disease	Cisplatin–pemetrexed	6.9 + 4.2 months; HR 0.58 (95% CI 0.43–0.78)	Immature data	Yes	2; considerable	V; insufficient	4; considerable
PROFILE 1007 (REF.[68])	Crizotinib; NSCLC with *ALK* rearrangements, second line, stage III–IV disease[d]	Docetaxel	3 + 3.7 months; HR 0.49 (95% CI 0.37–0.64)	Not meaningful owing to crossover	Yes	2; considerable	III; moderate	4; considerable
MDX010-20 (REF.[69])	Ipilimumab; melanoma, second line, metastatic disease	gp100	NA	6.4 + 3.7 months; HR 0.69 (95% CI 0.56–0.85)	NA	2; considerable	IV; minor	4; considerable
BRIM-3 (REFS[70,71])	Vemurafenib; melanoma with *BRAF* mutations, first line, metastatic disease[d]	Dacarbazine	1.6 + 4.7 months; HR 0.26 (95% CI 0.20–0.33)	9.7 + 3.9 months; HR 0.70 (95% CI 0.57–0.87)	NA	2; considerable	III; moderate	4; considerable
BREAK-3 (REF.[72])	Dabrafenib; melanoma with *BRAF* mutations, first line, metastatic disease[d]	Dacarbazine	2.7 + 2.4 months; HR 0.30 (95% CI 0.18–0.51)	Not meaningful owing to crossover	Yes	ND; uncertain	III; moderate	4; considerable
EMBRACE[73]	Eribulin; breast cancer, third line, metastatic disease	Investigator's choice of chemotherapy	NA	10.6 + 2.5 months; HR 0.81 (95% CI 0.66–0.99)	NA	3; minor	IV; minor	2; minor
CLEOPATRA[74,75]	Pertuzumab; $HER2^+$ breast cancer, first line, locally recurrent unresectable or metastatic disease	Trastuzumab–docetaxel	12.4 + 6.1 months; HR 0.62 (95% CI 0.51–0.75)	40.8 + 15.7 months; HR 0.68 (95% CI 0.56–0.84)	No	2; considerable	III; moderate	4; considerable
EMILIA[76]	Trastuzumab emtansine; $HER2^+$ breast cancer, second or later lines, unresectable locally advanced or metastatic[d]	Lapatinib–capecitabine	6.4 + 3.2 months; HR 0.65 (95% CI 0.55–0.77)	25.1 + 5.8 months; HR 0.68 (95% CI 0.55–0.85)	Yes	2; considerable	II; considerable	4; considerable
TROPIC[77]	Cabazitaxel; CRPC after docetaxel, metastatic disease	Mitoxantrone	NA	12.7 + 2.4 months; HR 0.70 (95% CI 0.59–0.83)	NA	3; minor	III; moderate	2; minor
COU-AA-301 (REF.[78])	Abiraterone; CRPC after docetaxel, metastatic disease	Prednisone	NA	10.9 + 3.9 months; HR 0.65 (95% CI 0.54–0.77)	NA	2; considerable	III; moderate	4; considerable
AFFIRM[79]	Enzalutamide; CRPC after docetaxel, metastatic disease	Placebo	NA	13.6 + 4.8 months; HR 0.63 (95% CI 0.53–0.75)	Yes	2; considerable	III; moderate	4; considerable

Table 2 (cont.) | **Examples of different health technology assessments of value for EMA-approved anticancer treatments**

Trial	Treatment and disease setting	Comparator arm	mPFS (control arm + increase in experimental arm)	mOS (control arm + increase in experimental arm)	HRQOL favours experimental arm?	Assessment (score and meaning in terms of clinical benefit)		
						GBA benefit[a]	HAS ASMR[b]	ESMO MCBS[c]
ALSYMPCA[80]	Radium-223; CRPC, late line and bone pain, metastatic disease[d]	Placebo	NA	11.2 + 3.8 months; HR 0.70 (95% CI 0.55–0.88)	Yes	2; considerable	IV; minor	5; major
VELOUR[81]	Aflibercept; CRC, second line, metastatic disease	FOLFIRI	4.7 + 2.1 months; HR 0.76 (95% CI 0.66–0.87)	12.1 + 1.4 months; HR 0.82 (95% CI 0.71–0.94)	NA	3; minor	V; insufficient	1; insufficient
CORRECT[82]	Regorafenib; CRC, third and later lines, metastatic disease	Placebo	NA	5 + 1.4 months; HR 0.77 (95% CI 0.64–0.94)	NA	3; minor	V; insufficient	1; insufficient
REGARD[83]	Ramucirumab; gastric cancer, second line, advanced or metastatic disease	Placebo	NA	3.8 + 1.4 months; HR 0.78 (95% CI 0.60–1.00)	NA	3; minor	V; insufficient	2; minor

ASMR, Amélioration du Service Médical Rendu; CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; ESMO, European Society for Medical Oncology; FOLFIRI, folinic acid, fluorouracil and irinotecan; GBA, Gemeinsamer Bundesausschuss (German Federal Joint Committee); HAS, Haute Autorité de Santé (French High Health Authority); HRQOL, health-related quality of life; MCBS, Magnitude of Clinical Benefit Scale; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; ND, no data; NSCLC, non-small-cell lung cancer. [a]Benefit assessment of medicinal products performed by the GBA. Every new drug must go through an early benefit assessment within 6 months of its launch in the German market. The GBA decides whether the new drug confers an additional benefit over existing therapies. The magnitude of additional benefit is classified as major (1), considerable (2), minor (3), non-quantifiable (4), no additional benefit (5), or less benefit (6). Price negotiations begin after a final decision is announced by the GBA. The scores displayed in the table were extracted from: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/. [b]Improvement in actual benefit (AMSR) assessed by HAS. This scale evaluates the therapeutic improvement offered by new drugs over existing therapies. The magnitude of improvement is classified as major (I), important (II), moderate (III), minor (IV), or non-existent (V). The scores displayed in the table were extracted from: https://www.has-sante.fr/. [c]The ESMO MCBS classifies new drugs as A–C (with A and B considered as substantial benefit) in the curative setting, and as 1–5 (with 4 and 5 considered as substantial benefit) in the non-curative setting. According to ESMO, drugs providing substantial benefit should be streamlined for accelerated assessment of value and cost-effectiveness. The scores displayed in the table were extracted from: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards. [d]Crossover from the control to the experimental arm was allowed.

be reluctant to put a drug on the market without a reasonable prospect of marketed use.

In some situations, however, uncertainties about available options might be sufficient to justify the approval of potentially suboptimal treatments. For instance, a new drug can be approved on the basis of results from clinical trials using a control intervention that has recently been supplanted by a superior treatment[27,28]. Examples include the common use of chlorambucil as comparator in patients with treatment-naive chronic lymphocytic leukaemia (instead of ibrutinib)[29] or of the melphalan–prednisone chemotherapy backbone in patients with transplant-ineligible multiple myeloma (instead of lenalidomide combinations)[30]. In those situations, approval might be granted provided that the differences are not striking and a 'place in therapy' can be envisaged for the new agent on the basis of the available evidence and the preference of different stakeholders. This situation also reflects the reality that, as better drugs are introduced, old drugs are not automatically removed from the market, even if proven inferior, and might remain the preferred option for some patients and physicians in specific situations (for example, owing to contraindications, patient preferences or restrictions posed by the health-care system on the basis of different considerations). Unless leaving inferior drugs on the market results in a clear and substantial risk to public health, re-evaluation of the place of older and potentially inferior treatments among the available options is left to the health-care systems, authors of clinical guidelines and clinicians. This consideration is particularly important when, owing to prohibitive costs, new drugs are not necessarily available for reimbursement. Thus, in the current framework this apparently counter-intuitive approach seems justified on the basis of the different roles of regulators in assessing and describing benefits and harms, and other stakeholders prioritizing available treatment options according to their preferences.

When debating the value of anticancer drugs, distinguishing between patient preferences and the societal perspective is important. For example, a drug with established efficacy in ~50% of patients and a demonstrated equally important detriment in the other ~50% would be of no interest from a societal perspective if the aim was to maximize health benefit in the whole population and biomarkers to prospectively determine which patients would benefit from the drug were not available. Nevertheless, the attitude of a patient with a high degree of certainty of having a poor outcome and no other available treatments might be different. In this theoretical example, a well-informed patient might decide to take the risk of harm in the hope of a benefit, however uncertain, on the basis of personal preferences[31]. This theoretical example is unlikely to happen because the societal gain is typically positive or negative but rarely exactly zero, although it illustrates the distinction between individual and societal perspectives.

Should regulators protect patients from 'gambling against the odds' of a beneficial treatment? We argue that, given the different perspectives, a central decision at the regulatory level seems less justified provided that regulators can adequately inform subsequent decisions, such as the doctor–patient decision or societal decisions on resource utilization. This view seems to conflict with the fact that

Box 1 | **Role of the EMA and FDA in drug authorization**

EMA

The EMA is the agency responsible for the evaluation of marketing authorization applications submitted through the 'Centralized Procedure', issuing recommendations and providing the basis for the authorization of medicines in Europe. The EMA continuously monitors and supervises the safety of medicines that have been authorized in the EU. When the EMA issues a positive recommendation, the European Commission subsequently makes a legally binding decision. The Centralized Procedure is valid in all EU member states plus Iceland, Liechtenstein and Norway, and it is compulsory for drugs in oncology and some other medicine areas (such as the treatment of HIV infection, viral diseases, neurodegenerative disorders, autoimmune disorders and diabetes or advanced therapies). The EMA is not responsible for the authorization of clinical trials; or aspects related to pricing, reimbursement or availability of medicines. Before an authorized medicine is made available to patients, decisions about pricing, reimbursement and availability take place at the national and regional levels in the context of the national health-care system of each country. The EMA has no role in these decisions, although it collaborates with HTA bodies across the EU in terms of communication to facilitate the HTA and the provision of joint advice to applicant companies.

FDA

This federal agency under the US Department of Health and Human Services is responsible for ensuring the safety and efficacy of all medicines, vaccines, blood transfusions, medical devices, tobacco products, and many other products for human use. The FDA is not involved in pricing and reimbursement of medicines but, unlike the EMA, is involved in the approval of clinical trials.

drug regulation was put in place precisely because of the perception that patients and clinicians are not well equipped to assess the effects of drugs by themselves. Why, then, should regulators not decide on their behalf? In this context, we wish to stress the role of regulators in protecting other decision makers by scrutinizing the data using their technical skills and expertise, and communicating their assessment, rather than deciding on behalf of other stakeholders.

Should regulators prioritize the societal perspective over that of patients? According to the current EU framework for pharmaceuticals, EMA regulatory approvals should not take economic considerations into account; this responsibility is exercised by the national competent authorities[4,32]. This approach gives wide autonomy to member states to decide on cost-effectiveness and prioritize different interventions according to national health-care objectives and budgets. Accordingly, the EMA has not been delegated the responsibility for determining whether or not a new drug will be beneficial within the context of the health-care system of each member state. This national evaluation involves complex decisions, for example, regarding resource allocation and prioritization, among others. Thus, the broader societal perspective is placed within the competence of national health-care systems and not within that of drug regulators. The situation in the USA is somewhat different because Medicare, one of the major public health insurance programmes in that country, has a limited ability to decline funding of drugs approved by the FDA (BOX 1). This situation is not without its own difficulties in the case of expensive drugs that challenge the system (such as aducanumab, intended for the treatment of Alzheimer disease)[33,34].

Yet, the perspectives from patients and society are not as conflicting as it might seem. A lot of common ground exists between efficacy, effectiveness and relative effectiveness, and this is an area in which regulatory assessment can inform the HTA (FIG. 1). For instance, although regulators formally base their evaluation on the ideal scenario of 'controlled' trials, they also evaluate the generalizability of trial results to 'real-world' settings, both in terms of efficacy (for example, in the intent-to-treat principle for the primary efficacy analyses) and harms (such as risk of off-label use or medication errors)[35]. In practice, a high level of agreement between both scenarios is expected, although divergence will be inevitable in the case of costly drugs that benefit a low number of prospectively unidentifiable patients. While cost has a major role in creating this conflict, agreement on evidentiary standards can narrow the gap between the ideal and the real-world settings.

To address the aforementioned gap, in 2010 the EMA and European Network for Health Technology Assessment (EUnetHTA) initiated a collaboration following a mandate that the High-Level Pharmaceutical Forum announced in 2008 (REF.[36]). The objective of the EMA–EUnetHTA collaboration is to improve the efficiency of processes and conditions for timely access of patients to effective medicines. The first step was to improve the way information was presented in the European public assessment reports in order to better address the needs of HTA bodies. In 2013–2015, areas of collaboration included joint scientific advice and early dialogue involving regulators and HTAs, development of scientific and methodological guidelines, generation of post-licensing (or post-authorization) data, and facilitating availability of clinical trial data[37]. Since 2015, additional areas of interaction have included a single process for parallel consultation between EMA and HTA bodies (launched in 2017), initiatives to facilitate patient and clinician engagement in decisions, definition of 'unmet medical need' for the purpose of setting priorities, and refining the wording used to define treatment-eligible populations in therapeutic indications, to name only a few.

The EMA also piloted a programme called Medicines Adaptive Pathways to Patients (MAPPs) to provide a systematic framework for multistakeholder agreement on data collection during drug development, licensing and post-marketing. The aim of the MAPPs programme is to optimize patient access and evidence generation to meet the objectives of different stakeholders in a timely fashion[38].

What outcomes do regulators consider?

In assessments of the benefit–risk balance of anticancer drugs, regulators consider outcomes that are considered clinically important and convincing. Traditionally, these outcomes have included clinical efficacy end points (such as OS and PFS), and all the various toxicities associated with each drug. Symptom improvement and HRQOL have also had a key role in some regulatory decisions. Objective response rate, although not considered a clinical benefit end point in its own right, has frequently been used for approvals of agents tested in single-arm trials, but only in the cases of dramatic activity, high unmet need, acceptable toxicity, and an overall positive benefit–risk balance based on the totality of the data[39] (TABLE 1).

What constitutes an important outcome in the long term is a matter of judgement. In making this judgement, regulators need to consider patient preferences and how individuals might value different outcomes. In the past, regulators have sought expert advice from patients regarding their preferences. While informative, relying on the input of a few representatives might not be reflective of the preferences of the wider patient population. Evidence-based studies of patient preferences might provide a more complete picture and, therefore,

these approaches are being explored in the regulatory context[40].

Regulators can also approve drugs on the basis of incomplete information on outcomes that are important to other stakeholders. This scenario is not unusual in situations of high unmet need, in which the emphasis for regulators has been transparent communication of effects and uncertainties and early approval but requiring data collection after approval. The approval of ceritinib for the treatment of *ALK*-rearranged non-small-cell lung cancer or blinatumomab for the treatment of CD19-positive acute lymphoblastic leukaemia, both on the basis of single-arm data[41,42] followed by the submission of confirmatory data from RCTs[43,44], are examples in which regulators approved drugs on the basis of 'dramatic activity' in the absence of complete information on long-term outcomes[45]. These examples are not infrequent and, indeed, several drugs have been approved on the basis of data from non-randomized trials or from trials with primary efficacy end points other than OS[46]. Another example is if certain outcomes are not measured by study design. Renal cell carcinoma is an interesting example, because the primary clinical end point in most trials is PFS. This choice of end point creates a problem for stakeholders that require an estimation of the treatment effect on OS because, in most trials, patients who do not respond to treatment with the comparator medicine (frequently an obsolete regimen or placebo) are allowed to crossover to the experimental arm[47].

In some cases, defining the value of an anticancer drug might require such long follow-up durations that, unless early access were granted, this would result in substantial delays for patients with high unmet medical need. One example is the use of tamoxifen for adjuvant treatment of hormone receptor-positive breast cancer. Initially, this drug was regarded as highly priced and of questionable value[48–50]. More than 20 years later, evidence supporting its value in terms of long-term survival advantage and cost-effectiveness for health-care systems is available[51]. Direct estimates of the magnitude of long-term OS benefit of new drugs are often lacking at the time of approval. Legal provisions have enabled a conditional marketing authorization whereby companies must submit further data after approval to fill any existing knowledge gap[52]. Paradoxically, whilst regulators steer towards early access to drugs for patients in need, this approach might adversely affect the reimbursement process because HTAs require extensive data on outcomes that are unavailable at the time of approval, such as OS[46].

Should regulators only approve drugs when sufficient data on several outcomes are available to satisfy all stakeholders? If this was the case, the potential loss of opportunities to access promising new drugs would be difficult to bear. Perhaps the 'price of early access' can be addressed through conditional reimbursement mechanisms, although these approaches have not been used very often or fully explored[53]. For example, in 2006, a conditional reimbursement scheme was instituted in the Netherlands for bortezomib for the treatment of patients with relapsed and/or refractory multiple myeloma. The scheme allowed early access to the drug, but conditional on the obligation to gather real-world evidence and actual costs in daily practice[54]. The aforementioned MAPPs programme is being piloted to facilitate early access of patients to promising new drugs by an iterative development plan, for example, involving gradual expansion of the target population (perhaps starting from a population with a high unmet medical need). In this programme, the collection and use of real-world data after marketing authorization complements data from clinical trials and informs updates to regulatory labels and to other stakeholders[55,56].

Can regulators help other stakeholders?

To help subsequent decisions, regulators must communicate complete information about all relevant outcomes to other stakeholders. In the EU, this mechanism is currently achieved using a standardized format to report outcomes from pivotal clinical trials as well as a structured approach to communicating benefits and harms[7,57]. The latter includes descriptions of data and value judgements, and a table in which all the key favourable and unfavourable effects are listed, together with uncertainties and strength of evidence ratings. The table easily lends itself to the application of quantitative approaches for decision analysis, such as multi-criteria decision analysis that explicitly evaluates multiple conflicting criteria in decision making, or approaches that explicitly incorporate patient preferences.

Glossary

Benefit–risk evaluations
Together with evaluation of the 'quality', 'safety' and 'efficacy' of a new drug, the evaluation of the benefit–risk balance is the cornerstone of the scientific opinions of regulatory agencies (including the EMA) when assessing new drug applications. This evaluation is based on the balance between the favourable effects (benefits) of a medicine against its unfavourable effects (harms, commonly referred to as 'risks'). Regulatory agencies can only recommend authorization of medicines with a positive benefit–risk balance. In conventional marketing authorizations, regulatory agencies do not evaluate the benefit–risk balance of medicines in the context of all approved drugs for the same indication, but instead base their assessments on the 'absolute' benefit–risk (exclusively the benefits versus the harms from the drug).

Cost-effectiveness
Cost-effectiveness analysis compares the relative costs and relative effects of two or more courses of action. Effects can be measured, for example, in years of life gained from the intervention or number of surgical procedures avoided[85].

Effectiveness
This term refers to the extent to which an intervention is able to cause the intended pharmacological effects when provided under the usual circumstances of health-care practice, also referred to as 'in real life'. Effectiveness is distinguished from efficacy to refer to the smaller magnitude of effects often assumed or observed at the population level when the medicine is provided under the usual circumstances compared with the ideal circumstances of a controlled clinical trial setting (owing, among other things, to patient selection or monitoring)[84]. This concept is mainly used in the context of health technology assessment and is not a regulatory requirement for a marketing authorization of new medicines.

Efficacy
This term generally refers to the ability of a medicine to cause the intended pharmacological effects (referred to as 'benefits' or 'favourable effects', as opposed to 'harms', 'risks' or 'unfavourable effects') under ideal circumstances. In oncology, efficacy is often measured directly using clinical outcomes such as overall survival in randomized controlled trials. Efficacy is often distinguished from 'activity', typically measured in single-arm trials and evaluating a pharmacodynamic effect that is not necessarily associated with a clinical effect, such as tumour shrinkage on imaging. Efficacy is also often distinguished from 'effectiveness'[84].

Health technology assessment
(HTA). Systematic evaluation of the properties and effects of a health technology, addressing its intended and unintended consequences, and aimed at informing decision-making. HTAs involve evaluation of clinical effectiveness, safety, cost-effectiveness and, when broadly applied, societal, ethical and legal aspects. A major application of HTAs is in informing reimbursement and coverage decisions by insurers and national health-care systems.

Relative effectiveness
Comparison of an intervention with available treatments — that is, this term refers to the extent to which an intervention does more good than harm compared with one or more alternative interventions under the usual circumstances of health-care practice. The concept differs from 'effectiveness' owing to its comparative nature[84]. A similar distinction exists for efficacy and relative efficacy. This concept is mainly used in the context of health technology assessment and is not a regulatory requirement for a marketing authorization of new medicines.

Similar structured frameworks have been implemented in other regions[58,59]. For even more transparency and to further support the provision of clinical guidance, the EMA has established a policy of proactive publication of the documentation about clinical trials submitted by applicant companies[60,61].

Regulators and HTA bodies might also have a shared interest in defining the evidence that must be collected before and after approval. For example, evidence from clinical trials might be complemented with post-approval observational data. Examples of the latter are data from studies using disease registries to identify the natural history of the disease, resource utilization and compliance with the prescribed treatment, or from studies assessing efficacy and safety in real-world settings[62,63]. Similarly, data from registries and data sharing initiatives might be used to produce external controls in order to corroborate the evidence from non-randomized studies. The collection of efficacy and safety data from programmes facilitating early access and off-label use could also supplement clinical trial data. Other recommended post-approval studies could seek to identify biomarkers (or other markers) for improving patient selection[64]. In the current legal framework, a marketing authorization can be granted if the benefit–risk balance is positive but not necessarily optimal, and thus the larger problem of treatment optimization (for example, of dose and treatment duration) goes beyond the remit of regulators. This important quest is currently left mainly to academic initiatives, and are challenging in terms of trial design and often conducted in the absence of dedicated resources or support from the company marketing the drug[65]. Indeed, the approval of new drugs holds a prominent place in the drug development debate, whereas the gains obtained from trials investigating treatment optimization generally receive little attention. The development of a framework for studies addressing patient-centred treatment optimization goes beyond the scope of this Perspective, but its public health importance cannot be overemphasized.

Conclusions

Transparency about the objectives and values of different stakeholders (patients, payers, regulators and clinicians) is essential to understand their decisions when judging the value of anticancer treatments. A single definition for this concept does not exist, a fact that reflects the degree of variability of different priorities among the different stakeholders. Drug regulators make decisions based on value judgements that are (and will probably remain) patient-centred, and thus might differ from those made from a societal perspective. Rather than attempting to reconcile conflicting definitions and objectives, understanding all the different perspectives is important to ensure that they do not lead to marked inefficiencies, such as multiplication of trials and requirements that would lengthen and stifle the clinical development of promising new drugs. Furthermore, clarity about the purpose and perspective of any value definition is needed to avoid confusion when different stakeholders debate the value of new treatments. As the approaches for determining and communicating value evolve, the views of different stakeholders might become more aligned, further improving data generation and treatment optimization. Yet, the availability of new drugs is incompatible with the limited budget of most regional health-care systems. In this situation, the views of patients in urgent need of treatment options will continue to conflict with those looking for value-for-money to contain health-care budgets. The quest for a sustainable pricing policy has become more urgent than ever.

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Author contributions

F.P., U.W., D.P., N.W. and J.D. researched data for the article; all the authors discussed the manuscript contents; F.P., U.W. and J.D. wrote the article; and all the authors reviewed it before submission.

Competing interests

The authors declare no competing interests.

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