

Oncology Drug Development and Value-based Medicine

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Executive Summary

An explosion of innovative science, sustained R&D investment and the clinical successes of a new wave of targeted therapies have transformed the oncology landscape. Hopes for understanding and controlling lethal cancers have never been higher, yet the challenges of bringing a product to market and achieving optimal market success remain undiminished. Clinical proof – once sufficient foundation for product success in oncology – today must be complemented with compelling demonstration of treatment “value”. In this paper, John Doyle and Brian Huber argue the intrinsic need to redefine the clinical trial process to ensure that appropriate data are generated throughout the clinical trial process to support the overall pharmacoeconomic value of a new drug and meet a future demand for value-based medical practices.

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Introduction

Cancer drugs constitute the second biggest category of drugs sold in the US. Worldwide, sales of cancer drugs are forecast to grow steadily, driven by the aging population and by opportunities for earlier therapeutic intervention using more effective therapies, which open the door for possible long-term disease management and control.

Recent years have seen tremendous therapeutic innovation, particularly as the new molecularly targeted agents have entered clinical practice, offering hope of improved outcomes for subsets of patients.¹ Increasing cancer “survivorship” is starting to transform the approach to many tumor types, from one of acute treatment offering marginal patient benefits towards the possibility of chronic disease management. This has resulted in a change of focus to one of total patient care encompassing quality of life (QoL) issues. There is also increasing pressure from patients and their advocates for better access to affordable treatments that promise improved disease control. Patient affordability is increasingly considered by physicians, given the trend of rising costs and longer duration of care.²

These transformations in cancer management, and in patient and societal attitudes towards cancer treatments, have many parallels with the story of HIV management. In the 1980s, HIV infection led to almost certain death on emergence of AIDS. However, over the past 20 years HIV infection has become a chronic disease for those fortunate enough to afford access to antiretroviral therapy. That transition was possible not only through the development of new and innovative medicines and their use in effective combinations but also through the genotyping and phenotyping of the virus, close monitoring of treatment progress, and evaluation of best treatment sequencing. Radical changes in access to antiretroviral agents in the developed world were expedited by two factors. Firstly, peer pressure from patients, advocates, and clinical champions, and secondly, changes in the way that regulators and payers considered the approvals and funding of these agents.³ Our progress in shifting cancer to a controllable disease is not nearly as advanced – not least because “cancer” is a plethora of different diseases and because many tumors advance with stealth, such that their first presentation is often late-stage disease. Nevertheless, the endeavor is the same and the signs are that innovative oncology treatments have and will evolve some cancer treatments into long-term disease management and thereby change the way drugs are developed, approved, and valued.

Over the same 20-year period that has seen HIV medicine shift from acute to chronic care, there has also been a transition towards a value-based approach to assessing new drugs worth beyond their purely clinical attributes. Medical innovation in cancer, as in HIV, alters the economics of disease management. Value of treatment is no longer gauged according to simple, drug cost analyses but requires more holistic, sophisticated evaluation of determinates of overall cost of care and long-term benefits. The aforementioned conversion to chronic therapy, intensifying competitive landscape, and rise of targeted therapeutics for niche patient populations all converge to complicate the value paradigm in cancer care.

Historically, cancer drugs, like the early antiretroviral agents, enjoyed a “special status” because of their role in the acute treatment of usually an incurable disease with life expectancies measured in months to a few years. This “special status” permeated clinical practice where new drugs were very rapidly evaluated in man, sometimes with a paucity of scientific rationale. This “special status” also permeated regulatory approval processes and marketing authorization as well as reimbursement policies. In fact, the cost and value of new cancer treatments were rarely at issue. Oncology became such a specialist sector because of the high unmet needs. Payers would typically defer to oncologists in their network when establishing coverage and reimbursement policy. Policy and common practice would historically provide unfettered access to drugs, as most of these drugs would only be used for very short periods of time – often only providing marginal benefits.

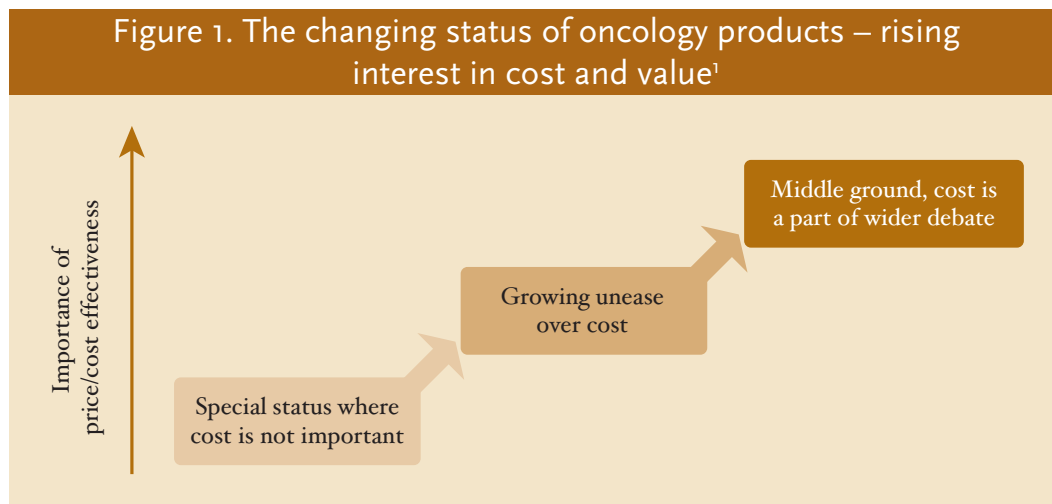
Now, new targeted drugs, usually used in multiple and complex drug combinations, are starting to bring clinically meaningful improvements for certain groups of patients with cancer. Treatment considerations in cancer are now much more complex and multi-factorial, involving:

- > *screening and selection of patients for treatment*
- > *choosing and combining drugs based on mechanisms of action that match with tumors’ molecular etiology*
- > *selecting treatments (and combinations) that optimize both long-term outcomes and future treatment options*
- > *safety and QoL considerations*
- > *the costs and pharmacoeconomics of treatment choices, including health technology assessment (HTA) agencies guiding coverage, reimbursement, and pricing*
- > *adherence with prescribed medications (especially oral)*
- > *regulatory and commissioning hurdles affecting reimbursement and patient access to new therapies and indications*

These considerations complement considerations of clinical efficacy and build a picture of the value of a drug or intervention – a perceived or actual value – which becomes married to the agent’s clinical pedigree, and part of its character.

Cancer continues to be a “politically and emotionally sensitive” disease. Efforts to seek better treatments are applauded, but emerging oncology treatments are not immune to the universal shift in medicine to focus on overall treatment value. Value is an economic construct that is inherently driven by the appraiser – or customer. Recent global economic factors aside, the advent of new and more expensive drug treatments has led a range of stakeholders (patients, clinicians, payers, policy makers, and society) to add their voice and perspective on the value of treatment innovation in oncology. Value-based medicine (VBM) is seen as the next, progressive step in the evolution and maturation of simple evidence-based medicine (EBM). This emergence of VBM has important implications for continued, successful drug development and innovation in oncology (Figure 1).⁴⁻⁶

Oncology treatments are not immune to the universal move in medicine to focus greater attention on treatment value.



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Value-based medicine is about more than just managing drug costs, constraints on healthcare spending, health-economic evaluation, reimbursement issues, and the rise of HTAs. Its emergence and evolution in oncology is part of a broadening debate on a host of topics, including the quality of cancer care, access to treatments, and the differing stakeholder expectations of drug therapy.⁷⁻⁹ The value of a treatment is already being shaped and formed through HTAs and inputs into the design of insurance policies, with risk–rewards balanced based on the healthcare providers and technologies demonstrating measurable value.¹⁰

Value-based medicine is about more than just managing drug costs.

This white paper considers the evolution towards value-based practice, the components of VBM and its significance in oncology. Stakeholder perspectives on value in oncology and case studies offering lessons and examples are also provided.

Oncology Drug Development

Over the past 2 decades, there have been both startling successes and spectacular clinical failures in the quest to develop new oncology therapeutics. An optimist would cite the enormous progress made in the understanding of the science of cancer and list an array of ground-breaking new drugs that have transformed treatment paradigms – a list that includes rituximab, trastuzumab, cetuximab, bevacizumab, erlotinib, and imatinib to name but a few. However, the oncology field is also littered with failures (Table 1), including:

- > *compounds that have initially shown promise but failed in pivotal and expensive phase III trials*
- > *an R&D effort that has proved more expensive, and with higher risks, than that of other therapeutic areas*
- > *high failure rates in trial settings that reflect a continued incomplete understanding of the complex etiology of certain diseases and of patient characteristics that confound appropriate patient selection into the crucial trial testing ground*

Table 1. Failure rates in oncology drug development remain high¹

Phase of development	Cancer drugs terminated in Phase ¹	Non-cancer drugs ²
Phase I	27%	17%
Phase II	60%	46%
Phase III	33%	29%
Regulatory authorization rejection	9%	11%

¹ N = 164 compounds

² N = 402 compounds

Adapted from: Natanson L. Innovative Strategies for drug development. Deloitte Recap LLC, 2010.

It is also interesting to note that the vast majority (78%) of new oncology drugs receive their initial licensure for orphan indications.¹¹ As we move from evidence-based to value-based practice, the evidence required to support use of novel agents will be redefined.

Evidence-based Medicine

Rational EBM is not a new concept. EBM has been defined as “a systematic approach to analyze published research as the basis of clinical decision making” and “the conscientious and judicious use of current best evidence from clinical care research in the management of individual patients”.¹² By applying the best available evidence to clinical-decision making,¹¹ EBM assesses and uses clinical outcomes, derived through strict scientific method and sound medical practices, to draw conclusions on the clinical worth of a medical treatment.^{13,14}

Clinical studies are the basis of EBM but all investigational studies are not created equal. The strength of evidence varies from study to study. Indeed, the strongest evidence comes from systematic review – or the collective overview – of multiple randomized, blinded, controlled trials in homogenous patient populations appropriately followed up.¹⁵ After that, reports from individual phase III randomized controlled trials (RCTs) – the regulatory benchmark for all new therapeutics – are the highest ranking evidence supporting a drug’s efficacy. In contrast, patient testimonials, case reports, and even expert opinion have little value as proof because of the placebo effect, the biases inherent in observation and reporting of cases, difficulties in ascertaining who is an expert, and more.¹⁶⁻¹⁸ Between the gold-standard RCTs and anecdotal evidence exists a vast range of quasi-experimental and observational research designs that might provide meaningful insights to real-world practice patterns, costs, and outcomes. Whereas these naturalistic studies excel in generalizability or external validity, their internal validity may be compromised by bias and confounding. This is noteworthy in that value-seeking research endeavors often will deploy an observational design in an attempt to mimic real-world treatment conditions and patient populations. Indeed, a great body of literature has documented the marked difference in cancer-trial populations versus cancer-patient populations. Healthcare stakeholders, such as payers, have taken notice of this dichotomy and have instituted their own studies in an effort to compare new treatments to the existing gold standard of care – otherwise known as comparative effectiveness research.

In oncology R&D, rigorous EBM has been promoted as the driving force to guide medical practice. Clinicians are expected to adopt the principles of evidence-based practice while maintaining clinical judgment and therapeutic integrity. The National Comprehensive Cancer Network (NCCN) Guidelines are designed to follow the principles of EBM and are often cited as the gold standard for best practice in oncology.¹⁹ Accordingly, oncology drug developers need to consider the NCCN requirements and evaluation process in conjunction with the Food and Drug Administration’s (FDA) demands for evidence.

Prior to EBM, there were examples of drugs gaining approval on tentative grounds such as novel mechanism of action conferring theoretical benefits, and approvals based on phase II datasets where hard clinical endpoints were not demonstrated – all reflecting the desperate desire to have something, rather than nothing, to offer certain groups of patients with previously untreatable cancers. Even today there are approved anticancer drugs in use that have no evidence base that is considered vital by current standards. An example is the use of doxorubicin to manage primary liver cancer, a practice now fading with the advent of better locoregional treatment and use of targeted biologicals. The move towards EBM has been productive, ensuring patients get drugs that work and are within the bounds of acceptable tolerability given the risks of cancer itself.

Trial-based Research – the Foundation to Evidence-based Medicine

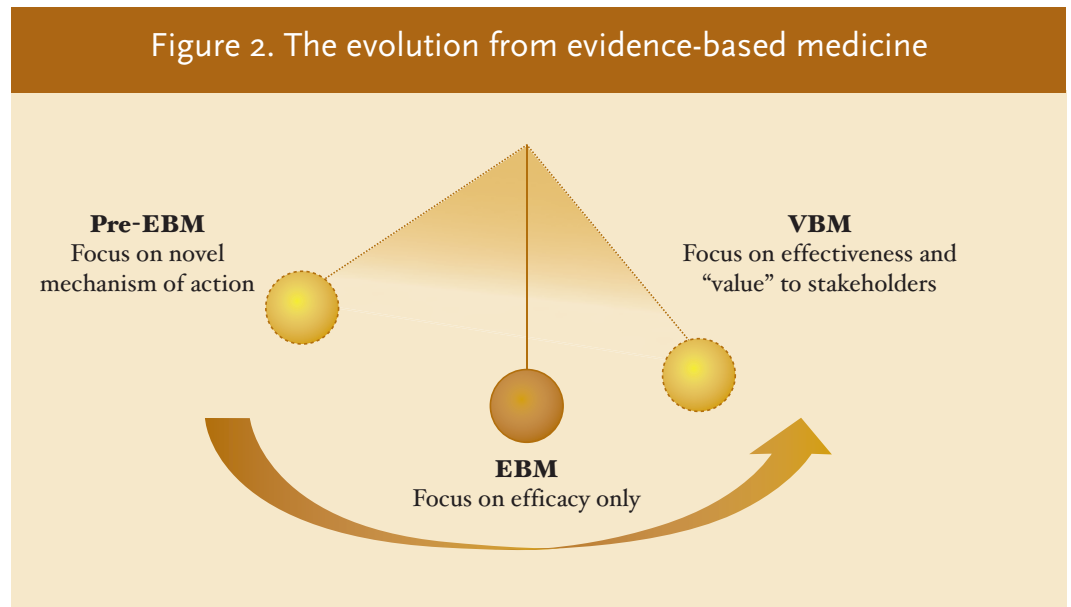
The route to drug approval is via EBM and both trial-based research and the regulatory practices for drug approval and licensing. Study designs and registration strategies are often dictated by the evidence base, and in turn contribute to the evidence base.

The job of a registration trial is to secure a drug license yet the evidence base in support of the drug treatment continues to grow after approval and during real-world use of the product. Observational research focused on real-world use across large, diverse populations is necessary to fully develop the risk:benefit profile of a drug. The need for this post-marketing surveillance research is amplified in oncology because of the heterogeneity of practice patterns and drug combinations, and by the fact that the types of patients recruited in trials – a select and often uncomplicated group – are often very different from those met in real clinical practice.

Traditional registration studies are performed in select patient groups and designed and powered to answer clear objectives using recognized endpoints, assumed from the evidence base to have clinical relevance. Consequently, RCTs might not always reflect real-world practice or be relevant to assessing the risk:benefit ratio of treatment in older and sicker patients who do not meet the ideal profile for inclusion in a clinical trial.

The Endpoints that Matter in Oncology

The era of EBM now ensures that new cancer drugs are tested and approved for their effect on clinically meaningful endpoints. The pendulum has swung toward endpoints such as progression-free-survival (PFS) and – the Holy Grail in oncology – overall survival (OS) (Figure 2). However, within EBM there is little consideration of the impact on patient QoL or other measures of value.



Today, although some of the targeted agents with compelling evidence have been fast-tracked for approval – for example, Glivec® (imatinib) was FDA-approved in May 2001 for treatment of chronic myeloid leukaemia (CML) within 2 months of license application on the basis of three small open-label trials – most regulators require phase III proof of efficacy based on standard clinical endpoints and EBM.¹ In contrast, Sprycel® (dasatinib) received an initial approval for the treatment of CML from the FDA in 2006. Data from a phase III randomized, open-label dose-optimization study were required to obtain full approval, which was received in 2009.

Before the advent of evidence-based medicine, many of the cytotoxic chemotherapies now used in routine oncology practice were often approved on the basis of phase II data.

Transitioning from a Clinical Evidence Focus to a Clinical Value Focus

The choice of primary endpoint in oncology is dictated by the cancer and its stage. While improvement in OS is the ideal, often proof of an increase in PFS, or similar index of delayed disease progression, is used as the means to evaluate drug benefits. Increasingly, patient-reported outcomes are being added to clinical trials to capture the patient perception of value. We expect payer-driven endpoints to be adopted in a similar fashion, as biopharma companies interact in the same way with HTA agencies as they do with regulators during drug development to take stock of their unmet needs and evidence requirements.

Despite our best efforts, current evidence-based trial design approaches may not be sophisticated enough to capture and collect all the data needed to differentiate the disease segments where novel therapies can show real value. In fact, new clinical science must be able to identify the parameters and have the methodologies that need to be factored into value assessment. The relative total value of a new treatment as an advance in a cancer indication must be shown, as must its comparative value – to other available treatments, other management options, and even the option of no treatment. This last option – no treatment – may seem at odds with the goals of cancer care but for patients with terminal disease palliative care might be more appropriate and of better value than treatments offering little clinical benefit and risk of diminished QoL due to treatment side effects. Decisions about what is best and of value in cancer often come down to personal choice and views on treatment worth, as well as the bigger value picture afforded by EBM and even VBM.

As VBM becomes more important as a means of differentiating between treatments and evaluating the role for therapy in different patient groups, the features important for determining the overall value of an intervention will include:¹

- > *long-term cost–benefit assessments – overall value in terms of total costs and total benefits*
- > *relative total value compared with other management options*
- > *the impact of therapy on service provision (e.g. need for additional nursing staff, beds, new diagnostics/monitoring tests to support use of the drug)*
- > *treatment convenience and compliance for patients – is the new agent more acceptable to patients and are they more likely to comply with therapy?*
- > *long-term risk-benefit analysis incorporating patient satisfaction/utility*

Value-based Medicine and Practice in Oncology

Clearly, EBM will continue to be the foundation for the evaluation of new cancer therapies. As such it will be the cornerstone for continued improvement in medical care. However, EBM does not allow us to explicitly compare or quantify specific values of interventions. Value-based medicine gives a more accurate measure of the stakeholder-perceived worth of a therapy than EBM alone. In doing so, VBM allows practitioners to deliver higher quality of care than EBM.

By focusing exclusively on fundamental clinical evidence, but not overall value, EBM may either overestimate, or underestimate, the value of a cancer intervention. For example, EBM will primarily focus on the clinical benefit of additional time of life gained from a cancer treatment. The quality of that extended life is often not quantitatively evaluated, yet in many circumstances the total value of the remaining life may be significantly decreased by the cancer treatment. Patients' life expectancy may increase from 7 to 10 months and the "value accrued over remaining life" can be calculated in terms of a quality-adjusted life year (QALY). The QALY measure aims to give an idea of how many extra months or years of life (of reasonable quality) a patient might expect to gain as a result of treatment. Drug treatment costs per QALY can then be calculated.²⁰ The QALY tool applied to a life-threatening condition therefore combines a measure of improvement in survival with any changes in QoL and then determines the treatment cost to gain that QALY. If that treatment significantly compromises the QoL (for example, by inducing severe vomiting, increasing the risk of infection, or causing mouth ulcerations that affect normal eating) those extra 3 months of life will yield a much lower QALY score. In such circumstances, EBM can overestimate the value of a cancer therapy.

There are also instances where EBM can underestimate the value of an intervention. Treatments with no additional effect on OS compared to the standard treatment might be deemed of low benefit by EBM, yet could offer better QoL to the patient through having fewer side effects, or by eliminating the need for frequent monitoring, hospital visits for infusions, or reducing the move to a second- and third-line therapy at a later stage in disease progression. These factors could result in an overall positive value for the new treatment despite no clinical survival benefit.

Value-based medicine requires that value components are built into drug-development programs early.

Crucially for biopharma companies investing in oncology R&D, VBM requires that value components are built into drug-development programs early.¹ New drugs need to demonstrate not just clinical efficacy and safety but also economic and value proof points throughout drug development. Ideally, clinical, economic, and humanistic evidence can be generated to corroborate a product's value proposition from multiple angles to multiple stakeholders. This compendium of evidence needs to then be customized and translated to each stakeholder category to optimally communicate value to all customers.

Changing Perspectives on Drug Development

Every one of us involved in drug development and commercialization needs to plan for a future where EBM, health-economic evaluation, and outcomes research are used together to inform views on the value of drug innovations. The way clinical studies are designed and executed and the types of dossiers produced to support clinical and value claims needs to change.

Value-based medicine is emerging as a means for clinicians, patients, payers, and policy makers to assess the total and objective value of a treatment intervention from the stakeholder, rather than from a purely clinical perspective.^{1,4-7} Value-based medicine extends and complements EBM rather than replaces EBM (Figure 3). It adds an economic and value perspective and is better able to assess and compare total value between different treatment options (Figure 4).

Value-based practice complements rather than replaces evidence-based medicine and evidence-based practice.

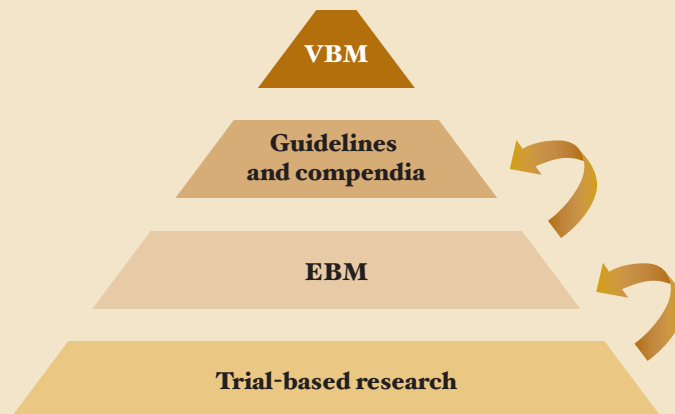
Figure 3. Value-based medicine is an extension of evidence-based medicine

Evidence-based medicine (EBM) – quantitative patient clinical data solely in treatment setting (not total patient value or societal benefit)

Value-based medicine (VBM) – quantitative patient clinical data + additional value parameters = quantitated total value and pharmacoeconomic benefit from a patient and societal perspective.

Figure 4. The value pyramid

Stakeholder assessment of oncology treatments is based on building blocks of persuasive data, starting with proof-of-treatment efficacy gained through trial-based research, accumulation of an evidence base, clinical appraisal, and consensus guidance on the role of treatment in care pathways, culminating in a value-assessment of treatment worth.

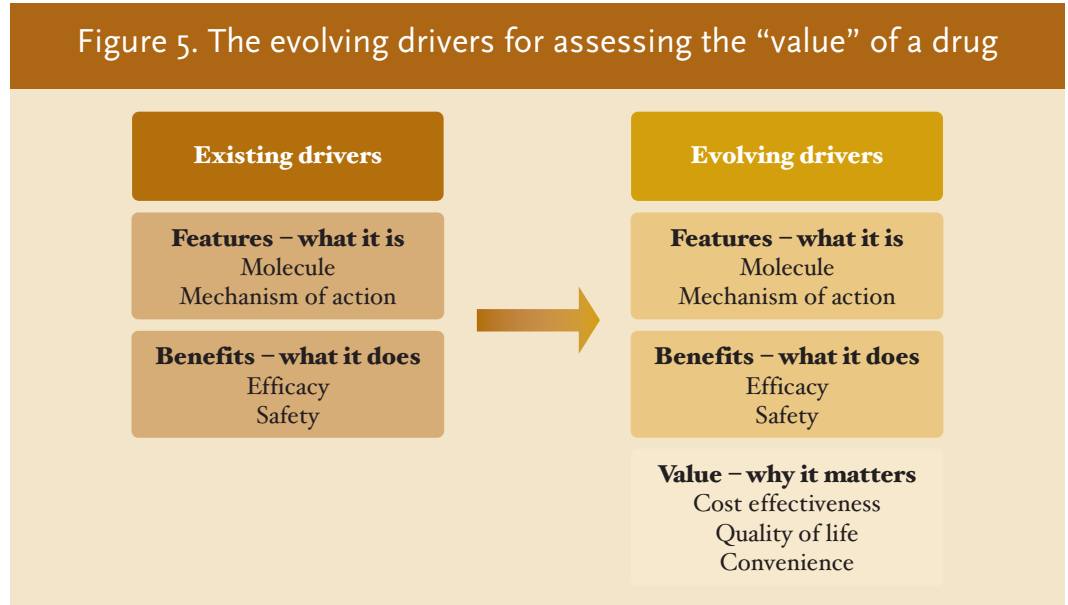


Adapted from: Brown MM, Brown GC, Sharma S. Evidence-based to value-based medicine. American Medical Association Press, 2005.

New Term – Old Principle

The term VBM is relatively new, but the practice of making value judgments in oncology is well established. Like EBM, a term which arose out of a need to coin an existing approach to assessing data, we predict that VBM will soon become part of the medical lexicon and its importance in oncology will drive adoption of VBM. However, the parameters that go into value assessment and the methodology to quantitate these parameters are continuing to be refined (Figure 5).

We predict that value-based medicine will soon become part of the medical lexicon.



Value-based Medicine – Multiple Stakeholders and Decision Makers

In oncology, where novel drug treatments may prolong life by a matter of only months, the value of that extension is viewed differently by different stakeholders. Indeed, the whole question of what assessments, outcomes, and endpoints should be made and collected in order to appraise the benefits, risks, and ultimately the value of a cancer treatment is a matter of debate.²¹ Health-related QoL is increasingly important within approvals and during HTAs.¹ In palliative settings, treatments that allow patients protracted PFS or QoL improvements or maintenance might be welcomed by some stakeholders yet dismissed as of little value by others.

The rise of value-based medicine recognizes that oncologists and other medical specialists are not the only arbiters of the value of a therapy.

The rise of VBM recognizes that oncologists and other medical specialists are not the only arbiters of the value of a therapy.^{1,4-7} Patients, physicians, other healthcare providers, independent regulators, governmental agencies, third-party payers, advocacy groups, and social media drivers (including internet commentators and participants in health-related internet forums) all have a view that influences and at times determines drug development, product registration, product uptake, and ultimately the final value assessment of the therapy.

In essence the stakeholder views have many common threads – all want to reduce the burden of cancer and prolong a patient’s life with sufficient quality.

- > *The patient has the most vested interest in this goal.*
- > *Advocacy groups may champion best management and fair access to new drugs and often push against EBM and value arguments in their desire to allow patients facing life-threatening conditions every hope for a better outcome.*
- > *Physicians want to offer their patients the treatment option that offers the best outcome.*
- > *Healthcare providers must choose the best treatments within their system of provision and budgetary constraints.*
- > *Independent regulators must show fairness and diligence in assessing the risk:benefit ratio of new treatments according to their standard methods of appraisal.*
- > *Governmental agencies are accountable for policy and direction on best spend and practices to ensure good health for the overall population.*
- > *Third-party payers must get the best value from available funds when agreeing to support prescription choices.*

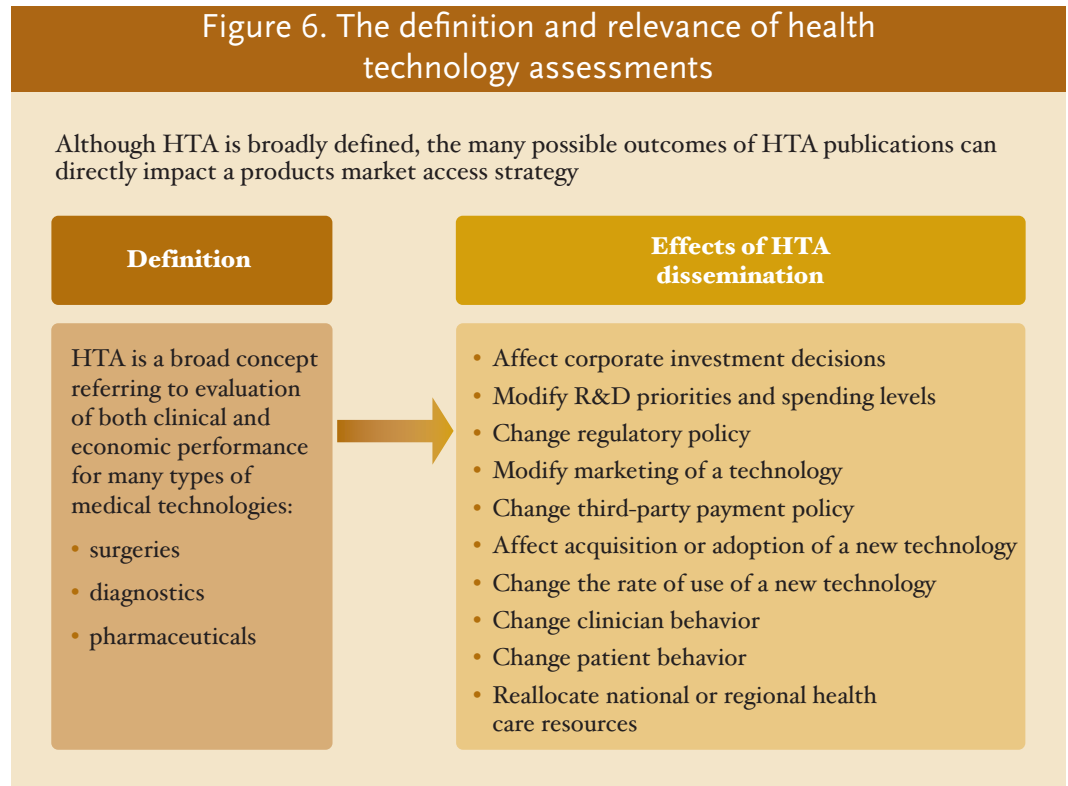
The evolution of VBM also reflects the shift away from a purely product-orientated approach rooted in science and efficacy data to a broader assessment of treatment worth that incorporates pharmacoeconomics, therapy management and compliance issues, and patient QoL. Once a product is launched, its value is governed by the healthcare system where it is used. As such, we need to evaluate healthcare organizations and processes to identify the optimal “point of entry” to the system in order to ensure system value appreciation.

Pharmacoeconomics and Cost Effectiveness Analysis of New Medicines – A Top-line Overview

In recent years there has been a significant focus on payer demand and governmental agency policies to contain healthcare spending by assessing treatment cost effectiveness. Within EBM, pharmacoeconomic studies have evaluated new approaches based on the cost (in monetary terms) and effectiveness (expressed in monetary, efficacy, and health-related QoL terms) of a new treatment. The value drivers used within the assessments relate specifically to drug efficacy and safety. In contrast, VBM takes a wider perspective and includes additional factors such as long-term clinical outlook and prognosis, and final outcomes such as functional status, QoL, and productivity. As a result, VBM will help to identify those drugs that offer the most overall “value” to patients and disregard those treatments that do not meet the appropriate pharmacoeconomic standards. Rationing is not a driver for VBM. However, VBM will identify those treatments of most value enabling healthcare resources to be more appropriately allocated to achieve the optimal patient value.

Health Technology Assessments – Growing Application

There is growing application of HTA to license-approved products as a means of measuring cost effectiveness. In 13 countries across Europe and in Canada, Australia, and New Zealand, national bodies have been established to advise or decide on public funding of licensed drug therapies, with many using HTA tools to reach decisions on whether treatment costs should be reimbursed. Not only are countries funding local HTAs, they are referencing more international HTAs in their value appraisals. Despite this burgeoning of HTAs as a cost-effectiveness tool, there is no single method or single application of this device, and often the processes of appraisal lack transparency (Figure 6).



In the UK, the National Institute for Clinical Excellence (NICE) uses HTAs to assess cost-benefit of newly licensed agents and has traditionally fixed a bar of £30,000 incremental cost per QALY for treatments to prove cost effectiveness. However, in 2009 NICE issued supplementary advice which raised the bar for end-of-life therapies (i.e. therapies indicated in patients where life expectancy is less than 24 months, where there is no alternative treatment with comparable benefits, and when the patient population affected is small [rare cancers]).

The influence of NICE extends beyond the UK borders and decisions made by this body affect views on the reimbursement of new therapies across Europe and beyond.

Health Technology Assessments in the US

The new US healthcare reform bill is expected to result in an additional 32 million Americans joining the US healthcare system in 2014. Therefore, the value of costly oncology therapies is likely to undergo increased scrutiny with respect to decisions concerning coverage in the future. Further use of HTAs and increasing application of comparative-effectiveness research (CER) is expected in an attempt to move from current models of care that reward quantity of care rather than quality of care.^{1,4,22} Compounding the public \$1.5 billion mandated by federal health reform legislation, the private sector is also sponsoring and implementing CER studies in an effort to determine the relative value of new technology versus the current gold standard.²³ The next step anticipated in oncology value assessment is greater use of cost–benefit comparisons – where the value of a treatment intervention is weighed against other available therapies.¹

The next step anticipated in oncology value assessment is greater use of cost–benefit comparisons.

In the past, the Centers for Medicare and Medicaid Services (CMS) have infrequently deployed “coverage with evidence development” in national coverage decisions, where a product may be granted “conditional coverage” for a limited period of time during which a manufacturer may aggregate evidence of value demonstration.²⁴ However, with the anticipated increase in healthcare costs, it is foreseeable that “coverage with evidence development” may be implemented more frequently.

Most recently, the US government announced that it is to assess the value of Dendreon’s immunotherapy, Provenge®, as a treatment for prostate cancer to determine if its coverage is “reasonable and necessary”.²⁵ Provenge was recently approved by the FDA for the treatment of patients with asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer (CRPC), having previously been rejected despite a unanimous recommendation by the expert advisory panel. The approval was based on a trial of 512 patients, which demonstrated an increase in OS of 4.1 months in the Provenge versus placebo arm of the trial.²⁶ The expected cost of Provenge is \$93,000, equating to about \$23,000 per added month of survival, a cost which compares favorably to other oncology products used in similar settings. The assessment of Provenge by CMS marks a landmark event in US reimbursement history given the coverage implications for a new life-extending cancer treatment and may portend a paradigm shift from EBM to VBM. In the case of Provenge, it could be argued that a VBM appraisal by CMS might trump an EBM appraisal by the FDA. Perhaps recognizing the perception of competing interests, a memorandum of understanding has been issued jointly by the FDA and the CMS to explore a parallel review process.²⁷

Comparative Effectiveness

Costs and cost effectiveness of innovative, life-extending oncology drugs can appear high but the comparative cost effectiveness of these treatments with other medical interventions needs to be considered. As shown in Table 2, the cost per QALY gained from a switch to an aromatase inhibitor to achieve better disease control (at around \$23,000), and even the costs of using erlotinib to manage pancreatic cancer, appear modest when compared with other medical interventions.²⁸

In a year when \$1.1 billion has been trunched by the American Recovery and Reinvestment Act for comparative-effectiveness research, there will be greater focus on comparative cost effectiveness and biopharma will need to step up and be armed to make arguments supporting the relative cost effectiveness of their offer. Focused research explicitly investigating “comparative effectiveness” has been incorrectly perceived as a central strategy to ration and thereby control healthcare costs.²⁹ In reality, “comparative effectiveness” is not intended to ration, but rather to discriminate value. A good example of this is an extensive analysis of cost and patient value in colon cancer treatment. In this analysis, there was no definitive correlation between overall spending and patient value in terms of clinical outcomes. Landrum et al found in areas where healthcare spending was above the

Comparative effectiveness is not intended to ration, but rather to discriminate value.

“average” for colorectal cancer, there were two counterbalancing practices.³⁰ In some practices that exhibited higher than average spending, there was a greater use of inappropriate chemotherapy, which had little positive clinical benefit while increasing adverse effects, a net adverse outcome for patients. Counterbalancing this, in other practices that exhibited higher than average spending, there was also a correlation for the use of appropriate but expensive adjuvant chemotherapy, which had an overall positive effect on clinical outcomes. Taken in isolation, an inappropriate conclusion from these data would be that increased area-level medical spending is not correlated with improved patient outcomes or quality, thereby supporting the case for spending reductions in high-spending regions. This inappropriate conclusion would be reached if the analysis was restricted to simple EBM. However, VBM would indicate that some practices that exhibited higher than average spending performed services that resulted in real value to patients and other services that resulted in negative value to patients. VBM would provide the granularity to discriminate between these services to assess patient value to eliminate the “negative-value” services while encouraging the “positive-value” services. The ultimate result of this is having better clinical outcomes at a lower overall cost to patients with colorectal cancer.

Table 2. Cost per quality-adjusted life-year gained from selected clinical strategies²⁸**

Switch to an aromatase inhibitor for early-stage breast cancer vs. continued tamoxifen	\$22,900
Implant a cardioverter-defibrillator (primary prevention) vs. continued medical management	\$37,400 to \$77,200
Perform fusion surgery for degenerative spondylolisthesis with spinal stenosis vs. conservative management	\$120,000
Prescribe trastuzumab for metastatic breast cancer vs. standard chemotherapy	\$150,000
Prescribe erlotinib for advanced pancreatic cancer vs. gemcitabine alone	\$370,000 to \$500,000
Perform helical computed tomographic screening for lung cancer in 60-year-old former heavy smokers vs. no screening	\$2,300,000

*Values are given in 2008 U.S. dollars, with adjustment for inflation according to the Consumer Price Index. Numbers are the ratios of the added cost per person to the gain in QALYs per person.

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Modeling Value and Cost Effectiveness

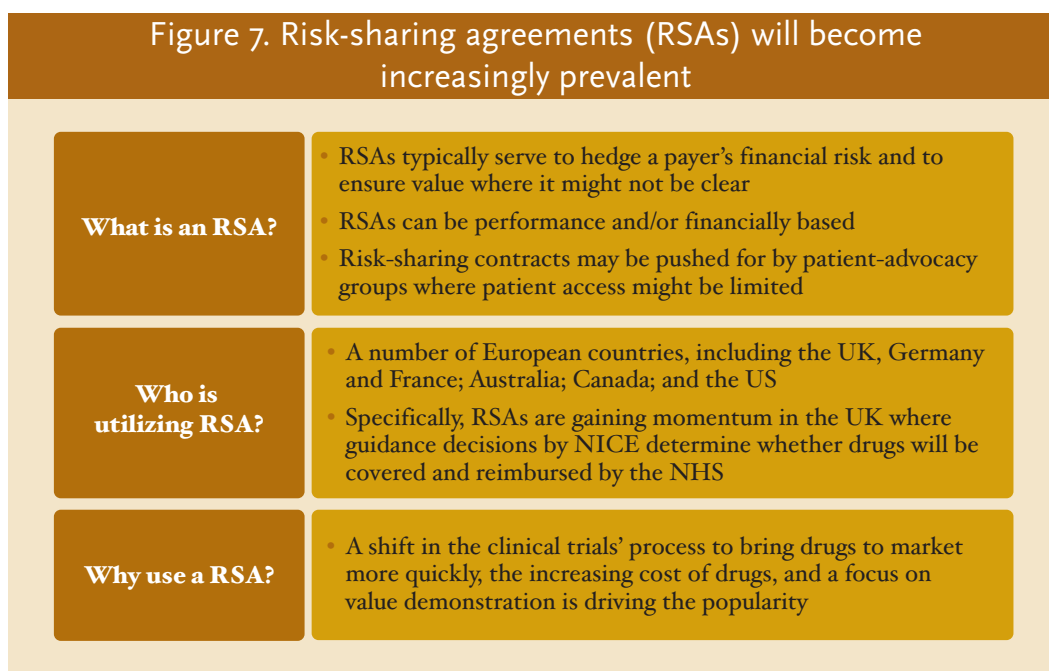
NICE is often held up as an agency which has broken much ground in the arena of modeling the value and cost effectiveness of new therapeutics. While an exhaustive review of its processes and procedures is outside the scope of this paper, NICE effectively applies a formula during its HTA-appraisal process, based on incremental costs per QALY gained, and has a threshold above which drugs are deemed too costly for the UK National Health Service (NHS) to reimburse. In oncology, application of the QALY to assess newly licensed treatments has been controversial.¹ This process has seen EBM-supported and licensed products – many of which offer new and improved outcomes for patients – struggle for reimbursement and market share.

In oncology, application of the QALY to assess newly licensed treatments has been controversial.

Rejections Based on Short Overall Survival Benefit

In August 2008, NICE delivered the preliminary assessment of a multi-technology appraisal of treatments for metastatic renal cell carcinoma (RCC) – declaring that Sutent® (sunitinib), Avastin® (bevacizumab) (+ interferon), Nexavar® (sorafenib), and Torisel® (temsirolimus) were not cost-effective options. NICE acknowledged that the treatments were clinically effective and that there was a lack of therapeutic alternatives in RCC, a disease of poor prognosis, but did not concede that therapies offered a cost-effective option over no intervention.

Months of debate and discussion ensued, during which time patient access to licensed clinically proven treatment was severely limited. Eventually in January 2009, NICE reversed its decision on Sutent cost effectiveness after Pfizer submitted additional survival data and agreed to cover the costs for the first 6-week cycle of treatment in a cost-sharing scheme (Figure 7). The Velcade® (bortezomib) risk-sharing contract between Janssen and the NHS may have served as a precedent case to this deal and future deals designed to “warranty” the effectiveness of cancer drugs.



Other agents were not successful, notably Nexavar® (sorafenib), the first targeted agent to show efficacy in RCC was hampered in its quest for funding by a phase III study design that compared Nexavar with placebo (rather than interferon, the sometime standard of care) and by early study termination and patient cross-over from placebo to active treatment which confounded evaluation of OS data. The OS at the final analysis of the intention-to-treat population was reported as 17.8 months vs. 15.2 months for sorafenib and placebo, respectively (HR 0.88, 95% CI 0.74–1.04, p=0.146).³¹

Another NICE HTA rejection exemplifies the problems faced in proving cost effectiveness of novel therapies in rare diseases, with poor prognosis and no current management option beyond palliation. Nexavar has been shown to extend survival in hepatocellular cancer (HCC) by more than 2.8 months with a predicted OS benefit of 6.1 months.³² NICE calculated an incremental cost-effectiveness ratio of £64,800 per QALY and advised that treatment should therefore not be funded by the NHS. There are an estimated 700 patients with HCC suitable for Nexavar treatment. This low number of patients was not a factor in assessing the cost-impact of funding Nexavar treatment in the UK, and even following a decision to reconsider use of the QALY threshold for end-of-life therapies, Nexavar remains licensed in the UK for HCC, supported by the Hepatobiliary UK Group (HUG) of clinical experts as a new standard-of-care therapy yet unapproved by NICE for reimbursement.

The NICE model and the drive towards HTAs and related-value assessments is already coloring VBM in Europe and in the US.

Health Technology Assessments – A Comparison With Regulatory Appraisals

Application of HTAs, as performed by bodies such as NICE, occurs after regulatory approval and licensure of new therapeutic agents. As such, the success of a new drug is no longer judged exclusively at regulatory approval.

The impact of an HTA approach to drug evaluation on future regulatory processes is unknown. The FDA and European Medicines Agency (EMA) will continue to use EBM and in oncology the endpoint of extended OS remains a key therapeutic goal. As VBM begins to permeate and shape clinical decision making, other factors such as QoL, which are already computed with HTAs, might begin to influence regulatory approvals.

What are the Lessons for Oncology Drug Development?

The rising growth in HTAs and their current role in many countries in assessing treatment value using QALY-based methods serve as an important lesson not only for licensed drugs seeking funding but also for drug development in oncology.

The emergence of the HTA highlights the importance of including outcome data within trial designs and underscores the importance of capturing data that can be used to support value propositions for products in clinical development.

Health-related Quality of Life

Clear differentiation of new oncology products requires a greater focus on QoL and patient perspectives on therapy. These factors need to be considered in the clinical trial process in preparation for regulatory submission.

Health-related QoL outcomes are designed to consider both the benefits of therapy and the impact of treatment side effects and toxicity on patient QoL.

Capture data that can be used to support value propositions for products in clinical development.

Clear differentiation of new oncology products requires a greater focus on QoL and patient perspectives on therapy.

Historically, QoL endpoints would be demoted to secondary or tertiary status in trial design or even estimated post hoc (i.e. quality-adjusted time without symptoms or without toxicity [QTwiST]). Clinical trials of future oncology products need to consider OS and other clinical endpoints deemed meaningful for a given cancer (PFS – progression free survival; TTP – time to progression; ORR – overall response rate), safety endpoints, and measures of generic and disease-specific QoL. These outcome “channels” should be prioritized based on indication characteristics such as:

- > *tumor type (stage/grade)*
- > *epidemiology*
- > *severity of disease (morbidity)*
- > *age of onset*
- > *unmet medical need*

Clinical trials of future oncology products need to consider overall survival and other clinical endpoints deemed meaningful for a given cancer, safety endpoints, and measures of generic and disease-specific quality of life.

Target Patient Subgroups

The value equation for an oncology product may also be changed by assessing the impact of therapy in particular patient subgroups.¹ Such evidence has already been persuasive to regulators and has appeal to payers keen to channel therapies and their costs towards the patients most likely to benefit from therapy. However, while retrospective analysis to exclude non-responding subgroups from studies with positive outcomes might offer a route to drug approval, positive results from post-hoc analysis of population subgroups from negative or non-significant studies are unlikely to be the basis for approvals. Identifying and addressing heretofore under-served patient populations may be a beneficial by-product of this targeted patient-group strategy.

Value from the Stakeholders' Perspective

As mentioned, the definition of value differs between various stakeholder groups. An understanding of each groups' perception of value is required for successful launch of a new agent.

Patients and Public

New treatments for cancer allow many patients to be treated as outpatients, where they assume greater responsibility for their own treatment. Many patients today and in the future will bear a substantial portion of the costs of treatment directly. As a group, patients with cancer are keen to understand their options and play a role in making value decisions over treatment choice. As patients assume more responsibility for administration and payment for cancer drugs, it will be imperative to assess the drivers and obstacles to medication adherence.

Both patients and the public need to understand more about how drugs are developed in oncology and more about the relative risks and benefits of treatments and their options in management. These risks and benefits need to be appraised from acute, chronic, and long-term perspectives and relative to other healthcare interventions. This need for improved understanding is important as patients are given more responsibility and say in their therapy. They need to appreciate the clinical rationale and the value of treatment.

Drug manufacturers need to consider a future where product dossiers aimed at communicating product value – in the broadest sense – are tailored not just for clinicians, formularies, regulators, and policy makers but also for patients and patient-support groups.

Clinician and Prescriber

Clinicians are also moving cautiously towards value-based practice,⁷ understanding that they have a role in ensuring value in oncology. While many clinicians will remain most comfortable dealing with hard clinical endpoints and EBM, they have a role in helping patients understand and assess treatment options and their value.²

Healthcare Providers

Healthcare providers are likely to appreciate and recognize the added value that VBM brings to EBM. Charged with providing a health service, complex beyond simple provision and underwriting of drug costs, healthcare providers are likely to embrace VBM as a means of evaluating the place of new oncology treatments within both cancer care and the broader remit of medical care provision.

Regulators

As discussed, the move towards VBM may in time affect regulatory decision making, with regulation and HTA-type processes coming closer together as part of drug approvals. Within the evolving regulatory environment, patient-reported outcomes are increasingly being incorporated into product claims and revised guidance for the industry is now available from the FDA.³³ In future, there will be an increasing need for standardization of the evidence required to support drug approval. In recognition of this, a memorandum of understanding has been issued jointly by the FDA and the CMS to explore the potential for a parallel review process.²⁷

Payer

As described throughout this paper, the status of oncology treatments has changed from a position where the price and value of therapies was rarely questioned, to a situation of broader debate around the health, pharmacoeconomic, and societal value of the innovation.

The innovator (the biopharma manufacturer) and developer of new products and the payer both have a keen interest in the price of products. Payers increasingly will only pay premium prices for products deemed to be truly innovative. Now and increasingly in the future, manufactures will have to demonstrate to payers the value of their innovation in particular disease settings and market niches – using clinical rationale and cost effectiveness arguments.

Governments

Governments already acknowledge the need for VBM, as witnessed by a global move towards mechanisms to assess the health economic impact and comparable cost effectiveness of new innovations. As previously highlighted, cancer is a political disease, a major killer and a global health target that governments cannot ignore. Healthcare planning that includes VBM assessment of new cancer treatment modalities is of prime interest to governments of all political persuasions.

Communicating Value Propositions

In a future colored by value-based practice, evidence dossiers in support of products in clinical development will need to include value proposition materials tailored to suit each of the stakeholders whose views affect the uptake and commercial success of a product. Value dossiers describing the methods and results of outcomes research will be as important as clinical evidence dossiers, adding to the case supporting drug efficacy, safety, and value.¹

Evidence dossiers in support of products in clinical development will need to include value proposition materials tailored to suit each of the stakeholders whose views affect the uptake and commercial success of a product.

Summary and Conclusions

Value-based medicine is not about cutting costs. It is about improving efficacy and cost effectiveness of therapy. Value-based practices are increasingly important in oncology. Clinicians, patients, payers, and policy makers welcome innovation in oncology but all are under pressure to choose treatments that offer not only the best clinical outcome and risk:benefit ratio but also the best cost–benefit for their investment in treatment. The trend to embrace value assessments as part of drug review and appraisal will not be limited to drugs that have gained a license on the basis of traditional trial-based research and EBM. The trend has and will extend to affect the way that drugs are studied and developed. Successful drugs in the future oncology marketplace will be those that account for and prove clinical efficacy and safety, while presenting data that support a value proposition for their real-world role in particular indications and patient groups.

The clinical value of oncologic therapy will always be determined at the physician–patient level of decision making. The public health value of cancer therapy is a new concept and requires appraisal at the population level of decision making. The inputs and outputs of such decisions are interlinked and yet distinct. Biopharma must recognize and investigate this multi-level decision-making process to determine the value thresholds and evidence requirement for their drugs in development.

In short, the future of successful drug development in oncology will require closer and earlier convergence of clinical and commercial planning, to ensure all new agents have a mature and plausible value proposition as a key element of their overall profile.

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