Defining and Measuring the Affordability of New Medicines

Antonanzas, Fernando; Terkola, Robert; Overton, Paul M.; Shalet, Natalie; Postma, Maarten

Published in:
Pharmacoeconomics

DOI:
10.1007/s40273-017-0514-4

Publication date:
2017

PharmacoEconomics (2017) 35:777–791
DOI 10.1007/s40273-017-0514-4

SYSTEMATIC REVIEW

Defining and Measuring the Affordability of New Medicines: A Systematic Review

Fernando Antoñanzas[1] · Robert Terkola[2,3] · Paul M. Overton[4] · Natalie Shalet[5] · Maarten Postma[3,6,7]

Published online: 5 May 2017

Abstract

Background In many healthcare systems, affordability concerns can lead to restrictions on the use of expensive efficacious therapies. However, there does not appear to be any consensus as to the terminology used to describe affordability, or the thresholds used to determine whether new drugs are affordable.

Objectives The aim of this systematic review was to investigate how affordability is defined and measured in healthcare.

Methods MEDLINE, EMBASE and EconLit databases (2005–July 2016) were searched using terms covering affordability and budget impact, combined with definitions, thresholds and restrictions, to identify articles describing a definition of affordability with respect to new medicines. Additional definitions were identified through citation searching, and through manual searches of European health technology assessment body websites.

Results In total, 27 definitions were included in the review. Of these, five definitions described affordability in terms of the value of a product; seven considered affordability within the context of healthcare system budgets; and 15 addressed whether products are affordable in a given country based on economic factors. However, there was little in the literature to indicate that the price of medicines is considered alongside both their value to individual patients and their budget impact at a population level.

Conclusions Current methods of assessing affordability in healthcare may be limited by their focus on budget impact. A more effective approach may involve a broader perspective than is currently described in the literature, to consider the long-term benefits of a therapy and cost savings elsewhere in the healthcare system, as well as cooperation between healthcare payers and the pharmaceutical industry to develop financing models that support sustainability as well as innovation.

Electronic supplementary material The online version of this article (doi:10.1007/s40273-017-0514-4) contains supplementary material, which is available to authorized users.

✉ Fernando Antoñanzas
fernando.antonanzas@unirioja.es

[1] Department of Economics, University of La Rioja, C/La Ciguena 60, 26004 Logrono, Spain

[2] College of Pharmacy, University of Florida, Gainesville, FL, USA

[3] Unit of PharmacoTherapy, Epidemiology and Economics (PTE2), Department of Pharmacy, University of Groningen, Groningen, The Netherlands

[4] Beacon Medical Communications, Brighton, UK

[5] NAS Healthcare Solutions, Surbiton, UK

[6] University Medical Center Groningen, Institute of Science in Healthy Aging & healthcaRE (SHARE), University of Groningen, Groningen, The Netherlands

[7] Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Key Points

Although affordability concerns can lead to restrictions on the use of expensive efficacious therapies, there is little consensus as to how affordability should be defined or measured.

This systematic review has identified a number of different definitions of affordability in the literature, but little to suggest that the price of medicines is assessed together with their value to individual patients and their impact on healthcare system budgets.

In contrast to current approaches, managing the affordability of new medicines may require consideration of the whole 'drug life', including downstream benefits to patients and potential savings in healthcare resource use, in addition to prices.

Cooperation between payers and the pharmaceutical industry is needed to ensure that innovative medicines that benefit patients can be developed and financed while maintaining the sustainability of healthcare systems.

Future payment models may include financial arrangements that distribute the cost of a new drug over a longer period, as well as patient-access schemes, price–volume agreements, risk-sharing arrangements and concerted public-private initiatives.

1 Introduction

In recent years, the development of new medicines has transformed the management of a number of diseases. However, the substantial improvements in clinical outcomes generated by the use of new targeted agents in the fields of oncology and infectious diseases, among others, are often associated with very high costs [1, 2]. Consequently, concerns exist as to the sustainability of drug prices, and for many healthcare systems affordability is a barrier to granting access to high-value pharmaceutical therapies [3], particularly given the lack in many countries of a clear definition of the value of healthcare products [4].

Despite financial pressures, in most European countries, the main factors in reimbursement decision making by health technology assessment bodies are therapeutic improvement compared with existing treatments and cost effectiveness, typically expressed as cost per quality-adjusted life year (QALY) gained [5]. Budget impact analysis is typically conducted alongside cost-effectiveness analysis, and is often used in regional and hospital decision making [6], but may not always be taken into account at a national level. For example, the National Institute for Health and Care Excellence (NICE) in England estimates the budget impact of new technologies in both the main Technology Appraisal Programme and the Highly Specialised Technology Programme (which assesses drugs for very rare conditions), but only the latter incorporates the analysis into the decision-making process [7]. It is possible, therefore, for highly efficacious therapies to be cost effective according to established cost per QALY thresholds but, if the eligible population is large, to be unaffordable within the healthcare system budget.

Where the cost of new treatments is a concern, a number of mechanisms have been used to overcome affordability issues, including discounts, price–volume caps, performance-based risk-sharing schemes and managed entry agreements [8]. However, the last two of these have little effect on the sustainability of healthcare system finances [9]. In addition, in some countries, special drug funds have been established to ring-fence funding for certain expensive therapies; this approach has been controversial, with concern over a potential detrimental effect on care for patients with other diseases [10, 11], and in England, the Cancer Drugs Fund has recently been reformed and now operates as a managed access fund [12].

Overall, from an academic perspective, we perceive substantial variation in the approaches taken to managing affordability issues among countries [5], and there does not appear to be any consensus on the terminology used to describe affordability, or the thresholds used to determine whether new drugs are affordable. It is therefore important to investigate how healthcare systems define and manage affordability, to explore the potential for industry and healthcare authorities to work better together, for example, by developing innovative commercial models, which may include patient-access schemes, tax benefits and concerted public-private initiatives.

The aim of this systematic review was to investigate how affordability is defined and measured in healthcare. Although affordability of health insurance and out-of-pocket payments are important topics, given the high costs associated with some recent therapies, for this review we have focussed on the affordability of new medicines.

2 Methods

2.1 Searches

A series of systematic literature searches was conducted on 19 July, 2016. Full terms used in the searches are listed in

Supplementary Tables 1 and 2. MEDLINE, EMBASE and EMBASE alert databases were searched using Dialog™ (ProQuest, Ann Arbor, MI, USA). The main search strategy included multiple free-text terms covering affordability or budget impact, combined with terms referring to definitions, thresholds and restrictions, as well as affordability terms in the Medical Subject Heading and Emtree thesaurus indices. Search results from each database were limited to studies published from 1 January, 2005. No restriction on publication language or article type was applied. The EconLit database was searched using the American Economics Association interface (https://www.aeaweb.org/econlit/) for articles describing affordability or budget impact. EconLit search results were restricted to journal articles published in English from 1 January, 2005.

2.2 Screening

Search hits from the three databases were combined, and duplicates were removed using EndNote software (Thomson Reuters, New York, NY, USA). Two levels of screening were conducted by a single reviewer. At the first level, remaining duplicate articles and conference abstracts were removed and the titles and abstracts of articles identified were screened for eligibility. Articles were included if they described a definition of affordability with respect to new medicines, or referred to a relevant definition published elsewhere. Articles presenting definitions of affordability of health insurance, or describing the affordability of medicines from the perspective of individual patients were excluded (e.g. opinion surveys; studies using individual incomes as part of a measure of overall affordability were not excluded). Full-text versions of articles that passed title/abstract screening were retrieved for further review. At the full-text review stage, studies not meeting the inclusion criteria were excluded (Supplementary Table 3).

2.3 Data Extraction and Citation Searching

Definitions of affordability were extracted from all included references. Where studies referred to a relevant definition of affordability published elsewhere, citations were followed and the cited references were screened for inclusion in the review; no restriction on publication date or article type was applied to references identified through citation searching.

2.4 Additional Web Searches

Manual searches of European health technology assessment body websites, as well as the websites of National Health Service England, the International Society for PharmacoEconomics and Outcomes Research (ISPOR) and the American Society of Clinical Oncology, were conducted to identify stated policies or methods for assessing affordability. For health technology assessment body websites, individual product assessments were not searched. Similarly, for professional societies, conference proceedings were excluded. A full list of websites searched and the search terms used is presented in Supplementary Table 4.

2.5 Conceptual Model

There is no established conceptual framework describing the terminology and application of the concept of 'affordability'. For the purposes of this review, we propose a scheme that allows the interactions of several factors related to the concept. As a starting point, we consider the definitions of the *Oxford English Dictionary*: "ability to be afforded; inexpensiveness; the cost or price of something" [13]. Of these, "ability to be afforded" and "inexpensiveness" involve some form of comparison or confrontation between different aspects. Applying these definitions to the public healthcare system, we interpret affordability as incorporating the idea of permission to do something; i.e. the ability to, in this case, spend public money on drugs depends on the budget approved by parliament. The most straight-forward idea of affordability, therefore, is the question of whether the cost of a new medicine (incorporating the price of the drug together with the patient population size and the need for additional resources such as tests, devices and healthcare personnel to put the new treatment into practice) can fit within the healthcare budget of a given jurisdiction.

When considering the concept of value, for example, as recently analysed by Antoñanzas et al. [4], further aspects of affordability arise. New drugs can be assumed to provide value in terms of efficacy and safety, as guaranteed by the registration and market authorisation processes. However, a drug may have further important attributes, which may make major or minor changes to its overall value. For example, in addition to clinical efficacy, a drug may generate highly significant improvements to health-related quality of life, show a high degree of cost effectiveness or provide further benefits that are hard to quantify within an assessment of therapeutic benefit. If such further values are conceived to be highly relevant, a drug classed as unaffordable based on costs and budget impact may be reconsidered, and potentially the necessary additional resources will be identified. Notably, such additional resources may result from displacement of other less effective treatments. As a consequence, an expensive drug that stretches the budget but is valued highly might still be considered affordable. As an example, we might consider sofosbuvir for hepatitis C, which many countries were able to find

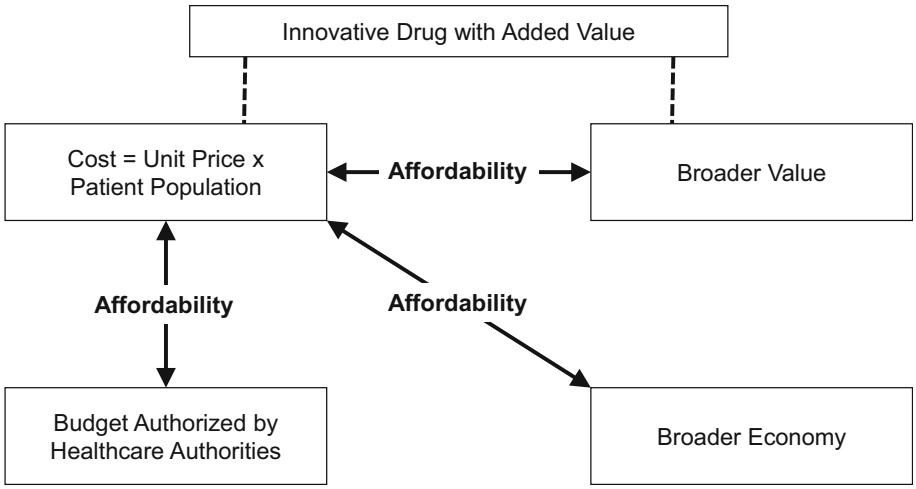

Fig. 1 Conceptual model classifying types of affordability (the *double-sided arrows*) of an innovative new drug with added value (efficacy and safety), where various segments confront one another. Segments are: cost, broader value of the drug (see text for explanation), healthcare budget and the broader economy

resources to finance despite clearly exceeding the available budget by doing so. Notably, the extent to which involvement of the broader value of a drug in the affordability discussion is accepted differs among countries.

Along these lines, to structure our results, we have developed a conceptual model, with affordability considered as a holistic concept of confronting segments within the healthcare system and the broader economy (Fig. 1). Initially, it is noted that a new drug with added value (efficacy and safety) is inherently linked to costs (volume times unit price) and to a set of broader values, such as health-related quality of life, productivity gains, displacement of other drugs, potential reduction in waste and cost effectiveness. The double-sided arrows in the graph cover the three types of affordability that we can differentiate upfront: (1) costs confronting the authorised budget for healthcare; (2) costs confronting broader value, often summarised in the incremental cost-effectiveness ratio (ICER); and (3) costs confronting the broader economy (potentially in addition to one or both of the former categories). These three types of affordability issues are not mutually exclusive, and for many new products more than one will be relevant; here, however, we use this framework as a means of separating the various approaches expected in the literature.

3 Results

3.1 Search Results

In total, 1755 articles were retrieved in the database searches. After removing duplicates from the records, the titles and abstracts of 1709 unique articles were screened. In total, 64 articles were identified as being potentially relevant to the review objectives, and full-text versions were obtained where possible (of the 29 potentially relevant studies indexed as conference abstracts, posters or presentations were obtained for 15; the remainder were assessed as abstracts only). Of the 64 potentially relevant articles, 45 were excluded (including 23 of the 29 conference abstracts; reasons for the exclusion of articles at the full-text review stage are presented in Supplementary Table 3). Citation searching identified a further six potentially relevant references, of which one was excluded following a full-text review. In total, 24 references passed the screening stage and were included in the review. Additional web searches identified a further three references. The flow of studies through the screening process is shown in Fig. 2.

3.2 Published Definitions of Affordability

In total, 27 published definitions of affordability were included in the review (Table 1) [14–40]. The identified definitions corresponded to the elements of our conceptual model (Fig. 1) as follows: five definitions described affordability in terms of the value of a product [14–18]; seven considered affordability within the context of healthcare system budgets [19–25]; and 15 addressed whether products are affordable in a given country based on economic factors [26–40].

3.2.1 Affordability: Definitions from a Product Value Perspective

In total, four studies described the affordability of new drugs in terms of cost-effectiveness thresholds [14–17]. Of these, two referred to a World Health Organization (WHO) criterion for economic value, with ICERs of less than three times the gross domestic product (GDP) per QALY described as affordable [14, 15]. In addition, in an

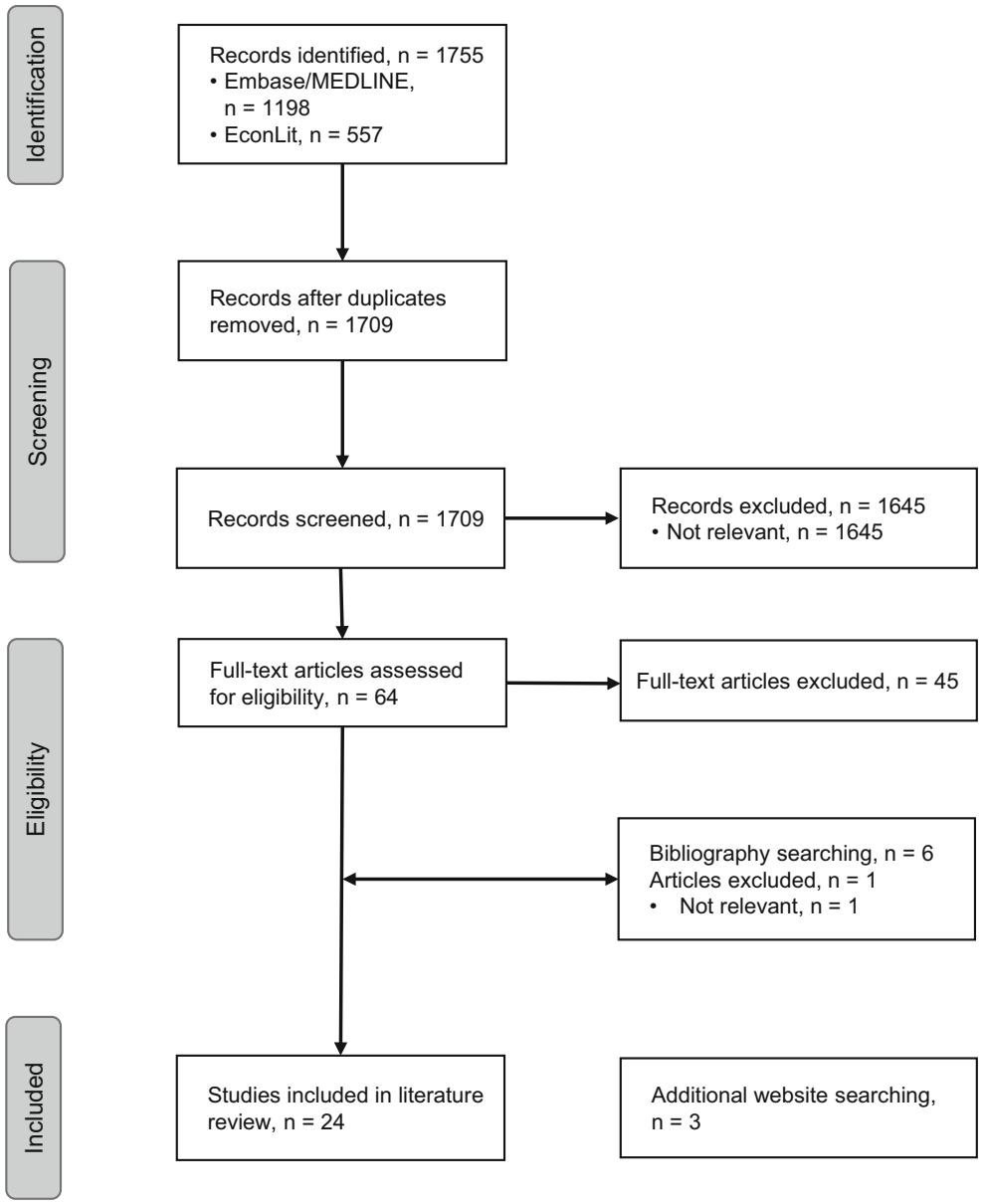

Fig. 2 PRISMA diagram. PRISMA, Preferred reporting items for systematic reviews and meta-analyses diagram

assessment of the cost effectiveness of oseltamivir for influenza treatment, a willingness-to-pay threshold of ¥6,000,000 per QALY was described as affordable in Japan [16]. Similarly, an Australian study modelling the cost effectiveness of cognitive-behavioural therapy and antidepressant drugs for major depression used Australian $50,000 per QALY as an affordable threshold for the healthcare system [17]. None of these studies addressed the potential impact of these thresholds in the case of products with a very large population of eligible patients. In addition to cost per QALY, in England, NICE considers broader aspects of the value of new products, and suggests that the appropriate maximum acceptable ICER to be considered should be that of the opportunity cost of programmes displaced by new, more costly technologies [18].

3.2.2 Affordability: Definitions from a Healthcare System Budget Perspective

Comparative affordability of drugs in different countries was addressed by two references [19, 20], both of which used the acquisition cost of the drug divided by healthcare expenditure per capita to assess relative affordability in each country. An evaluation of biologic treatments for rheumatoid arthritis in central and Eastern Europe found that countries with lower levels of healthcare expenditure

Table 1 Definitions of affordability identified in the published literature

Study, year	Study description	Definition of affordability
Definitions from a product value perspective		
Dranitsaris et al. 2011 [14]	Estimate affordable cost for new oncology therapy in India (hypothetical example)	Approach used to determine affordable cost for new medicines involved establishing thresholds for economic value based on multiples of per capita GDP: ≤1× per capita GDP per QALY would be very cost effective; 1–3× per capita GDP per QALY would be cost effective; >3× per capita GDP would be cost ineffective [Source: WHO]
Mauskopf 2012 (poster) [15]	Review of the principles of prevalence-based economic evaluation	Affordability was based on cost/QALY thresholds set at a percentage of per capita GDP [Source: WHO]
Nagase et al. 2009 [16]	Assessment of the cost effectiveness of oseltamivir for influenza treatment in Japan	"Willingness-to-pay level of ¥6,000,000 ($50,000) … is commonly accepted as an affordable threshold"
Vos et al. 2005 [17]	Assessment of the cost effectiveness of interventions for major depression in Australia	"[ICER was] … well below the threshold of $A50 000 we use in the ACE-MH studies as 'affordable'" [Source: Assessing Cost-effectiveness—Mental Health project]
National Institute of Health and Care Excellence, England [18]		Given the fixed budget of the NHS, the appropriate maximum acceptable ICER to be considered is that of the opportunity cost of programmes displaced by new, more costly technologies
Definitions from a healthcare system budget perspective		
Orlewska et al. 2011 [19]	Cross-sectional study of the availability of biologic therapies for rheumatoid arthritis in central and Eastern Europe	Affordability was compared among countries using an affordability index, calculated comparing the relative healthcare expenditures per capita (as an index) to the relative price index, using Poland as the basis. A higher index indicates greater difficulty affording goods and services
Zueger and Becker, 2013 (conference abstract) [20]	Comparison of the affordability of new therapies for HIV/AIDS and oncology treatments in Brazil to USA and OECD	Two affordability measures were used to compare drug costs in Brazil with other OECD countries: (1) Cost as a proportion of GDP per capita (2) Cost as a proportion of healthcare spending per capita
Jørgensen and Kefalas, 2015 [21]	Review of European (EU5) reimbursement processes for advanced therapy medicinal products (cell and gene therapies)	No specific definition reported, but authors describe budget impact thresholds as follows: In France, population sizes drive the conditions of the price/volume agreements with the pricing authority (CEPS). Furthermore, for therapies that aspire to have ASMR I–III, only therapies that have an expected annual revenue of >€20 million are required to undergo cost-effectiveness analysis by CEESP In Germany, therapies with orphan indications (and expected annual revenues <€50 million) are assumed inherently to have added benefit, are exempt from the early benefit assessment, and can therefore enter straight into price negotiations. Furthermore, therapies in any indication, with expected annual revenues <€1 million avoid both the early benefit assessment and national price negotiations, and can be priced freely [Source: G-BA, Legifrance]

Table 1 continued

Study, year	Study description	Definition of affordability
Haute Autorité de Santé, France [22]		…cost-effectiveness analyses should also be submitted … for drugs and medical devices deemed to be innovative and likely to have a significant impact on the statutory national health insurance expenditures … A significant impact on the health expenditure has been defined as: An expected € 20 million (VAT included) or greater annual sales revenue during the second full year of marketing across all indications; or an impact on the organisation of care, professional practices or patient care conditions
Mauskopf et al. 2013 [23]	Review of NICE appraisal reports to investigate link between budget impact and decisions	Empirically: mean (maximum) adjusted potential budget impact for drugs that were recommended without restrictions was £20.3 million (£46.0 million) compared with £49.8 million (£108.2 million) for those recommended with restrictions and £71.1 million (£135.8 million) for those not recommended [Source: NICE]
Agenzia Italiana del Farmaco, Italy [24]		The extent to which medicines and further healthcare products are available to the people who need them at a price they/their health system can pay (adapted from [41])
Souliotis et al. 2016 [25]	Development of questionnaire and conceptual framework for mapping access to health care across EU-28 countries	Affordability: "a system for financing health services so people do not suffer financial hardship when using them"
Definitions related to the broader economy		
Institute for Clinical and Economic Review 2015 (presentation) [26]	Description of the Institute for Clinical and Economic Review framework for assessing value	Theoretical basis of the potential budget impact threshold: The amount of net cost increase per individual new intervention that would contribute to growth in overall healthcare spending greater than the anticipated growth in national GDP +1% Based on state (Massachusetts/Maryland) and ACA legislation A potential budget impact for an individual drug estimated to contribute significantly to cost growth above this threshold serves as an "alarm bell" for greater scrutiny and for efforts to maximise health system value (budget impact threshold set at double average cost growth per new molecular entity) [Source: Institute for Clinical and Economic Review] *The authors note that this definition is intended to be used in combination with data on long-term cost effectiveness*
Bozkaya et al. 2016 (presentation) [27]	Comparison of ASCO and Institute for Clinical and Economic Review frameworks for assessing value in oncology in USA (hypothetical example)	Refers to the Institute for Clinical and Economic Review's calculated budget impact threshold of US$904 million [Source: Institute for Clinical and Economic Review]
Schlander and Schwarz 2005 [28]	Macroeconomic analysis to assess the affordability of healthcare spending in Germany	The border of affordability is the point at which increasing healthcare spending will reduce spending in non-healthcare areas. The limit of affordability would be reached when the annual increase of health spending would fully absorb the growth of GDP available for consumption

Table 1 continued

Study, year	Study description	Definition of affordability
Cameron et al. 2009 [29]	Assessment of the prices, availability and affordability of medicines in 36 developing and middle-income countries, using WHO/HAI data	Affordability is estimated using the salary of the lowest paid unskilled government worker to establish the number of days' wages needed to purchase courses of treatment for common conditions [Source: WHO/HAI]
Cameron et al. 2012 [30]	Assessment of the prices, costs and affordability of new medicines for anti-epileptic drugs in 46 countries	Treatment affordability was estimated as the number of days' wages that the lowest paid government worker would need to purchase a month's supply of anti-epileptic drugs [Source: WHO/HAI]
Helfer et al. 2012 [33]	Cross-sectional survey to assess affordability of drugs for chronic diseases in six cities in Rio Grande do Sul, Brazil	Affordability was estimated as the number of salary days required for a worker receiving the national minimum wage to buy, in a private pharmacy, the amount of medication required for 1 month of treatment [Source: WHO/HAI]
Iyengar et al. 2016 [35]	Comparative study of prices, costs and affordability of new medicines for hepatitis C in 30 countries	[Affordability is calculated as] … the duration of time that an individual would need to work (earning the average wage of the general population) to obtain sufficient income to pay for a full course of treatment fully out of pocket
Jingi et al. 2014 [31]	Cross-sectional survey of the affordability of drugs for CVD in Western Cameroon	Affordability was estimated using median medicine and the salary of the lowest paid unskilled government worker, and calculating the number of days' wages required to pay for investigation tests and to purchase a 1-month course of treatment. Treatments costing 1 day's wage or less (for a 30-day supply of medicine) were considered affordable [Source: WHO/HAI]
Lemus and Rivas 2013 (conference abstract) [34]	Cross-sectional survey of the affordability of anti-hypertensive medicines in Mexico	The affordability of treatments was calculated by comparing the total cost of medicines with the daily official minimum wage, to calculate the number of days' wages required to pay for 1 month of therapy
Ngorsuraches and Chaiyakanm 2015 [32]	Cross-sectional survey of the affordability of single-source drugs in Thailand	Three affordability measurements were calculated: The catastrophic approach was based on the ratio between drug cost and income The impoverishment approach focussed on overall income left after purchasing drugs In the WHO/HAI method, one day's wages for the lowest paid unskilled government worker was considered the affordability threshold for a month's supply of medicine [Source: WHO/HAI]
Niëns et al. 2012 (WHO bulletin) [36]	Modelling study investigating approaches for measurement of the affordability of patient payments for healthcare (India and Indonesia used as examples)	Three definitions described: Impoverishment: the proportion of the population that, after spending on a good/service, drops below a relevant poverty line Catastrophic spending: the proportion of the population that would spend more than X percent of their income to pay for a good/service WHO/HAI method: the number of days' wages the lowest paid unskilled government worker needs to spend to procure a course of treatment of a particular medicine *The authors note that the requirement for thresholds to be established based on normative or arbitrary choices may be problematic*

Table 1 continued

Study, year	Study description	Definition of affordability
Niëns and Brouwer 2013 [37]	Review of methods of measuring the affordability of patient payments for healthcare (Indonesia used as an example)	Three definitions described: Impoverishment: the proportion of the population that, after spending on a good/service, drops below a relevant poverty line Catastrophic spending: the proportion of the population that would spend more than X percent of their income to pay for a good/service WHO/HAI method: the number of days' wages the lowest paid unskilled government worker needs to spend to procure a course of treatment of a particular medicine *The authors note that the requirement for thresholds to be established may be problematic given unequal income distributions*
O'Donnell et al. 2008 [38]	Book: Analyzing Health Equity Using Household Survey Data	"A popular approach has been to define medical spending as 'catastrophic' if it exceeds some fraction of household income or total expenditure in a given period, usually one year"
Mokaya et al. 2015 (conference abstract) [39]	Cross-sectional survey to assess affordability of Parkinson's disease therapies in Kenya	An affordable price was the amount per month that could be set aside by the lowest paid government worker to purchase a month's supply of drugs, after deducting an average amount of basic monthly expenses [Source: WHO/HAI]
Homedes and Ugalde 2015 [40]	Cross-sectional study of affordability of new medicinal products (approved by FDA in 2011–12) in Latin America	Healthcare expenditure >5 or 10% of total household income is considered to be unaffordable. Income was measured as monthly minimum wages; average monthly per capita income; monthly household net-adjusted disposable income; and monthly household financial wealth *The authors note that the use of average incomes may be misleading*

ACA Affordable Care Act, *AIDS* acquired immunodeficiency syndrome, *ASCO* American Society of Clinical Oncology, *ASMR* Amélioration du Service Médical Rendu, *CEESP* Commission Evaluation Économique et de Santé Publique, *CEPS* Comité Économique des Produits de Santé, *CVD* cardiovascular disease, *FDA* Food and Drugs Administration, *G-BA* Gemeinsame Bundesausschuss, *GDP* gross domestic product, *HAI* Health Action International, *HIV* human immunodeficiency virus, *ICER* incremental cost-effectiveness ratio, *NHS* National Health Service, *NICE* National Institute of Health and Care Excellence, *OECD* Organisation for Economic Co-operation and Development, *QALY* quality-adjusted life-year, *VAT* value added tax, *WHO* World Health Organization

did not necessarily have lower prices for biologics; consequently, the variation in affordability among countries was greater than the variation in prices [19]. The second comparative affordability study also assessed drug affordability as a fraction of GDP per capita, and found that using this approach oncology treatments consumed 2–20 times the amount of available funding in Brazil, compared with USA and other Organization for Economic Cooperation and Development countries [20].

A related concept, budget impact thresholds for new products, was described in three sources [21–23]. A review of European reimbursement processes noted that in France, products with an Amélioration du Service Médical Rendu of I–III are only required to undergo a cost-effectiveness analysis if they are expected to have an annual revenue of more than €20 million [21]; this approach is consistent with the definition of affordability identified on the Haute Autorité de Santé website [22]. Similarly, in Germany, products with expected annual revenues of <€1 million (<€50 million for products with orphan indications) are exempt from undergoing early benefit assessment [21].

The Agenzia Italiana del Farmaco also takes an approach based on healthcare system budgets, describing affordability, using a definition adapted from the WHO, as the extent to which medicines and further healthcare products are available to the people who need them at a price they or their healthcare system can pay [24, 41]. A further study defined affordability as a system for financing health services so people do not experience financial hardship when using them [25].

3.2.3 *Affordability: Definitions Related to the Broader Economy*

An approach proposed by the US Institute for Clinical and Economic Review was described in two references [26, 27]. In this theoretical approach, a budget impact threshold for a new medicine is calculated as the amount of net cost increase per individual new intervention that would contribute to growth in overall healthcare spending greater than the anticipated growth in national GDP plus an additional 1% [26]. The calculation involves an estimation of the annual growth in drug spending in healthcare, divided by the number of new approvals per year—products associated with a budget increase of twice the mean cost growth per new product would require a higher level of scrutiny than those with a lower budget impact [26, 27]. For example, US healthcare spending on drugs was calculated to be US$410 billion in 2015–2016. With an estimated GDP growth of 2.75% (plus 1%), the healthcare system can in principle afford US$15.4 billion of additional drug spending. This additional expenditure must cover an average of 34 new approvals, equating to US$452 million per new drug, and setting a budget impact 'alarm bell' of US$904 million [26]. Although this definition of affordability relates to economic factors, the Institute for Clinical and Economic Review Value Assessment Framework links this calculation to comparative clinical effectiveness, cost effectiveness, and the consideration of other benefits and disadvantages; this study therefore spans more than one of the affordability issues shown in Fig. 1.

A similar approach was taken in a German study assessing the affordability of overall healthcare spending through macroeconomic analysis [28]. In this study, the limit of affordability was defined as the point at which increases in healthcare spending would necessitate reductions in spending in non-healthcare areas. In this theoretical framework, the upper limit for annual increases in healthcare spending would equal the growth in GDP. Affordability is therefore dependent on economic growth [28]. However, this study did not address the affordability of individual new therapies.

In total, nine studies described a definition of affordability related to that used by the WHO and Health Action International, in which affordability is measured by the number of days' wages the lowest paid unskilled government worker needs to spend to procure a course of treatment with a particular medicine [29–37]. Although the WHO definition refers to a course of treatment, five studies described the number of days' wages needed to obtain a month's supply of medicine [30–34], with two suggesting that a single day's wage could be considered the affordability threshold [31, 32]. Other variations on this definition used the national minimum wage [33, 34] or the average wage of the general population [35]

A further two definitions were reported in multiple references [32, 36–38]. In the catastrophic spending approach, affordability was measured as the proportion of the population that would spend more than a set percentage of their income to pay for a product [32, 36–38]. Alternatively, in the impoverishment approach, affordability was assessed as the proportion of the population that, after spending on a product, drops below a relevant poverty line [32, 36, 37]. The authors of two of these studies note that the requirement for thresholds to be established based on normative or arbitrary choices may be problematic given unequal income distributions [36, 37]; a further issue with the impoverishment approach is that no consensus exists as to how the poverty line should be determined [37].

In addition, two studies described definitions that were variations on the WHO/Health Action International approach [39, 40]. In a cross-sectional survey of the affordability of Parkinson's disease therapies in Kenya, it was suggested that an affordable price would be the amount per month that could be set aside by the lowest paid government worker to purchase a month's supply of drugs, after deducting an average amount of basic monthly expenses [39]. Similarly, the authors of a cross-sectional study in Latin America suggested that healthcare expenditure costing more than 5 or 10% of household income could be considered unaffordable [40]. In this study, approaches to measuring income included monthly minimum wages, average monthly per capita income and monthly household net adjusted disposable income; however, the authors noted that the use of average incomes may be misleading [40].

4 Discussion

In total, the systematic search found 27 definitions of affordability. Of the identified definitions several, particularly the WHO approach based on individual incomes [29–37], were referred to by multiple sources.

Overall, the definitions identified covered all three aspects of affordability identified in our conceptual model (Fig. 1), with affordability described in terms of the value of a product [14–18], within the context of healthcare system budgets [19–25] and, within a given country, based on economic factors [26–40]. As expected, given the holistic nature of affordability in healthcare, many of the identified studies covered more than one of the possible aspects. Among studies investigating affordability from an economic viewpoint, there was a significant divide between those taking the perspective of the healthcare system (or the economy as a whole) [26–28] and those measuring the

affordability of treatment on the basis of individual patients' incomes [29–40]. In general, this divide appears to reflect the countries studied, with low- and middle-income countries, in which out-of-pocket payment for healthcare is common, more likely to use the individual income approach. Only a few studies were identified that combined aspects of individual income with a healthcare system perspective, by assessing affordability of new therapies in terms of cost as a proportion of GDP [20], or of cost per QALY, with per capita GDP used to set willingness-to-pay thresholds [14, 15]. As has been shown elsewhere, the affordability of healthcare products does not depend solely on available GDP, but is affected by efficiency (e.g. some countries may spend more than others to achieve the same health outcomes) and price (both drug prices and overall purchasing power parity vary among countries) [42].

In general, there was little in the literature to indicate that the price of medicines is considered alongside both their value to individual patients and their budget impact at a population level. Several references referred to explicit or implicit thresholds (or calculations) for the amount that can be afforded without restrictions or additional evidence generation [21–23, 26, 27], suggesting that in these frameworks, value may be scrutinised only in cases with a high budget impact. Affordability was considered solely in terms of cost effectiveness by two studies [16, 17], with set cost per QALY thresholds defined as the limits of affordability, but without an assessment of the potential impact of this approach in the case of products with very large patient populations.

Use of cost per QALY thresholds as a measure of affordability is somewhat surprising because without consideration of the number of eligible patients (for example, through budget impact analysis) the ICER for a new product does not determine whether it can be afforded. Cost-effectiveness calculations can be useful support for policy decisions, and are an important means of comparing different medicines. Analyses of this type may also aid in evaluating the impact of a new medicine in terms of therapies displaced. Economic evaluation also typically fails to consider broader aspects of value that influence affordability, such as innovation (e.g. a new mechanism of action that may lead to new therapeutic targets), the reduction of waste (freeing resources to make other drugs affordable) and the recently described concept of medical reversal, whereby evidence generated in trials of a new therapy may contradict existing clinical practice [43]. These concepts are not at the core of affordability, but may serve to modulate or inform the decision-making process, particularly in cases in which the crucial elements of the efficacy and safety of new products are modest or unclear.

In England, NICE has suggested that cost per QALY thresholds should correspond to the opportunity cost of programmes displaced by new technologies [18], but it is unclear how effectively this approach is followed in practice. A consultation process was initiated in October 2016 to consider proposed changes to NICE procedures, including formalising a £20 million budget impact threshold above which a commercial agreement to reduce costs between a manufacturer and National Health Service England would be mandatory [44]. A similar revenue ceiling, of €250 million in the first year after launch, has been proposed in Germany, which currently allows free pricing of medicines for 12 months [45]. A budget impact limit is already in operation in the Netherlands, where an ICER calculation is required for drugs with a predicted budget impact in excess of €2.5 million, suggesting that costs below this limit can be considered affordable [46]. Similarly, in France, the criteria for an economic assessment to be performed include a threshold of €20 million in annual revenue, above which a product is considered to have a significant impact on the health insurance budget [47].

One interesting example of the integration of affordability elements into the decision-making process for new health technologies comes from New Zealand. The Pharmaceutical Management Agency (PHARMAC) framework covers four dimensions (need, health benefit, cost and savings, and suitability), which are assessed from three points of view: clinical (including existing treatments, clinical efficacy and population size); economic (including economic evaluation results and evaluation of opportunity costs) and commercial (including price competition processes and reference pricing) [48]. The goal of this approach is to cope with the affordability issues that constrain decisions and optimise use of the budget allocated to health services.

Overall, how affordability is considered varies considerably according to the perspective of various stakeholders, including individuals, hospitals and national healthcare systems. While it is essential that healthcare systems seek to obtain good value for money, an approach to managing affordability based mainly on reducing costs may impact patients' access to effective treatments, and could potentially reduce the incentives for innovation [49]. Addressing the challenge of affordability to ensure not only that healthcare provision is sustainable but also that it continues to improve may require a broader perspective than is often taken in assessments of new products, for example, by assessing savings in other areas of the healthcare system that result from provision of an expensive therapy using the drug budget. The use of budget silos to manage healthcare expenditure is a common practice in many countries, but can be an obstacle to accessing new medicines [6]. By contrast, investigation of the efficiency of a new product using cost-effectiveness modelling can look across budget

silos to generate results in terms of costs per health outcome that can support decisions on affordability from the perspective of a single patient (although for the target population as a whole, budget impact considerations may offer a different view). For many new medicines, it is likely that a balance of these approaches will be needed to understand the affordability of the product from a practical perspective. Where affordability decisions rely on the level of clinical efficacy demonstrated in randomised controlled trials to generate savings elsewhere in the healthcare system, one challenge will be the potential for real-world outcomes to differ from those demonstrated in controlled conditions. Joint initiatives between pharmaceutical companies and healthcare systems to develop methods for capturing and evaluating real-world data in a timely manner are overdue.

The ISPOR has recently published good practice guidelines for budget impact analysis [50]. Although the main perspective taken is that of the budget holder, the ISPOR guidelines recommend that budget impact analysis takes into account the effects of an intervention on other healthcare resource use, for instance, an intervention for human immunodeficiency virus infection that maintains a patient's CD4 count at a high level may reduce the cost of treating opportunistic infections. Similarly, the guidelines suggest that while time horizons of 1–5 years are common in a budget impact analysis, longer time horizons may be needed to assess cost savings that may arise in the future, for example, interventions that cure chronic hepatitis may prevent cirrhosis or liver cancer in the future [50]. In addition, reducing the need for liver transplants for patients with hepatitis could increase the availability of livers for patients with end-stage liver disease as a result of other causes [51].

The link between affordability and the broader value of healthcare products is not straightforward. Value in healthcare is a vague and highly subjective concept [4], and may include benefits that are hard to capture through economic evaluation. When pharmaceutical companies develop innovative products that improve the treatment available to patients, the expectation is that this activity will produce the return on investment necessary to fund further research and the costly process of bringing future drugs to market [52]. In turn, society benefits from the development of effective new treatments. For example, it has been estimated that in USA, statin use costs approximately US$300 billion in the period 1987–2008, but had a social value of $1.25 trillion; social value is defined as the quantity of resources, in monetary terms, that society would be willing to give up to retain the survival gains resulting from therapy [53]. Where the value of new therapies in terms of health benefits is modest or uncertain, low sales may lead to reduced reinvestment in future products. Therefore, a trade-off exists between the flexible application of affordability criteria and incentives for the pharmaceutical industry to develop new research processes.

The concept of affordability implicitly incorporates the idea of a reference temporal framework. A decision affecting a whole population group may not be affordable when an intervention first becomes available, but high costs may be managed by targeting different subpopulations each year to distribute the cost over a longer period, making the global decision affordable. This type of downscaling has frequently been used by healthcare systems to manage the affordability of new technologies, for example, when new vaccination and screening programmes have been implemented or when new therapies have been introduced for some diseases. However, such approaches, even if patients with the greatest need can be prioritised, may reduce the benefits of the intervention. For instance, in addition to the future benefits of curing chronic hepatitis described above, it is likely that the rapid treatment of all eligible patients could lead to a substantial reduction in transmission of the disease, but is challenging for healthcare systems owing to the high up-front costs of, for example, sofosbuvir [54].

The temporal aspect of affordability is also visible in the cascade of actions that takes place when a drug loses patent protection (exclusivity). Changes in prescription are frequent, reflecting the market response to new prices that make the drug more affordable; furthermore, therapeutic guidelines may change the drug's position in the treatment algorithm, acknowledging the new value that the drug, with its reduced price, has for the healthcare system. These changes reflect the importance of affordability considerations to the sustainability of healthcare systems. As above, the temporal context affects affordability, with high-priced drugs with modest value in terms of additional health benefits for patients being unaffordable initially, but becoming affordable after patent expiry.

Part of the solution may be innovative financing models: these could take the form of payment-over-time systems, particularly in the case of products that can prevent the spread or worsening of disease. For instance, it has been suggested that amortisation of the high up-front cost of sofosbuvir over a period of years could allow healthcare systems to avoid having to prioritise patients for treatment (and consequently forgo some of the benefit of reducing disease transmission), while limiting the short-term financial impact [54]. To manage affordability issues in the future, it is likely that payers will need to work with the pharmaceutical industry to develop arrangements that reward innovation, while ensuring the sustainability of the healthcare system.

One area associated with high treatment costs, but also with the potential to help manage the affordability of care, is personalised medicine [55, 56]. Targeted therapies designed to act upon the specific molecular pathways underlying individual patients' disease (particularly in oncology) are

typically associated with high drug acquisition costs. However, changing from a treatment pathway in which all patients receive the same therapies to the use of targeted agents in appropriate subsets of patients may ultimately lead to lower costs overall, both through reduction in the use of other medical resources as a result of improved outcomes [57], and through the avoidance of treating patients with therapies that are not effective for their disease [58].

From a long-term global perspective, it has been suggested that separating the cost of research and development and the price of a drug could increase affordability and incentivise innovation [59]. In this model, development of a new innovation that has a positive impact on health would be rewarded, not through exclusivity (as is the case with the present patent system), but through a system of prizes. Patents would therefore be considered to constitute a right to be rewarded via prizes; in exchange for the prize, the winner would allow other companies to sell the product competitively, at a price equal to the marginal cost [60].

This review has some limitations. First, the systematic search was limited to references from 2005 onwards, and some older definitions may have been excluded. However, no date restriction was applied to the citation search, and it is likely that any older definitions that were still considered to be useful would have been identified in this way. Second, although no language restriction was applied to the MEDLINE and EMBASE searches, the EconLit search was restricted to articles published in English, and it is possible that some relevant economic literature published in other languages may have been missed. Third, relevant conference abstracts were included when identified in the systematic search, but for practical reasons no search was conducted of conference abstracts not indexed in the MEDLINE or EMBASE databases. However, abstracts from ISPOR conferences are indexed in EMBASE, and these are likely to be the conferences most relevant to the affordability of healthcare products.

This systematic review has focussed on the affordability of new medicines by healthcare systems. Affordability pressures also exist in other areas of healthcare provision, as well as with regard to the affordability by individuals of health insurance (particularly in USA [61]) and of co-payments for expensive therapies (particularly in developing countries, but also in Europe [62] and USA [1]). Further work will be needed to investigate how affordability is defined and managed in these areas.

5 Conclusions

This systematic review has found affordability to be defined in a number of different ways, but little to suggest that the price of medicines is considered alongside both their value and their budget impact. Cost-effectiveness analysis is commonly used to assess new drugs, but even highly cost-effective products may not be affordable if their budget impact is large. However, recent changes in England, Germany and the Netherlands suggest that a greater emphasis is being placed on cost effectiveness in the case of technologies with a large budget impact.

To date, establishing a fair balance that encourages innovation and the development, mainly by pharmaceutical companies, of superior medical technologies, without compromising the overall provision of healthcare as a result of budgetary crowding-out effects, has been challenging. In the future, managing the affordability of healthcare may require a broad perspective that can consider the long-term benefits of a therapy and cost savings elsewhere in the healthcare system. Cooperation between payers and the pharmaceutical industry is also likely to be needed to develop pricing systems that produce fair prices and financial arrangements that support the sustainable development of innovative medicines; these may include patient-access schemes, tax benefits, concerted public-private initiatives and potentially changes to the patent system for pharmaceuticals.

Author contributions All authors designed the study, analysed the results, reviewed all draft versions of the manuscript and approved the final version for submission. Paul Overton conducted the systematic review and wrote the manuscript.

Compliance with Ethical Standards

Funding This work was supported by Novartis Pharma AG (Basel, Switzerland) under the AGORA initiative (Advisory Group On Reimbursement and Access, a European Think Tank aiming to optimise access for patients to innovative treatments).

Conflict of interest Fernando Antoñanzas, Robert Terkola and Maarten Postma have received honoraria and travel support related to this study from Novartis Pharma AG under the AGORA initiative. At the request of the AGORA Think Tank, support for the systematic review was provided by Paul Overton (Beacon Medical Communications Ltd) and Natalie Shalet (NAS Healthcare Solutions Ltd), whose organisations received project funding from Novartis Pharma AG. Maarten Postma has received research grants and honoraria from various pharmaceutical companies, unrelated to this study.

Data availability All data generated during this study are included in this published article and its supplementary information files.

References

1. Siddiqui M, Rajkumar SV. The high cost of cancer drugs and what we can do about it. Mayo Clin Proc. 2012;87(10):935–43.
2. Rosenthal ES, Graham CS. Price and affordability of direct-acting antiviral regimens for hepatitis C virus in the United States. Infect Agents Cancer. 2016;11:24.

3. Abboud C, Berman E, Cohen A, et al. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. Blood. 2013;121(22):4439–42.
4. Antonanzas F, Terkola R, Postma M. The value of medicines: a crucial but vague concept. Pharmacoeconomics. 2016;34(12):1227–39.
5. Kanavos P, Vandoros S, Irwin R, et al. Differences in costs of and access to pharmaceutical products in the EU, 2011. http://www.lse.ac.uk/businessAndConsultancy/LSEConsulting/pdf/pharmaceuticals.pdf. Accessed 4 Mar 2016.
6. Garrison L, Towse A. The drug budget silo mentality in Europe: an overview. Value Health. 2003;6(Suppl. 1):S1–9.
7. Brockis E, Marsden G, Cole A, Devlin N. A review of NICE methods across health technology assessment programmes: differences, justifications and implications. Office of Health Economics Research Paper 16/03 2016. https://www.ohe.org/publications/review-nice-methods-across-health-technology-assessment-programmes-differences. Accessed 14 Nov 2016.
8. Carone GSC, Xavier A. Cost-containment policies in public pharmaceutical spending in the EU. 2012. http://ec.europa.eu/economy_finance/publications/economic_paper/2012/pdf/ecp_461_en.pdf. Accessed 14 Nov 2016.
9. Hollis A. Sustainable financing of innovative therapies: a review of approaches. Pharmacoeconomics. 2016;34(10):971–80.
10. Claxton K, Martin S, Soares M, et al. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. Health Technol Assess. 2015;19(14):1–504.
11. Haycox A. Why cancer? Pharmacoeconomics. 2016;34(7):625–7.
12. NHS England. Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund). 2016. https://www.england.nhs.uk/wp-content/uploads/2013/04/cdf-sop.pdf. Accessed 23 Aug 2016.
13. Oxford English dictionary. Oxford: Oxford University Press; 2009.
14. Dranitsaris G, Truter I, Lubbe MS, et al. Improving patient access to cancer drugs in India: using economic modeling to estimate a more affordable drug cost based on measures of societal value. Int J Technol Assess Health Care. 2011;27(1):23–30.
15. Mauskopf JA. Prevalence-based versus incidence-based economic evaluations for the assessment of new health care interventions. Value Health. 2012;15(4):A170.
16. Nagase H, Moriwaki K, Kamae M, et al. Cost-effectiveness analysis of oseltamivir for influenza treatment considering the virus emerging resistant to the drug in Japan. Value Health. 2009;12(Suppl. 3):S62–5.
17. Vos T, Corry J, Haby MM, et al. Cost-effectiveness of cognitive-behavioural therapy and drug interventions for major depression. Aust N Z J Psychiatry. 2005;39(8):683–92.
18. National Institute of Health and Care Excellence. Guide to the methods of technology appraisal 2013. https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. Accessed 4 Oct 2016.
19. Orlewska E, Ancuta I, Anic B, et al. Access to biologic treatment for rheumatoid arthritis in Central and Eastern European (CEE) countries. Med Science Monit. 2011;17(4):SR1–13.
20. Zueger P, Becker R. The affordability of oncology and HIV/AIDs technologies in Brazil compared to the United States and other OECD countries. Value Health. 2013;16(7):A684.
21. Jørgensen J, Kefalas P. Reimbursement of licensed cell and gene therapies across the major European healthcare markets. J Mark Access Health Policy. 2015;3:1–12.
22. Haute Autorité de Santé. Methods for health economic evaluation. http://www.has-sante.fr/portail/jcms/c_2035665/en/methods-for-health-economic-evaluation. Accessed 4 Oct 2016.
23. Mauskopf J, Chirila C, Birt J, et al. Drug reimbursement recommendations by the National Institute for Health and Clinical Excellence: have they impacted the National Health Service budget? Health Policy. 2013;110(1):49–59.
24. Agenzia Italiana del Farmaco. Glossary. http://www.aifa.gov.it/en/glossary/20/lettera. Accessed 22 Aug 2016.
25. Souliotis K, Hasardzhiev S, Agapidaki E. A conceptual framework of mapping access to health care across EU countries: the patient access initiative. Public Health Genom. 2016;19(3):153–9.
26. Institute for Clinical and Economic Review. Evaluating the value of new drugs and devices. 2016. http://icer-review.org/wp-content/uploads/2016/02/Slides-on-value-framework-for-website-v4-13-16.pdf. Accessed 4 Oct 2016.
27. Bozkaya D, Migliaccio-Walle K, O'Day K. Assessing prescription drug value in the united states: a hypothetical example comparing ASCO and ICER framework outcomes. Value Health. 2016;19(3):A1.
28. Schlander M, Schwarz O. Affordability of increasing health care expenditures in Germany: a macroeconomic analysis. Gesundheitsokonomie Qualitatsmanagement. 2005;10(3):178–87.
29. Cameron A, Ewen M, Ross-Degnan D, et al. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. Lancet. 2009;373(9659):240–9.
30. Cameron A, Bansal A, Dua T, et al. Mapping the availability, price, and affordability of antiepileptic drugs in 46 countries. Epilepsia. 2012;53(6):962–9.
31. Jingi AM, Noubiap JJN, Onana AE, et al. Access to diagnostic tests and essential medicines for cardiovascular diseases and diabetes care: cost, availability and affordability in the west region of Cameroon. PLoS One. 2014;9(11):1–10.
32. Ngorsuraches S, Chaiyakan K. Equitable prices of single-source drugs in Thailand. Appl Health Econ Health Policy. 2015;13(4):389–97.
33. Helfer AP, Camargo AL, Tavares NU, et al. Affordability and availability of drugs for treatment of chronic diseases in the public health care system. Rev Panam Salud Publica. 2012;31(3):225–32.
34. Lemus F, Rivas R. Afforda bility of antihypertensive treatment in Mexico. Value Health. 2013;16(7):A705.
35. Iyengar S, Tay-Teo K, Vogler S, et al. Prices, costs, and affordability of new medicines for hepatitis C in 30 countries: an economic analysis. PLoS Med. 2016;13(5):e1002032.
36. Niëns LM, Van de Poel E, Cameron A, et al. Practical measurement of affordability: an application to medicines. 2012. http://www.who.int/bulletin/volumes/90/3/10-084087/en/. Accessed 4 Oct 2016.
37. Niëns LM, Brouwer WBF. Measuring the affordability of medicines: importance and challenges. Health Policy. 2013;112(1–2):45–52.
38. O'Donnell O, van Doorslaer E, Wagstaff A, Lindelow M. Analyzing health equity using household survey data. 2007. http://siteresources.worldbank.org/INTPAH/Resources/Publications/459843-1195594469249/HealthEquityFINAL.pdf. Accessed 4 Oct 2016.
39. Mokaya J, Gray WK, Walker RW. Mapping the availability, price and affordability of drugs used to treat Parkinson's disease in Kenya. Move Disord. 2015;30:S427.
40. Homedes N, Ugalde A. Availability and affordability of new medicines in Latin American countries where pivotal clinical trials were conducted. Bull World Health Org. 2015;93(10):674–83.
41. World Health Organization. A model quality assurance system for procurement agencies. 2007. http://apps.who.int/medicinedocs/documents/s14866e/s14866e.pdf. Accessed 25 Jan 2017.

42. Jönsson B, Persson U, Wilking N. Innovative treatments for cancer in Europe: value, cost and access. IHE report. Lund: IHE; 2016:2. http://www.ihe.se/innovative-treatments-1.aspx. Accessed 12 Jan 2017.
43. Prasad V, Cifu A. Medical reversal: why we must raise the bar before adopting new technologies. Yale J Biol Med. 2011;84(4):471–8.
44. National Institute for Health and Care Excellence and National Health Service England. Proposals for changes to the arrangements for evaluating and funding drugs and other health technologies appraised through NICE's technology appraisal and highly specialised technologies programmes. https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/technology-appraisals/NICE_NHSE_TA_and_HST_consultation_document.pdf. Accessed 15 Nov 2016.
45. Bloomberg. Bayer warns planned German price curbs may restrict drug access. https://www.bloomberg.com/news/articles/2016-11-14/bayer-warns-planned-german-price-curbs-may-restrict-drug-access. Accessed 5 Dec 2016.
46. Morel T, Arickx F, Befrits G, et al. Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries. Orphanet J Rare Dis. 2013;8(1):198.
47. Toumi M, Remuzat C, El Hammi E, et al. Current process and future path for health economic assessment of pharmaceuticals in France. J Market Access Health Policy, [S.l.], v. 3, June 2015. http://www.jmahp.net/index.php/jmahp/article/view/27902. Accessed 25 Jan 2017.
48. PHARMAC. Fact sheet #4: making funding decisions. 2016. https://www.pharmac.govt.nz/assets/factsheet-04-making-funding-decisions.pdf. Accessed 19 Apr 2017.
49. London School of Economics. Tender loving care? Purchasing medicines for continuing therapeutic improvement and better health outcomes. 2016. http://eprints.lse.ac.uk/67824/. Accessed 10 Nov 2016.
50. Sullivan SD, Mauskopf JA, Augustovski F, et al. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. Value Health. 2014;17(1):5–14.
51. Jena AB, Stevens W, Gonzalez YS, et al. The wider public health value of HCV treatment accrued by liver transplant recipients. Am J Manag Care. 2016;22(6 Spec No.):Sp212–9.
52. Tufts Center for the Study of Drug Development. Briefing: cost of developing a new drug. 2014. http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014..pdf. Accessed 20 Apr 2017.
53. Grabowski DC, Lakdawalla DN, Goldman DP, et al. The large social value resulting from use of statins warrants steps to improve adherence and broaden treatment. Health Aff (Millwood). 2012;31(10):2276–85.
54. Kleinke JD, McGee N. Breaking the bank: three financing models for addressing the drug innovation cost crisis. Am Health Drug Benefits. 2015;8(3):118–26.
55. Schleidgen S, Klingler C, Bertram T, et al. What is personalized medicine: sharpening a vague term based on a systematic literature review. BMC Med Ethics. 2013;14(1):55.
56. Draghia-Akli R. Enabling personalized medicine in Europe: a look at the European Commission's funding activities in the field of personalized medicine research. Per Med. 2012;9(2):151–5.
57. Lee JK, Kim DW, Keam B, et al. The impact of molecularly targeted treatment on direct medical costs in patients with advanced non-small cell lung cancer. Cancer Res Treat. 2015;47(2):182–8.
58. Ansari D, Tingstedt B, Andersson R. Pancreatic cancer: cost for overtreatment with gemcitabine. Acta Oncol. 2013;52(6):1146–51.
59. Antonanzas F, Juarez-Castello C, Rodriguez-Ibeas R. Pharmaceutical patents, R&D incentives and access to new drugs: new ways of progress at the crossroad. Eur J Health Econ. 2011;12(5):393–5.
60. Antonanzas F, Rodriguez-Ibeas R, Juarez-Castello CA. Should the patent system for pharmaceuticals be replaced? A theoretical approach. Expert Rev Pharmacoecon Outcomes Res. 2014;14(5):617–26.
61. Zallman L, Nardin R, Malowney M, et al. Affordability of health care under publicly subsidized insurance after Massachusetts health care reform: a qualitative study of safety net patients. Int J Equity Health. 2015;14:112.
62. Organisation for Economic Co-operation and Development/Europena Union. Health at a glance: Europe 2014. doi:10.1787/health_glance_eur-2014-en. Accessed 15 Nov 2016.