Affording the Future?

The role of cost effectiveness thresholds in determining NHS patient access to high quality care in the post-Brexit era

Summary

• Worldwide, life expectancy at birth has increased by 30 years in the last 100 years. New medicines and vaccines, combined with other health care advances, have accounted for approaching half this progress. Continuing advances in the prevention and treatment of cancers and the neurological and musculoskeletal diseases (as well as in controlling continuing infectious threats) could ensure that virtually everyone will in the second half this century be able to live in good health into their 80s, baring relatively rare exceptions. But there are concerns about the affordability of new treatments, and whether or not societies will choose to fund the research needed to develop them or afford the costs of their universal supply.

• In cost effectiveness analysis (CEA) cost effectiveness thresholds can define the maximum payable for an additional Quality Adjusted Life Year (QALY). Recent evidence indicates that NICE normally regards ‘new QALY’ costs (also referred to as Incremental Cost Effectiveness Ratio or ICER values) of up to £30-£40,000 as providing sufficient ‘value for money’ for NHS patient use. This threshold can vary but above it treatments are not usually recommended. For comparison, nursing home care for people living with a limited quality of life often costs over £50,000 a year, while British public ‘willingness to pay’ based estimates indicate an incremental QALY value of around £60,000.

• Calculating QALY values is by no means an exact science, and there is no agreed way of calculating cost effectiveness thresholds. NICE has a Highly Specialised Technologies (HST) programme that does not depend on ‘cost per QALY’ estimates. The logic of this partly relates to the fact that while the costs of developing ‘ultra-orphan’ treatments can be close to those for commonly used products the volume of QALYs generated will, given limited patient numbers, be much lower. But the HST approach has been used to evaluate only a few very rarely used treatments.

• The principle that cost effectiveness thresholds should vary according to the context in which new QALYs are being generated deserves wider recognition. It is not in the public’s interests to expect the prices of all innovative therapies to fall within ‘one size fits all’ parameters. Rigid approaches deprive people of treatments that are in budgetary impact terms affordable, especially when total pharmaceutical outlays can be limited by other means. The Pharmaceutical Regulation Scheme (PPRS) caps the cost of all medicines supplied to the NHS under its terms.

• The use of narrowly defined measures of value combined with relatively low cost effectiveness thresholds can conflict with the NHS’ duty to provide good care for everyone. It sometimes leads to people feeling that they have to beg for treatments that their doctors believe could benefit them. Well-structured policies could and should avoid such service failings, not least because once the costs of developing and licensing new treatments have been incurred the macro-economic savings derived from not supplying them to NHS patients can be much smaller than is often assumed. International experience indicates that a more humane system would be affordable.

• The proportion of NHS resources spent on pharmaceuticals has been around 10 per cent for approaching 50 years. The economics of areas like anti-cancer treatment supply are complicated by the fact that such medicines are normally first used alone to treat late stage disease. Yet their optimum ‘cost per QALY’ value is likely to stem from using them with other drugs in earlier stage therapy. This can be why novel medicines are dismissed as ‘merely adding weeks to the end of life’. Research based companies need to generate income relatively soon in the life cycles of innovative products, while intellectual property rights still apply. Yet often their products’ full value only becomes apparent after they become low cost generic products. This tension often underlies pricing concerns.

• Some researchers have argued that the incremental cost effectiveness threshold employed by NICE should be cut to below £15,000 per QALY. Others reject such recommendations as being based on inadequate data,
The techniques used to measure quality of life and value health outcomes are subject to many limitations. In some circumstances they risk discounting the lives of people living with mental or physical disabilities. There is also a danger of systematically exaggerating the opportunity costs of using products like innovative medicines and vaccines. Unlike labour intensive services, pharmaceutical products typically drop in price after the intellectual property rights awarded to incentivise further R&D spending expire. CEAAs factor in ‘life cycle’ related savings.

The NHS was established to provide equitable and appropriate care for everyone, rather than to provide an especially low cost health service. If policy makers are unduly influenced by recommendations based on narrow value measures like QALY’s coupled with low cost effectiveness thresholds they will undermine community wellbeing. Wider dimensions of value, including giving hope to people living with conditions that are presently incurable and the long term socio-economic and industrial benefits that life sciences related research and product use generates, should be taken into account.

Nations like France, Germany and the US spend 1.5-2 per cent of their GDPs on pharmaceuticals. The British figure is about 1 per cent. The UK spends 10-20 per cent less of its national income on health and social care than France, Germany, Sweden and The Netherlands. America spends twice as much of its GDP on healthcare than the UK.

Reducing the cost effectiveness thresholds used by NICE to less than half their current value would put UK patient access to innovative treatments further behind that enjoyed by similarly affluent populations elsewhere in Western Europe and North America. Driving down health and social care spending to levels below those seen in other comparably wealthy nations without checks on the improper use of ‘single purchaser’ market powers could damage British research and industrial investment in the post-Brexit environment.

There is no ‘scientific’ way of setting cost effectiveness thresholds. The reason why the WHO recommends that QALY-like Disability Adjusted Life Years (DALYs) should be valued at three times per capita GDP as opposed to the one-to-one ratio presently used by NICE may relate to the fact that the WHO acts as a health improvement advocate rather than a rationing agency. Economists who advocate very low NHS cost effectiveness thresholds risk perpetuating under-investment damaging the wider economy. Such deficits may be difficult to prove until after substantive harm has been caused.

With its relatively strong research base, Britain stands to lose from driving down the prices paid for innovative medicines and vaccines in the affluent world. But defending the value of research based products requires meeting the needs of people in poorer communities. Policy makers should support low cost access to essential medicines in such settings, without unethically seeking to cut the prices for innovative products paid by the NHS in order to avoid making proportionate contributions to global pharmaceutical research, development and supply costs.

**Recommendations**

- England and the other UK nations should seek to achieve flexible and humane approaches to valuing and supplying innovative treatments which promote equity and foster high levels of public and patient confidence without generating unaffordable costs. National and international examples of good practice, including recognised strengths of the PPRS and the achievements of countries like France and Sweden, should be built on in order to combine greater freedom for ‘case by case’ decision making on the cost effectiveness of medicines offered for NHS use while assuring overall health care system affordability. Pharmaceutical assessment methods should themselves be as cost effective as possible.

- Future policies ought to enable seriously ill NHS patients to have timely and assured access to treatments such as anti-cancer and rare disease medicines in ways consistent with taxpayers’ interests in the quality and affordability of health care and ongoing industrial investment in R&D and manufacturing. The UK’s pharmaceutical sector record has to date been strong. It could become stronger through linking greater sensitivity to health service user and wider community needs with more emphasis on constructive partnership working between public and private sector organisations.

- Economists make simplified models of the world in order to aid the pursuit of greater wellbeing. Rationally used, measures such as QALYs and ICERs support the identification of efficient and effective choices. But if health economists, or others using their findings in areas like the value of reducing pain or extending life, come to dogmatically believe that their work provides an absolute guide to achieving optimal patterns of health care funding and activity they may endanger the health, wealth and wellbeing of people in the communities they seek to serve. Politicians, health professionals and other stakeholders should actively avoid such risks.
Introduction

NICE was first formed as the National Institute of Clinical Excellence a little over seventeen years ago, in April 1999. Some sources suggest that it was originally destined to be called the National Institute of Cost Effectiveness but claim that title was rejected by the New Labour politicians of the day because it sounded money oriented, as opposed to care focused. Others deny that any such attempts were made to ‘sugar the pill’ of NICE’s establishment.

The truth or otherwise of this debate is uncertain. However, beneath the surface of these conflicting assertions it is undeniable that the language of health economics has since the start of the 2000s become commonly used throughout the NHS. In large part because of NICE’s international reach, it is also being increasingly heard in health care settings elsewhere in Europe and the world. Terms such as QALYs (Quality Adjusted Life Years) and ICERs (Incremental Cost Effectiveness Ratios) have become a familiar part of day-to-day discourse about what treatments should or should not be seen as offering enough value for money to warrant health service users having access to them.

This is in some ways a desirable development. Health care resources are – as in any other sector – finite. It is rational to try to use them to optimum effect, even if the extent to which NICE and other appraisals as currently undertaken can support the delivery of this goal is questionable. Critics of health economists believe that their work too often involves the creation of simplified models of complex problems in order to permit the exclusion of uncertainty and the generation of solutions that can be presented as being ‘scientific’ and hence unquestionable, but are in reality disputable and lacking in the depth of understanding needed to provide reliable prescriptions for the future.

There are also concerns about how well the cost effectiveness study based findings underpinning decisions on access to NHS care are understood by stakeholders such as the patients and clinicians at the heart of service delivery, or politicians making ‘higher level’ choices on behalf of their communities. The quality of most if not all NICE’s work is widely seen as good. Yet there is arguably a need for greater public insight into the principles and methods on which cost effectiveness studies are based and via which their findings applied. Otherwise a danger exists that proposals which might be questionable from an informed public interest standpoint will be accepted without critical consideration, while potentially more beneficial opportunities are neglected.

Against this background this report is primarily concerned with the setting and impacts of cost effectiveness thresholds as used by HTA (Health Technology Assessment) bodies. These can be said to define ‘cost per QALY generated’ ceilings. Put simply, treatments which create new units of health gain for amounts of money below the maximum level set are recommended as cost effective by agencies like NICE. Those with costs exceeding the chosen threshold are judged unaffordable.

The first sections below briefly explore the nature of pharmaceutical products as economic goods and offer an outline of the development of health economics and cost effectiveness analysis to date, along with a description of how measures like QALYs and ICERs are derived. They also provide observations relating to how and why the methods used for determining the value of medical innovations and setting affordability thresholds in countries such as the US, France and Germany differ from the approach presently adopted in Britain.

One of the practical challenges facing those seeking to ensure that the use of health economics based techniques generates optimal ‘value for money’ and avoids causing needless harm is that there is no theoretically based, or even generally agreed, way of working out how cost effectiveness thresholds should be calculated. The fact that, as has been claimed in relation to NICE’s work (see Timmins et al, 2016), they may ‘just emerge’ should be a cause for caution, if not a degree of alarm. It means that in some instances NHS patients could be being denied access to life enhancing and/or extending therapies for essentially arbitrary reasons. In others there is a possibility of paying ‘too much’ for treatments that might be obtained for less.

Questions relating to further protecting public interests in investing in research and development and maintaining a healthy pharmaceutical sector while keeping total costs down to levels which allow optimal public access to existing health technologies are considered towards the end of this report. Before this, however, there are a number of introductory points to be noted. The first link to the fact that this analysis is not intended to add to the already extensive technical literature relating to cost effectiveness analysis in the health sphere.

The latter is only fully accessible to a small and in some respects isolated body of specialists. Individuals interviewed during the preparation of this document said that critical discussion of the thinking and assumptions underpinning health economics is largely confined to those whose careers depend on practicing it. It is apparent that many people responsible for key decisions in the health service have little understanding of how cost effectiveness based

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1 The organisation is now called the National Institute for Health and Care Excellence. The terms cost effectiveness and affordability are sometimes used interchangeably. However, a treatment judged cost effective on an individual care focused ‘cost per QALY yielded’ basis may be seen as unaffordable at the overall health system level and vica versa, in part depending on the total number of potential beneficiaries involved.

2 In total 20 semi-structured interviews were undertaken in the period between February and September 2016. Most of the respondents involved were health economists or individuals with related health sector expertise.
recommendations are made. In some instances confusions as basic as mistaking high ICER values for the amounts actually paid for products such as medicines occur. Hence this contribution seeks to provide an overview of how the current situation has evolved, and the importance of issues like the setting of cost effectiveness thresholds for not only individuals like Ministers but also to members of health professions and the wider public interested in achieving better health and health care.

**Investing for the future via current care provision**

Other introductory considerations range from the scale of the future health gains that bio-pharmaceutical science based advances in fields such as genetics and epigenetics will eventually generate through to, in the present UK context, the implications of the recent ‘Brexit’ vote for health care and the overall British science base. If, as some fear, the consequences of leaving the EU will in the medium to long term lead to reductions in the capacity of this country to fund public enterprises there will further downward pressures on costs of all types. At worst, providers of health related goods and services in the UK will have to face continuing ‘austerity’ coupled with increased cultural isolation. Yet against this restoring the performance of the economy is likely to demand increased public and private investment in research and development in high technology areas, conducted in ways that allow good communication and joint working with ‘cutting edge’ centres throughout Europe and other world regions (Freeman and Kwarteng, 2013).

To put today’s challenges in the wider human development context, in the century or so between the start of the 1914-18 conflict and the present day the world’s population rose four-fold, from around 1.7 billion people to over 7 billion. Against this 5 billion plus increase, the UK’s total population expanded by 20 million. In the same period life expectancy at birth has been extended by approaching 30 years in rich and poor countries alike. Such dramatic gains have led to population ageing, and to major changes in the nature of the demands facing health care providers like the NHS.

This progress has been achieved despite tragedies ranging from wars to the impact of tobacco smoking on world health, and the burden of death and disability caused since 1980 by the HIV pandemic. Even in sub-Saharan Africa, with its continuing burdens of high maternal, infant and child mortality, the average new-born girl or boy can today expect to live about 60 years. This is a decade longer than the average life expectancy at birth recorded in Edwardian Britain at the height of its Imperial power.

Environmental and allied improvements, from better access to clean water to enhanced food availability, have played a dominant role in driving demographic and epidemiological change. However, better medicines and vaccines have also been important. Together with advances in areas such as surgery, products ranging from antibiotic, antiviral and antihypertensive drugs through to polio and other forms of immunisation have probably accounted for approaching 50 per cent of the global health gains seen over the course of the last hundred years (Craig et al, 2014).

Notwithstanding concerns about the extent to which poorer individuals and populations have sufficient opportunities to benefit from modern treatments, this represents a fundamental contribution to the wellbeing of humanity. The affordability of the ‘pharmaceutical revolution’ has in part been assured because when initially expensive new medicines and vaccines lose intellectual property protection and manufacturing technologies become more efficient their prices fall markedly. At the same time knowledge about the best use of pharmaceutical products increases as they reach market maturity, not only amongst health professionals but also – as and when counter-productive barriers to wider public learning can be overcome – amongst their end-point consumers.

Such factors help account for the relative stability of NHS pharmaceutical costs as compared to gross health service outlays shown in Figure 1. It has been predicted that during the current century nearly all premature deaths amongst children and adults in middle and early later life could, barring events such as accidents, become preventable (Peto, 2015). However, achieving this historic turning point will require not only the establishment of adequately resourced universal health care systems throughout the world. It will also need much ongoing research and development investment in generating better technologies for the prevention and treatment of conditions such as vascular diseases and the cancers, together with improved therapies for disorders like – for instance – multiple sclerosis and Alzheimer’s Disease.

Complex communities such as modern Britain inevitably have potentially conflicting interests in spending enough on pharmaceuticals to drive desired levels of private and linked public investment in high risk development projects and, against this, in keeping drug and vaccine prices and gross spending as affordable as possible. This tension underlies debates on how ‘fair’ prices for medicinal and allied goods can best be determined and explains why concerns relating to the setting of cost effectiveness thresholds in HTA evaluations have important implications for everyone.

3 It is possible, for example, for a medicine to have an Incremental Cost Effectiveness Ratio/ICER value of, say, £50,000 per QALY but have an actual supply cost of under £5,000 per course if the comparator intervention used is a low cost generic product. In such circumstances, critics claim, useful and modestly priced innovations can be excluded from use, and whole areas of research exposed to a CEA study induced ‘blight’.
At one stage the calculations undertaken by Claxton at al suggested an ICER figure similar to that of Alan Williams’ ‘cockshy’ of £18,000, which was the UK per capita GDP in the early 1990s.

The validity of such claims and the approach used to calculate this lowered cost effectiveness threshold and the consequences of failing to adopt it has been disputed by other commentators (Barnsley et al, 2013; Karlsberg Schaffer et al, 2014). In the world’s other leading industrial nations there is little likelihood of such recommendations gaining credence. But if it were accepted in this country it would dramatically cut NHS willingness to pay for medicines and other medical technologies, and put UK pharmaceutical sector policies at an increased distance from those of the US, Japan and other parts of Western Europe.

The UK vote to leave the European Union may, as already indicated, lead to a further increase the perceived need for cost reductions throughout the public sector. Recent action taken in relation to instituting competitive tendering for Hepatitis C treatments (see Box 1) could come to exemplify the type of cost saving intervention that will be increasingly employed in the pharmaceutical arena. They may risk undermining NICE decision and the functioning of the Pharmaceutical Price Regulation Scheme5. However, the establishment and work of the Accelerated Access Review (AAR, 2015) has illustrated governmental level awareness of the importance of the life sciences to the UK’s economic future and the value of appropriate investment in pharmaceutical R&D funded via company earnings, as well as by direct State payments.

This report does not attempt to speculate about the possible impacts of the AAR, or on how the responsibilities of, and interfaces between, NICE, the PPRS, NHS England and other agencies should in future evolve. But it is worth emphasising that in raising questions about the strengths and limitations of “cost per incremental QALY” based methods in determining what medicines or other innovative products the NHS should be prepared to afford it is not intended to suggest here that there ought to be no limits on the amounts that publicly funded healthcare providers pay for such items.

Whenever monopsonist (single) or other very large health care purchasers are dealing with private pharmaceutical suppliers who are – by virtue of patents and other intellectual property rights granted to promote public interests in funding research and developing better products – temporary monopolists, there will inevitably be tensions and disputes. The occurrence of such phenomena should not be taken as evidence of a failing system, or necessarily of fault on either side. But they underline the need for values, procedures, rules and regulations that help maintain a reasonable balance between incentivising innovation and preventing excessive spending.

5 The PPRS is negotiated between the Department of Health (acting on behalf of all the UK nations) and pharmaceutical industry representatives. It has during the last half century been central to containing overall pharmaceutical spending in Britain. It is normally re-negotiated every five years, with the Association of the British Pharmaceutical Industry (ABPI) representing the interests of participant member companies.

Sources: OHE and the Kings Fund

Medicines in a Complex Policy Environment

The available evidence indicates that NICE has in the last few years regarded £30-£40,000 as being the ceiling amount that the NHS should pay for an incremental – as distinct from an average – QALY (Dakin et al, 2015), albeit the cost effectiveness thresholds used vary by up to 50 per cent between settings. For reasons discussed below there is, for example, in many countries a willingness to pay more for each unit of utility/benefit generated by treatments for rare conditions than there is for QALYs derived from other therapies. NICE has also applied a higher affordability threshold in the context of end of life care.

However, recent MRC supported investigations by University of York and other academics have argued for a lower health sector cost effectiveness threshold. York based health economists, most notably the late Professor Alan Williams, were in the past central to developing the “cost per QALY” based approach to cost effectiveness analysis and in lobbying for its use in the UK and elsewhere. Williams himself suggested a ceiling figure of around £18,000 per incremental QALY in the 1990s (Williams, 2005). The subsequent work of Professor Karl Claxton and others at one time favoured the imposition of a cost effectiveness threshold of £13,0004, although a figure of £15,000 has since been more widely quoted (Claxton et al 2015a, 2015b, 2016). These authors say that lives are being lost in the UK because money being spent on pharmaceuticals could be more productively allocated.

The validity of such claims and the approach used to calculate this lowered cost effectiveness threshold and the consequences of failing to adopt it has been disputed
Box 1. Curing Hepatitis C

There is presently no vaccine for Hepatitis C, a viral infection first identified at the end of the 1980s. It presently affects some 150 million people world-wide, or one in every fifty members of the global population. It is most common in Egypt, where past attempts to control schistosomiasis (a parasitic condition which can sometimes lead on to bladder cancer) caused it to be spread via the re-use of contaminated needles. But it is also found in affluent settings such as the US. About three million Americans are living with a chronic Hepatitis C infection.

The virus is mainly spread through blood to blood contact. This means that in countries like the UK rates are highest in groups such intravenous drug users and people who have received concentrated blood Factor products derived from donors’ contributions. However, other routes, including mother to baby transmission, also exist. About three quarters of those infected develop a chronic liver infection. In this group 5-10 per cent of those who are untreated will ultimately lose their lives as a result of cirrhosis or liver cancer. Hence the recent marketing of medicines such as sofosbuvir (Solvadi), dasabuvir (Exviera) and ombitasvir and grazoprevir (Zepatier) is of considerable public health significance.

Depending on the Hepatitis C genotype involved and the availability of diagnostic resources and additional treatments, these new therapies (Solvadi became available during 2014) can cure well in excess of 90 per cent of cases. Before 2014, medicines costing about $50,000 in the US could successfully treat only about 35 per cent of those chronically infected Hepatitis C patients offered them. This resulted in a ‘cost per cure’ of approaching $140,000 (Scannell, 2015). The availability of Solvadi cut this figure closer to $90,000.

Even so, it was widely alleged that the cost of new Hepatitis treatments would make health care unaffordable in America and elsewhere. Solvadi’s quoted launch price (not including discounts) was $85,000 per 12 week course. Although the cost per incremental QALY generated by using sofosbuvir was even at its full list price in a variety of clinical instances relatively low, many commentators feared it was excessively expensive. A minority of campaigners claimed (citing earlier problems encountered in the HIV pandemic context) that it showed that granting intellectual property rights for innovative pharmaceuticals is unsustainable.

However, without provisions such as patents it is doubtful as to whether or not today’s range of antiviral medicines would exist. It should be also noted that in countries such as Egypt Solvadi is available (on a Ramsey pricing basis – see main text) at about $300 per course. Because later stage chronic infection treatment is more or less as effective as early stage therapy it is in addition worth recording that the entire cohort of people with living with Hepatitis C in economically advanced nations need not be treated in any one decade, let alone any one year.

In fact, competition between alternative innovative medicines with both the same and differing modes of action has, in combination with professional approaches to medicines purchasing, already acted to rapidly reduce costs. NHS England has recently announced a programme designed to treat 10,000 individuals a year at a total cost of £190 million, implying ‘a cost per Hepatitis C cure’ of about £20,000 (well under $US 30,000).

The imposition of a cap on the number of NHS patients able to access any NICE recommended therapy may be questioned. But from a wider perspective this progress illustrates how initial ‘cost anticipation’ driven reactions to the availability of new pharmaceutical treatments can be unduly negative. There needs to be more constructive preparation for new technology introductions. Over time the costs of effective anti-viral medicines will fall further. Used appropriately, they will greatly reduce the financial and other burdens imposed by Hepatitis C and could in some settings come close to eradicating the disease.

The Hepatitis C treatment issues described here are unique. Yet similar lessons can be drawn from many other areas. For example, NICE was in part created because of fears in the 1990s that then new beta interferon based treatments for multiple sclerosis would prove excessively costly. Even when, after much potentially counter-productive public controversy, a risk sharing/Patient Access Scheme was established in 2002, some critics argued that it represented an unduly costly and pointless investment. But there is now evidence that such therapies are both affordable and cost effective (Palace et al, 2015; Torjesen, 2015).

The opening of a market for disease modifying MS therapies may also have been instrumental in encouraging the introduction of other more effective interventions. Likewise, initial British ‘health economics/ evidence based care’ linked opposition to supplying Herceptin (trastuzumab) in the treatment of early stage breast cancer is an example of what might in retrospect be said to have been an ill-judged response likely to harm public and patient interests.
To avoid financial chaos, systems like the NHS and the organisations within it must keep their outlays within their allocated budgets. Given that pharmaceuticals reportedly account for up to 13 per cent of total NHS costs⁶ there is a need for reliable price and/or total cost controls. Nevertheless, there is also a strong common sense case for saying that assessing the value of bio-pharmaceutical and allied innovations should involve considering societal benefits that go well beyond those immediately enjoyed by individuals receiving health care, or just those stemming from their personal contributions to their families’ prosperity and the wider economy.

To the extent that NICE's cost effectiveness based judgements, alongside the approach adopted in the PPRS, currently represent the closest thing Britain has to a strategy for driving the development of its bioscience based industries it is important to ensure that the methods used for assessing value are as well-based as possible. The future is not, of course, predictable, and no sort of data manipulation can ever generate absolute answers to questions like ‘how much ought to be spent on bio-pharmaceutical research via government grants and spending on today’s pharmaceutical products in order to meet future patient and NHS care provider needs?’ Even so, it is from a logical standpoint true that the long term gains from investments in the life sciences (including spending in areas like, for instance, cancer therapeutics) may well encompass fundamental contributions to fields ranging from sustainable energy generation to food production, over and above those directly relevant to improving patients' health.

The fact that pharmaceutical and allied R&D is a bridgehead to the future deserves recognition in judgements relating to what spending on innovative pharmaceutical products is ultimately ‘worth’. Awareness of the importance of this conclusion should not be swamped by the findings of narrowly based technical studies that at best only partially reflect reality.

Social dimensions of value

The professions traditionally concerned with supplying and using medicines, vaccines and other pharmaceutical goods have, rightly, primarily been interested in their physical and clinical properties. Examples of these include storage characteristics and the pharmacological mechanisms that give rise to treatments’ abilities to prevent, ameliorate and cure illnesses. Yet since the middle of the twentieth century there has been a growing awareness of the additional psychological, social and economic dimensions of pharmaceutical products. For instance, popular films and books like The Third Man and The Constant Gardener have highlighted the potential for drugs – as potentially life-saving but also hazardous items of trade that can be costly but are also light and easy to transport – to on occasion serve not to relieve suffering but instead to facilitate exploitation.

In a similarly sociological vein, vaccine ‘scares’ have periodically tapped in to deep rooted hopes and fears in ways which distort behaviours and undermine personal and collective interests. The recent, sometimes misleading, debate around statin use has parallel features (Collins et al, 2016). There is now a better understanding than ever before of the psychological determinants of medicines use, and how the balance between an individual’s beliefs about the benefits of taking medicines and her or his fears regarding problems like side effects influences medicine taking behaviour (Horne et al, 2013). Even today not all health professionals fully appreciate the implications of the fact that the way people elect to use treatments is a fundamental determinant of their effectiveness.

In the immediate economic context there are across social settings as disparate as those of the US and the UK also ambiguities relating to the costs of medicinal and related treatments as against perceptions of their value. New pharmaceuticals are sometimes seen as unduly expensive. Yet at the same time people often attach a high priority to being able to access them, even when evidence of their efficacy is relatively weak.

Concerns about ‘drug’ prices are linked to the economic fact that pharmaceuticals are not like gold, which is of high value because of it is of inherent scarcity and because it has aesthetic as well as commercially useful physical properties. Once their high costs of development – including those of failed research projects – have been met, pharmaceuticals can usually be made in as much volume as is required. Once adequate production capacity has been established the marginal costs of producing pharmaceutical products are normally much lower than the average costs – it is in some respects cheaper to supply a lot than a little. This means that the financial barriers to their universal supply are in the medium to long term likely to be much less significant that those associated with problems like setting up the labour intensive diagnostic and care facilities needed to ensure that entire populations can access appropriate therapies.

In addition, unlike high technology products such as jet engines and computers, medicines do not have multiple parts. They typically contain only a limited number of pharmaceutical quality ingredients. Exceptions exist, but such factors typically combine to make it possible for competent organisations to copy pharmaceutical products relatively cheaply, once the intellectual property rights (IPRs) that permit innovators to fund new research have expired. This may prove increasingly true with biological molecule products, as well as for small chemical molecule based treatments.

⁶ Full accounting for discounts and allied factors reduces this figure to close to 10 per cent.
The resultant differences in the prices of IPR protected pharmaceuticals as compared to ‘true generics’ sold at near commodity cost can understandably drive fears that, despite their being heavily regulated, research based pharmaceutical companies’ profits are excessive. Yet the available evidence from sources such as the European Commission (EU 2012, 2015) is that once the level of research investment risk is taken into account the pharmaceutical industry is no more profitable than is to be expected on the basis of data from other industrial sectors. In addition, the fact that pharmaceutical costs fall as their IPRs expire means that worries about the rising costs of medicines as a proportion of total health care outlays are often exaggerated.

The NHS’ record is not alone in illustrating this last point. At the macro-economic (large scale) level pharmaceutical spending now, on average, stands at around 15 per cent of national health care costs, or approaching 1.5 per cent of the typical OECD country’s GDP – see Figure 2. The proportion of World Gross Product (WGP) spent on both health care and on medicines and allied products (the latter fraction now stands at an estimated 1.3 per cent) has moved upwards in recent decades, mainly because of greater outlays in emergent economies. But in Britain – where total pharmaceutical spending is about 1 per cent of GDP – and other Western European and North American States the basic year-on-year picture is more stable than is often assumed.

### Optimising affordable access

Similar comments can be made in relation to individual therapeutic areas, including cancer care. This last is at present amongst the fastest changing of all high technology fields. In the UK there has despite evidence of the positive social value of cancer research and anticancer treatment use (see, for instance, Salas-Vega and Mossialos, 2016) been considerable controversy about the cost and overall affordability of anticancer medicines, stimulated in part by concerns that NHS patient access to early diagnosis and new treatments is poor as compared to that enjoyed elsewhere in Western Europe and North America.

Fears about NHS treatment quality can be exaggerated. But it is true that the UK spends significantly less per capita on anticancer products than countries like France, Germany and the US (Jonsson et al, 2016). It is also accurate to say that despite spending having increased in England since 2010 anticancer medicines still account for about 1 per cent of NHS costs and 0.1 per cent of Britain’s GDP. Even in the highest spending countries such outlays account for little more than 0.2-0.3 per cent of GDP. Such sums are large but very far from unaffordable.

Observations like these raise questions about how much individual drug price controls are causal in determining total pharmaceutical spending levels, as against more difficult to identify cultural and economic forces. For example, on occasions measures that drive down the prices and/or use of some specific products can drive up other costs. And even when item-by-item pricing approaches are judged to have major effects on the total amount of money spent on pharmaceuticals, doubts also exist as to whether or not cost effectiveness study based interventions per se are likely to reduce or increase gross spending levels. Associated points include:

- **effective medicines use often requires patient-interest focused professional guidance.** Simply enabling people to take pharmaceuticals freely, without due regard to diagnostic indications and individual response variations, could obviously prove harmful. Professionals like pharmacists make important inputs to enhancing health outcomes by curbing the inappropriate use of the medicines and allied products at the centre of their expertise, as well as by positively promoting their beneficial consumption. From an economic perspective such factors make health care provision and medicines supply within it an unusual, if not uniquely ‘special’,
market. From an overall cost effectiveness standpoint systems characterised by relatively high unit prices for innovative medicines balanced by lower than average usage levels sometimes perform better than low price, higher volume, models;

- providing good health care for populations often requires resource transfers between more and less advantaged groups. This too has important implications for medicines pricing and supply, nationally and internationally. In the latter context, for example, if privately funded pharmaceutical R&D is taken to be an essential complement to publicly financed life sciences research, there is a strong ‘Ramsey pricing’ case in favour of the view that the cost effectiveness thresholds used in relation to medicines in better-off environments and population groups should be higher than those applied in less prosperous settings. But even in the EU there have been difficulties in translating such theoretical insights into agreed methods of adjusting for GDP variations. On the global stage there are challenges involved in seeking to ensure that countries like the UK do not seek to ‘free ride’ on the back of nations which permit higher pharmaceutical expenditures in order to avoid contributing fairly to the world-wide biomedical research effort;

- NICE has conducted important work, consistent with the spirit of the NHS as a pioneering tax funded universal health care system. But its approach to determining the cost effectiveness of innovative medicines is not beyond criticism. For example, NICE guidelines have helped to define good quality care standards at the global as well as the national level (Rawlins, 2016). The organisation’s recent work on topics like treating people living with multiple diagnoses can also be seen as ground breaking. Its multiple and single drug cost effectiveness assessments in addition have the potential to protect against the misuse of monopsony purchasing powers, as well as ‘over-pricing’ risks. However, they lack public interest linked industrial policy dimensions and a fully satisfactory long term health improvement perspective; and

- the role of prices in markets for innovative products is very different from that of ‘market clearing’ in a commodity supply context. Value as judged by ‘cost per incremental QALY generated’ estimates is not necessarily the best determinant of what prices should be in the case of treatments that can be regarded as linked steps taken on a continuing path towards achieving the final end of 100 per cent effective prevention or cure rates. A more dynamic approach might, for example, involve paying more per unit of utility gained in periods where progress is slow and difficult as compared with those when it is easier to achieve rapid advances, or in contexts where the type of suffering yet to be alleviated is inherently more serious than others. Hence relieving even minor forms of arthritic pain in older men is important, but it is materially different from improving advanced breast cancer outcomes in younger women. It is debatable whether or not relieving any number of cases of limited pain should ever be seen as more important than saving lives.

In markets for commodities like, say, wheat, prices are (subject to interventions intended to assure quality and continuity of production) appropriately set by the forces of supply and demand. When there are shortages of such items their prices rise and increased production is encouraged. During gluts prices fall. Scarcity, along with consumers’ ability and willingness to pay, can in such circumstances be said to dominate the concept of ‘value’. Hence water is typically cheap while gold – despite not being vital for life – is expensive.

But products like new medicines and vaccines are not sold in ‘near perfect’ markets in which achieving the greatest immediate good for the largest possible number of individuals is universally accepted as the most important objective. With regard to research activity, for instance, the public’s interests may be best served by incentivising behaviours aimed at achieving sustainable, long-term goal oriented, progress in ‘serious’ disease contexts, rather than more immediate forms of benefit.

To translate this into more personal terms, an individual living with a cancer might be as or more concerned with promoting the ongoing development of treatments that will in future protect her or his children or others in their community than with extending their own survival. This does not necessarily mean to say that they would not

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7 Frank Plumpton Ramsey, whose brother Michael was long after Frank’s premature death to become Archbishop of Canterbury, was born in 1903 and died of what would today be a treatable kidney disorder in 1930. However, in his short life he was able to make a number of important contributions to mathematics, philosophy and economics. Ramsey pricing theory shows that monopoly suppliers of goods like medicines can contribute most to public welfare and their own profits by segmenting markets and charging higher prices to affluent consumers and lower ones in poorer communities. Provided prices in the latter markets do not fall below marginal supply costs producers are not subsidising less advantaged communities by offering products at affordable prices. However, to work effectively Ramsey pricing strategies can demand secrecy and/or restrictions on the free movement of goods in order to mitigate pressures for uniformly low prices.

8 In the run up to NICE’s establishment there were fears that the then new erectile dysfunction treatment Viagra could impose unacceptable costs on the NHS, even though in cost per QALY terms it offered good value for money. The then Secretary of State Frank Dobson imposed NHS supply limits before NICE was formed. This can be taken to illustrate an underlying approach at some variance with publicly stated beliefs in the appropriateness of ‘cost per QALY’ cost effectiveness thresholds. NICE subsequently established its reputation by early rulings on the supply of the anti-influenza medicine Relenza, which it judged to be non-cost effective as a treatment for NHS use in normal conditions.

Affording the future?
want treatment. But their reasons for wanting it may be very different from those implied by conventional economic models, which see people as primarily motivated by a desire for direct (and largely immediate) personal gains.

Advocates of the ‘York/NICE’ approach typically believe that incentivising research for the future is best facilitated by rewarding the makers of recent innovations that generate ‘new QALYs’ on a pro rata basis, within relatively rigidly defined cost effectiveness parameters (Claxton, 2007). Such a strategy may be consistent with a desire to maximise crudely defined health care efficiency at any one point in time. But critics may claim that it is simplistic if not arrogant to suggest the productivity of major bio-pharmaceutical research investments is likely to be directly influenced by the way health economists evaluate products already on the market. If this interpretation is accepted then the time and money presently being put into conducting detailed ‘cost per new QALY’ studies might well be better spent on other activities more directly linked to welfare generation.

The translation of research and development effort into better health outcomes is an inherently uncertain process, regardless of how individuals and groups are financially motivated. It might therefore be concluded that within the broad envelope of resources taken to be available for rewarding private sector pharmaceutical innovation in the UK and more widely, more effort should be applied to understanding alternative ways of supporting productive investment. For instance, it might be that a different strategy for judging which innovations are affordable could seek to ensure that, assuming integrity of intent, earnings are more evenly spread than current arrangements permit.

A ‘big winners take all’ approach, via which those who by good fortune have developed widely applicable products can profit very significantly, while those who invest with good-will but in ‘total QALY’ terms make less viable discoveries can in effect be denied market access, is not ideal in the modern setting. An approach that reduces the perceived long term risks of investing in high quality/high risk research and radical new treatment developments could help protect public interests in ongoing therapeutic improvement and ensuring that potentially beneficial treatments are not needlessly left unsold and/or unused.

As discussed later, one approach to achieving this end could be to amend the present use of threshold levels in interpreting cost effectiveness findings. The aim of such a reform would be to foster more flexible ways of permitting NHS patient access to innovative treatments that are of high scientific and other forms of worth but which benefit only limited numbers of people without increasing gross health service costs to an unsustainable extent.

**Pursuing Value in Health Care**

The origins of present day economic thought stretch back a thousand years and more. For instance, the concept of a ‘just price’ as one based on the necessary costs of making a physical product or offering a service in part stems from the work of theologians such as Thomas Aquinas in the middle-ages. The approach he took in the thirteenth century was linked to the then already long-held belief that ‘usury’ – including charging interest on loans, as well as making profits over and above those needed to maintain an existing business – is morally wrong. Even today, such ethical perceptions underlie opposition to medicine pricing models based on the willingness and ability of individuals and communities to pay for beneficial treatments, rather than calculations that embody an explicit formula for determining the ‘correct’ value of such products in relation to the health gains they generate and/or the costs of their manufacture.

However, the birth of economics as a modern discipline is conventionally located in the ‘age of enlightenment’ which accompanied the start of demographic and epidemiological transition in Northern Europe. In the UK it was linked to the work of individuals such as Adam Smith and David Ricardo. In the last 200-300 years the power of monarchs and aristocrats, supported by military and religious institutions, to determine the allocation of societies’ resources has faded. In the place of feudal dogmas relating to the divine right of Kings to rule their subjects concepts such as ‘opportunity costs’, ‘equilibrium prices’, ‘market imperfections’ and ‘comparative advantage’ have emerged to help guide thinking about how money can best be spent.

Economic thinking embodies the imperative that scarce resources should be used as efficiently as possible to produce valued goods and services, instead of being ‘squandered on second best choices’. However, doing this in practice is in complex plural societies easier much said than done, and in the health arena it is only since the birth of the NHS and other advanced health care systems in the era following the end of World War II that ‘health economics’ has developed in its present form.

Notwithstanding interest shown in ‘medical economics’ in the 1930s, the most generally accepted starting point for health economics was the work of Americans such as Selma Mushkin and Kenneth Arrow (1963) at around the start of the 1960s. This timing happened to coincide with the Thalidomide tragedy in Europe. Their initial analyses were associated with the realisation that health can be regarded as a form of personal capital that individuals invest in and spend during their lives, and with the post-war recognition of the importance of rational, evidence supported, decision making in public policy formation and implementation.
Another American step forward took place in 1972, when the Office of Technology Assessment (OTA) was formed. This had the mission of advising Congress about the value of new technologies and the costs and benefits of providing them to the US public. In fact, its health related work proved of interest to many other audiences, nationally and internationally. But because of domestic opposition the OTA was closed down in 1995, during President Clinton’s first term. The United States’ national level withdrawal from a world-leading role in HTA from the mid-1990s onwards subsequently permitted NICE and other European bodies to assume a more dominant position than might otherwise have been possible.

One of the reasons why economists were slow to address the health sector was that it was not until the late 1940s that health outlays started to account for a significant, and continuously rising, percentage of total spending in the world’s richer economies. The late development of health economics was also linked to the authority of doctors over the allocation of health care resources.

The ability of the medical profession to control its environment is now – in the UK perhaps more than any other country outside the former USSR – more restricted than it was in the past. Yet even in the immediate post-WW II period medical power was still in some ways comparable to that of aristocrats and priests before the social revolutions of the nineteenth and early twentieth centuries (McKinlay and Marceau, 2002; Freidson 1970, 2001). Until stronger managerial systems supported by State inspired regulations emerged, this meant that there was little perceived need for economic evaluations to identify ‘best choice’ health care developments. Indeed, it might be suggested that even today health economics has a disappointingly restricted role outside the field of mathematically oriented ‘cost per QALY’ pharmaceutical technology appraisals.

Examples of early British developments included the formation of the then exclusively ABPI funded Office of Health Economics (OHE) in 1962, soon after the Thalidomide crisis broke.9 On the government side the initial employment of economists at the Department of Health took place at the end of the 1960s, while the first publication in this country on what has been termed a ‘QALY type’ measure by Coulter et al took place in 1971 (Hurst, 1998).

However, for the purposes of this document perhaps the most important event to record was the appointment of Alan Williams as a senior lecturer at the University of York in 1964, and as a Professor from 1968. Apart from a brief period at the Treasury, Professor Williams spent the rest of his life in York, up to his death in 2005, developing his contributions to health economics. This involved him working with an exceptional group of local colleagues and other collaborators (most notably the UCL psychiatrist Professor Rachel Rosser, who before her premature death developed a special interest in quality of life assessment) to in a step-by-step way create the basis of the methodology that has been used by NICE since its inception in 1999 (Williams, 2004; 2005).

Part of the reason for the success of what is now the National Institute for Health and Care Excellence is that, unlike some other politically inspired health service innovations, it was from its inception able to draw on and refine a heritage of over forty years of research, evidence gathering and concept construction. Arguably the single most important step along this long path of intellectual innovation was the introduction of the QALY (Zeckhauser and Shepard, 1976).

Understanding QALY based cost-effectiveness evaluations

Economic evaluation methodologies exist on a spectrum that stretches from cost-minimisation analysis (CMA) to cost-benefit analysis (CBA). The former is of value in comparing different interventions that produce the same outcomes. In such instances it is a relatively simple task to find the lowest cost way of achieving a desired end point. However, if different technologies generate different types of benefit it is more difficult to identify ‘first best’ as against ‘second and third best’ opportunities for spending the resources available.

In the face of this challenge, cost-benefit analysis seeks to convert all the inputs and outputs involved in health care (including tangible factors like labour costs and ‘intangible’ ones such as the value of pain relief and the generation of hope for individuals and families living with threats to their lives) and other forms of activity into monetary terms. The findings that result are usually adjusted to take into account the fact that people normally value immediate benefits more than those that may or may not materialise in the future, albeit in the health context discounting can be queried. For instance, anti-smoking campaigners might say it is likely to lead to an undervaluing of the future distress that a predictable proportion of smokers (and those around them) will experience when they are disabled or dying as a result of conditions such as heart disease, COPD and/or cancer, as compared to the immediate relief nicotine addicts get from tobacco use.

The advantages of CBA include being able to tailor studies to fit specific circumstances, and offering ways of comparing and contrasting the value of different types

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9 The OHE’s Swedish counterpart, the Institute for Health Economics (IHE), was not created until 1979. The early formation of OHE was linked to the establishment of the then Voluntary Price Regulation Scheme (the VPRS, which was the progenitor of today’s PPRS) in 1957 and concerns as to how its evolution could be influenced at the time of its initial renegotiation in 1962. OHE’s development was also shaped by the global changes in the pharmaceutical sector precipitated by reactions to the inadequately regulated sale of Thalidomide for use by pregnant women. This background gave OHE more independence than might otherwise have been the case and fostered a degree of innovative creativity.
of outcome obtainable from similar levels of investment in radically different fields. Because the findings of such studies are expressed in monetary terms they tend (despite the fact that welfare benefits may never exist as hard cash) to be more credible with politicians and the public than ‘softer’ philosophical or sociologically based recommendations. However, conducting good cost benefit analyses requires considerable resources. Further, because high quality CBAs are often complex, they can still leave policy makers feeling uncertain or vulnerable as to what they ought to do when faced with testing decisions about which competing options should or should not receive funding.

**The origins of NICE**

No form of economic analysis can provide unequivocal answers to questions about whether or not it is right for prosperous communities to leave people with diseases like, say, Morquio syndrome sub-optimally treated, whatever the costs of better care (see Box 2). Nor can economic studies offer definitive responses to queries about how much profit it is right for a company to make from marketing a new medicine or questions on how much of their wealth societies should channel into seeking science based advances that will to an unknowable degree benefit future generations. These are ethical issues that require informed logical discussion and good judgement rather than empirical analysis alone.

Nevertheless, there was in high level British political circles in the 1980s and 1990s – stimulated by fears about the possible tax funded costs of new treatments for non-communicable diseases like multiple sclerosis – a growing desire for a robust, financially affordable but publicly credible, means of guiding NHS drug spending decisions and making rationing choices. Sufficiently authoritative interventions would be difficult for critics to challenge and might hence be able to cut short politically troublesome disputes. Appropriately structured, they could also serve to help ensure that the UK pharmaceutical sector is not underfunded as a result of unduly negative pricing policies.

A recently published study entitled *NICE: a Terrible Beauty* (Timmins et al, 2016) describes some of the background to the establishment of NICE and associated attempts by bodies such as the Office of Fair Trading.

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**Box 2. Treating Morquio syndrome**

Morquio A (MPS IV A) is an ultra-rare metabolic condition which is part of a group of diseases known as mucopolysaccharidoses. It is often caused by spontaneous genetic mutations as distinct from familial inheritance, and presently affects under 100 people in England. Morquio A is associated with short stature and spinal and other skeletal problems, and with symptoms such as pain. Life expectancy amongst those severely affected has been only 20 years.

However, in 2014 a drug called elosulfase alpha (Vimizim) was licensed. The full value of this treatment is not as yet known. Yet there is evidence of its benefitting those included in a trial involving 35 UK patients and some 140 others that was financed by its producer, a company called BioMarin. Because of the small global market the unit cost is high. The US launch price was about £250,000 a year. But given a likely uptake of less than 1 patient per million population the budgetary impact of providing such pharmaceutical care should be affordable, even if discounts were not available.

Given the severity of its impacts on families as well as individuals, there is a strong ethical case for offering such care. A number of countries in Europe and elsewhere moved swiftly to assure access to Vimizim after it was marketed. But in England negotiations involving NHS England and NICE took in the order of 18 months to complete. This distressed some carers and patients seeking treatment and because of media coverage of their plight it did little to promote public confidence in the NHS. The welfare costs of this are difficult to estimate. But they were probably in excess of the financial savings made by not acting more promptly.

There is now a Managed Access Arrangement for Vimizim treatment in place in England. Other UK countries have put in place comparable provisions (Roberts et al, 2016; Roberts, 2016). The English scheme presently involves a little under 50 patients. They have each signed contracts which oblige them to attend hospital based assessments at least once every four months, and to provide information about their health and quality of life on a regular basis. If patients fail to respect the terms of their contract or if insufficient evidence of benefit emerges they risk having their NHS funded access to elosulfase alpha stopped. This rigour should mean that mistakes like the CDF’s failure to be able to demonstrate the value of enhanced anti-cancer drug access – see main text – will not be repeated, and that the medical care available to NHS patients with Morquio syndrome is of high quality. However, for some patients it may seem a very controlling approach.

Two other Managed Access Agreements have since the pioneering Vimizim agreement been set up. They relate to treatments for Systemic Lupus Erythematosus (SLE – a potentially life threatening auto-immune condition) and Duchenne muscular dystrophy. DMD is a recessive X chromosome linked muscle wasting disorder which, like haemophilia, normally affects only boys. As more effective rare disease treatment options emerge MAAs are likely to prove an important model for the future. However, it is to be hoped that other groups of vulnerable NHS users will not have to experience the fear and sense of needing to beg for access to care that some of those affected by Morquio syndrome have endured.
In essence, the main steps towards developing the ‘cost per QALY’ approach as employed by NICE today involved:

- defining a unit of utility or value suitable for application throughout the field of health care provision. Quality Adjusted Life Years (QALYs) are calculated by multiplying the length of extra life in years a treatment generates by the improved or dis-improved quality of life associated with that survival gain as measured on a scale of 0-1. So-called DALYs (Disability Adjusted Life Years, most prominently employed by the WHO) are worked out in a related way, although that methodology involves an elaborate age weighting function (Sassi, 2006). The first studies to effectively popularise the QALY concept were published in the 1980s, along with suggestions that average or, it was later argued, marginal (or incremental – see below) QALY cost based ‘league tables’ can act as a guide to which services provide best overall value, and hence which new forms of treatment most deserve investment;

- developing reliable ways of measuring the quality of life enjoyed by people living with differing levels of mental and physical distress and, on the basis of this, measuring the cost per QALY gained as a result of new forms of care. The widely employed 3 level EuroQol 5 Dimension instrument for assessing perceived quality of life was made available at the start of the 1990s. A five level version (the EQ-5D-5L) has been introduced over the past five to ten years (see Box 3). The way quality of life research has traditionally been conducted has been via panels of healthy individuals who are asked to value alternative health states from an ‘objective’ viewpoint. However, there is now evidence that having direct experience of varying types of distress and inconvenience, some forms of which can be accommodated more successfully than others, can change health state perceptions (Kanavos, 2016).

It is also worth noting that calculating QALY yields involves attaching utilities to differing states of being alive, rather than valuing acts that visibly save lives or delay death. Yet life-saving has a special value in most if not all societies. Although this is a contested field (Round, 2012; McHugh et al, 2015) such social facts imply that an additional value should be given to the provision of life saving/extending interventions in contexts like end of life care. What is unquestionable is that some people believe that all lives are equally worth saving, whatever their supposed quality and anticipated duration, while others believe that age and quality of life related weightings can ethically be applied in assessing how much it is ‘worth’ spending on treating one person as opposed to another; and

- setting criteria for how ‘cost per QALY data’ can be used to decide which forms of care or treatment can or cannot be funded. Many but not all economists who accept the value of
Box 3. Measuring Quality of Life and the Pursuit of Value Based Pricing

The EuroQual 5D (EQ5D) has since 1990 been the main instrument used in most British and many other health economics studies of health related quality of life (QoL) issues. It involves, as its title suggests, asking people to rate health states in relation to five domains – mobility as measured by walking ability; self-care in relation to washing and dressing; the capacity to undertake usual activities in the work, domestic and leisure contexts; pain and allied discomfort levels; and anxiety and/or depression experienced. The original 3L version asked respondents to rank their assessments at one of three levels – no problem, a moderate problem or a severe problem. The more recent 5L version adds two more intermediate points into this assessment framework. Hence it significantly increases the number of QoL related health states the EQ5D can describe.

A second part of the EQ5D employs a visual analogue scale to enable individuals’ judgements be recorded as single ‘scores’, with the most negative state imaginable being rated 0 and the best 1. Data generated via these tools can be used to scale quality of life related preferences, so that differences attributable to treatment conferred benefits can be given a relative value. With the addition of the time dimension and cost data this permits QALY values to be determined. Cost effectiveness thresholds can then be applied in order to make affordability judgements for individual treatments.

Such measuring techniques may be seen as relatively crude but are nevertheless robust. EQ5D applications are capable, at least within given cultures, of providing consistently reproducible findings when panels of healthy individuals are asked to rate different conditions. However, recent research has shown that having direct experience of disease and disability can change preferences. People are more able to adjust to problems such as not being able to dress independently than they are to adapt to ongoing pain or psychiatric distress.

Concerns have also been expressed that the EQ5D may not adequately record quality of life dimensions such as relief from fatigue or side effect fears that are known to be important to many patients, and that it ignores value dimensions such as the contributions to economic and societal development derived from using medicines in ways that result in increased investments in research and manufacturing that feed back into wellbeing. It has been suggested that using techniques such as Multi Criteria Decision Analysis (MCDA) could help to correct shortcomings in calculating QALY values (Thokala et al, 2016). However, the extent to which such alternatives provide answers that differ significantly from those generated via studies using the EQ5D or similar instruments is debatable. Whatever the methodologies employed, if researchers restrict their attention to assessing narrowly defined individual health benefits as against societal level public health and wellbeing variables they will always generate similar overall findings, even if their recommendations as to which individual products offer best value vary.

In the period following the ‘Lansley’ NHS reforms announced in 2010 it was hoped by some that new approaches to determining ‘value based’ prices (VBPs) for pharmaceutical products supplied to the NHS would resolve problems being encountered in areas like anti-cancer drug supply, which the CDF (see text) was intended temporarily to contain. In essence, policy makers were seeking to establish a new consensus as to how weighting QALY calculations could and should satisfy the concerns of all the stakeholders in the pharmaceutical research, development, supply, purchasing and use process.

In theory this might be possible, even if in the NHS arena there are inherent tensions between cash limited, publicly funded, buyers and IP holding private sellers. But the VBP initiative’s objectives were not in practice achieved for reasons touched on in the main text of this report, and because of political naivety coupled with the fact that the beliefs and interests of some of those charged with developing a viable model may have precluded the pragmatic compromises needed. Success would arguably have required integrating estimations of the long term ‘public health and wellbeing’ dimensions of the value of using medicines and investing in public and private biopharmaceutical enterprise with narrower empirical measures of the short term individual health gains generated by taking innovative treatments. It may also have demanded new ways of systematically addressing the ‘affordability, profit and volume’ trade-offs involved in medicine, vaccine and diagnostics supply.

cost effectiveness analysis in improving health service efficiency agree that setting either explicit or implicit cost effectiveness thresholds is a necessary step. However, comparatively few would say that such thresholds should be rigidly applied, or that aggregated data based ‘cost per incremental QALY’ figures ought to be the only factor taken into account when deciding what services should be made available. Averaged observations do not necessarily reflect individual experiences. In addition, it may be argued that in effect telling (by applying defined cost effectiveness thresholds) the providers of new treatments the maximum amount they can charge might in some instances increase rather than decrease spending levels. In other circumstances rigid cost effectiveness thresholds could stop some patients receiving treatments that could reasonably be regarded as affordable on a budgetary impact basis, especially when total pharmaceutical outlays are capped.
The proponents of ‘cost per QALY’ based approaches often believe that although NICE does not set the prices of patented or other IP protected medicines and is not responsible for purchasing items that are obtained by the English NHS, its work nevertheless serves to promote a form of ‘value based’ pharmaceutical pricing. This, such commentators suggest, might not only generate financial savings for the NHS and benefits the wider economy, but also provide the research based pharmaceutical industry with the best possible incentives to produce more effective medicines.

One implication of such thinking is that, without NICE, research based companies would focus on the production of items which lack therapeutic utility but which because of market imperfections could prove more profitable than clinically more significant alternatives. However, the likelihood of this being true is limited. Other problematic assumptions relate to factors like the speed at which the NHS adopts innovations.

**Box 4. The UK PPRS**

Prior to the establishment of the Pharmaceutical Price Regulation Scheme in 1962, a predecessor initiative called the Voluntary Price Regulation Scheme (VPRS) was set up in 1957. Framed in the period shortly before the Thalidomide tragedy, this linked domestic pharmaceutical prices to those of exported items because it was at that time thought that health service willingness to pay for medicines should be guided by the prices paid on the world ‘free market’. But by the early 1960s attitudes had become more critical. The PPRS introduced more assertive controls. It has since evolved into a system for limiting company earnings and the costs incurred in areas ranging from management and spending on marketing to research and medical information provision as they relate to the supply of branded medicines to the NHS.

Proponents of the PPRS say that it effectively addresses both the health service’s need for economy and medicines affordability and wider public interests in fields such as maintaining innovators’ legitimate rights to set their products’ prices and encouraging export oriented enterprise. However, critics have argued (see OFT, 2007) that it in the past allowed branded medicine and allied product prices to fall out of line with their value to NHS patients. This, it was alleged, caused distortions in health service resource allocation and activity that might have ultimately cost lives.

Such charges have an at best uncertain validity. Provided PPRS and allied controls ensure that the total costs of NHS drug supply are within agreed limits, claims that other areas of health and social care are being deprived of funding because of medicines outlays could be misleading. It might be more appropriate to say that governments have simply chosen not to fund some other areas, like health related social care, to an adequate level. The latest version of the PPRS places an explicit ceiling on the overall amount of money spent on pharmaceutical products in the ambit of the scheme. As described in the main text, there have from an industry viewpoint been concerns that discounts returned to the Department of Health, which are currently in excess of £500 million, are not repaid to the agencies directly paying for medicines. This could be encouraging the under-use of some treatments for no real health service saving.

Not all companies and/or products are covered by the PPRS. Even so, the fact that the gross cost of the majority of the medicines purchased the NHS is being contained via mechanisms other than detailed product-by-product pricing interventions is worth emphasising, not least from an NHS user’s perspective. Patients and their representatives are primarily concerned with ensuring that everyone who might reasonably hope to benefit from licensed treatments can enjoy access to them. Pharmaceutical expenditure capping systems linked to appropriate ‘excess earning’ repayment arrangements may help facilitate this, albeit there can be no ‘magic bullet’ solutions to resolving all NHS pharmaceutical cost linked tensions. In the case of budget capping strategies stakeholders would need to agree methods for ensuring that the overall quantum of money being spent represents an acceptable percentage of GDP, and that the income available to competing companies is fairly distributed in relation to their innovative and wider medicines supply related performance.

**Differing National Approaches**

The extent to which beliefs like those outlined above are valid in the current health care environment is explored further towards the end of this report. Before that, however, some wider questions relating to British, European Union Member State and other national policies on medicines pricing and cost control are considered.

In England, topical pharmaceutical sector issues have recently included the major changes in the role and working of the Cancer Drugs Fund first announced by the Cameron/Clegg administration in 2010 in the wake of a Conservative election commitment to improve cancer drug supply to NHS patients. The delayed publication of the final report of the Accelerated Access Review (AAR) has also been of significant interest. The AAR was established in March 2015 with, as its title suggests, the objective of finding ways of enhancing NHS patient access to innovative drugs and associated products.
Additional areas of debate have included the pricing of generic medicines that have only one producer and are shielded from competitive pressures within the NHS supply chain and the future of the PPRS. The latter offers a framework that embodies approaches to branded medicine pricing and overall NHS spending limitation which may be seen as alternatives to, or at least valuable complements to, ‘cost per QALY’ based strategies – see Box 4.

Improving cancer care

The CDF was created because of popular concerns that the NHS has in some respects under-performed in the field of cancer care. The most important shortcomings of the latter arguably relate to late and insufficiently precise cancer diagnoses. Yet at around the time of the May 2010 general election there was also evidence that in England and Wales NICE was, despite the introduction of an end-of-life care cost effectiveness threshold weighting, refusing on cost effectiveness grounds to recommend many anti-cancer medicines that other European countries were providing for their citizens. This threatened to undermine trust in the NHS as a care provider. Given the special position of the health service in British politics such fears put pressure on elected policy makers, who in earlier years had witnessed Tony Blair’s politically successful interventions in the area of breast cancer treatment.

In the period from 2011-2015 the CDF helped to increase per capita NHS spending on anti-cancer medicines in England to around the EU average. In that period its annual outlays rose from around £200 million to in the order (including budget overspends) of £400 million. (In total, anti-cancer medicines now cost the NHS in excess of £1,500 million a year.) The rise in CDF spending was therefore significant, if in headline terms little more than the aggregated NHS spending increases reportedly incurred in the context of ‘single source’ generic medicines outlays – see The Times, 2016.

More broadly, the CDF’s costs between 2011 and 2015/16 also need to be seen against the exceptional scientific advances being made in oncology at this point in history and falls in spending in other, more mature, areas of pharmaceutical care. Total pharmaceutical spending expressed in manufacturers’ prices did not rise as a percentage of all NHS outlays in the period 2010-15. It rather remained at just on 10 per cent of all health service costs. Claims that the CDF had become ‘unaffordable’ might therefore be seen as to a degree disingenuous, even though it was unquestionably imposing strains on the newly created NHS England’s specialised services commissioning budget.

The available data suggest that up to its restructuring in July 2016 the CDF was benefiting about 20,000 individuals a year. However, its impacts on health outcomes have not been systematically quantified. Because of this failing, coupled with the challenge the CDF was offering to both NICE’s decision making process and NHS England’s budgetary control, it has now been ‘repurposed’ to act as a mechanism for facilitating the managed introduction of anti-cancer medicines that are at the time of their initial marketing judged to lack enough evidence to determine their cost effectiveness. How well this radically new arrangement will work in practice is uncertain. It contains a number of controversial provisions11. But for the purposes of this analysis the most important observations to be offered include:

- **anti-cancer drug development programmes often take decades to reveal the full value of innovative treatments, especially when they can most effectively be used in combination with other agents in curing early stage illnesses.** The data employed to gain initial marketing approvals typically relate to the observed effects of new treatments in slowing the progression of late stage, terminal, cancers. This is not always explained to patients and the public. It may on occasions be why new anticancer medicines are discerned as ‘merely adding weeks to the end of life’. Given the limited periods that IPRs apply for before generic competition commences, the need to generate income relatively early in the life cycles of anticancer medicines in a period when evidence of their cost effectiveness is unlikely to be complete can be potent force underlying pricing disputes; and

- **since the 1990s the focus of pharmaceutical innovation has shifted from high volume use, relatively low unit price, medicines supplied in the primary care setting towards lower volume use, higher unit price, treatments most commonly prescribed in specialist hospitals.** This trend, which is reflected in the data shown in Figure 3, means that although overall primary care medicine costs have fallen with IP expiries, hospital and other specialised care budget holders have faced difficulties. The fact that in recent years ‘invisible’ discounts have via the PPRS mechanisms referred to in Box 4 been received centrally rather than locally has exacerbated such trends. The role played by the

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11 Bodies such as Breast Cancer Now and Prostate Cancer UK (2016) have warned that this country’s overall approach to HTA and anticancer medicines pricing/purchasing may prove sub-optimal. The new (England only) CDF arrangements set a cap on spending on the new anti-cancer medicines included in its remit of some £340 million per annum, which is about the same amount as the CDF budget that was exceeded in 2015. Companies that are responsible for investing in cancer care improvement will be required to compensate the NHS for over spending. There is a risk that as well as selectively disadvantaging NHS users with cancer and doctors seeking to provide them with the best possible treatment this could discourage further investment in the field, especially if other nations were to follow England’s lead.
CDF should be understood in this context, as well as that of the fundamental scientific advances presently taking place in areas such as immuno-oncology.

It is sometimes suggested that continuing advances in cancer care will threaten to undermine the affordability of the NHS. However, NHS spending on anti-cancer medicines of all types is no more than 20 per cent of total cancer service costs, and the latter – as in other health care systems – account for little more than 5 per cent of NHS outlays (Jonsson et al, 2016). Hence NHS anticancer drug spending currently stands at around 0.1 per cent of GDP.

Even if this proportion temporarily rises as more effective treatments are marketed, counter-balancing savings will be made as other pharmaceutical costs fall and age specific cancer-related outcomes improve. In this context it is of note that amongst people below the age of 60 cancer mortality rates have already halved since the 1970s (Cancer Research UK, 2016). Contrary to common political assumption, population ageing per se has not in recent decades been a major driver of increased health care costs in countries like the UK. In developed communities delaying death also delays much health spending (Gill and Taylor, 2012).

**Figure 3. Trends in NHS hospital and primary care spending on pharmaceuticals**

<table>
<thead>
<tr>
<th>Year</th>
<th>% of total NHS Pharmaceutical costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>39%</td>
</tr>
<tr>
<td>2013</td>
<td>41.2%</td>
</tr>
<tr>
<td>2014</td>
<td>43.5%</td>
</tr>
<tr>
<td>2015</td>
<td>45%</td>
</tr>
</tbody>
</table>

Source: IMS and ABPI

**Accelerating Access**

Turning to the AAR, key points to highlight relate to the value of pharmaceutical enterprise in the light of British, European and global health and industrial and scientific development interests. These are broader than just those linked to the immediate capacity of the NHS to generate additional QALYs. Informed submissions to the AAR inquiry have recommended the introduction of more flexible and timely approaches to assessing the full community-wide value of new medicines and agreeing affordable prices (Pisani and Lee, 2016).

Such changes, coupled with developments like a greater use of the MHRA’s Early Access to Medicines Scheme (EAMS), could help restore confidence that the availability of innovative treatments to NHS patients and clinicians is in line with that enjoyed by the citizens of countries like France and Germany. However, this will not be the case if reductions in cost effectiveness thresholds like those recommended by Claxton et al (ibid) were to be adopted by NICE, or in one way or another imposed by other agencies responsible for purchasing products like innovative vaccines and medicines for use in NHS specialist care settings.

The work of Claxton and his colleagues involved attempts to estimate the average cost of each new QALY generated by existing NHS services. They argued that lives and/or wellbeing will be lost unless the figure they derived for the latter is used as a ceiling for the amount the health service is prepared to pay for each incremental QALY generated by innovations like new anticancer medicines.

Other sources, such as Barnsley et al (2013), have offered detailed technical critiques of this research and the quality of its conclusions. Their findings are not repeated here. But it is worth highlighting the fact that even commentators who are highly sympathetic to need to control NHS pharmaceutical costs have questioned the wisdom of lowering NICE’s cost effectiveness thresholds. (See, for example, Raftery, 2014.) None of the individuals interviewed during the preparation of this analysis accepted that a case for a radical lowering of existing NICE cost effectiveness thresholds has successfully been made. Some said that even maintaining them at existing levels could, without the introduction of new flexibilities to permit higher thresholds in some contexts, prove damaging to the UK public’s interests.

It was noted, for example, that other government backed research initially undertaken in the transport context found a ‘willingness to pay’ based incremental QALY value of up to £60-70,000 (Mason et al, 2009; Towsse, 2009). This is four times the health sector limit advocated by Claxton et al. US sources consistently indicate higher threshold figures, while in the UK nursing...
home care for people living with illness and disability often costs in excess of £50,000 a year in the UK.

One interviewee was in addition particularly concerned that the York University study in question reported wide variations in the cost per incremental QALY incurred in differing areas of health service provision. In some fields it is well over £1 million. In others it is less than £5,000. Against this, it is reasonable to ask why, unless other unstated assumptions are being made, the ceiling value set for introducing innovative pharmaceutical products designed to address unmet needs should be confined to a (questionably estimated) average NHS ‘incremental QALY production cost’ of around £15,000.

Further to such questions there is, as already indicated, evidence that the cost effectiveness of pharmaceutical treatments rises as their IPRs expire. Their prices fall as their life cycles proceed (Pistollato, 2015) and the expertise needed to optimise their use grows. Such observations imply that it would be appropriate to accept ‘market entry’ prices for innovative medicines with indications for as yet inadequately treated conditions that represents a cost per incremental QALY well above any estimated average NHS cost effectiveness level. It would be unfortunate if the fact that the health service is tax funded because it is seen as exceptionally important by the UK electorate were to end up meaning that the community’s marginal propensity to spend on health services and/or products is significantly lower than that observed in many areas of private consumption, some of which are positively harmful to health.

**CEA in Europe and the US**

In the wake of the establishment of NICE, many other countries formed organisations that seek to contribute to determining the affordability and equitable provision of new medicines and other health related products and services. Sweden, for instance, has an unusually long tradition of evidence based public administration. A body called the Swedish Council of Technology Assessment in Health Care (the SBU) was first set up in 1987 (Jonsson, 2009). But it was not until 2002 that a specific Pharmaceutical Benefits Board was established. Now known as the Dental and Pharmaceutical Benefits Agency or TLV, this plays a central part in the processes of establishing ‘value based’ medicine prices.

However, the extent to which the TLV or other European agencies operate in ways which are directly comparable to NICE’s approach should not be overstated. The Swedish body, for example, can claim to be more open to making adjustments in its judgements based on the specifics of each case. It may on occasions accept ‘costs per incremental QALY’ that are in excess of twice the normally reported NICE ceiling (that is, in the order of €100,000) without resorting to employing a special evaluation methodology that is significantly different from that in day-to-day use (Wallström, 2016). This is on occasions cost increasing. However, satisfaction with Swedish health care is relatively high and as a proportion of health spending reported pharmaceutical costs in Sweden are a little below the UK level. At the same time overall health care costs expressed as a percentage of GDP are only marginally higher, albeit social care spending is significantly greater than in Britain.

Other examples of European bodies that undertake health technology assessments include the French National Authority for Health (the Haute Autorité de Santé, or HAS), which in its current format has existed since 2004, and the German Institute for Quality and Efficiency in Healthcare (IQWiG). This was also set up in 2004. Substantial health economics expertise relating to the evaluation of medicines has also been developed in countries ranging from the Netherlands and Spain to Italy and Poland. Yet despite some convergent trends the detailed ways of working adopted in each of these national settings can once again be said to differ significantly from NICE’s tightly focused ‘cost per marginal QALY’ methodology.

In Poland, for instance, the cost effectiveness threshold used is – in line with WHO recommendations relating to the affordability of Disability Adjusted Life Years – three times the per capita GDP. However, despite the economic growth enjoyed since the country entered the European Union this last figure remains much lower than that recorded in most of Western Europe. Because of this, Polish Governments appear to have been more sensitive to issues such as minimising spending on imported as opposed to domestically produced items than is the case in the UK.

In Italy, by contrast, the setting of a defined affordability threshold is normally avoided. This allows greater freedom for confidential price negotiations (EIU, 2015). Likewise in France, despite what appears to be a growing acceptance of QALY’s as a measure of value in the health sector, greater attention is given to factors such as the views of professionals on the scientific and clinical value of new medicinal products and, in line with the Napoleonic tradition, to the precise legal provisions in place for defining the rights of citizens and the powers of governmental agencies (Remuzat et al, 2013; Barron et al, 2014). There is evidence that the quality of French...
health care is valued highly by people living there. NHS users’ views on the services available to them in most contexts reflect lower levels of satisfaction.

In Germany there is a relatively strong commitment to ensuring that new pharmaceutical and allied technologies are accessible via the social insurance funds in operation there as rapidly as possible (Gissel, 2013). This can initially involve accepting relatively high prices for innovative medicines with original modes of action, although over time the ‘efficiency frontier’ based strategy adopted in Germany acts to drive costs down across the board. The system is not reliant on ‘cost per QALY’ calculations for achieving increasing efficiency. Both Germany and France spend more of their national wealth on health and social care than the UK. Yet there is no economic evidence to indicate that this means that their populations would benefit from the reallocation of some of the resources currently employed on health related services and products to other areas.

Box 5. The Value of the Pharmaceutical Industry

In the UK there is a danger of spending on pharmaceuticals by the NHS being seen as just a cost to the public purse, rather than as a robust source of value to society. In addition to the health gains that medicines and related products deliver, recent data show that British and other pharmaceutical companies made a £3 billion positive contribution to the balance of trade in the period leading up to the Brexit vote. The research based pharmaceutical industry accounts for about 25 per cent of all UK private R&D spending (companies currently spend some £4 billion a year on British based projects) and directly employs 70,000 people. This is a relatively small workforce compared with areas such as high street retail. Yet in per capita terms pharmaceutical company employees contribute more to the UK economy than those working in any other major sector.

Multiplier effects mean that the gross value delivered to the UK economy is several times greater than the trade surplus generated. Industry spending and profits in addition contribute to the incomes of institutions like pension funds and the work undertaken by Universities and health research oriented voluntary sector organisations, all of which are vital to the UK economy’s health. Even so, evidence generated via interviews conducted for this analysis suggests that some health economists believe that the nation’s best interests could be served by pushing down pharmaceutical prices to levels substantially below those currently paid in most other economically developed nations.

Such commentators may argue that this would benefit patients seeking NHS treatment and that, because of the excellence of the British research environment, investment in UK based pharmaceutical company activities and clinical trials will not be adversely affected. ‘Free-ride’ advocates may also believe that because America spends so much more that the UK on pharmaceutical research and development the worldwide rate of biomedical progress will not be significantly slowed if Britain fails to make proportionate inputs to the global research based pharmaceutical industry’s income.

However, the view taken here is that such arguments are unethical and unrealistic. There is a strong counterbalancing case in favour of the view that Britain should, relative to its GDP, contribute as much to the costs of private pharmaceutical R&D and global supply as countries like Japan, the US, France and Switzerland. Public support for this is in part signalled by the fact that UK per capita voluntary contributions to ends such as charitably funded cancer research are amongst the highest in the world.

American critics of the fact that the US spends in the order of 2 per cent of its GDP on pharmaceuticals on occasions point to the fact that (notwithstanding the recent Obama reforms) health care there has been inequitable and relatively inefficient, and that access to medicines amongst poorer groups can on occasions be wanting. There is some substance in such concerns, even if structural US health sector failings cannot be attributed to pharmaceutical costs per se. As a proportion of total American health outlays these account for little more than 10 per cent. What is more clearly true is that the US economy receives net benefits from not only pharmaceutical industry company investment and profits, but also from being a world centre of life sciences research and product manufacturing. Positive interactions between privately and publicly funded research efforts have helped achieve this position.

Switzerland’s population, despite its much smaller size, also enjoys considerable benefits from its pharmaceutical industry, as does that of Eire in respect of manufacturing. However attractive the research settings that Britain may continue to offer, there is a risk that the cumulative impacts of conflicts about pricing and allied issues could discourage further pharmaceutical industry investment. This will be especially likely if the post-Brexit economic environment proves more challenging than optimists hope. Dropping the cost effectiveness threshold used in NICE or other assessments used to determine NHS patient access to pharmaceutical care would almost certainly prove counter-productive. But if the Britain’s responses to the hazards it faces are adequately planned and implemented there is no reason to doubt that it will be able to enjoy pharmaceutical sector successes comparable to those seen in the US and Switzerland.
Turning to North America, both Canada and the US are also relatively high spenders on health care and within that on pharmaceuticals as compared with the United Kingdom. Canada has since the start of 1980s made significant investments in health economic studies and developing methodologies for assessing the cost effectiveness of new medicines and allied technologies. Canadian Courts have also in the past challenged the extent to which IPRs owned by American research based companies apply in their jurisdiction.

However, absolute per capita spending on pharmaceuticals in Canada is amongst the highest in the world (OECD, 2015). It is also well above that of the UK when expressed in GDP percentage terms. The reasons for such apparent discrepancies in part relate to the Provincially based system of health care financing, which increases pressures on politicians to ensure high quality care in ways that are responsive to local needs and preferences. There also appear to have been perceived interests in permitting relatively high prices for domestically produced generic medicines.

In the case of the United States the available data show that, like France, it allocates around 2 per cent of its GDP to purchasing medicines and associated products and services, as against the 1 per cent recorded in the UK. The extent to which this advantages as opposed to imposing a burden on the American public is debateable – see Box 5. But from a long-term macro-economic perspective there are strong arguments in favour of the view the US spending on products derived from biomedical/biopharmaceutical research benefits the overall American economy. A strong pharmaceutical sector funded via both private and public investments generates returns at many levels.

One of the most important factors to highlight is that, as noted earlier, for the 20 years or so since the closure of the Office of Technology Assessment the development of publicly supported cost effectiveness research has been limited in the US. This has been linked to beliefs that ICER based restrictions on the affordability of treatments supplied to patients living in varying states of health could prove discriminatory, and may harm the interests of not only individuals but also those of research based industry and the wider US community.

American medical and economic though leaders such as Professor Milton Weinstein have argued that an extended use of cost effectiveness analysis and allied techniques could play a positive role in improving the efficiency of the US health sector. Yet at the same time they have warned that the narrow UK focus on ‘cost per QALY’ driven assessments linked to low cost effectiveness thresholds could prove counter-productive (Weinstein, 2010; 2011).

In future initiatives such as the establishment of Patient-Centred Outcomes Research Institute (PCORI – which was formed following the passage into law of President Obama’s Affordable Care Act in 2010) – may establish a new balance between rewarding and promoting innovation and defending public interests in equity and population-wide access to good quality care in the US. Yet achieving this is likely to demand progressively more sophisticated approaches to applying concepts such as cost-effectiveness thresholds (Dubois, 2016). If attained, such advances would be likely to have global impacts, as well as the potential to further improve health in less advantaged sections of America’s domestic population.

Science, dogma or pragmatism? Determining cost effectiveness in a changing world

Factors such as national cultures and political preferences and interests play a complex role in not only setting overall health care spending levels but also how alternative opportunities within different health sectors are valued and funded. Because of the nature of the phenomena being studied both academic traditions and more transient ‘thought fashions’ can have a major influence on the observations made by, and the findings of, social scientists. This may be as true for economic results expressed in ‘hard’ monetary terms as it is for the products of ‘softer’ disciplines such as medical sociology and moral philosophy.

While not denying the desirability of trying to inform health sector decision making with rational economic assessments, or the need for mechanisms which ensure the budgetary stability of public and private services, the discussion below highlights questions relating to the assumptions and practices that exist in areas like the setting of cost effectiveness thresholds used in HTA studies. Given that this area is often poorly understood (Culyer, 2015) it seeks to further develop themes raised in the opening sections of this report, with the goal of casting light on how current approaches might further evolve in order to serve future health related public interests better than is currently the case.

How much should be spent on health care?

At first sight the total amount spent on the NHS may seem to have little to do with how much bodies like NICE say an additional QALY is worth. It might, for instance, be thought that while macro-level health service spending is set by political exigencies linked to the election cycle and events like the 2008 financial crisis or Britain’s withdrawal from the European Union, research on whether or not
life-prolonging treatments are ‘cost effective’ should be
grounded in fundamental considerations.

From a practical perspective the linkage between
total health service costs and what NICE or other
agencies take to be the maximum acceptable value
of an incremental QALY is indeed tenuous. But from a
theoretical standpoint the two should in fact be closely
related. It might, for instance, be suggested that if it
could be shown on a UK public willingness to pay
basis that an additional Quality Adjusted Life Year is
on average ‘worth’ £50,000 then total NHS spending
ought to be set to reflect such observations. (This value
varies between social classes. The UK system might by
critics be said to be at risk of imposing willingness to pay
values characteristic of poorer social groups across the
board, rather levelling up. See sources such as Hammitt,
2002; Baker et al, 2010; and Donaldson et al, 2011 for
discussions of how the social value of QALY’s might be
best determined.)

However – as people in organisations like NHS England
may well fear – the politically determined affordability of
such an approach could not necessarily be guaranteed.
It is therefore more likely to be argued that the overall
amount of money made available for health care should
set the ‘price’ of each new unit of health gain.

Adequate data on the incremental NHS costs of generating
health gains across the health sector as a whole remains
lacking. Yet this thinking underpins recommendations
in favour of cutting the amount payable per additional
QALY produced to £15,000. This approach is therefore
highly questionable, in part because it is impossible ever
to know accurately what the overall amount of ‘marginal’
health gain the NHS currently generates is, or could be
were the health service optimally organised.

In reality there is evidence that ICER values vary greatly
within all health care systems (Neumann et al, 2014).
From a dynamic developmental viewpoint it might be
judged beneficial to pay more for QALYs derived from
technology based advances that are likely to lead on,
directly or indirectly, to step changes in health care
productivity than for extra QALYs provided via extending
services in static fields. This approach implies that no
single ‘correct’ marginal QALY value can be calculated,
and that pragmatic judgements need to be made on
a case-by-case basis. Similar arguments can also be
raised, for example, in relation to the value of exporting
items like medicines, and to the importance of generating
hope amongst individuals facing serious illnesses that
cannot at present be satisfactorily treated.

Regarding the overall cost of the NHS, the UK has from
the 1960s had a track record of spending less of its GDP
on health and associated social services than many
other similarly prosperous Western European nations.
Fully reliable international comparisons do not exist, and
exaggerations should be avoided (ONS, 2016). But it is
reasonable to estimate that England allocates some 10-
20 per cent less of it wealth on health and health related
social care than countries such as France, Germany and
the Netherlands. These have social insurance based
systems, while the NHS is (together with Local Authority
services) overtly funded from central taxation.

At the same time UK health care costs are closer to half
the GDP level recorded in the US. However, America
spends less of its wealth on other forms of welfare. It is
arguable that its high use of private funding, alongside
a public spending level comparable to that in Britain,
means that for sections of the population its health
care system remains – notwithstanding Obamacare –
less fair and effective than is the NHS. Paradoxically,
some commentators implicitly argue that if people in
the UK value the equity aspects of having a tax funded
health service more highly in relation to variables such
as encouraging innovation or economic growth than
do Americans, this justifies setting relatively low cost
effectiveness thresholds.

Because raising taxes is frequently unpopular with
voters and those seeking election, this line of thought
suggests that it is ‘right’ to be much more parsimonious
with taxpayers’ money than with private or compulsory
insurance raised funding. Such a bias could be taken to
legitimate spending less on health and social care than
comparably wealthy nations with other health service
financing systems. Within Britain it could also be seen as
a reason for being significantly more careful with ‘NHS
£s’ than people are when buying items like ‘fast-foods’
or alcoholic drinks14.

However, the NHS was not created during the 1940s
to keep per capita health spending down to levels
below those recorded in nations like modern Germany,
or to ensure that the services it offers are much more
cost effective than those available in other parts of
the economy. Arguably the UK electorate was instead
focused on creating universal access to the best
possible standard of comprehensive care for citizens of
every class.

There is also evidence that the war-time planners
and members of the subsequent Attlee government
hoped that NHS policies would help keep Britain at the
forefront of biomedical research and linked industrial
development. The rationale for this related to being able
to pay for enhanced ‘post-Imperial’ era domestic welfare
provisions. To the extent that these goals still represent

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14 The UK population currently spends about 20 times as much on
‘fast food’ purchases like take-away meals as the NHS does on
anticancer pharmaceuticals. Out-of-pocket outlays on items like
alcoholic beverages are of a similar magnitude, even after tax.
They represent more than twice the total costs of all forms of
NHS cancer care. However, it is anti-cancer medicines rather than
items like tobacco products that are more commonly said to be
unaffordable.

Affording the future?
British voters’ aspirations and preferences they provide further grounds for disputing claims that calculations based on current NHS spending levels offer reason for lowering NICE’s present cost-effectiveness thresholds.

Put succinctly, Britain ‘nationalised’ health care funding (as distinct from all aspects of its provision in the community) because it was believed it to be especially important. Efficiency is desirable. But it would be a counter-productive result if in the twenty first century pursuing an equitable approach to paying for health care in the aftermath of Hitler’s war were ultimately to cause British investment in health related services to be significantly lower than would have been the case had a Bismarkian or US style insurance model been favoured in its place. Unless those responsible for conducting and using cost effectiveness studies understand the implications of this observation and are prepared to guard against the hazards it suggests there is a possibility that they will, through actions like accepting unduly low incremental QALY affordability thresholds, undermine public interests.

Is a QALY always worth a QALY?

Some but not all health economists believe that ‘a QALY is a QALY’ in the sense that, in order to maximise the efficiency of health care, the NHS should always pay the same amount for each additional unit of health gain, whatever the context in which it is produced. However, others think this a questionable approach. In addition to the problems inherent in setting appropriate cost effectiveness thresholds, the reasons why multiplying the average duration for which a treatment benefits individuals by the additional quality of life (QoL) generated cannot provide a consistent measure of value relate to:

- the challenges involved in quality of life measurement, coupled with concerns about any implied assumption that extending the lives of individuals fortunate enough to have good underlying health is worth more than providing similar benefits to groups of people who because of persistent illness or permanent disability are unable to recover from illness so fully;
- the growing importance of low incidence diseases and the benefits of ‘orphan’ treatments in societies that have successfully controlled many more common disorders, and the fact that at given points in history communities may rationally elect to prioritise some forms of health care research and development over others;
- the fact that health related benefits and their sequelae are experienced not only by individuals during their lifetimes, but indirectly by families and wider communities over longer periods;
- the need, in part due to the complex interactions between population health and macro-economic performance and the potential impacts of pharmaceutical purchasing decisions by monopsony buyers on research and manufacturing investment, to foster coherent policies on the development of the UK’s life science based industries and their future capacity to enhance national income; and
- the weaknesses of inflexible ‘evidence based’ approaches in fields characterised by high levels uncertainty, where appropriate policy formation rests on the exercise of intelligence, good probabilistic judgement, rationality and consistent ethical purpose rather than the mechanistic interpretation of empirical information.

This does not seek to be a technical paper, and not every dimension of the issues identified above can be explored here15. However, some commentators concerned with the value as opposed to the quality of life argue that, subject to the varying personal choices of the individuals involved in any given episode of care, duration of life should take precedence over the avoidance of disability. In assessing the utility of medical interventions it is reasonable to attach more ‘worth’ to those which improve survival and confer freedom from problems such as chronic pain than those that only improve survival to a similar degree. But because QALYs confute the length of individuals’ lives with their externally perceived quality their use may risk treating some types of patient inequitably.

People who are living without significant health problems are likely to attach a relatively high value to avoiding states like being unable to dress or wash independently, or having to live with learning or other disabilities (see Box 3, page 14). Yet this does not mean that those experiencing such conditions find being alive worth any less than do people with the good fortune of living without them. Even if special safeguards can mitigate the danger of unfairly treating – of failing to treat – less advantaged people, concerns about the potential for discrimination may cast doubt on the QALY based ICER concept as a reliable arbiter of utility throughout health and social care.

Parallel to this, it might also be argued that the age at which an extra QALY is gained by an individual affects

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15 Other potentially important questions relate to whether or not people in need of treatments that can be life-saving or disability preventing but which are judged insufficiently cost effective for NHS provision should be entitled to financial compensation up to the level implied by the mean cost effectiveness threshold used in making rationing decisions. It is also debateable as to whether individuals who are not in receipt of any form of expensive care should be entitled to having more resources allocated to their treatment for a new indication than would be so in instances where patients are already receiving high cost therapies for other conditions. However, the equity related policy implications of ‘disconnects’ between assessing the cost effectiveness of individual treatments as against the relative cost effectiveness of treating different groups of people requesting NHS care are not explored here.
its value. Alan Williams suggested this when he argued, 
rightly or wrongly, that people should when they reach 
their 70s accept that they have had a ‘fair innings’ and 
not seek to access costly health care to the same extent 
as younger individuals (Williams, 1997). Even if his work 
in this area is only taken to mean that older individuals 
have fewer potential QALYs to lose than younger ones 
it carries disturbing implications for those who favour of 
‘age blind’ welfare policies.

Another illustration of one QALY not necessarily being 
worth another relates to saving the life of a new born 
infant as compared with that of her or his mother. In 
affluent societies the projected life expectancy of the 
baby would normally be significantly longer than that 
of the mother. Hence the number of conventionally 
calculated QALYs generated by saving the infant would 
outweigh the number yielded by saving the mother. But 
the ‘real world’ costs generated by losing a parent or an 
as yet childless adult with a formed mind and established 
social links may reasonably be thought to be far higher 
than those caused, however tragically, by the loss of an 
infant with an unformed identity.

Turning to orphan disease treatments, it can be less costly 
to develop medicines or other therapies for rare disorders 
than it is to discover and prove the safety and efficacy of 
new treatments for common conditions. This is especially 
likely to be so when there is a ‘re-purposing’ established 
medicines, and when it is judged inappropriate to factor 
in the sunk costs of research project failures into that of 
particular innovations. However, it is broadly true to say 
that all novel therapies have high costs of development, 
regardless of their volume sale and the total number of 
QALYs they will generate during the period for which 
IPRs apply.

Given relatively low marginal production costs and the 
fact that the fundamental social purpose of accepting 
premium prices for recent innovations is to facilitate 
further R&D investment, this means that from the 
provider-side standpoint the cost per QALY produced is 
likely to be orders of magnitude higher in the rare disease 
context than in that of commonly used therapies. For 
some health economists the volume of welfare produced 
is the key issue from a public interest viewpoint. They 
may say that if the costs of developing treatments for 
rare disorders make them uneconomic when cost 
effectiveness thresholds are set at standard levels it 
would be right either for manufacturers not to make 
them or for the NHS not to offer them. But from a health 
service user and equitable public policy perspective this 
can be strongly challenged.

At worst there stands to be a damaging mismatch 
between orphan disease related legislation designed 
to encourage research investment in fields regarded 
as social priorities, and purchasing policies which 
impede public access to effective products after their 
development costs have been incurred. Relevant 
considerations include the fact that in aggregate ‘rare’ 
diseases today affect many millions of people across 
the world. Once effective treatments are developed they 
will normally, after IPR expiry, continue be available at a 
relatively low cost for the remainder of history, or at least 
up to the point when better solutions emerge.

In that there are profound uncertainties surrounding what 
any one biopharmaceutical research and development 
project will ultimately lead to, and that some innovations 
will eventually prove much more productive than any 
early assessment could reasonably anticipate, it may 
also be suggested that approaches that encourage the 
research community to concentrate on prevalent disease 
mechanisms rather than a broader range of scientific 
opportunities could in the long term prove less efficient 
than ‘wider spectrum’ R&D incentivisation strategies. 
In countries such as France the case for rewarding 
scientific excellence in addition to health gain generation 
has received stronger recognition than has been so in 
Britain.

Regarding orphan products a number of HTA agencies 
have also, to a degree at least, recognised the case 
for paying much more per QALY (say, for instance, 
five to ten times more) in some rare disease contexts 
than is normally judged appropriate. NICE has a highly 
especialised technologies (HST) evaluation programme 
which allows for this contingency. However, it is limited 
to examining only a small number of cases in any one 
year, and the cut-off line between treatments that qualify 
for special consideration and those that do not appears 
to have been set in a restrictive manner.

To the extent that this initiative represents an acceptance 
that ‘rare disease QALYs’ should be seen as, in the short 
term at least, having a special value it serves patient 
and public interests. Nevertheless, the current situation 
leaves open a number of questions as to how cost 
effectiveness threshold setting flexibilities ought to be 
undertaken by responsible bodies.

This in turn leads on to how UK industrial policy, to the 
extent to that it exists and is desirable, ought to be linked 
to NHS medicines purchasing strategies. It is sometimes 
argued that health service budget holders should only be 
concerned with obtaining narrowly defined health returns, 
and that discrete mechanisms like fiscal interventions 
should be engaged when there are perceived national 
interests in fields such as further incentivising private 
sector research and development investment.

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16 When a drug has been developed to the point of licensing the 
extent of the global savings to be made by not supplying it in 
any given market is contestable. This is in part because even in 
the most heavily regulated settings research based companies 
may reasonably seek to attain target levels of return on capital 
by charging more for other items. Put more positively, reducing 
the likelihood of effective but low volume sale medicines failing 
to generate revenues could reduce the global cost of risk capital 
and so generate savings that counter-balance increased costs.
There is a significant case for measures such as the ‘patent box’ provisions put in place by Gordon Brown’s last Labour administration. They were seen as splitting the domestic income stream available to research based companies between the ‘health value’ generated directly from health service sales and ‘wider societal value’ revenues linked to taxation arrangements.

Such provisions may have boosted UK investment levels in some instances. However, such strategies (the genesis of which was to a degree linked to the original establishment of NICE) could prove problematic as the twenty first century unfolds. This is partly because their application (which can reduce corporation tax payments) might risk causing structural distortions in British based industry. Facilitating reductions in visible NHS pharmaceutical purchasing prices could also in time encourage other comparatively prosperous countries with fewer direct interests in pharmaceutical and wider biomedical research to impose reduced prices for innovative therapies without making counter-balancing fiscal adjustments.

The potential impacts of such trends on world-wide public (health) interests are difficult to estimate. But they could prove significantly negative. In such circumstances one possible means of bringing industrial and health policy approaches into closer alignment could involve upwardly revising the cost effectiveness threshold(s) applied when using ‘cost per QALY data’ to determine the affordability of innovations. If achieved in an internationally structured manner (ie by linking permitted pricing levels more consistently to GDP levels in away acceptable to all the stakeholders involved) this could open the way to the more effective use of Ramsey pricing – see previous sections – in promoting equitable global access to medicines while maintaining adequate research and development spending (Danzon et al, 2011).

Observers who because of the many uncertainties involved question the value of national industrial strategies and/or internationally co-ordinated attempts to improve global access to medicines and foster research investment are likely to dismiss the need for such interventions. Yet there can be little rational doubt

Box 6 From Edward Jenner to Checkpoint Inhibition – the Evolution of Immunology

In 1796 Edward Jenner experimented on an eight year old boy called James Phipps, the son of a landless labourer who from time to time worked as Dr Jenner’s gardener. James was first inoculated with cowpox pust and then exposed to smallpox. This fortunately successful preventive intervention established Jenner as the discoverer of vaccination and eventually opened the way to effective smallpox control across the world. The disease was finally eradicated in the late 1970s, albeit some weaponised smallpox virus stocks may still be in existence.

Despite that fact that the ethics and design of Jenner’s lone child trial might well seem questionable from today’s standpoint his work played a significant part in opening the way to the subsequent contributions of scientists such as Louis Pasteur, followed by those of twentieth century pioneers of immunology such as Sir Frank Macfarlane Burnet and Sir Peter Medawar. The advent of anticancer vaccines and medicines such as today’s checkpoint inhibitors can be linked back to a knowledge chain forged over hundreds of years.

Even Jenner’s initial contribution was not as original as is sometimes portrayed. In developing vaccination he was building on long standing English folk law and semi-formal medical knowledge about the preventive effects of cowpox, as well as drawing on ancient knowledge of variation. The latter, which involves exposure to live smallpox virus in small doses, had already been intermittently practiced in countries such India, China, Iran and Turkey for upwards of a millennium. It was famously introduced into England by Lady Mary Wortley Montague on her return from Istanbul (where her husband was Britain’s ambassador) in about 1720, thirty years before Jenner’s birth. Her brother died of smallpox in 1713. This loss motivated Lady Mary to protect her children and the wider community.

Such examples illustrate the fact that the reputations of ‘great women’ fortunate enough to win acclaim are often gained from standing on the shoulders of generations of long forgotten, but nevertheless important, predecessors. In the context of pharmaceutical product development and scientific progress more generally this understanding emphasises the value of seeing innovation as a single incremental process conducted over time, rather than a dis-linked series of transient, fragmented, events.

Economists typically focus on assessing the utility of individual developments while offering little or no insight into the long term human realities and societal probabilities surrounding investment in areas like the life sciences, or why alternative forms of immediate consumption may be of less significant value. In the complex environment of the modern world, where for the first time in history large populations are threatened by having too much rather than too little food, those responsible for designing medicines price and cost control strategies should arguably seek to take account of the importance of adequately incentivising all the (unpredictable) steps needed to maintain the evolutionary cascades leading to better disease treatments. In areas like cancer care public interests are unlikely to be served by focusing just on retrospectively rewarding ‘major breakthroughs’ as measured by their ICER values alone.
that channelling resources into areas like biomedical innovation as opposed to, say, unhealthy levels of food consumption should benefit humanity. One of the more serious criticisms of current approaches to economics is that they can encourage affluent communities to consume ‘as if there were no tomorrow’. A related point to stress is that pharmaceutical and associated life science advances are not just isolated events. As discussed in Box 6, they can be seen as links in a single chain of historical development.

Whose needs count most – is the ‘right’ aim to maximise total QALY production?

Following on from the above, the philosophy underlying NICE’s use of QALY’s in conducting its medicines appraisals and offering recommendations regarding the treatment of NHS patients is essentially utilitarian. The theory Jeremy Bentham developed in the late eighteenth and early nineteenth centuries posits that, in the absence of divine guidance, public policies should seek to promote the greatest happiness determined good for the greatest number of people. UK governance traditions are to a significant degree based on this pragmatic maxim, coupled with the principles of free market economics. At heart such thinking assumes that the ‘natural’ pursuit of happiness coupled with the uncompromising pressures of economic competition and selection at the individual and social group levels offers the best chance of wellbeing.

But for voters and policy makers concerned with the formation of just, stable and adaptable societies, and valuing behaviours that do not leave vulnerable members of the community to suffer avoidably, utilitarianism may be judged wanting. Late twentieth century commentators such as John Rawls (1999) have argued that socially just administrations should seek to ensure that the life opportunities enjoyed by the least advantaged sections of society do not fall below a universally acceptable set of minimum standards.

If this position is accepted it adds weight to the view that in the health sector cost effectiveness analyses should be conducted in ways that will serve to increase investment in the treatment of rare and/or more severe diseases, particularly when progress appears scientifically possible. At the present time this includes fostering treatments for less frequent and more serious forms of cancer, as well as more common disorders such as multiple sclerosis and Alzheimer’s Disease. In the short term this may generate only a limited quantum of patient benefit. Yet it can be rationally predicted that the societal returns from continuing to invest in such fields will increase exponentially in future decades, in ways that will over time benefit the entire (global) population.

One implication of this is that the conventional proposition that maximising the immediate number of QALYs generated by NHS spending is in line with the public preferences is challengeable. Health and social care funders and providers may need to do more to confirm the appropriateness of resource allocations in line with values such as equity and concern for the wellbeing of coming generations.

Even in the period of relative poverty during and immediately after WW II a spirit of altruism arguably underpinned support for the creation of NHS. Some human values development theories (see, for instance, Inglehart and Welzel, 2005) suggest that since then, as Britain has grown richer and more secure, individual and collective willingness to safeguard minority interests and invest for the future should have grown stronger. To the extent that this is actually the case current policies in areas such as promoting health service efficiency and incentivising innovation will need to be revisited to ensure that they fully reflect public preferences in high priority welfare fields.

Are the opportunity costs of using IPR protected medicines and vaccines systematically over-stated?

Patents and other forms of intellectual property right are central to the model of privately funded pharmaceutical innovation that first emerged at the end of the nineteenth century and reached a zenith since the introduction of products such as insulins and penicillins as commercial entities. Some critics of the status quo, often citing delays in supplying effective HIV treatment to people in regions such as sub-Saharan Africa in the 1990s and early 2000s, argue that IPRs delay access to medical innovations. They conclude that other forms of R&D funding should be instituted.

Yet presently IPRs play an essential role in the mixed, mutually dependent, system of public and private funding that underpins not only the research based pharmaceutical industry but also the life sciences based research undertaken in settings like Universities and research charities. As already described, this inevitably means that new pharmaceutical products are more expensive than mature products, except when special action is taken to assure their affordability. Yet unlike the case with labour intensive forms of health care the prices of pharmaceutical products fall over time as IPRs expire and knowledge about their optimal mass use matures.

Naive interpretations seek to explain such trends in terms of successful innovators retrospectively recovering their costs (Scannell, 2015). More sophisticated observations see the social utility of high initial returns on successful pharmaceutical innovations more in terms of incentivising the investment of risk capital in new research and
development programmes needed to create the next generation of treatments. However, for the purposes of this discussion the most important issues relate to the question of whether or not the cost effectiveness thresholds used in evaluating items like new medicines should, were it accurately and meaningfully calculable, be set at the average ‘cost per additional QALY’ for the health service as a whole.

A number of the weaknesses of the case for reducing the cost effectiveness thresholds NICE presently uses in medicines evaluations have already been discussed. One important point worth re-emphasis here is linked to the fact that over their useful lifetimes the average cost of most pharmaceutical products is well below their launch price (Pistollato, 2015).

It follows from this that if regulatory or other agencies were to impose the same cost effectiveness threshold on new medicines and allied items value calculation as they would – assuming they were they similarly controlled – on labour dependent innovations where real costs (in line with GDP growth) tend to rise over time it would significantly distort the choices made. This could discourage pharmaceutical innovation and inhibit dynamic and optimally productive change in the way health gains are generated.

Unless ‘whole life’ approaches to understanding the costs and benefits of products such as new medicines are employed the opportunity costs of using such technologies relative to alternative ways of improving health care are going to be significantly over-stated. The precise size of the effects engendered by IPR expiries and mature product genericisation depend on many variables. Some economists may say that the uncertainties involved are too great to permit meaningful life time cost projections. But this does not mean that policy makers can afford to ignore such realities.

It is not unreasonable to suggest that taking into account life cycle effects could, independently of other factors, justify the cost effectiveness thresholds applied in assessing innovative pharmaceutical products at the time of their launch being several times the levels observable elsewhere in the health sector, much less in the wider economy.

Are defined cost effectiveness thresholds needed?

Within the model devised by health economists in York and elsewhere, cost effectiveness thresholds are vital for translating ‘cost per incremental QALY’ data into decisions as to whether or not a given medicine or other treatment can be recommended for NHS patient use. During the research undertaken for this analysis stakeholders stressed that NICE already exercises a degree of flexibility in deciding what it regards as affordable. But it is in general true to say that the current English approach is more tightly focused on applying a narrowly defined – and relatively low – QALY cost ceiling than is so in other comparable countries. The extent to which this difference is dogmatically driven, as opposed to rationally informed, is debatable.

As previously discussed there is, for example, in Germany a stronger emphasis on ensuring timely public access to new pharmaceutical technologies, even when they are costly at launch. It is only subsequently that increasing attention is paid to enhancing the efficiency of the clinical care available (Perleth et al, 2009). This implies a pragmatic acceptance that incremental cost effectiveness ratios should vary significantly between therapeutic fields, depending on the technical challenges and therapeutic opportunities relevant at any given point in time.

American public policy makers have typically discouraged the use of aggregated ‘cost per QALY’ data to make decisions on treatment entitlements, while recently accepting that comparative effectiveness studies can have an important to play in the delivery of good quality personal care. Interviews undertaken with US based economists who believe that cost effectiveness analysis could and should in future have an extended role indicate that the British example is seen as having some strengths, but that – notwithstanding the variations acceptable to NICE – its rigidity would make it unacceptable to many Americans doctors and patients. Respondents highlighted the theoretical problems inherent in defining incremental cost effectiveness thresholds, and suggested that creating situations in which patients feel that they have to beg for access to effective treatments should be regarded as repugnant in any setting.

Similar responses were received from respondents in Europe, including in nations such as France and Spain. In Italy, for instance, there is likely to be awareness of ‘cost per QALY’ information. But it is not normally used to formulate explicit recommendations about the medicine prices health care providers should pay. This could in some instances help reduce expenditures to levels below those which health technology assessments might indicate are acceptable, albeit at the possible cost of sacrificing public interests in incentivising R&D spending. In relation to this a British source recalled a Treasury contact saying that if it was certain that incurring higher pharmaceutical costs would stimulate increased research or other investment in the UK this would be a price worth paying, but that they could not be sure this would be the result of relaxing NHS rationing/cost effectiveness criteria. Additional money might instead flow to centres in settings like the US.
Life is inherently uncertain. However, especially in contexts where personal relationships and the opinions of key decision makers remain vitally important, there is good reason to think that the UK, despite the present strength of its public sector science base and NHS linked research assets, will become a less favoured research and clinical trial investment destination if its approach to pharmaceutical pricing and supply is – as compared to the policies of other nations or groups of nations – perceived as being unduly self-interested and demonstrably over-regulated.

Switzerland’s record underlines the fact that Britain’s limited size does not mean that the decline in its position as a leading centre for international company investment in pharmaceutical innovation and manufacture seen in recent decades has, as some may believe, been inevitable. Nor should it be taken to imply that, given good governance, a future strengthening of the country’s performance will prove impossible, despite challenges like those linked to Brexit and the likely move of the European Medicines Agency away from London.

Introducing more flexible approaches to conducting cost effectiveness analyses and making NHS medicines use recommendations could help create a more positive environment. This might encourage not only existing or potential foreign investors in the UK but also NHS clinicians, together with patients and families who hope to be able to access novel and more effective treatments. The remainder of this paper explores the ways in which achieving these ends might be addressed in ways consistent with assuring the financial viability of the health service and limiting total pharmaceutical costs to affordable levels.

Adapting for the Future

This report is centrally concerned with the setting of cost effectiveness thresholds in health technology assessment, particularly in the pharmaceutical care context. There are many issues that require investigation in this context (Karlsberg Schaffer et al, 2016). Yet important though the work of bodies such as the National Institute for Health and Care Excellence and the impact of its CEA studies is, their contributions to medicines evaluation and use represent only a limited part of the UK system for controlling pharmaceutical expenditures and promoting improvements in care quality and outcomes.

As Figure 4 in part serves to illustrate, other key elements of the structure in place in England include the PPRS, NHS England and Trust based purchasing activities in the area of specialised care and the wider work of NHS pharmacists and doctors as they are involved in buying, supplying and guiding the use of pharmaceutical products at the national, regional and local levels. In primary care the Drug Tariff sets generic medicine prices,
while community pharmacists’ profits on supplying NHS medicines are limited by a claw-back system which returns a proportion of their profits to the Department of Health. This is intended to stimulate low cost purchasing by independent professionals, while also ensuring savings for the publicly funded system.

Fiscal provisions can additionally influence research and other investment decisions by private ‘non-NHS family’ companies that supply the health service with medicines. The challenge now facing this country, given tensions like those associated with Britain’s changing relationship with the European Union, is to try to ensure that all the above elements work together to protect national and international interests in improving health and increasing prosperity. The discussion below does not recommend in detail how a new national industrial strategy might try to maintain or further strengthen this country’s pharmaceutical sector and wider life-science capabilities. But it does seek to identify key issues and indicate potentially beneficial directions of change, given the following initial propositions:

- **the primary, if not exclusive, goal of pharmaceutical sector actors should be to promote health gain and provide comprehensive and well trusted treatment care access for everyone.** Private companies must make profits to survive, and public health care providers need to ensure that their costs do not exceed their ability to finance their commitments. But without the confidence of the public they should in partnership be serving neither ‘side’ can successfully fulfilling its mission. To the extent that the pursuit of narrowly defined efficiency in the NHS can create situations in which people fear they are not being offered the best possible treatment in a timely manner, the current situation requires reform;

- **short term problems ought not to suppress awareness of the long term gains which progress in developing pharmaceutical and allied life science technologies will contribute.** Current investments in biopharmaceutical and allied research by both public and private agencies will, over and above the immediate value of incremental therapeutic improvements, serve as bridgeheads to future life science advances which, as the twenty-first century unfolds, will play vital roles in fields beyond health care per se. Realistic attitudes to the present utility of new health technologies and the pricing of innovative products must of course be adopted. Yet as debate in areas like climate change and energy generation indicates, policy makers ought also to be mindful of long term, community wide, challenges that will require solutions dependent on life sciences related expertise;

- **the UK has an interest in the further development of the global market for medicines and allied products in ways that are sensitive to the needs of all communities.** From a national perspective Britain, with its relatively strong research base, stands strategically to gain from the returns generated by innovative medicines and vaccines robust relative to those of supplying commodities. But defending the value of intellectual property and further investment in R&D cannot be sustainably achieved in ways that are antipathetic to the welfare of those members of the world population who currently stand to gain most from extending the affordable provision of universal health care.

There is as has already been described a strong public interest case for using ‘Ramsey pricing’ in global medicines supply. This could allow the prices paid for new treatments by patients and public health systems in the world’s poorer countries to be close to the marginal costs of their production, while richer individuals and nations pay higher amounts in accordance with their wealth. Such strategies, along with complementary health service developments, could help resolve access to treatment related inequalities and support ongoing pharmaceutical sector investment.

To this end there is a moral as well as a political case for saying that the UK ought not to attempt to ‘free ride’ on the back of spending on medicines by nations like the US or France, albeit every effort should be made to prevent outlays on clinically inappropriate treatments. The view taken here is that cost effectiveness analyses of not only pharmaceutical product use but also of issues like investing in medical and nursing education should explicitly take into account global health care concerns, alongside local welfare interests. If this is accepted it implies that, subject to the appropriately regulated pursuit of efficiency, the total quantum of money spent on pharmaceuticals in the UK should, as a proportion of GDP, be comparable to that spent by other nations with similar levels of income. Related arguments exist in contexts like, for instance, ensuring that the NHS does not use its market power to drive down the wages of groups such as nurses to such low levels that it becomes reliant on staff trained in less developed settings.

To date the performance of the British pharmaceutical sector in the R&D context has been good. However, in other industrial areas the UK’s research and development investment outlays have, as a proportion of GDP, generally been below the levels reported by leading OECD countries and the target level for all EU Member States set by the European Commission for 2020. If in the years leading up to and following Brexit government revenues fall, or do not grow as fast as was previously hoped, and public health service funding consequently faces new curbs, under-investing in the pharmaceutical sector could represent a growing threat.
The role of the Pharmaceutical Price Regulation Scheme

The PPRS has since the 1960s provided a framework that has not only limited the cost of medicines and other pharmaceutical products to the NHS, but has also encouraged productive research investment and moderated spending in areas such as the promotion of medicines sold to the health service. Despite criticisms from agencies such as the now dissolved Office of Fair Trading (ibid – the OFT may at one time have seen its own survival as linked to the promotion of ‘value based’ pricing for NHS medicines) the stated objectives of the PPRS can be seen as firmly in line with rationally defined public interests.

Some critics may say that in the past linking the ceilings placed on industry returns to the (historic) value of companies’ assets in the UK might on occasions have encouraged ‘excessive’ local investment. However, the current (2014) version of the PPRS (which does not apply to the sale of non-branded generic/off-patent items) provides an overall NHS spending cap. This, along with other provisions, offsets such hazards. There is reason to argue that, especially in a post-EU environment, the UK should seek to build on the successes of the PPRS rather than to dismiss it as redundant. One possible way of seeking to achieve this might be through further guaranteeing NHS market access for all licensed medicines supplied via the terms of the Scheme to help assure that appropriate clinical needs are met.

‘Overspends’ on the total budget for medicines and allied goods supplied under the terms of the PPRS are presently returned by ABPI member companies to the Department of Health. This has proved controversial for a number of reasons. One is that the rebates paid under this arrangement (which are presently in excess of £500 million a year) are not, visibly at least, returned to the hospitals and primary care organisations directly responsible for purchasing medicines.17 This decreases their willingness to fund novel treatments, even in circumstances where the marginal cost to the NHS as a whole of providing better care is effectively zero.

The impact of total expenditure capping is also limited by the fact that the PPRS does not cover all innovative medicines use. However, the idea of maintaining a broad cost containment framework within which companies can compete for sales to the NHS has a number of attractions. Not the least of these is that over time the type of cost effectiveness based medicines evaluation used by NICE could be employed to distribute income fairly between rival companies and help ensure that the total spent on their products remains at a reasonable level, rather than to limit seriously ill NHS patients’ access to innovative treatments that they and their doctors believe may benefit them.

Centrally controlled purchasing

In the last 20 years there has been an accelerating trend towards fewer new medicines being marketed for high volume use in primary care as against the introduction of products suitable for relatively low volume use in specialist hospital and allied settings. The percentage of total NHS pharmaceutical costs incurred by the hospital sector is now close to 50 per cent, as compared to about 20 per cent in the years between the 1950s and the end of the 1980s. At the same time NHS England is tightening structures and procedures relating to central and regional contracting for medicines in order to drive down costs while preserving what it sees as the best affordable service quality. In some cases NHS England may also limit the numbers of people being treated in order to contain spending, notwithstanding NICE recommendations on NHS patients’ entitlements.

From a health service management perspective there is arguably a robust case for such policies, especially in areas outside the ambit of the Pharmaceutical Price Regulation Scheme. However, as well as limiting costs the role of the PPRS includes curbing the inappropriate exercise of monopsony purchasing powers.

Its stated objective is to balance public interests in NHS medicines being as affordable as possible against the benefits associated with a successful pharmaceutical industry. NICE’s interventions, despite the criticisms sometimes made of them, can be seen as seeking a similar balance. But beyond NICE and the PPRS centralised purchasing programmes driven only by a desire to obtain the lowest possible prices could become focused on expenditure minimisation in ways that counter-productively limit clinicians’ freedoms to prescribe optimum treatments for their patients, or in other undesirable ways restrict consumer choice and the extent to which pharmaceutical companies can generate earnings from IP protected products sold for NHS use.

This risk should neither be over-stated nor ignored. One possible means of checking the possible future impacts of medicines purchasing programmes that may in time come to be managed by external commercially motivated entities (as opposed to internal, professionally directed NHS agencies) might be for NICE to be given a strengthened statutory role in monitoring and regulating all NHS pharmaceutical supply contracts made outside the ambit of the PPRS, and using its expertise to protect public interests on both sides of the pharmaceuticals provision equation. Part of the purpose of this would be to ensure that in the coming era of more personalised

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17 Scotland has been able – for reasons some may feel have been indirectly linked to a high level political desire to maintain the viability of the Union – to use its pharmaceutical sales rebates to enhance access to new treatments. But this has not been overtly so in the rest of the country.
‘precision’ medicine aimed at preventing or where possible curing complex conditions like lung and other cancers, NHS clinicians are as well placed as possible to ensure that their patients can access timely, optimally specified, treatment.

Current approaches do not consistently guarantee this. Arguably, when health economics was new to the NHS its application necessarily involved overriding professional preferences which were inadequately informed and insensitive to the benefits of improving health service resource use. But given developments like those embodied in the present version of the PPRS and the changes in clinicians’ education and attitudes that have since taken place there are more opportunities to take a facilitative approach to guiding the choices made by health service users and their advisers.

Recognising this could open the way to health economics in the UK interfacing more effectively with disciplines ranging from clinical pharmacy and health psychology to medical sociology in order to comprehensively and equitably address the challenges of health care related resource allocation. Optimising value is today more likely to demand strengthening rather than limiting the decision making capacity of individual health professionals seeking to deliver patient-centred services (Porter, 2010).

**Improving the ways in which cost effectiveness thresholds are set and applied**

The quality of much public debate about the long term returns to be derived from bio-science based research and the standards of medicines supply and use in Britain could be improved. On occasions what can reasonably be judged a positive national success is presented as a costly, corrupted, failure. The adverse consequences of such false negativism are rarely explored, let alone communicated effectively to public and political audiences. The view offered here is that broadly based economic studies could, when adequately undertaken and their findings constructively presented, help correct such shortcomings.

With specific regard to the role of cost effectiveness thresholds in determining NHS patient access to treatment a key message of this analysis is that calculating the value of new therapeutic options via estimating their incremental QALY related costs is by no means an exact science. Over and above problems like the potential of aggregated data to obscure the differing outcomes experienced by people receiving the same forms of care, many of the assumptions made in the process of calculating the benefits that innovative technologies can bring to individuals – let alone their families, communities and the global population – are highly contestable.

What is measured is often measured imprecisely, while dimensions of value that are not measured may well be ignored altogether. It is widely said in quality management that only that which is measured is delivered, but that the things which are most important to groups such as patients are often too difficult to measure (Taylor, 1996). This can also be the case in economic evaluations.

Relatively minor methodological variations in the way variables like quality of life are assessed or weighted are unlikely to change the ‘answers’ provided by CEAs by any great amount. Yet more robust challenges to the ‘York paradigm’ which has dominated British health economics in the last few decades could result in much larger value estimation re-adjustments. Examples of the latter might include estimating the non-discounted long term society-wide value of new means of improving health and preventing curing conditions like, for instance, Parkinson’s disease, multiple sclerosis or Alzheimer’s disease.

In instances when large State funded or mandatory insurance funded purchasers are buying innovative, IPR protected, pharmaceutical products from single source suppliers sophisticated mechanisms for resolving pricing disputes in a public interest focused manner have an essential role to play, especially as the viability and desirability of international reference price based systems is coming under increasing scrutiny (Persson and Jonsson, 2016). The politicians and others responsible for establishing NICE and subsequently for promoting ‘value based’ medicines pricing were at heart seeking to as authoritatively as possible resist challenges to NHS rationing decisions, and/or to establish fair prices in a ‘science based’ way. Yet CEA derived conclusions cannot provide absolute answers to any of the questions at the centre of such matters.

Respondents interviewed during the preparation of this report suggested that even Ministers are not always adequately aware of the limitations of ‘cost per QALY’ based prescriptions. Some observers believe that undue influence over policy formation relating to an important industrial sector may on occasions have been exercised by groups ideologically hostile to the role of private companies in the health arena.

Understood and used with sufficient good-will, ‘cost per QALY’ estimates support patient and population focused decision making. But there is also reason to fear that narrow and yet over-detailed approaches to calculating whether or not novel medicines offer sufficient value for money for NHS use can waste time, resources and effort. Despite the good intentions of health economics pioneers like Alan Williams and the positive contributions that NICE has made, one of the main conclusions offered here is that the ‘cost per QALY’ centred pursuit of efficiency has at best played an uncertain role in determining NHS user access to pharmaceutical
innovations in an equitable and affordable manner. There is evidence (see, for example, Jonnson et, 2016) that in some instances it has delayed access to treatments and played a part in needlessly depriving patients of the best possible personal care.

The evidence available also suggests that some other countries are presently doing better than Britain in maintaining patient and public confidence in the quality and affordability of health and social care they provide, and in providing an environment that is conducive to synergistic private and public investment in pharmaceutical and wider biomedical innovation. The introduction of more flexible and humane approaches in fields like the application of cost effectiveness thresholds in determining medicines affordability could – as exemplified in settings like Sweden – be an important step towards achieving British arrangements which are more consistently patient and clinician friendly than at present, yet which are still capable of effectively controlling public expenditures on medicines and allied products.

Conclusion

People have been using medicines derived from plant and other sources ever since homo-sapiens evolved some 250,000 years ago. In the 5,000 years or so during which written records have developed early pharmacopeias initially drew together ancient folk-wisdom. They subsequently opened the way to progressively more scientific approaches to guiding the uses of drugs – as poisons as well as potential cures – and understanding their biological actions.

The immediate progenitors of modern medicine and today's health care professions were formed in the nineteenth and early twentieth centuries. However, it has only been in the period following the second World War and, in the UK, after the creation of the NHS that the research based pharmaceutical industry as it is currently formed came into existence.

The advent of medicines such as systemic antibiotics18, antipsychotics and blood-pressure lowering agents, together with products like polio vaccines, was initially accompanied by a wave of optimism about the potential of pharmaceuticals to transform national and global health. But at the end of the 1950s the Thalidomide tragedy precipitated a political reaction which led to increasingly stringent regulatory provisions, which it was hoped would assure the safety and efficacy of novel pharmaceutical treatments.

The need to conduct extensive tests and clinical trials greatly increased the cost of developing new medicines and vaccines. It also led to the build-up of a unique data base relating to the benefits of pharmaceutical innovations.

This twin increase in spending and information opened the way to the ‘birth’ of health/’pharma’ economics and, since 2000, the creation of NICE as the cornerstone of health economics based Health Technology Assessment in the UK. In the half century or so between the 1960s and the present new approaches pioneered by both industry and academia have changed the way the utility of medicinal and other treatments is evaluated. The power of doctors treating patients to allocate health care resources has decreased, while the influence of managers and others involved in the ‘higher level’ allocation of NHS money has risen.

Along with other factors, such shifts in their external environment have also led to major changes in the form and functioning of research based pharmaceutical companies. The nature of the research and marketing challenges they face has shifted, and they are more globally oriented and socially accountable than at any previous time in their existence.

The factors that are causal in driving the evolution of complex systems are often difficult to identify with any significant degree of confidence. The judgment offered here is that the impact of cost effectiveness studies on total health spending and patterns of health and social care delivery has been less extensive than their architects are likely to have wished. But despite its limitations health economics as a discipline has – together with the wider HTA and patient empowerment movements – served to promote more reflective and critical attitudes to the use of health care resources, especially in the context of medicines supply. This has improved some forms of care delivery, even though the inflexible application of CEA based findings can lead to needlessly rigid restrictions on the practice of medicine, particularly in rapidly developing areas.

In circumstances in which the monopolistic providers of goods such as innovative medicines are selling to monopsonistic purchasers like the NHS, elaborate mechanisms for finding pricing solutions and determining total outlays are often required. The system which has to date emerged in the UK – the specific nature of which is linked to the functional culture of the NHS as a tax rather than insurance funded universal care system – has a number of strengths. It has, for instance, facilitated the promotion of therapeutic advances in ways that limit inappropriate prescribing and curb undue spending on medical entertainment. However, Britain stands out against other developed countries as having an unusually narrow focus on ‘QALY based’ cost utility analysis.

18 Topical antibiotics have a much longer history. For example, penicillin and other moulds were used in folk medicine for centuries before Sir Alexander Fleming’s famous observations.
Historically, the NHS has long been a relatively low cost care system which tends to be a parsimonious user of innovative pharmaceuticals. If in the context of accessing new medicines and vaccines the amount the NHS is willing to pay per ‘marginal QALY’ were to fall dramatically from current levels this would make the UK a progressively less attractive place in which to introduce new medicines. It could discourage further industrial investment in clinical and other British based research, especially if withdrawal from the EU diminishes the wider importance of the UK’s economy and culture.

Successfully combatting such dangers will demand the introduction of more constructive and thoughtful ways of controlling pharmaceutical costs, that simultaneously promote improved health outcomes and incentivise therapeutic innovation. In looking towards the continuing evolution of health economics, and within it cost effectiveness analysis as employed by HTA agencies, an important part of the task ahead will involve further refining the use of QALY based value estimates in order to stop their application causing avoidable harm to groups such as those in need of low volume sale ‘cutting edge’ medicines, while at the same time respecting the need to ensure ‘value for money’ and the overall affordability of the health service.

With specific regard to setting and using cost effectiveness thresholds, positive progress will also require moving on from imposing tightly defined ‘cost per QALY’ ceilings towards making tailored judgements, consistent with the fundamental values and goals of the NHS and the empathetic provision of personalised health and social care. Achieving further shifts away from a ‘one size fits all’ approach will involve producing contextualised cost and benefit analyses that are more sensitive to individual and community values than present forms of CEA. There will also need to be mechanisms for ensuring that new purchasing methods are not used to drive down the amounts paid by the NHS for innovative medicines to unsustainable levels after the ‘fourth hurdle’ of demonstrating cost effectiveness has been negotiated.

The qualitative research findings summarised in this report also highlight a widespread belief that increased flexibility should be combined with a strengthened commitment to protecting NHS users from feeling that they need to beg for treatments that might save or extend their lives. Well-structured policies could and should avoid such service lapses, not least because once the costs of developing and licensing new treatments have been incurred the scale of the macro-economic savings to be derived from not supplying them to all patients who could benefit from them is normally much smaller than is often assumed. International experience indicates that a more humane system would not only be affordable at the national level, but could send better ‘market signals’ to research based pharmaceutical companies and publicly funded research organisations.

Private companies, like public sector agencies and health professionals, respond to financial incentives. Innovations that give high levels of individual benefit to large numbers of people should in total earn more than less impactful developments. Yet the added value of rare disease medicines and scientifically important treatment advances should not be underestimated. In relation to protecting public and patient interests in affordable therapeutic evolution suggestions that the quality of future pharmaceutical research will hinge primarily on ensuring that new treatment prices are rigidly linked ICER values calculated to several (both costly and questionable) decimal places and implemented via the use of relatively inflexible cost effectiveness thresholds lack credibility.

There is also no reason to believe that halving the cost effectiveness thresholds used to evaluate whether new health technologies are suitable for NHS use would benefit current or future patients or the wider economy. Introducing more flexible and pragmatic strategies for rewarding positive intention, managerial competence and scientific excellence alongside the delivery of health gain is much more likely to enhance welfare. Such measures could and should be coupled with appropriate overall spending caps and robust guarantees of equitable service provision for those most in need of effective care.

Similar conclusions can be drawn in the wider context of evaluating non-pharmaceutical forms of health and social care advance. The economic imperative of seeking increased efficiency is legitimate in the sense that everyone wants to generate as much value as possible from the resources at their disposal. Yet in the uncertain reality of the human condition there can be no simple way of achieving this end in health care. If (as is perhaps inevitable given that ultimately – like beauty – value exists uniquely in each beholder’s eye) efficiency is measured in only partially satisfactory ways its uncritical pursuit could inflict heavy costs.

Economists make simplified models of the world in order to aid the pursuit of prosperity and wellbeing. Rationally and compassionately employed, measures such as QALYs and ICERs usefully inform choices. But if health economists, or those seeking to apply their findings on topics like the value of reducing pain or extending lives, come to think that their findings provide an absolute guide to achieving the chimera of ‘true efficiency’ they risk making serious mistakes. They would be putting their faith in all too fallible social science constructs ahead of the tangible, clinically directed, relief of suffering, the generation of hope and the step-by-step evolution of better treatments for people who are themselves facing severe illness or who are having to live with threats to those for whom they care.
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