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Article

Treatment Is Worth a Lot – But Just How Much?

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Abstract
More than at any other time in history, science offers enormous potential to transform the prevention, diagnosis and treatment of many diseases. However, patients are urgently awaiting new therapies – and too often not getting them. And researchers and companies also face significant development obstacles as only one in ten drugs entering clinical trials ever makes it over the finish line. This article looks at the issues involved in bringing innovation into healthcare systems from a political and policy level. It takes a close look at Health Technology Assessment (HTA) across Member States, how it is working and, more to the point, how it isn't, and how it often serves to stymie the introduction of new medicines by undermining the European Medicines Agency (EMA). The article argues that the EU could strengthen HTA cooperation via a common framework, and promote higher quality and fairer assessments; while joint work could reduce duplication of efforts, and promote better synergies as well as better use of Member States' resources. The author also takes an in-depth look into criticism of private-sector pricing of innovative medicines in the light of discussions about what constitutes "value" in the context of new treatments – a discussion that shows no signs of abating – while advocating enhanced contact and the need for compromise between all stakeholders in the great value debate.

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Three New Factors Affecting Health

One of the major changes in the context for healthcare in recent years has been the new emphasis on cost. For decades, healthcare spending rose steadily in the developed world, in line with the growing prosperity that permitted many countries to continue funding wider coverage of the new diagnostic and treatment regimens that medical science offered [1].

But three factors have radically modified that equation in the last decade, giving new prominence to getting the full picture of the value of treatment.

The most obvious new factor is the ageing of the population. Now the burden on health and social security spending is greater than ever before because people are living longer – thanks in many cases to the advances in healthcare [2]. They are living longer, but also suffering more disease, and for longer, with consequent strains on the resources to supply care. The skewed distribution of healthcare demand is well known, with the vast majority of spending concentrated in the final years of life as health declines, and as co-morbidities and acute and often sustained interventions proliferate [3].

The second factor is the slowdown in economies in much of the developed world – and particularly in Europe. Strains were becoming apparent even before the crunch of 2007–2008, but the crisis that precipitated is still reverberating across the member states, with growth sluggish or even negative, and prospects still sombre for recovery [4].

The consequent emphasis on austerity puts all public spending under the microscope, and health and social security, as a major heading in every member state's budget, has unsurprisingly been the focus of many economy drives – as the European Semester exercise demonstrates year after year, with its critical comments on inefficiencies and inadequacies in national budgets [5].

The third factor, and the one closest to this special edition, is the tsunami of scientific, technological and medical progress in the current millennium. Massive progress and a massive change in the economics of treatment. Treatments that may save lives or restore lost quality, but that are the consequence of huge and investment-intensive efforts in research [5]. Since much – even most – of this progress is driven by the private sector, the issue of funding has risen, rightly or wrongly, to the forefront of debate [6].

If it were just a bigger and older population, or just times of austerity, that were the new elements, it would already be hard enough to find the right answers. But when it is both a bigger and older population and austere conditions for public finances, then throwing into the mix the additional element of often costly new diagnostic and treatment options is the equivalent of putting a match to a powder-keg [7].

So on the threshold of the third decade of this new century, society and its appointed leaders, faced with numerous new and valuable, but often costly, diagnostic and therapeutic options, are recognising that new treatments are worth a lot, but are inevitably posing the question of just how much they are worth [8].

The question is obvious, but finding answers to it is not so easy.

Putting a Value on New Treatments

An accurate evaluation is itself going to depend on a number of factors. One is information – and information that is accepted and is trusted. Another is an agreed system of criteria for analysing the information and assessing the options – agreed, and trusted by all stakeholders.

The corollary is that no solutions can be found, no response to the challenge will be satisfactory, without trust – trust in the information, and trust in the systems.

So what sort of mechanisms can make it easier to establish that trust? Part of that has to be a better understanding from the outset of where each of the distinct stakeholders is coming from [9].

Innovators have their own view of the world: they are conscious of the potential merits of their innovations, and of the efforts expended to achieve them; if they are private-sector innovators (as so many of them are), they will also have their own view of what sort of reward they deserve, both for the individual innovation, and for maintaining the expensive infrastructure that makes innovations possible [10].

Regulators bring their own approach to the issues. They are essentially gatekeepers on what it is desirable for the public to be offered. They operate on the basis of standards of quality, safety and efficacy for the goods and services that are proposed as serving the public interest [11].

Healthcare systems have their own world view too. They want to maximise the public health opportunities for the widest populations, and will deploy as far as they are able the most appropriate tools – or what they deem the most appropriate tools – to achieve that. But they have another constraint that they operate under: the need to respect the budgets they are allocated by their respective political authorities.

So while they function on the basis of a public mandate, they are unable to automatically provide the public with every innovation that might be desirable for achieving health benefits. Among the innovations that the regulators approve, they often have to make choices, selectively providing what seems to them the best mix within limited resources [12].

And society in general also has a part to play in this complex mix. Social expectations, social values, the way society feels (or articulates a feeling) about balancing individual needs against public needs, about rewarding innovation, about priorities in public spending, etc. all contribute to the climate in which healthcare systems – and indeed regulators and innovators – make their own choices and plan their own strategies [13].

Contact and Compromise

No one simple answer is going to work. Private enterprise innovators may want maximum returns, but that flies in the face of what healthcare systems (and those who pay for them) want – which is the most economical way of providing healthcare for all, and therefore requires tough choices and tight budgeting; and that may in turn clash with the desires of many in the general public, who favour access to every innovation that may do them good, irrespective of the price; and who may even, in extremis, clash with regulators' desire for dependable safety when caution may delay or prevent access to a promising innovation.

So everyone is going to have to make some compromises [10].

How is that best achieved, when the further apart these distinct constituencies are, and the less they know about the constraints the other stakeholders are subject to, the harder it is going to be to find answers that make the most sense to all of them.

So plenty of contact between them, and from the early stages of the processes that each of them is engaged in, is likely to ease the tensions before they become irreconcilable. Such early dialogues among all stakeholders will allow them to interact with each other, and will help build the common understanding that is the basis for trust [14].

The EU can provide a framework for this – and if it so chooses, it can do so with a framework better than any that exists at present.

This would help to permit more fruitful discussions once an innovative product or service moves out of research and beyond regulatory approval, and reaches further down the decision path to the point where the issue is what cost should be attached to acquiring that product or

service. A highly performing framework would help discussions of what people attach value to, and of how to apportion the different priorities of different groups or sub-groups of stakeholders [15].

It would be possible to clarify what value means to patients (the priceless benefit of the chance of deferring death, or of a complete cure, or of relief from suffering), or to society (a better chance for all of retaining health, or privileged access for certain groups – very old, very young, very disadvantaged, suffering from very rare or very common diseases, or better hopes for the economy as a whole by shortening periods of disease-based absence from work or keeping the population healthier for longer), or to innovators (a sharper understanding of what is involved in research and the difficulty of sustaining it), or even investors and entrepreneurs, so influential in the innovation cycle (and who may choose to invest in property or aviation or ICT if the returns from life sciences are too low).

This is all fine in theory. But so far, in practice, it is not happening optimally.

Criticism of Drug Pricing

The question of how to assess value is a matter of great public interest, and is a regular on the conference circuit, in the European Parliament, among patients and among scientists, and even nowadays in the EU Health Council [16]. And when paying for innovative medicines and diagnostics is the focus, the debate can at worst be characterised by a degree of animosity, even suspicion and hostility, that is unhelpful to achieving the best outcomes for public health [17].

A highly critical report on access to medicines, discussed in the European Parliament's health committee in late 2016, was a classic set-piece confrontation between drug industry supporters and sceptics, with more than 600 amendments tabled by MEPs, ranging from downright dislike of the private sector and alleged profiteering from high prices, to staunch backing for the industry's innovations.

In the end, the critical tone of the so-called Soledad Cabezon report was heavily neutralised by the time it was adopted by the full Parliament in 2017, but it saw hundreds of deeply hostile proposed amendments from MEPs with no love for private sector involvement in healthcare [18].

The critical tone towards healthcare innovation was evident also in conclusions agreed by the EU Health Council under the Italian presidency, after months of hostile comment among Member States triggered in particular over the prices being charged for an innovative treatment for hepatitis C [19]. Again, the final conclusions were less outspoken than much of the preceding criticism, but there was no disguising the depth of feeling among those Member States anxious over the tough choices that high-priced innovations were obliging them to make.

Similar concerns led to similar outbursts from Member States during the Netherlands presidency, and again conclusions contained demands – albeit, again diluted – for tough reviews of drug firms' pricing practices, and have led to a formal review by the Commission of the role of incentives in drug innovation. And the same critical tone was evident in the most recent ministerial review of access to medicines, during the Health Council at the end of the Maltese presidency in June this year [20].

Meanwhile, some Member States, feeling that individually they are unequal to the power of the big innovative drug firms when it comes to negotiating prices, have started to work together to present a more united front. The most advanced example is the BeNeLuxA collaboration, in which the Benelux countries have been joined by Austria, but similar initiatives have since been taken by southern European countries in the June 2017 Valletta declaration, and in ad hoc collaborations between countries in the Balkans and the Baltics [21].

Not all the action is antagonistic. European drug industry leaders and many national health authorities have been meeting in an informal grouping over the last year, in a bid to find consensus approaches to the thorny issue of balancing reward for innovation with budgetary discipline.

And there are some excellent examples of attempts to square the circle by regulators themselves. The European Medicines Agency (EMA) has been playing a leading role in promoting early dialogue with innovators, and in promoting the exploration of more flexible authorisation procedures, known as adaptive pathways, to give innovative products a better chance to prove their worth.

Independently, Belgium and France are both operating their own forms of early release and reimbursement of innovations, under carefully controlled conditions, and in the UK NICE has pioneered new approaches to assessing the merits of potential innovative therapies. The trend is catching on in other Member States too [22].

The Role of HTA

The range of initiatives to find the right balance between costs and benefits of innovation also extends to public private partnerships to promote more efficient – and thus hopefully more cost-effective – innovation, such as the IMI, and the corporate world also continually seeks to streamline its research costs by mergers and acquisitions and by imaginative licensing deals with smaller innovators [23].

And of course there is, at the heart of current discussions about resource allocation for innovative treatments and diagnostics and procedures, the work of health technology assessment authorities.

Health Technology Assessment (HTA) is a multidisciplinary process that – at its best – presents information about the medical, social, economic and ethical issues related to the use of a new health technology in a systematic, transparent, unbiased and robust manner.

HTA can inform decision-makers on the formulation of safe, effective health policies that achieve best outcome and value for money for patients, health professionals and health systems [24]. It aims to answer questions such as: Is the technology effective? For whom does it work? What costs are entailed? or How well does it work compared to alternative technologies?

In recent years most Member States have introduced some form of HTA, typically to measure the added value of a new technology – pharmaceuticals, medical devices, medical and surgical procedures and other measures for disease prevention, diagnosis or treatment used in healthcare, and to compare it to existing technologies [25].

As the European Commission itself says, HTA "is a very useful tool, as it helps Member States to decide which health technology to favour at national/regional level. It also helps Member States to keep their health budgets under control, as products with no or limited added value cannot expect to be reimbursed or to obtain high prices. Last but not least HTA encourages industry to invest in innovation with substantial added benefits for patients" (source: Commission survey as part of 2017 consultation) [26].

But even the Commission, for all its enthusiasm, recognises that at present the concept is not working as well as it should. It says:

At this stage, the vast majority of HTA are carried at national/regional level, i.e. EU Member States assess the new technology according to its national legislation. This leads to duplications of efforts for Member States and industry which translate in unnecessary costs throughout the HTA process. It can also lead to diverging results/outcomes (i.e. health technologies available earlier in some countries compared with others), which in turn can result in limited business predictability for industry and delayed access for patients.

And although Member States have begun pilot work on sharing best practices on how HTA is carried out, and a limited number of joint HTA reports have been prepared, "the use of these results is still decided at national level. In practice this has meant that the joint reports have not (yet) been used on a large scale" [27].

The significant scientific, technical and economic expertise required, which is itself costly, and which is not available in all Member States, means that even advanced Member States cannot assess all new technologies. This has triggered current reflections on strengthening EU cooperation for HTA, in particular for the period beyond 2020 [28].

HTA offers great opportunities to promote efficiency and effectiveness of healthcare. It promotes sustainability in the healthcare system but also the use of innovative products directly benefiting patients. It contributes to the Commission priorities on jobs, growth and investment, and on a deeper and fairer internal market, and enhances reliance on evidence-based policy-making [29].

But HTA can perform best when that process is seen to be impartial and is coherent. And for that to happen, all stakeholders have to be involved – and that ranges from innovators themselves to regulators, patients, healthcare professionals and, crucially, payers. If innovation prospects are discussed at an earlier stage, earlier feedback from other stakeholders could guide innovators and reduce some of the risks of major investments being wasted [30].

In addition, everyone involved has to play their role correctly.

HTA Encroachment is Not Helping

If HTA authorities begin to move beyond their role of advice on the value of a technology, and instead encroach on the role of regulators by re-evaluating safety and efficacy of products, confusion inevitably results.

This is particularly disruptive when therapies approved by the EMA are challenged – or rejected – purely for cost-containment reasons. This amounts to denying, restricting or delaying patient access to safe and efficacious treatment. It also undermines the credibility of the EMA and damages public faith in regulatory system – a crucial consideration at a time when scepticism is mounting on other issues, such as public uptake of vaccination.

It can even lead to scientifically and ethically questionable demands for additional trials – even for double-blind placebo trials in cases where there is no approved therapy, or in indications where disease awareness is limited and patient populations are miniscule [31].

The HTA encroachment into the regulatory domain can also imperil the effectiveness of successful policies such as the EU orphan drug scheme. Orphan Drug Designations were created to foster needed incentives for developing treatments and cures for rare and ultra-rare diseases, and the scheme offers incentives including 10 years of market exclusivity, and protocol assistance.

The merits of the scheme are well established. In the US, prior to the introduction of the scheme there in 1983, only 38 drugs specifically to treat orphan diseases had been approved, but from then until May 2010, the FDA approved 353 orphan drugs and granted orphan designations to 2,116 compounds. As of 2010, 200 of the roughly 7,000 officially designated orphan diseases have become treatable [32].

In the EU, a medicine can qualify for orphan designation when it is intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating, for which the EU prevalence is no greater than 5 in 10,000 (or marketing of the medicine would generate insufficient returns to justify the investment needed for its development), and for which no adequate diagnosis, prevention or treatment has been authorised. The designation implies a finding of added clinical benefit by EMA.

It signifies that the drug in question has demonstrated, to the satisfaction of the regulators at the EMA – composed of national experts – a significant benefit to those impacted by the condition which it was designed to treat. This should be recognised by HTA authorities – but this is often not happening [33].

An official attempt was made in 2012 to overcome this problem, in a proposal to update the EU's 1988 rules on transparency of national pricing and reimbursement systems. This included a provision that HTAs should not question safety and efficacy assessments by marketing authorisation authorities. For a range of (largely unrelated) reasons, the proposal was not ultimately adopted, but it demonstrates a clear understanding of the need to address the issue at the EU level [34].

As things stand at present, Member States are increasingly straying from their mandate to determine value for money, and are increasingly second-guessing the safety and efficacy of EMA-approved therapies for pure cost containment reasons.

National HTA authorities in the EU Member States should, therefore, recognise that drugs which have been granted an orphan drug designation have already demonstrated one of the key elements of the HTA assessment. Failure to do so, and requiring an HTA re-assessment, undermines one of the important incentives provided by the designation. It also adds another hurdle to providing treatment that can really be life-saving and life transforming for patients suffering from rare diseases [35].

Research organisations with particular concern for patients with rare diseases wrote recently to the EU seeking further intervention. Its signatories said they "fully appreciate the need to ensure that public funds are spent and allocated wisely and efficiently," and it recognised that "HTA authorities can play a role in this process, by properly recognising the value for money and benefits for patients of these therapies."

But, it went on, HTA agencies, by questioning the safety and efficacy of medicines already assessed at European level, "only create additional burdens and red tape that ultimately discourage innovation and undermine the incentives set up at European level to foster the development of treatment for rare diseases, thereby putting at risk the chances to address the outstanding unmet medical needs in this disease area" [36].

The fault does not lie entirely in one direction. The situation is occasionally complicated by individual drug firm policies. When policies are driven predominantly by motives of profit maximisation and share-price support, the picture can become distorted. Allegedly, some firms have taken advantage of the underlying confusions to submit marketing authorisation applications to the EMA even where there is little chance of success, but where a high volume of applications has the effect of driving up the share price [37].

The Need for a Common Framework, and Future Initiatives

The entire HTA exercise is at a crucial tipping point in Europe.

Over the last decade or so the EU has sought to develop HTA coordination and support mechanisms together with Member States. One of the results has been the design and establishment, in 2006, of the EUnetHTA, a widely recognised network and community developing common assessment methodologies, information tools and starting to produce joint reports, and benefiting (by 2019) from around €23 million under the Health Programme managed by DG SANTE. The EU's research programme FP7 has also granted €11 million for research projects in this field, and the IMI also dedicated resources for HTA-related initiatives [38].

But with more than 50 HTA national and regional agencies in the Member States, there is high fragmentation leading to duplication of efforts, lack of standardisation and coordination.

While joint work at EU level has been carried out, and its added value has been recognised, the uptake at national level has been variable, leading to duplication of additional costs for both Member States and industry. This does not help in securing the sustainability of healthcare systems, and is an obstacle to the development and introduction of innovative products, particularly in the fields of nano-medicines, personalised medicine and Big Data.

The lack of a common EU framework imposes high costs on technology developers, notably as regards the requirements for additional clinical data to demonstrate effectiveness and ultimately on patients due to delayed access to new, potentially more effective treatments [39].

A parallel HTA network, in existence since 2013, brings together DG SANTE and European health ministries to provide strategic guidance on avenues to reinforce cooperation. The EU's efforts have yet, however, to deliver real results [40].

Recognising the urgency of the situation, the EU is preparing a new position on the way ahead, based on extensive consultations over the last year and more [41].

The challenges in the HTA field, as well as the need to promote growth, create new jobs and increase EU competitiveness, suggest the need for a qualitative increase in the Commission's efforts to support Member States that can promote convergence, avoid duplication, and ensure a better use of resources through joint work and its full uptake by Member States.

This could deliver improved sustainability of healthcare systems, through decisions based on better evidence when using new cost-effective technologies (pharmaceuticals, medical devices, preventive or treatment methods) or discarding old, ineffective technologies [42].

It could achieve better health outcomes, by using well-assessed technologies and providing faster access to innovative technologies for the benefit of patients [43].

It could also support innovation and growth in the internal market, by ensuring a level playing field for companies, increasing business predictability and reducing administrative burden, such as conflicting clinical requirements for health technology developers [44].

It could strengthen HTA cooperation, to promote higher quality and fairer assessments; joint work can reduce duplication of efforts, promote better synergies and thus lead to a more efficient use of Member States' resources.

It would require setting up a permanent HTA technical coordination mechanism, with consistent EU funding support, and with a stronger mandate for urging uptake of joint work between Member States. The EMA could initially host and facilitate the technical coordination, and could capitalise on synergies with the regulatory function and create opportunities for further cooperation [45].

For the longer term, the EU initiative should explore other options, since HTA will increasingly cover a wider array of technologies beyond the current remit of EMA.

Above all, whatever form the new system takes, it is vital that it confers trust, and obliges stakeholders to work on the basis of accurate information. Earlier dialogues and better integrated frameworks are needed so that the stakeholders (all stakeholders) can interact with each other. If the EU is to realise its own potential for effective coordination, then this urgent case provides a perfect opportunity for it to show what it can do when working at its best.

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