

# Changing HTA Paradigms

## 1. Introduction

This paper is intended to inform discussion for the 2016 HTAi Policy Forum meeting on the subject of "Changing HTA Paradigms".

The overall objective of the meeting is to explore significant developments in the paradigm or approaches to health technology assessment (HTA) that have been introduced in response to the evolving needs of patients, payers, providers, technology producers and health care systems. A number of potentially relevant types of development were identified through discussions at and following the 2015 Policy Forum meeting (see Table 1). Following a Policy Forum scoping meeting in June 2015, two key areas for discussion at the 2016 meeting were identified: "Rethinking scientific dialogue and multi-stakeholder engagement" and "Rethinking value, affordability and access".

The purpose of this Background Paper is to explore the principles and practices in these thematic areas.

The information in this report attempts to capture arguments and key developments from recent relevant published and "grey" literature sources. It has benefitted greatly from comments on earlier drafts from Forum and other HTAi members. Nevertheless, this is a rapidly developing and complex area, and there may still be important developments and ideas that have not been included. A journal paper will be developed following the 2016 meeting to contribute further to the wider discussion.

Section 2 of this paper describes the background to the choice of this topic, including an overview of the scoping and other relevant discussions. Section 3 explores the theory and practical examples related to Theme 1 - "Rethinking scientific dialogue and multi-stakeholder engagement" - as well as related challenges. Section 4 does the same for Theme 2 - "Rethinking value, affordability and access". Sections 5 and 6 suggest questions and issues to guide discussions within each Theme and review the intended outputs and outcomes of the Forum meeting.

## 2. Background

The 2015 Policy Forum meeting focused on “Improving the effectiveness and efficiency of evidence production for HTA”. The meeting suggested that HTA “has an important role to play in helping improve evidence production”. However, it was also suggested that, in doing so, the HTA paradigm needs to be more agile and adaptive and to move beyond simply providing information to support one-off decisions and play a more active role in aligning stakeholder perspectives and activities across the product lifecycle and helping the health care system understand the potential of innovations and how practice may need to change to ensure that their potential value is realized.

Participants referred to the need to innovation in HTA to deliver this enhanced role, and recognized that this is closely related to more broad reforms in health care and the need for valuable technologic innovation. Related to this, Policy Forum members also recognized current health systems and HTA processes may need to re-think fundamental concepts of value and affordability, as new high-value technologies that require significant upfront investment present challenges for health systems.

In the discussions at the 2015 HTAi Policy Forum meeting, members began to conceptualize what an innovative approach to HTA means, and identifying needs and trends under this new paradigm. Table 1 – which was developed following the meeting - attempts to capture key features of this “Changing HTA paradigm”.

Table 1. The Changing HTA paradigm: A step change in HTA.

| Current HTA approach   | Innovating in HTA   |
|--|---|
| Patient involvement  | Patient driven priorities   |
| Focus on the technology (single and multiple technology assessments)                 | Focus on disease pathology and patient pathway  |
| Unilateral stakeholder liaison (manufacturer-regulator), absence of service delivery | Multi-lateral stakeholder dialog and collaboration, including health service delivery perspective   |
| Focus on 'front end' innovation  | Whole technology life cycle - from entry to exit  |
| Scientific advice  | Scientific dialogue   |
| Review of submitted evidence   | Aligned, co-produced, real-time, real world data  |
| Data/evidence for regulatory approval  | Data/evidence for holistic value assessment (regulatory, payer and health service delivery)   |
| Continued methodological development   | Continued methodological development  |
| HTA meaningful for regulators and payers   | Translation of outputs of HTA in clinical practice (meaningful for clinicians and patients)<br>Enhancing the reach of HTA to clinical practice                                      |
| Analyzing organisational implications  | Better integration and information of service delivery issues and planning (add info on what is needed in health care system to deliver)  |
| HTA process complex and time consuming   | HTA process agile and adaptive across the life cycle  |
| Static HTA: a single episode at one point in life cycle                              | Dynamic HTA: continuous/updated assessment. System and resources keep pace as data become available and when/if things change during the life cycle                                 |
| HTA confined to assessment of Health Technologies                                    | HTA beyond the confines of traditional HTA using its approach to support and improve health care service  |
| HTA and value of innovations   | HTA and value and affordability of innovations (how health system can have the capacity to absorb the current and projected level of innovations)                                   |
| HTA linked with payers   | HTA linked with health system, with those responsible for allocating resources. HTA as a convener of all parties on how health system needs to develop to get value from innovation |
| HTA in a budgetary and health system decision making with a short term perspective   | HTA taking a medium long term perspective in informing health system decision-making  |

In short, a new HTA paradigm is characterized by:

- A more agile and adaptive HTA process across the life cycle of technologies, reacting quickly to new and real life data when it becomes available or when changes in the technology life cycle emerge;
- Assessment methods and language that go beyond incremental cost-effectiveness ratios, incorporating meaningful results for clinicians and patients;
- Where information on what the health system and patients need from innovation, and what the health system may need to do to get value from it, is discussed through a lens of health services delivery and product lifecycle, through multi-lateral stakeholder dialog and collaboration that addresses health needs and product conceptualization, through development, evaluation, introduction, and appropriate use in a changing landscape as other developments come on stream.

At the Policy Forum Scoping Meeting in June 2015, breakout groups explored various aspects of innovation in HTA and participants described five key thematic areas where innovation is most likely to be happening or is needed. These were 1) HTA engagement with payers and health systems and a move toward more sophisticated approaches to multi-stakeholder engagement; 2) New approaches to scientific dialogue, particularly between HTA bodies and industry but also involving other stakeholders including regulators, providers and patients; 3) How HTA can influence the pipeline and priorities of research and development, either private-sector or public-sector funded; 4) The use of adaptive/lifecycle approaches to technology management; and 5) The increasing need to use real-world data – topics

It was recognized there was significant overlap between these themes, and that some – for example using real world data – had been discussed in recent meetings. As further scoping and feedback occurred, it also became apparent that it would be difficult to find good examples of significant innovation in all aspects of HTA, and also difficult to have a detailed discussion of all areas during the limited time available at a Policy Forum meeting. Therefore, it was decided that the 2016 meeting should focus on two themes that had not been the main focus of earlier discussions and where it was felt that there was significant current activity and/or interest.

These 2016 meeting Themes are: ***“Rethinking scientific dialogue and multi-stakeholder engagement”***; and ***“Rethinking value, affordability and access”***. Case studies have been carefully selected and developed from those suggested by Forum members to illustrate important new developments and/or key challenges in each Theme.

## 3. Rethinking scientific dialogue and multi-stakeholder engagement

### 3.1 Theory and Principles

HTA organizations around the world have been making efforts in recent years to increase engagement for a variety of purposes. A first notable activity has been efforts to increase patient involvement and engagement. In more established HTA processes, as well as jurisdictions where liberal democratic processes for administration prevail, patient and community preferences and social values are increasingly being considered “evidence” to be incorporated into HTA reports.<sup>1</sup> Patient organizations appear to see these interactions as positive.<sup>2</sup> This in turn has seen increased understanding and education among organizations of patient representatives of the value of engagement.<sup>3</sup> Patients are also being increasingly involved in interactions with evidence producers that feed into HTA processes<sup>4</sup> including considerable investment in patient-centred comparative effectiveness research in the US<sup>5</sup> as well as global drug development by the private sector.<sup>6</sup> The recently developed “HTAi Value and Quality Standards for Patient Involvement in HTA” is a response to the need for principled approaches to collaboration and consultation with patients and citizens.<sup>7</sup>

This move to more “patient-driven” priorities and better engagement with patients is now similarly being observed with other key stakeholders, including regulators<sup>8</sup>, industry, and most recently care providers. The need for improved coordination between regulators and HTA was highlighted by increasing use of “fast track” regulatory approaches and calls for “adaptive licensing” by European regulators<sup>9</sup>, with a subsequent recognition that all stakeholders, including HTA bodies would need to be involved in these processes if they were to achieve their goals. This broader “adaptive approach” to introducing drugs and medical devices was the subject of the 2014 HTAi Policy Forum.<sup>10</sup>

A final hurdle, highlighted in the Policy Forum deliberations, is effectively engaging with care providers, health system administrators, and regional or local health service managers. Many jurisdictions have attempted to resolve what is sometimes a natural tension between effective decision-making at a local (micro or meso) level versus effective stewardship of technology at a policy (or macro) level. These levels

- 1 Sally Wortley, Kathy Flitcroft, and Kirsten Howard, “WHAT IS THE ROLE OF COMMUNITY PREFERENCE INFORMATION IN HEALTH TECHNOLOGY ASSESSMENT DECISION MAKING? ACASE STUDY OF COLORECTAL CANCER SCREENING,” *International Journal of Technology Assessment in Health Care*, September 17, 2015, 1–8, doi:10.1017/S0266462315000367; Jennifer A. Whitty, “An International Survey of the Public Engagement Practices of Health Technology Assessment Organizations,” *Value in Health* 16, no. 1 (February 2013): 155–63, doi:10.1016/j.jval.2012.09.011.
- 2 Marie-Pierre Gagnon et al., “Introducing the Patient’s Perspective in Hospital Health Technology Assessment (HTA): The Views of HTA Producers, Hospital Managers and Patients,” *Health Expectations: An International Journal of Public Participation in Health Care and Health Policy* 17, no. 6 (December 2014): 888–900, doi:10.1111/hex.12010; Mylène Tantchou Dipankui et al., “Evaluation of Patient Involvement in a Health Technology Assessment,” *International Journal of Technology Assessment in Health Care* 31, no. 3 (January 2015): 166–70, doi:10.1017/S0266462315000240.
- 3 Eric Low, “POTENTIAL FOR PATIENTS AND PATIENT-DRIVEN ORGANIZATIONS TO IMPROVE EVIDENCE FOR HEALTH TECHNOLOGY ASSESSMENT,” *International Journal of Technology Assessment in Health Care*, November 20, 2015, 1–2, doi:10.1017/S0266462315000434.
- 4 “How Should We Involve Patients in Research and Innovation? - Authored Articles - GOV.UK,” accessed December 21, 2015, <https://www.gov.uk/government/speeches/how-should-we-involve-patients-in-research-and-innovation>.
- 5 Lori Frank, Ethan Basch, and Joe V. Selby, “The PCORI Perspective on Patient-Centered Outcomes Research,” *JAMA*, August 28, 2014, doi:10.1001/jama.2014.11100.
- 6 Anton Hoos et al., “Partnering With Patients in the Development and Lifecycle of Medicines: A Call for Action,” *Therapeutic Innovation & Regulatory Science* 49, no. 6 (November 2015): 929–39, doi:10.1177/2168479015580384.
- 7 “HTAi: Values and Standards,” accessed November 27, 2015, <http://www.htai.org/interest-groups/patient-and-citizen-involvement/pcig-home/values-and-standards.html>.
- 8 H-G Eichler et al., “Adaptive Licensing: Taking the next Step in the Evolution of Drug Approval,” *Clinical Pharmacology and Therapeutics* 91, no. 3 (March 2012): 426–37, doi:10.1038/clpt.2011.345; Don Huseureau, Chris Henshall, and Jamil Jivraj, “Adaptive Approaches to Licensing, Health Technology Assessment, and Introduction of Drugs and Devices,” *International Journal of Technology Assessment in Health Care* 30, no. 3 (July 2014): 241–49, doi:10.1017/S0266462314000191.
- 9 Hans-Georg Eichler et al., “Relative Efficacy of Drugs: An Emerging Issue between Regulatory Agencies and Third-Party Payers,” *Nature Reviews. Drug Discovery* 9, no. 4 (April 2010): 277–91, doi:10.1038/nrd3079; Eichler et al., “Adaptive Licensing”; F Ehmann et al., “Gatekeepers and Enablers: How Drug Regulators Respond to a Challenging and Changing Environment by Moving toward a Proactive Attitude,” *Clinical Pharmacology and Therapeutics* 93, no. 5 (May 2013): 425–32, doi:10.1038/clpt.2013.14.
- 10 Don Huseureau, “ADAPTIVE APPROACHES TO LICENSING, HEALTH TECHNOLOGY ASSESSMENT, AND INTRODUCTION OF DRUGS AND DEVICES” 30, no. 3 (July 1, 2014): 241–49.

of decision-making have responsibilities and incentive structures that are not always fully aligned.<sup>11</sup> They may also require different types of information.

In a similar vein, there has been a recent move away in many jurisdictions from “traditional” clinical practice guidelines that pay little or no attention to costs and broader system implications to the development of care pathways,<sup>12</sup> based on HTA and quality considerations. This involved clinicians working in partnership with HTA<sup>13</sup> and those responsible for managing health care delivery at either a local or broader system level.<sup>14</sup> Some of these initiatives are born out of quality improvement initiatives that attempt to link payment and delivery to value and through utilizing disease-specific strategic or managed clinical networks.<sup>15</sup> Another significant driver in this effort is an increasing interest in hospital-based HTA approaches.

### 3.2 Current Activities and Relevant Cases

In the last 5 years, numerous HTA bodies have engaged in early scientific dialogue processes with manufacturers, often jointly with regulators. These developments have been brokered by both HTA and regulatory bodies and in some cases private sector consultancies, and generally welcomed by manufacturers who have increased their capacity for such dialogue through organizational changes, including merging outcomes research and market access processes and departments into “HTA” departments. For example, Australia piloted a process in 2009 that brought industry together with both the HTA body and the regulator to focus on matters of “common interest”.<sup>16</sup> It appears to have “provided early and clear signals to inform major development investments and the probability of successful market access”.<sup>17</sup>

Scientific dialogue focus on questions specific to particular products, or classes of products and/or disease areas (with topics such as the validation of new endpoints for the new treatment approaches). Although it has always been part of regulatory activity, it is anticipated that these advice processes will gain in prominence within HTA communities, as companies perceive barriers to access become more widely dependent on HTA.<sup>18</sup> In addition to formal scientific dialogue with HTA bodies, manufacturers are increasingly convening *ad hoc* boards with payer “proxies” (i.e., ex-payers or payer experts) to provide advice on clinical development programs for specific products and a number of private sector consultancies now run these “expert network” consultation services for manufacturers (e.g., NDAGroup, GLG).

11 Chantale Lessard, André-Pierre Contandriopoulos, and Marie-Dominique Beaulieu, “The Role (or Not) of Economic Evaluation at the Micro Level: Can Bourdieu’s Theory Provide a Way Forward for Clinical Decision-Making?,” *Social Science & Medicine* (1982) 70, no. 12 (June 2010): 1948–56, doi:10.1016/j.socscimed.2010.03.013; Ron Goeree and Vakaramoko Diaby, “Introduction to Health Economics and Decision-Making: Is Economics Relevant for the Frontline Clinician?,” *Best Practice & Research. Clinical Gastroenterology* 27, no. 6 (December 2013): 831–44, doi:10.1016/j.bpg.2013.08.016.

12 J. Lord et al., “Economic Modelling of Diagnostic and Treatment Pathways in National Institute for Health and Care Excellence Clinical Guidelines: The Modelling Algorithm Pathways in Guidelines (MAPGuide) Project,” *Health Technology Assessment (Winchester, England)* 17, no. 58 (December 2013): v – vi, 1–192, doi:10.3310/hta17580.

13 Gisselle Gallego, “SURGEONS’ VIEWS OF HEALTH TECHNOLOGY ASSESSMENT IN AUSTRALIA: ONLINE PILOT SURVEY” 29, no. 3 (July 1, 2013): 309–14.

14 Nicolas Martelli, “HOSPITAL-BASED HEALTH TECHNOLOGY ASSESSMENT FOR INNOVATIVE MEDICAL DEVICES IN UNIVERSITY HOSPITALS AND THE ROLE OF HOSPITAL PHARMACISTS: LEARNING FROM INTERNATIONAL EXPERIENCE” 29, no. 2 (April 1, 2013): 185–91.

15 Braden Manns et al., “Identifying Strategies to Improve Diabetes Care in Alberta, Canada, Using the Knowledge-to-Action Cycle,” *CMAJ Open* 1, no. 4 (October 2013): E142–50, doi:10.9778/cmajo.20130024; F. Lega and M. Sartirana, “Managed Clinical Networks: Scope, Evidence and Feasibility,” *International Journal of Clinical Practice* 65, no. 7 (July 2011): 725–27, doi:10.1111/j.1742-1241.2011.02686.x.

16 Michael Wonder, Martin E. Backhouse, and Edward Hornby, “Early Scientific Advice Obtained Simultaneously from Regulators and Payers: Findings from a Pilot Study in Australia,” *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 16, no. 6 (October 2013): 1067–73, doi:10.1016/j.jval.2013.07.007.

17 Ibid.

18 Oriana Ciani and Claudio Jommi, “The Role of Health Technology Assessment Bodies in Shaping Drug Development,” *Drug Design, Development and Therapy* 8 (2014): 2273–81, doi:10.2147/DDDT.S49935.

**Box 1: Early scientific advice processes internationally**

| International/Non-governmental  | Year of inception            |
|---|------------------------------|
| • Tapestry  | 2010 (now closed)            |
| • Green Park Collaborative International                                  | 2011                         |
| • IMI (Innovative Medicines Initiative, an EU Public-Private partnership) | 2015                         |
| <b>Europe</b>   |                              |
| • United Kingdom (NICE)   | 2009                         |
| • Sweden (TLV-MPA)  | 2009                         |
| • Germany (GBA)   | 2012                         |
| • Italy (AIFA)  | 2011                         |
| • France (HAS)  | 2012                         |
| • Netherlands (ZINL, ZINL-CEB)  | Tapestry: 2010 then EUnetHTA |
| • EUnetHTA  | 2011                         |
| • European Commission   | 2014                         |
| <b>North America</b>  |                              |
| • Canada (CADTH)  | 2015                         |
| • Green Park Collaborative (USA)  | 2011                         |
| • MaRS EXCITE (Canada)  | 2011                         |
| • FDA/CMS Parallel Review   | 2010                         |

An example of improved engagement that has received a lot of attention is the multiple early scientific dialogue projects run through EUnetHTA and the European Commission. Between 2012-15, 24 one-day, face-to-face, early dialogue meetings between HTA bodies and small to large drug and medical device companies occurred with the European Medicines Agency invited as an observer. During this time, the process and procedure for conducting early dialogues was revised several times.

In the USA, the FDA/CMS parallel review process, established in 2010, has also provided a means for early communication between HTA bodies and the medical device industry. Producers eligible for Parallel Review or interested in applying may also still request CMS' input on clinical trial design and other considerations by asking for CMS' participation in an FDA Pre-Submission meeting.<sup>19</sup> The MaRS EXCITE initiative (in Canada) takes this further by working further "up-stream" in the technology development process and collaboratively developing clinical development plans further "up-stream."<sup>20</sup>

Although dialogue between an HTA body and a company may be a helpful step towards understanding shared scientific judgments and what is important to demonstrate value, there has been an increasing awareness of the importance of dialogue with others affected, including patients, care providers, other HTA bodies and other companies. To this end, a number of key initiatives have included multi-stakeholder engagement to not only explore scientific judgments, but other facets of patient access to new therapies. The European Commission program, called Shaping European Early Dialogues (SEED) included regulators and patient representatives as observers along with a consortium of 14 European HTA bodies. As of this writing, eleven early dialogue procedures, that have taken place prior to major company decisions regarding clinical development, including 3 medical devices have been conducted through this program to date. Some have observed that multi-stakeholder involvement, and particularly that of clinicians, has been a key success factor with SEED.

19 Center for Devices and Radiological Health, "CDRH Innovation - Payer Communication Task Force (PCTF)," WebContent, accessed December 21, 2015, <http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhinnovation/ucm456149.htm>.

20 Leslie Levin, "EARLY EVALUATION OF NEW HEALTH TECHNOLOGIES: THE CASE FOR PREMARKET STUDIES THAT HARMONIZE REGULATORY AND COVERAGE PERSPECTIVES," *International Journal of Technology Assessment in Health Care* 31, no. 4 (January 2015): 207-9, doi:10.1017/S0266462315000422.



One participant in SEED noted that in the rare disease space, SEED “has had an immediate output for industry developers” – namely it has provided reassurance in current clinical development plans or called attention to places that need change. Incentive and impact from early advice is also due to the fact that some HTA bodies, such as the G-BA in Germany, offer an “official, non-binding, position” during face-to-face meetings. For pharmaceutical companies, this may be simply communicating the position of the G-BA on what is an adequate comparator (a small but important piece of information). Advice to device manufacturers is broader and encompasses issues of study design, clinical endpoints, comparators and regulatory issues. Formal evaluations of advice programs have recently emerged, including that of the Scottish Medicines Consortium.<sup>21</sup>

These same principles of multi-stakeholder interaction have been viewed as critical to the success of lifecycle approaches to the introduction and re-assessment of technology – the shift from one-off technology assessment to ongoing technology management.<sup>22</sup> Other non-governmental organizations, such as the IMI (Innovative Medicines Initiative, an EU Public-Private partnership) and MIT Center for Biomedical Innovation: NEWDIGS are exploring how initial introduction with on-going development, assessment and review of use can be accomplished using relevant stakeholder input along a continuum.

The Center for Innovation in Regulatory Science has also undertaken numerous initiatives since 2008 to better understand how these processes can work and gauge their impact. This includes systematically collecting information on scientific advice meetings and their impact on development from its participating members. Some of these data include “type of advice provider, timing, scope, and consistency of advice between different stakeholders and the reasons companies may not be compliant with the advice given.”<sup>23</sup> A survey of stakeholder attitudes is also currently being undertaken.

### Alzheimer’s disease

An example of engagement has been in the area of Alzheimer’s disease, where new developments in basic research catalyzed significant opportunities for commercialization of new therapeutic products by global pharmaceutical manufacturers. Yet despite the potential clinical significance of having new therapies that might prevent or delay the onset of symptoms, questions remained about the feasibility of investment required, economic impact, to what degree having new products aligned with patient and provider values, and how these would be implemented in practice. Producers of new drugs were faced with the costly uncertainty of creating new medicines that may be societally beneficial, but would challenge existing HTA frameworks, possibly not receiving reimbursement in line with the value of the potential benefits offered.

Alzheimer’s disease therapies also posed a real challenge in that costs and benefits would accrue over a longer period, would impact different budgetary siloes, and require data to support decreased reliance on caregivers and other health and public health system resources that would be challenging to measure. Several projects engaging multiple stakeholders were developed to address these challenges. In 2013, after 2 years of development, the Green Park Collaborative – International (GPC- I) pilot program released recommendations “regarding the selection criteria, interventions, comparators, outcomes, and follow-up employed in phase 3 and 4 trials of pharmaceutical therapies intended for use in patients with mild or moderate Alzheimer’s disease.”<sup>24</sup> The collaboration included input from numerous HTA bodies (CADTH, NICE, PBAC, HAS, EUnetHTA, NOKC), regulatory agencies (EMA, FDA), pharmaceutical companies (Lilly, Pfizer, Roche, Merck), HTA organizations, academics and policy experts.

21 C. Lee, M. Wasserman, and A. Arnaud, “Qualitative and Quantitative Analysis of The Scottish Medicines Consortium (Smc) Advice,” *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 18, no. 7 (November 2015): A549, doi:10.1016/j.jval.2015.09.1756.

22 Husereau, “ADAPTIVE APPROACHES TO LICENSING, HEALTH TECHNOLOGY ASSESSMENT, AND INTRODUCTION OF DRUGS AND DEVICES.”

23 “Stakeholder Survey: Early Scientific Advice,” *CIRS: The Centre for Innovation in Regulatory Science*, accessed December 21, 2015, <http://www.cirsci.org/stakeholder-survey-early-scientific-advice/>.

24 “CMTP - EE2,” accessed December 1, 2015, <http://www.cmtptnet.org/news-room/view/effectiveness-guidance-document-on-alzheimers-disease/>.



Alzheimer's has seen a similar focus by the Innovative Medicines Initiative (IMI), a large private-public sector partnership between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA), intended to improve access to innovative drugs for patients. Some initial IMI projects were successful in bringing HTA bodies, innovators, and payers together (although not with a specific mandate for scientific advice) to arrive at consensus regarding topics like the appropriate use of real-world evidence. Building on these, a number of IMI-sponsored projects have focused on various aspects of the clinical development of drugs for Alzheimer's. For example, one part of the BigData4BetterOutcomes (BD4BO) program, the "Real World Outcomes Across the AD (Alzheimer's disease) Spectrum (ROADS) to Better Care" project brought several major pharmaceutical companies together with national health system leaders, HTA bodies, and regulatory agencies to develop recommendations on appropriate AD-related outcomes. These included cognitive, functional, and behavioral endpoints that could be used in real-world research programs and data systems outside of clinical trials. A similar project, funded by the European Commission in the framework of the Public Health Programme, is the Alzheimer's COoperative Valuation in Europe (ALCOVE)

### **Better multi-stakeholder engagement**

The move toward better engagement among HTA bodies was first observed with patient and public/citizen engagement processes. Several HTA bodies in Scotland, Sweden, Denmark and the UK were among the first to develop processes for the involvement of patients in HTA.<sup>25</sup> Subsequent attention was then given to regulators and the need for coordination / collaboration – particularly in cases of drugs perceived to be high priority.

Subsequently, and despite HTA being a policy tool intended to support decisions, many perceived a disconnect between HTA and the decisions that payers were making, as a result of health system structures, evolving health system challenges and the need for flexibility in decision-making. The benefits of good engagement go beyond topic scoping and answering needed questions but extend to identifying health and health system priorities including the needs for innovative technologies, priorities for assessment amongst emerging technologies, the ways that the analyses and their conclusions can best be presented, and the implications of these for health care practice and organisation and the use of human, capital and recurrent resources. Clearly, payers and health system managers have an important role to play in HTA dialogue.

In Sweden, the reimbursement process is linked through the Dental and Pharmaceutical Benefits Board (Tandvårds-och läkemedelsförmånsverket), or TLV. The SBU (Statens beredning för medicinsk och social utvärdering) is an independent body that is able to provide HTA support to the TLV. There are also regional HTA bodies. The TLV has no responsibility for health care delivery budgets, which are decentralized to regional (city-based) councils. The Swedish process of payer engagement involves monthly meetings between all 21 county councils (the complete number of actual payers), the SBU and the TLV. The county councils have come together and are co-operating on horizon scanning activities, interpreting HTA reports, and priority setting for health economic based mini-HTA-evaluations. In particularly important cases this also leads to third party negotiations between the companies, the county councils and TLV. This improved process has also created the need for a strengthened approach to horizon scanning and forecasting.<sup>26</sup> As the first drugs in the pilot program are only now showing in reimbursement applications, it is too early to evaluate the impact of this process.

<sup>25</sup> Wortley, Flitcroft, and Howard, "WHAT IS THE ROLE OF COMMUNITY PREFERENCE INFORMATION IN HEALTH TECHNOLOGY ASSESSMENT DECISION MAKING?"; Low, "POTENTIAL FOR PATIENTS AND PATIENT-DRIVEN ORGANIZATIONS TO IMPROVE EVIDENCE FOR HEALTH TECHNOLOGY ASSESSMENT."

<sup>26</sup> [http://www.piperska.org/sites/default/files/Wettermark\\_Horizon\\_scanning\\_and\\_forecasting\\_in\\_Sweden.pdf](http://www.piperska.org/sites/default/files/Wettermark_Horizon_scanning_and_forecasting_in_Sweden.pdf)

### 3.3 Issues and challenges

There is still considerable uncertainty regarding the ultimate value and outcomes of engagement. However, many of these enhanced approaches to engagement have demonstrated that dialogue about scientific judgments and better engagement between HTA bodies, manufacturers and other key stakeholders is feasible and positively perceived by all parties. The ROADS Project is in its inception, having launched in October 2015. The Green Park Collaborative - International initiative reported that a "convergence toward shared understanding" occurred. However, they also reported that the international scope of the exercise created specific challenges – specifically the different structures and political factors related to health system stewardship created contextual problems. It also created logistical problems for teleconferencing and considerable expense and planning for face to face meetings.

Another related issue is the timing and resources that should be contributed to engagement at any given stage. There is a general recognition that engaging is a time and labor intensive effort for all parties and may not be required or worthwhile for all disease or drugs. For example, one analysis suggests that engagement may have little impact on HTA recommendations, even in technologies with high payer uncertainty and which have been conditionally approved.<sup>27</sup>

Other significant challenges to engagement include changing the nature of the HTA process from one that is reactive to one that is pro-active, engaging the relevant stakeholders across the whole life-cycle approach of products from health need and concept to mature adoption. This innovation in the HTA process will require significant time and resources and all parties, and those that finance their activities, will need to be convinced that it is a beneficial approach. These processes may reveal different views on what is important to different parties and bring all stakeholders out of a "comfort zone". There may also be differing views within HTA bodies and technology producers themselves, which will require reconciliation. Deciding who is qualified to lead and contribute to dialogue and how these processes are governed may require further thought.

Another significant challenge is having consensus on what information can be shared, and when, and the "non-binding" nature of advice; questions about whether joint collaboration is worth the effort and resources required. As these activities are intended to be societally beneficial and will likely be wholly or partially funded by the public, there may be expectation of transparency of the process and the clear declaration of conflict of interests. There may also be concerns about conflict of interest if the manufacturers themselves fund these processes. The sharing of information also calls attention to its ever-changing nature and the impermanence of advice based on changing information.

27 I. Lipska et al., "Does Conditional Approval for New Oncology Drugs in Europe Lead to Differences in Health Technology Assessment Decisions?," *Clinical Pharmacology and Therapeutics* 98, no. 5 (November 2015): 489–91, doi:10.1002/cpt.198.

## 4. Rethinking value, affordability and access

### 4.1 Theory and Principles

Increasing fiscal pressure across all health systems coupled with the realization that some technologies that HTA bodies consider both effective and cost-effective may not be affordable has led to a vigorous public debate in recent months about the concepts of value, affordability and access. Notably, drugs for chronic hepatitis C virus, which appear to be much more effective than previous regimens, were judged to have reasonable additional costs when compared to the value of their benefits (i.e., incremental cost per quality-adjusted life-years were below acceptable threshold limits).<sup>28</sup> Yet, in some jurisdictions, the investment required for full price treatment was not feasible.<sup>29</sup> Other products that represent substantial fiscal pressure include some oncology drugs<sup>30</sup>, drugs for diabetes, expensive drugs for rare diseases<sup>31</sup>, and some medical devices, such as stereotactic radiosurgery and radiotherapy, which require significant capital expenditure to realize reduced operational expenses; or possibly deep brain stimulation which, if it were to be used in larger populations could have a major budgetary impact. Other technologies that may soon emerge include therapies for Alzheimer's prevention and regenerative therapies (cures).<sup>32</sup>

There have been several responses to the introduction of therapies of high societal value but unmanageable budget impact: firstly, payers have had to increasingly rely on traditional approaches to managing funding and access, including limiting access to identifiable subgroups where therapy is most cost-effective,<sup>33</sup> and developing care pathways or rationing sequences of use (e.g., first line, second line therapy.) The latter approach brings further attention to the need for early dialogue between stakeholders, including those in the physician / caregiver involvement. An example of restriction with new hepatitis C treatments, where despite receiving a 50% discount on the price, the US Department of Veterans' Affairs had to restrict reimbursement to a proportion of their constituents infected with the virus.<sup>34</sup> Others have proposed dynamic pricing models or strategic procurement involving HTA as a more nuanced approach to these restrictions.<sup>35</sup>

Another traditional response that is increasingly used is that of product-listing agreements. Product listing agreements can be put in place to address both either payer uncertainty about effectiveness, costs or both. Sometimes these concepts are inter-related. In some cases, innovative access with evidence development (AED)<sup>36</sup> or "performance-based risk sharing" agreements have been employed. Both issues have also been already discussed in previous Policy Forum meetings.<sup>37</sup> This has been more straightforward for some diseases where populations are easily tracked and outcomes are not difficult

28 John W. Ward and Jonathan H. Mermin, "Simple, Effective, but Out of Reach? Public Health Implications of HCV Drugs," *The New England Journal of Medicine* 373, no. 27 (December 31, 2015): 2678–80, doi:10.1056/NEJMe1513245.

29 Andrea Messori, "Newest Treatments for Hepatitis C: How Can We Manage Sustainability?," *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 61, no. 12 (December 15, 2015): 1891–92, doi:10.1093/cid/civ667; Ohad Etzion and Marc G. Ghany, "A Cure for the High Cost of Hepatitis C Virus Treatment," *Annals of Internal Medicine* 162, no. 9 (May 5, 2015): 660–61, doi:10.7326/M15-0674.

30 Experts in Chronic Myeloid Leukemia, "The Price of Drugs for Chronic Myeloid Leukemia (CML) Is a Reflection of the Unsustainable Prices of Cancer Drugs: From the Perspective of a Large Group of CML Experts," *Blood* 121, no. 22 (May 30, 2013): 4439–42, doi:10.1182/blood-2013-03-490003.

31 Brian Godman et al., "Are New Models Needed to Optimize the Utilization of New Medicines to Sustain Healthcare Systems?," *Expert Review of Clinical Pharmacology* 8, no. 1 (January 2015): 77–94, doi:10.1586/17512433.2015.990380.

32 Don Huseareu, "How Do We Value a Cure?," *Expert Review of Pharmacoeconomics & Outcomes Research* 15, no. 4 (2015): 551–55, doi:10.1586/14737167.2015.1039519.

33 Douglas Coyle, Martin J Buxton, and Bernie J O'Brien, "Stratified Cost-Effectiveness Analysis: A Framework for Establishing Efficient Limited Use Criteria," *Health Economics* 12, no. 5 (May 2003): 421–27, doi:10.1002/hec.788.

34 Chip Reid CBS News December 1, 2015, and 7:23 Pm, "VA Can't Afford Drug for Veterans Suffering from Hepatitis C," accessed December 3, 2015, <http://www.cbsnews.com/news/va-cant-afford-drug-for-veterans-suffering-from-hepatitis-c/>.

35 E Nason and J Sproule, *Industry-Payor Agreements for Pharmaceuticals Background for Roundtable* (Edmonton, AB: Institute of Health Economics, 2011), [http://www.ihe.ca/documents/Industry-payor%20agreements%20for%20pharmaceuticals\\_v1%200%20\(2\)-1.pdf](http://www.ihe.ca/documents/Industry-payor%20agreements%20for%20pharmaceuticals_v1%200%20(2)-1.pdf).

36 T. Stafinski, C.J. McCabe, and D. Menon, "Funding the Unfunderable: Mechanisms for Managing Uncertainty in Decisions on the Introduction of New and Innovative Technologies into Healthcare Systems," *Pharmacoeconomics* 28, no. 2 (2010): 113–42.

37 "HTAi: About HTAi Policy Forum," accessed December 3, 2015, <http://www.htai.org/policy-forum/about-htai-policy-forum.html>; Karen Facey, "Improving the Effectiveness and Efficiency of Evidence Production for HTA in the Light of Current Trends in Drug and Device Development, Health System Funding, Regulation and HTA," *International Journal of Technology Assessment in Health Care* [in press] (2015).

to define.<sup>38</sup> For example, access to a new expensive medicine for cystic fibrosis (ivacaftor) was aided by already-established registries. Notably, the Australian Pharmaceutical benefits Scheme provided this new medicine through a pay for performance arrangement and based using its National registry.<sup>39</sup>

Other proposed innovative financing mechanisms have been licensing and bond mechanisms that have been created for financing existing interventions for developing countries.<sup>40</sup> For example, USD 6.5 billion from 23 countries was raised by The International Finance Facility for Immunisation scheme which was used to provide vaccines to countries with a lesser ability to pay more rapidly.<sup>41</sup> Other schemes include the Health Impact Fund, where pharmaceutical companies pledge to distribute innovations at cost in return for a performance-based reward<sup>42</sup> and a social impact bond being developed by the Ontario government to fund medical devices.<sup>43</sup>

Another response to “funding the un-fundable” has been to re-visit frameworks for assessing what is considered valuable.<sup>44</sup> This has included small proposals to consider broader metrics of societal value through to large-scale proposals that use societally relevant criteria with a departure from a strict focus on cost-effectiveness. In some jurisdictions, such as the UK, this has led to guidance on how to reconsider the value of health-related quality of life and length of life in the very young or with few years remaining. Many jurisdictions have similarly adopted frameworks for considering the value of therapies for rare diseases with high morbidity – although some, notably Canada, have suggested that all diseases be treated equally. More radically, some have proposed looking beyond cost-effectiveness and value for money within the budgets for particular conditions or for the health care system itself, to include wider opportunity costs for other activities impacted by higher health care spending when considering value of health care interventions.

These discussions have strengthened interest in some quarters on the possible use of multi-criteria decision analysis (MCDA) as a means of combining the range of factors that may be considered relevant to defining and determining value. Although some MCDA-based proposals have addressed the payer’s problem of scarce resources,<sup>45</sup> others have do not explicitly consider what payers are able to give up to achieve these wider benefits.<sup>46</sup> This is a departure from the concept of economic value where lost opportunities from investment can be explicitly characterized. Some of the challenges of implementing MCDA approaches are the increased complexity coupled with burden of administration – it remains to be seen if these approaches will become mainstream.<sup>47</sup> MCDA approaches have seen uptake in Central and Eastern European countries but there are few practical examples of MCDA being used for wider value frameworks outside of these.

Not surprisingly, these developments have led to debate about what represents a “fair price” for a technology –i.e., a price that provides a good return to investors, rewards and incentivizes innovation,

38 Louis P. Garrison et al., “Performance-Based Risk-Sharing Arrangements–Good Practices for Design, Implementation, and Evaluation: Report of the ISPOR Good Practices for Performance-Based Risk-Sharing Arrangements Task Force,” *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 16, no. 5 (August 2013): 703–19, doi:10.1016/j.jval.2013.04.011.

39 “Department of Health | Access to Kalydeco through the Pharmaceutical Benefits Scheme,” accessed February 13, 2015, <http://www.health.gov.au/internet/main/publishing.nsf/Content/MC14-000305-pharmaceutical-benefits-scheme-listing-of-kalydeco>.

40 “Overview - ABOUT IFFIm - International Finance Facility for Immunisation,” accessed February 14, 2015, <http://www.iffim.org/About/Overview/>.

41 Ibid.

42 “The Health Impact Fund: A Summary Overview | Incentives for Global Health,” accessed February 14, 2015, <http://healthimpactfund.org/the-health-impact-fund-a-summary-overview/>.

43 “The Way Forward on Social Impact Bonds,” MaRS, accessed November 30, 2015, <https://www.marsdd.com/news-and-insights/way-forward-social-impact-bonds-canadian-impact-investors-give-insights-new-report/>.

44 Norman Daniels, Thalia Porteny, and Julian Urritia, “Expanded HTA: Enhancing Fairness and Legitimacy,” *International Journal of Health Policy and Management* 5, no. 1 (2015): 1–3, doi:10.15171/ijhpm.2015.187.

45 Vakaramoko Diaby and Ron Goeree, “How to Use Multi-Criteria Decision Analysis Methods for Reimbursement Decision-Making in Healthcare: A Step-by-Step Guide,” *Expert Review of Pharmacoeconomics & Outcomes Research* 14, no. 1 (February 2014): 81–99, doi:10.1586/14737167.2014.859525.

46 Praveen Thokala and Alejandra Duenas, “Multiple Criteria Decision Analysis for Health Technology Assessment,” *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 15, no. 8 (December 2012): 1172–81, doi:10.1016/j.jval.2012.06.015.

47 Ibid.

and allows society to benefit to the full from the uptake of the technology.<sup>48</sup> While much of this debate is currently being conducted in the media and governments in parallel with formal HTA and pricing and reimbursement processes, in some jurisdictions attempts have been made to factor these considerations into the formal processes. These developments have also led to discussions about what constitutes “value” and what is affordable and how these concepts relate to each other. For example, despite a formal requirement to consider cost-effectiveness (as a proxy for value) in creating recommendations, there is considerable empirical evidence from Canada that positive decisions were more greatly influenced by price (a proxy for budget impact).<sup>49</sup>

## 4.2 Current Activities and Relevant Cases

### Value-based frameworks

The issue of providing access to needed and innovative (i.e. socially valuable) technologies that may be unaffordable has seen several concrete responses. Many of these have focused built upon a range of work in recent years to better understand value and its relationship to price and refine mechanisms to determine what payers are willing to pay and in what manner.

In Germany, for example, where pre-reimbursement price controls did not previously exist, concerns about unsustainable pharmaceutical expenditures led to the formal adoption of economic evaluation methods to inform negotiations for the reimbursement of new or relevant drugs within the Statutory Health Insurance System.<sup>50</sup> Despite these efforts, legislation was passed to freeze current prices of patented medicines and reorganized insured prices in 2010. Subsequently, the “Act to Reorganize the Pharmaceuticals’ Market in the Statutory Health Insurance System” (Gesetz zur Neuordnung des Arzneimittelmarktes in der gesetzlichen Kranken-versicherung [AMNOG ]) came into effect January 2011. The new legislation outlines a system that combines rapid, therapeutic benefit assessment with therapeutic reference pricing and negotiation.<sup>51</sup> It was intended to replace the need for formal economic evaluation.

In 2010, the UK Department of Health released an outline of the newly proposed value-based pricing system for public consultation. At the basis of the proposal was a price structure based on evaluations of cost-effectiveness for new drugs and a basic UK threshold, “reflecting the benefits displaced elsewhere in the NHS when funds are allocated to new medicines”.<sup>52</sup> Thresholds would then be adjusted where a medicine was marketed for “diseases with unmet need or which are particularly severe”, “medicines that can demonstrate greater therapeutic innovation and improvements compared with other products”; and “medicines that can demonstrate wider societal benefits.”<sup>53</sup>

Further studies were subsequently commissioned to measure the threshold, set up a system for ongoing monitoring,<sup>54</sup> examine how to capture and aggregate wider benefits, how to account for therapeutic improvements, and how the threshold should relate to price. The result of these efforts led to a 2013, Department of Health issuance to NICE with the terms of reference for ‘value-based assessment’ which asked NICE to consider other aspects of value, such as burden of illness and the wider societal benefits

48 William W. Chin, “A Delicate Balance—Pharmaceutical Innovation and Access,” *The New England Journal of Medicine* 373, no. 19 (November 5, 2015): 1799–1801, doi:10.1056/NEJMp1513227.

49 Angela Rocchi et al., “Common Drug Review Recommendations: An Evidence Base for Expectations?,” *Pharmacoeconomics* 30, no. 3 (2012): 229–46.

50 Gerber A, Stock S, Dintsiros CM. Reflections on the Changing Face of German Pharmaceutical Policy: How Far Is Germany from Value-based Pricing? *Pharmacoeconomics* 2011;29(7): 549–53; Gissel C. Pharmaceutical Pricing Based on Early Benefit Assessments. Value in Health. Conference: 17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2012 Washington, DC United States (2012); Gandjour A. Germany’s Decision Rule for Setting Ceiling Prices of Drugs: a Comparative Analysis with Other Decision Rules. *Applied Health Economics & Health Policy* 2011;9(2):65–71

51 Gerber, Stock, Dintsiros. Reflections on the Changing Face of German Pharmaceutical Policy: How Far Is Germany from Value-based Pricing?”

52 Department of Health, Medicines, Pharmacy & Industry Group16, *A New Value-based Approach to the Pricing of Branded Medicines: a Consultation* (London: Department of Health, UK, 2010)

53 Ibid

54 Claxton et al. Methods for the Estimation of the NICE Cost Effectiveness Threshold.

of new interventions, including productivity effects, into its methods so that they could be used in the appraisal and decision-making process.

NICE developed a methodology in response to this in March 2014<sup>55</sup>, suggesting a method to modify quality-adjusted life-years (QALYs) based on burden of illness. However, the suggestion to include measures of productivity was rejected based on concerns of equity. Instead, a proposal to examine wider societal impact, represented by the absolute difference in QALYs for patients receiving conventional care and the equivalent population without the condition was proposed. The idea was that the absolute QALY shortfall represents the reduced capacity of patients to engage with society as a result of having their condition. Other numerous shortcomings to QALY-based approaches have been highlighted over the years.<sup>56</sup>

There were several suggestions in the proposal as to how these measures could be used, including as a weight for the cost-effectiveness threshold, along with other considerations of certainty, degree of innovation, and non-health objectives of the NHS. After receiving extensive conflicting and negative feedback upon consultation, the proposal was largely abandoned. Among others, concerns were raised about ignoring notions of opportunity cost and the complexity of implementing the new system of appraisal. Announcing the outcome of this process in September 2014, NICE called for a new approach to managing the entry of new drugs into the NHS, "positioning NICE for a wider role in the way drugs are developed, evaluated and taken up in the NHS". In November 2014 the UK Government announced the Innovative Medicines and MedTech Review, to consider how to speed up patient access to cost-effective and innovative medicines, devices and diagnostics. The review commenced in March 2015 and is still ongoing.

Related to policy-based frameworks for value have been several recent attempts to communicate value to consumers and care providers. Notably, large medical societies and service delivery organizations, including (ACC–AHA), the American Society of Clinical Oncology (ASCO), Memorial Sloan Kettering Cancer Center (MSKCC), and the National Comprehensive Cancer Network (NCCN) have developed tools for patients and care providers to consider costs in decisions to choose. These tools create scores to assess value of treatment to patients.<sup>57</sup>

### Research programs to establish value

Beyond revisiting frameworks for evaluation, have been significant attempts to promote applied research of new technologies to resolve uncertainties significant to payers and establish value. For example, the Agenzia Italiana del Farmaco (AIFA) collects real-world data through web-based registries<sup>58</sup> as a means to resolving uncertainty and often linked to product listing agreements. This system recognizes the need to collect information "fit-for-purpose" and that meets the needs of its decision-makers. However it also highlights the impact that these arrangements can have on others, including patients and caregivers and the need for multi-stakeholder collaboration.<sup>59</sup>

In the US, the Patient-Centered Outcomes Research Institute (PCORI) Board of Governors \$83 million to fund 26 patient-centered, comparative clinical effectiveness research (CER) studies on numerous conditions including two (worth USD 29.5 million) focused on chronic hepatitis C virus (HCV) infection. The HCV studies are designed and implemented with the input of national advocacy organizations, major professional associations, payers, and other key patient and stakeholder groups. One of the

55 NICE, "NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE CENTRE FOR HEALTH TECHNOLOGY EVALUATION Consultation Paper Value Based Assessment of Health Technologies," accessed December 2, 2015, <http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/VBA-TA-Methods-Guide-for-Consultation.pdf>.

56 Marilyn Dix Smith, Michael Drummond, and Diana Brixner, "Moving the QALY Forward: Rationale for Change," *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 12 Suppl 1 (March 2009): S1–4, doi:10.1111/j.1524-4733.2009.00514.x.

57 Peter J. Neumann and Joshua T. Cohen, "Measuring the Value of Prescription Drugs," *The New England Journal of Medicine* 373, no. 27 (December 31, 2015): 2595–97, doi:10.1056/NEJMp1512009.

58 "Registri Farmaci Sottoposti a Monitoraggio," *Registri Farmaci Sottoposti a Monitoraggio* | AIFA Agenzia Italiana Del Farmaco, March 31, 2014, <http://www.agenziafarmaco.gov.it/content/registri-farmaci-sottoposti-monitoraggio>.

59 Husereau, "ADAPTIVE APPROACHES TO LICENSING, HEALTH TECHNOLOGY ASSESSMENT, AND INTRODUCTION OF DRUGS AND DEVICES."



studies, "Patient-Centered Models of HCV Care for People Who Inject Drugs", is intended to examine the impact of two complex interventions (patient navigators and directly observed treatment) to people who inject drugs (and are at a high risk of re-infection) to see where new drugs have the biggest impact.

### Special frameworks for rare diseases and regenerative medicine

Reflecting the issue of value and affordability are decisions regarding drugs for rare diseases. Although these drugs have traditionally been viewed as affordable (i.e., do not contribute to expenditure growth, despite "low-value" (by cost-effectiveness) standards they have also been viewed as needed (to do a lack of alternatives) despite being high-priced. Several international jurisdictions have developed special frameworks for considering the value of drugs and technologies for rare diseases (Box 2). For example, recent guidance from NICE on the evaluation of drugs for ultra rare conditions states that the Appraisal Committee "will also take into account what could be considered a reasonable cost for the medicine in the context of recouping manufacturing, research and development costs from sales to a limited number of patients."<sup>60</sup>

At issues will is the sheer number of them in development today that will create a condition of "salami slicing" where payers who have only been willing to reimburse due to relatively small budget impacts will likely resist when this accumulation of these small exceptions represents a large population and opportunity cost. The same issue is reflected with future regenerative (curative) therapies for a multitude of small populations; current estimates suggest almost 500 therapies are in development.<sup>61</sup>

#### Box 2: Special reimbursement frameworks for rare disease technologies

##### UK

- NICE has established a separate committee for "highly specialised technology".
- In addition to cost-effectiveness, the committee also considers the "nature of the condition (including morbidity/clinical disability with current standards of care; effect on caregivers' quality of life; current treatment options)" ; impact beyond direct health benefits (are there any such benefits, are costs/savings incurred outside of the NHS and PSS) ; and impact on delivery of the specialized service (staffing and infrastructure requirements such as training, planning for expertise).<sup>62</sup>
- Committee will also take into account what could be considered a reasonable cost for the medicine in the context of recouping manufacturing, research and development costs from sales to a limited number of patients

##### Scotland

- The SMC will consider additional factors when compelling clinical evidence is provided along with additional costs that are high. A Patient and Clinician Engagement process with new criteria for ultra rare diseases has been developed and is currently under review by government.
- This includes the life-threatening nature of disease; whether life expectancy or quality of life will improve substantially; what other therapeutic options are available; whether specific sub-group of patients will highly benefit; whether a disease condition can be stabilized or reversed; whether the new medicine bridges a gap to a definitive therapy; and whether the drug is an alternative to an unlicensed drug that is the sole treatment in use for a specific condition.<sup>63</sup>

60 <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/Highly-Specialised-Technologies-Interim-methods-and-process-statements.pdf>

61 "Alliance for Regenerative Medicine Releases Annual Industry Report Showcasing Impressive Sector Growth | Alliance for Regenerative Medicine," accessed February 14, 2015, <http://alliancerm.org/press/alliance-regenerative-medicine-releases-annual-industry-report-showcasing-impressive-sector>.

62 <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/Highly-Specialised-Technologies-Interim-methods-and-process-statements.pdf>

63 [http://www.scottishmedicines.org.uk/About\\_SMC/Policy\\_statements/Orphan\\_Drugs](http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Orphan_Drugs)



### Australia

- Australia has established a “rule of rescue,” which considers the following criteria: 1) There are no drug or non-drug treatments available in Australia for patients with the specific medical condition; 2) The medical condition is severe, progressive, and expected to result in premature death; 3) The medical condition applies to a very small number of patients; 4) The proposed drug qualifies as a rescue from the condition by providing worthwhile clinical improvement.<sup>64</sup>

### France

- France has had a National Plan for Rare Diseases since 2005 but has no specific framework for reimbursement of rare diseases. However, France will expedite a review if there is the following criteria are met: (a) new therapeutic modality, (b) high unmet need, (c) demonstrated efficacy/tolerability.

### Germany

- Germany has created a special provision (not a law or regulation) that states that “for small sample sizes, it is reasonable to accept a higher than 5% p-value (e.g. 10%) to prove statistical significance and to accept evidence from surrogate endpoints.” It also suggests surrogate endpoints must be valid, and that there is no reason to deviate from evidence hierarchies (i.e., using randomized controlled trials) when assessing the impact of drugs for small populations.<sup>65</sup>

### Canada

- CADTH has declared it will not create a separate process for rare disease drugs. However, CDR does have a special priority review process for drugs that meet a set of particular criteria, these are: “1) the drug is indicated or anticipated to be indicated for an immediately life-threatening or other serious disease; 2) the drug addresses an unmet medical need; 3) the drug offers substantial improvement in clinically important outcome measures of efficacy and effectiveness, when compared with other appropriate comparators.” This priority review procedure, which facilitates a faster review, may or may not apply to drugs for rare diseases.

### Explicit attempts to address affordability

Although current approaches to the assessment and reimbursement of expensive treatments for rare conditions are attempting to address budget impact and affordability explicitly, there are few examples of formal approaches to assess and reimburse “mainstream” technologies. In 2009, the UK introduced the Pharmaceutical Price Regulation Scheme (PPRS), a voluntary agreement that sought to relate rewards to companies to the levels of their investment in R&D and health system expenditure growth (a proxy for affordability) on particular products. The scheme has recently been modified to allow for more flexible pricing and patient access schemes.<sup>66</sup> More recently in the US, a value framework developed by the independent US Institute of Clinical Effectiveness and Review (ICER) has also attempted to show how affordability might be included formally in the routine assessment and decisions on reimbursement of technologies.<sup>67</sup>

The ICER Framework is being used to develop “value-based” prices for 15 to 20 FDA approved drugs over the next two years. Rather than being based on a cost-effectiveness threshold, these prices are based in affordability, and assuming that growth in expenditures on health cannot exceed theoretical limits linked to economic productivity. ICER defines “value-based price benchmarks as “The price range within which

64 <http://www.pbac.pbs.gov.au/section-f/f3-other-relevant-factors.html>

65 [https://www.iqwig.de/download/IQWiG\\_Methoden\\_Entwurf-fuer-Version-4-2.pdf](https://www.iqwig.de/download/IQWiG_Methoden_Entwurf-fuer-Version-4-2.pdf)

66 <https://www.gov.uk/government/publications/pharmaceutical-price-regulation-scheme-2014>

67 Peter B. Bach, “New Math on Drug Cost-Effectiveness,” *The New England Journal of Medicine* 373, no. 19 (November 5, 2015): 1797–99, doi:10.1056/NEJMp1512750.

all patients could be treated with reasonable long-term care value without adding short-term costs to the health care system that would contribute to health care spending growing faster than the overall economy.” ICER still looks at traditional cost-effectiveness thresholds as a proxy for “care value” but does not link prices to these. This approach is experimental and ICER has no formal authority within the US health care system, but the approach is attracting interest from a number of State and other US payers who are working with ICER to explore how an approach of this kind might be helpful in practice.

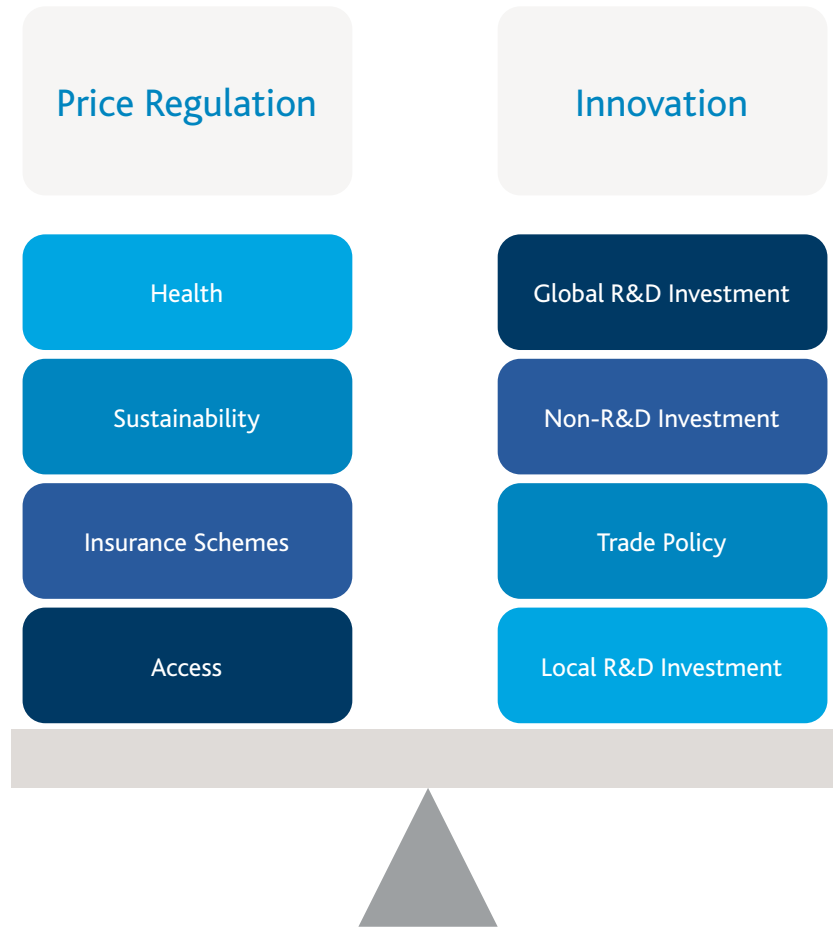
For example, ledipasvir/sofosbuvir combination therapy (Harvoni®) for chronic HCV infection had a US list price of approximately \$95,000 for 12 weeks of treatment. ICER, supporting the California Technology Assessment Forum (CTAF) concluded this was a “low” health system value despite a favourable incremental cost-effective ratio but due to its potential contribution to expenditure growth (5% in a single year). The recommended price range proposed by CTAF was \$34,000-\$42,000. Gilead Sciences, the maker of Harvoni®, subsequently announced it expected to provide a similar discount to payers.<sup>68</sup>

### 4.3 Issues and Challenges

This review of developing approaches to value, affordability and access illustrates the numerous challenges for payers, HTA bodies, industry and others. Some changes to pricing or coverage arrangements have come quickly in response to perceived concerns about health care sustainability – but they can be blunt instruments and may give rise to conflicting opinions about how prices should be determined, and whether there will be an adverse effect on innovation (Figure 1). While Germany was able to change prices arrangements quickly through what was perceived as needed legislation, the UK has still not arrived at a new framework for value and price, and no major system seems yet to have developed a way to factor affordability (in addition to cost or comparative effectiveness) into its routine consideration of the mainstream of technological innovation. The example of ICER suggests that there are technical solutions to this that may be of value to payers, but raises questions about the appropriate role in this area for a private organization with no accountability to insurers or government, and about whether (and if so how) a framework of this kind might be formally adopted (and if necessary modified) for use within a health system. There are also concerns that the traditional concept of value as separate from budget impact/expenditure is now lost with this approach.

68 Matt Seidner, “New Lower Prices for Gilead Hepatitis C Drugs Reach CTAF Threshold for High Health System Value | Institute for Clinical and Economic Review,” accessed December 2, 2015, <http://www.icer-review.org/new-lower-prices-for-gilead-hepatitis-c-drugs-reach-ctaf-threshold-for-high-health-system-value/>.

Figure 1: Relationships to be considered in pricing policy intended to foster innovation



The use of real-world evidence and other applied research to help to establish value is potentially beneficial both to payers (and the HTA bodies that support them) and industry. However, the timing of the research can be problematic, and considerable investment that may be required. A significant issue is how to decide who is responsible for creating and maintaining (financing) registries that are necessary for collecting real world data. There may also be fewer incentives to conduct research if health system budgets are not linked to research budgets. The UK National Institute for Health Research, for example, is part of the National Health Service, and has commissioned research in response to uncertainty in technology assessment.

## 5. Issues for Discussion at the 2016 Policy Forum Meeting

The break-out group discussions in the meeting may wish to consider the following questions

### 5.1 Rethinking Scientific Dialogue and Multi-Stakeholder Engagement

- a. What have we learned from work to date on scientific dialogue and multi-stakeholder engagement?
- b. When should dialogue start and how should it proceed over the lifecycle of the technology? What needs to be discussed and agreed at each step?
- c. When should dialogue proceed with a single HTA agency and when with multiple agencies?
- d. Which other stakeholders should be involved, and at which points in the dialogue?
- e. When is better to talk to different types of stakeholders individually and when together?
- f. What support may stakeholders require in order to engage and add value to, and derive value from, the process?
- g. How can the resource demands for HTA agencies and other stakeholder be managed and met? How can processes be streamlined? How can priorities be set for technologies where scientific dialogue will offer most value?
- h. How can we measure the impact and value of the process?
- i. Who should instigate, lead and manage the process of scientific dialogue?
- j. What authority should the process have? To what extent can the advice and commitments offered by HTA agencies and other stakeholders be morally or more formally binding? How do agreed courses of action need to be picked up by the manufacturer, HTA body and other stakeholders in order to get "traction"?
- k. Is it necessary to protect the confidentiality of some of the information that needs to be shared and, if so, how can this be achieved?
- l. Do the issues and preferred approaches differ for devices and drugs? If so, why and how?
- m. Do the issues and preferred approaches differ between high and middle/low income countries?

### 5.2 Rethinking Value, Affordability and Access

- a. When should discussions start on possible issues around value, affordability and access, and how should they proceed around and following market launch?
- b. Who should be involved in addition to manufacturers, payers and HTA bodies?
- c. To what extent is it possible or appropriate to use established mechanisms such as product listing agreements/patient access schemes and prioritizing access by disease severity/ability to benefit to manage costs that budgets cannot accommodate?
- d. What other approaches are feasible and appropriate in these circumstances?
- e. If the concept of "fair price" – i.e. a price that is "fair" to all parties – helpful? If so, what principles should underpin discussions/negotiations of this, and who should be involved in such discussions?
- f. What role (if any) can HTA play in agreeing value, affordability and access in addition to assessing benefits, costs and budget impact?
- g. Do the issues and preferred approaches differ for devices and drugs? If so, why and how?
- h. Do the issues and preferred approaches differ between high and middle/low income countries?

## 6. Outputs and outcomes of the 2016 Policy Forum meeting

The outputs of the February 2016 HTAi Policy Forum discussion will include:

- A factual note of points and issues raised in the discussions, by end of February 2016, to assist members in briefing colleagues within their organisations. This will be accompanied by copies of all slides used at the meeting (with the presenters' permission)
- A manuscript based on the discussion for submission to the International Journal of Technology Assessment in Health Care – possibly as part of a "mini-theme" on Innovation in HTA
- A panel session at HTAi 2016 to present IJTAHC draft paper and stimulate discussion with a wider group of stakeholders
- Presentations at other relevant national and international meetings by the Forum leadership team and Forum members.

Consideration will also be given to the presentation of outputs in novel ways to promote the work to a wider audience, and suggestions are welcome.

Intended outcomes from the 2016 Policy Forum meeting include:

- Improved understanding of the perceived need to re-think HTA – in general and in the specific areas of scientific dialogue and multi-stakeholder engagement, and of approaches to value, affordability and access
- Improved understanding of innovative approaches in these areas and the implications of these for how HTA can be undertaken and used in the future for the maximum benefit
- Understanding of the perspectives of different stakeholders on these issues and of how these can be addressed
- In the light of all the above, proposals for improvements to the traditional HTA process to allow it better to address the real needs of the current and future health care and innovation systems.

Aimed at:

- Meeting attendees and their organisations and networks
- All stakeholders in the wider HTA, health care and innovation community.

**Don Husereau**  
HTAi Policy Forum Scientific Secretary  
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