



# 2015 Policy Forum BACKGROUND PAPER

**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**

---

Karen Facey  
HTAi Policy Scientific Secretary 2014-2015

January 2015



Health Technology  
Assessment international

**This report should be cited as:**

Facey K. *HTAi Policy Forum 2015 Background Paper: 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*. Edmonton: Health Technology Assessment International; 2015.

## HTAi Policy Forum 2015

# 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

## 1. Context and Purpose of this Paper

---

The HTAi Policy Forum provides an opportunity for senior people from public and private sector organizations using health technology assessment (HTA) to support decisions or recommendations about product development and coverage to meet for strategic discussions about the present state of HTA, its development and implications for healthcare systems, industry, patients and other stakeholders (<http://www.htai.org/policy-forum/about-htai-policy-forum.html>).

This paper provides information to set the scene for the 2015 HTAi Policy Forum meeting on the subject of “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”.

The overall objective of the meeting is to develop and test model pathways for health technology evidence generation that are “as optimal as possible”, i.e. they can support timely HTA/coverage decisions, are efficient (taking cognisance of the evidence needs of other stakeholders and limitations to evidence generation), with an acceptable level of uncertainty for all stakeholders. A key challenge will be to recognise the trade-offs between earlier approval and uncertainty in evidence.

The purpose of this Background Paper is to present the “current trends” affecting different stakeholders or parts of the health system that might impact the way evidence can be generated for HTA/coverage. The aim is to share information among Policy Forum members in advance of the meeting, so that this material is taken “as read” and face-to-face discussions will focus on ways to improve evidence production for HTA.

The information in this report comes from a variety of published and grey literature sources mainly published in the past year, identified by the author, HTAi Policy Forum and Board Members and HTAi members.

Section 2 of this report describes the background to the choice of this topic, including an overview of past Policy Forum discussions. The following sections then cover the trends/challenges in:

1. Technology development and evidence generation for drugs and devices
2. Health system funding and organization that impact evidence generation for HTA
3. Regulatory approaches that impact evidence generation for HTA
4. HTA/coverage and regulatory interaction.

Section 7 presents trends and opportunities in evidence generation and sections 8 and 9 consider how these issues will feed in the HTAi 2015 Policy Forum meeting.

## 2. Background to the Topic

The 2015 meeting topic needs to be differentiated from past Policy Forum discussions<sup>1</sup>, so this section distils key elements from past Policy Forum papers that are relevant to discussion of evidence production for HTA to identify learnings and gaps that need to be addressed.

In 2008, the Policy Forum agreed the potential for harmonization of evidence requirements for clinical effectiveness, not only across HTA jurisdictions but also with regulators, whilst recognising that economic modelling and coverage decisions would still be context specific. In 2011, this theme was developed to clarify the different purposes of regulatory and HTA evaluations and encouraged emerging initiatives that provide joint scientific advice to manufacturers about study design and data requirements that might lower the overall burden of data collection for specific technologies. This included a proposal to extend such advice to cover specific medical conditions and methodological issues. It also recommended that discussions were needed with all stakeholders to better understand unmet health needs. The 2013 Policy Forum paper concluded that scientific advice should focus on how value should be demonstrated for HTA, taking account of the different stakeholder perspectives of value and the judgements involved in that determination.

Over the decade of the existence of the Policy Forum, there has been increasing pressure to deliver more timely HTA decisions, in particular at the point of market launch. This has led to a greater dependency on the evidence available at the time of licensing. Alongside this, there has been increased interest in the generation of evidence post-marketing in the real-world setting. So, the 2014 Policy Forum explored the implications of new adaptive approaches to licensing that evaluate an evolving evidence base, rather than at a single point-in-time. It identified the need to set priorities for adaptive approaches and stressed the need to examine evidence collection processes, consider the implications for different technologies and legal and ethical standards. It also recommended consideration of how stakeholders could contribute to the shared decision-making model that is implicit in adaptive approaches.

The 2007 and 2010 Policy Forum papers addressed what could be called “adaptive approaches to coverage” for technologies that could offer major benefits, but for which there are uncertainties in the evidence. Both outlined the circumstances in which managed entry agreements (MEA)/ coverage with evidence development (CED) might be used. They stressed that these approaches should be the exception and not the rule, being used where there are major uncertainties about key outcomes for which data could be collected within a realistic time period. The papers noted the challenges in operationalization of such complex administrative approaches and the need to evaluate their effectiveness. The 2009 and 2012 Policy Forum papers considered how HTA could be used in the next phases of the technology life cycle to optimize technology usage post coverage and in disinvestment decisions.

All Policy Forum papers sought to explore a dynamic approach to HTA that promotes appropriate, timely, and cost-effective use of technology making the best use of data over the technology life cycle, in collaboration with other stakeholders in the health system. However, there are concerns that evidence to support HTA is not being generated as optimally as it could be and that HTA is not responding to the continuing development of regulatory systems that are allowing even earlier licensing of products on the basis of phase II data. Hence the 2015 topic was chosen by Policy Forum members amalgamating two topics of “Improving the effectiveness and efficiency of evidence production” and “adapting HTA to recent trends in drug development”.

1 <http://www.htai.org/index.php?id=424>

## 3. Trends and Challenges in Technology Development and Evidence Generation

### 3.1 Drug Development

#### 3.1.1. Increasing Complexity of Clinical Research

The past decade has seen the translation of basic research on molecular characteristics, Antisense RNA interference, cell therapy, gene therapy and conjugated monoclonal antibodies into therapeutic innovations that are targeted to specific patients and disease sites, which can improve quality and length of life. It is also now a decade since the complete sequencing of the human genome. Although this has led to advances in diagnostic tests for predictive or prognostic applications, there remains a sense of dissatisfaction about the progress of personalised/stratified medicine in terms of its contribution to drug development and HTA<sup>2</sup>. The hope is that stratified medicine is not seen as “niching” a product or restricting patient choice but that it can help target appropriate patients and yield positive net benefit. However, to understand the predictive and prognostic properties of biomarkers to achieve this, new forms of observational research are needed to understand the associations between stratification of patient populations, risk, prognosis and outcome.

Development of new medicines is a long and rigorous process, which has become more costly and complex over the last decade. In 2011, 5,408 medicines were in development globally, with 833 of those in Phase III<sup>3</sup>. The attrition rate is high. Of the treatments that reach Phase III, one-third fail and only 20% of the products that are launched produce revenues that exceed average Research and Development (R&D) costs. A study in 2007, suggested that it costs an average of US\$1.2 billion to develop one new drug<sup>4</sup> and more recent studies estimate this to be higher. This is partly because the complexity of clinical trials has increased. In 2000-2003, the average number of clinical tests/ observations undertaken in a trial was 106, compared with 167 in 2008-2011, and the number of case report form pages increased from 55 to 171 over that period.<sup>5</sup>

This increased complexity decreases the effective patent life of a drug, thus reducing the “reward” for the industry. However, to encourage specific forms of research (e.g. in paediatrics) extension of patent is given.

The increasing complexity of clinical trials for regulatory purposes has meant that many involved in clinical research have been reticent to expand clinical studies to take account of the needs of HTA. Some companies have reorganised functions to ensure that market access is the ultimate goal, but not all have done this and there is still silo working between clinical research and market access in many companies, with little review of the overall efficiency of the research process to meet the needs of all stakeholders. In particular those that sign off protocols for Phase III (lead medic and statistician) may not be aware of HTA requirements or have the right skill sets to ensure these aspects are appropriately addressed.

2 O'Donnell J. Personalized medicine and the role of health economics and outcomes research: issues, applications, emerging trends and future research. *Value in Health*. 2013; S1-S3. (Editorial for Special Issue on Personalized Medicine).

3 Analysis Group. *Innovation in the biopharmaceutical pipeline: a multidimensional view*. Boston: January 2013.

4 DiMasi J, Grabowski H. The cost of biopharmaceutical R&D. *Is biotech different? Managerial and Decision Economics*. 2007; 28:469-79.

5 Getz K, Campo R, Kaitin K. Variability in protocol design complexity by phase and therapeutic area. *Drug Information Journal*. 2011; 45:413-20.

### 3.1.2 Partnerships to Improve Research

Some of the greatest clinical advances have been achieved through collaborative enterprises (ultrasound scanning, cloning, etc). Therefore it seems essential to see how inter sector collaborations can be fostered to improve the efficiency and effectiveness of health technology research. Some examples are described in this section.

In the U.S., \$95 billion was spent on medical research last year, but only 6% of clinical trials were completed on time, with a major challenge being the inability of centers to enroll sufficient patients. Part of the challenge is matching eligible patients to appropriate trials (and this becomes increasingly challenging with the development of stratified medicine). Clinical trial recruitment is a data-intensive task that often requires clinicians and researchers to manually cross reference patient data with criteria for thousands of available clinical trials. For centers like the US Mayo Clinic, which is currently conducting over 8,000 clinical trials, this is a major challenge. However, in partnership with IBM they are seeking to quickly and accurately match patients with appropriate clinical trials, using powerful data analytics to help clinicians quickly sift through millions of pages of clinical trial and patient data so that all eligible patients are considered for clinical trials<sup>6</sup>.

Health systems increasingly use the power of data analytics to monitor their performance and improve quality through linking data from a variety of sources to electronic health records. This is often achieved through multi-stakeholder consortia. One example of this is the Farr Institute in the UK, which provides the infrastructure to support safe use of patient and research data for medical research, and enables partnerships by providing a physical structure to co-locate National Health Service (NHS) organizations, industry, and academia<sup>7</sup>.

Another trend in the past decade has been the shared development of medicines as a result of mergers, acquisitions, joint development or in-licensing<sup>8</sup>. However this raises its own challenges, as a company may need to submit an HTA dossier for a product that it did not develop.

The scale and severity of the present Ebola outbreak with its 50% mortality rate, has resulted in a burst of scientific activity to find new treatments and vaccines with leniency for approval mechanisms given the extremely poor prognosis<sup>9</sup>. This is a very special case and may not provide insight to more usual situations. However an older, interesting example is that of combination treatment for HIV, which involved a collaboration of 16 companies with regulators to validate HIV RNA and CD4 as surrogate markers to enable conditional licensing.

### 3.1.3 Patient-centred Research

Another trend emerging in the pharmaceutical sector in 2014 has been the discussion of patient centricity and patient value. The aim is to realign drug development and company processes to be more patient centric, but this leads to interesting discussions about loss of power and the need for strong leadership to allow this form of partnership in research.

6 Hogan S. Watson helps Mayo clinic speed clinical trial research. Smarter Planet Blog. 8 September 2014. Accessed 22 September 2014.

7 [www.farrinstitute.org](http://www.farrinstitute.org) Accessed 22 September 2014

8 DiMasi J, Kim J, Getz K. The impact of collaborative and risk-sharing innovation approaches on clinical and regulatory times. *Therapeutic Innovation and Regulatory Science*. 2014; 48:482-7.

9 Fast-tracking treatments - The hunt for Ebola medicines is being accelerated. *The Economist*. 13 September 2014.

Lessons can be learned from public sector health research, looking at the developments in comparative effectiveness research (CER)<sup>10,11</sup>. The UK NHS research coordinating centre has over a decade of experience of involving patients in its processes and now evaluates whether a trial proposal has effectively engaged patients in its design and the intentions for involvement of patients in the conduct and interpretation of the study, all of which must be fully reported<sup>12</sup>. Meanwhile in the USA, patient engagement is considered crucial to the successful translation of CER. Furthermore it is recognised that CER may be enhanced by continuous patient engagement from selection of topics to question framing, selection of comparators and outcomes, development of analysis plan, agreement on data collection methods and review, interpretation and dissemination of results<sup>13</sup>.

The public sector also recognises the value of qualitative research more than has traditionally been the case in the private sector. Qualitative research can be undertaken in separate studies, or there is an increasing move to do it prior to or within Phase III trials, but this practice is not yet widespread<sup>14</sup>.

Patient organizations are also pushing for greater involvement in clinical research. Signposting of eligible patients to appropriate trials is seen as a key part of their remit. Some are taking this further by influencing study design to ensure that outcomes of importance to patients are measured (and where necessary developed). Myeloma UK has built a research network of 29 hospitals in the UK to improve patient access to experimental treatments whilst contributing to development of the evidence base for HTA.<sup>15</sup>

The European “PatientPartner” FP7 project, which involved all stakeholders concluded that patients have experiential knowledge generated through living with their condition, which is different from any scientifically generated knowledge. They recommended that patient organizations are the vehicle to communicate this real-life knowledge and that they should be actively involved in all aspects of clinical research, in order to ensure that the resulting therapies are better adapted to the needs of patients. PatientPartner developed a number of guidance documents to facilitate partnership between patient organizations, sponsors and investigators. They also recommended that a training programme about clinical research be created for patient organizations and that a European communication platform be developed to provide details of patient organizations, sponsors, investigators and their areas of interest in clinical research<sup>16</sup>.

The value of the early involvement of patient organizations in clinical trials was also mentioned in the FP7 Cooperation Work Programme stating that; “The early involvement of patients and their advocacy group in the planning, implementation and monitoring of a clinical trial is considered so that patients’ needs are appropriately considered. This may also increase the rate of enrolment of trial participants and can have a positive effect on the performance of a clinical trial.”

### 3.1.4 Data Transparency

Another important development in pharmaceutical research over the past few years has been the call for greater transparency and sharing of all clinical data. On the one side there has been concern that trials that show no benefit or report safety issues are not reported, but on the other side companies are frustrated by journals that will only publish trials that are deemed to be interesting and show benefit. This has led to the development of independent databases, where study protocols can be placed and thus traced to publication.

10 [http://www.nihr.ac.uk/funding/research\\_programmes.htm](http://www.nihr.ac.uk/funding/research_programmes.htm) Accessed 21 September 2014

11 <http://www.pcori.org/programs> Accessed 21 September 2014

12 INVOLVE. Briefing notes for researchers: public involvement in NHS, public health and social care research. INVOLVE, Eastleigh. 2012.

13 Mullins D, Abdulhalim A, Lavalley D. Continuous patient engagement in comparative effectiveness research. JAMA. 2012; 307; 1587-8.

14 O’Cathain A, Thomas K, Drabble S et al. Maximising the value of combining qualitative research and randomised controlled trials in health research: the QUALitative Research in Trials (QUART) study—a mixed methods study. NIHR HTA. 2014; 18: ISSUE 38.

15 Myeloma UK. Myeloma UK research update. Myeloma matters. Autumn 2014.

16 <http://www.patientpartner-europe.eu/en/project-outcomes/policy-recommendations> Accessed 30 December 2014.

Over the past few years, it has been recognised that such databases are not sufficient and since July 2014 it has been mandatory in Europe for sponsors of clinical trials to post results in a centralised database managed by the European Medicines Agency (EMA). At the outset, data have only been available to view on screen, but from October 2014 they will be downloadable for analysis for non-commercial research purposes. There has been much debate about this move, with concern from industry statisticians that results may not be analysed according to the strict analytical processes that were laid out in statistical analysis plans. So safeguards are needed that only suitably skilled professionals can access data and analyse the data for bona fide purposes.

In September 2014, NICE updated its Technology Appraisal process guide to strengthen the section indicating that it expects pharmaceutical companies to present all clinical trial data, and that if it didn't get all data, it would liaise with the regulatory authorities.

Some companies have already found robust mechanisms to make their clinical data accessible to researchers to allow investigation of appropriate scientific questions. For example, some companies give access to their data via the Yale University Open Data Access (YODA) Project, which makes data available to researchers in a sustainable way, to increase access to clinical research data and promote its use to generate new knowledge<sup>17</sup>.

As we move into this new paradigm of data sharing with an increased focus on re-analysis and meta-analysis of clinical trial data, there is a need for a more coordinated approach to data collection and management and there may be significant benefits from greater standardisation of protocols, outcome measures and data recording<sup>18</sup>.

### 3.1.5 Organising Evidence Generation to Suit the Needs of HTA

Roche has undertaken surveys and workshops to determine the usefulness of adopting the EUnetHTA HTA Core Model<sup>®</sup> as a tool for scoping out evidence and as structure to develop a repository to share HTA evidence with its affiliates<sup>19</sup>. Participants in Canada, France, Italy, UK, Netherlands, Germany and the global department agreed that use of the HTA Core Model<sup>®</sup> in its entirety—with all nine domains and the 135 assessment elements - was helpful. They felt that the assessment elements helped them understand how value is assessed in HTAs and also saw the usefulness of the HTA Core Model<sup>®</sup> to help drive a broader perspective on value for the company as well as for external stakeholders. They noted that the domains on the health problem and current use of the technology, the description of the technology, clinical effectiveness and costs and economic evaluation were critical for pricing and reimbursement, and that the ethical, organizational, social and legal aspects were often not considered sufficiently. The work also resulted in some considerations for refinements in the HTA Core Model<sup>®</sup>. The overall conclusion was that the HTA Core Model<sup>®</sup> could help structure the company's repository for HTA evidence, inform the development of checklists for evidence generation and highlight national and global evidence gaps. Work is underway to develop these tools by mid-2015.

17 <http://medicine.yale.edu/core/projects/yodap/> Accessed 18 December 2014

18 Association of the British Pharmaceutical Industry. Clinical trial transparency: technical standards for data sharing old, current and future clinical trials. ABPI. December 2013.

19 Gylmark M. HTA Core Model<sup>®</sup> as a Value Assessment Framework—Perspective of a global healthcare company. Presentation at EUnetHTA 2014 Conference.

## 3.2 Medical Devices/Diagnostics

In the device sector, a wide range of diagnostics to diagnose disease and optimize pharmaceutical therapy and medical devices that manage major morbidity and increase life expectancy or aid daily living have been developed.

### 3.2.1 Medical Devices

The development pathway for a medical device depends upon its regulatory classification (low risk class I devices such as thermometers, to high risk class III such as implantable devices) and the indications of use, which can be very broad across a range of conditions. Class III devices require clinical evaluations for regulatory purposes, whereas those in the lowest classes do not, so the only data available for assessment of such products is likely to be real world data.

The users of one device may be a specialised surgeon, whereas for other devices they will be used at home by the patient. For each device, their learning curve in terms of appropriate use of the device is important and will impact on the effectiveness of the device. Furthermore a device may be disruptive and require realignment of referral processes and health care delivery patterns.

When conducting clinical studies, a range of challenges arise. If the method of device delivery is different from the current standard of care, it may not be ethical to undertake a controlled trial and a sham treatment may actually lead to a negative effect and be worse than no treatment.

Furthermore, medical devices evolve rapidly, often every 18 to 24 months, with reduction in size, change in delivery system, technology refinement etc. This phenomenon is illustrated by the number of patents issued on medical devices. In 2012, more than 10,000 patent applications for medical devices were filed with the European Patent Office (EPO), equivalent to 7% of the total number of applications. This was more than any other technical field. Of these patent applications, 38% were filed from European countries and 62% from other countries, with the majority of applications filed from USA (42%). In comparison, around 5,400 applications were filed for pharmaceuticals and 5,300 in the field of biotechnology. Furthermore, over the last decade, the number of EPO filings for medical devices has doubled, whereas biotech and pharma patent applications were relatively stagnant.

These challenges in doing RCTs for medical devices are clearly noted by Parvizi and Woods as<sup>20</sup>:

- Medical device safety and effectiveness are, in part, determined by the user's skill and patient selection; training in the use of the medical device can substantially affect outcomes
- Ethical issues with 'sham' procedures when conducting comparative clinical trials, which are more challenging than placebo administration in pharmaceutical trials
- Inability to blind the user and the patient, potentially biasing outcome assessment
- Impracticality of repeating clinical trials for every design modification of a device, which might nevertheless alter the benefit-risk relationship in use.

As a result of all these issues, the evidence generation framework within which medical devices sits is very different to that of drugs. However, in 2012, MedTech Europe acknowledged the need to demonstrate improved healthcare outcomes, cost effectiveness and the socioeconomic value of medical technology to ensure sustainable, accessible healthcare and healthy ageing<sup>21</sup>. In this they called payers to recognise the value of medical technology through optimized market access and timely, appropriate funding, but recognized that more data are needed to illustrate the value of our technologies. To achieve this they state the need to engage stakeholder networks.

20 Parvizi N and Woods K. Regulation of medicines and medical devices: contrasts and similarities. *Clinical Medicine* 2014; 14: 6-12.

21 MedTech Europe. Contract for a healthy Europe. October 2012.

### **3.2.2 In-Vitro Diagnostics (Text Provided by European Diagnostics Manufacturers Association and Adapted by Scientific Secretary)**

In-vitro diagnostics (IVDs) are non-invasive tests used for diagnosis, screening, assessing predisposition and monitoring. They rely on biological samples, including blood, urine or tissue and provide information to make treatment decisions. Hence they are dependent on how information is used (by clinicians, by patients if self-testing) in the pathway of care and so IVDs have specific regulatory requirements that are different from those for medical devices.

IVDs do not interact directly with patients and consequently any risk posed to patients stems from the information that IVDs provide. With this in mind, much of the evidence generation that is required for regulatory approval is linked to the quality and performance of the information IVDs provide. The performance of an IVD is either the analytical performance (e.g. sensitivity to measure the analyte) or clinical performance/validity (e.g. diagnostic sensitivity).

For HTA, clinical utility is of interest, ie how an IVD supports decisions about patient management. Clinical utility has been described as including many elements such as acceptability, appropriateness; availability of treatments/interventions, and health economics, with multi-dimensions such as the value of information to avoid bad decisions and their impact at the socio-economic and organizational level, e.g. fewer days spent at the hospital if a test is being performed, and the value of knowing about a disease condition or status for the patient, in order to make reproductive decisions, etc. To obtain this information, linked evidence approaches are often used, with comparative studies of test accuracy combined in decision models with evidence from trials and follow-up from real-life studies.

### **3.2.3 Companion Diagnostics (Text Provided by European Diagnostics Manufacturers Association and Adapted by Scientific Secretary)**

Companion diagnostics play an essential role in personalized/stratified medicine assessing the appropriateness of a specific medical intervention for an individual patient, aiming to maximize the effectiveness of treatments and reduce adverse events and non-responders. They provide key information on a patient in relation to their eligibility for a targeted therapy based on the specific biomarkers of their disease.

### **3.2.4 Demonstrating Added Value of Medical Devices**

In June 2014, the Royal Netherlands Academy of Arts and Sciences published a detailed report that presents a variety of ways to generate evidence to establish the benefits of medical devices<sup>22</sup>. It is based on the premise that a one-size-fits-all approach is not appropriate for the wide range of medical devices that exist and that a targeted approach is needed based on the device specifications, context, users and patients. It notes that standard comparative effectiveness studies are methodologically challenging due to the interplay between device complexities, user skills and learning curve. It promotes collaboration amongst all stakeholders at an early stage to define the place of the device in the clinical pathway so that evidence from a range of technical, safety and clinical studies on a device can be linked to create a “network of evidence”. It suggests this is preferable to the standard hierarchy of evidence approach. Three main types of studies to develop evidence are outlined, those producing:

- Direct evidence of added benefits (including more novel randomised and non-comparative designs)
- Indirect evidence of benefit using an intermediate outcome with modelling (quantitative linking)
- Indirect evidence of benefit, adapting evidence from a different setting or different form of device (qualitative linking).

22 <https://www.knaw.nl/actueel/publicaties/evaluation-of-new-technology-in-health-care> Accessed 31 December 2014

## 4. Trends and Challenges in Health System Funding and Organization that Impact Evidence Generation for HTA

### 4.1 Comparative Review of Health Systems

The IHE Handbook of Health Economic Statistics<sup>23</sup> reports OECD data for 2010/2011 that give a picture of the operation of health systems across the globe and the context within which HTA sits. Health expenditure per capita ranges from US\$3,000 (9.1% GDP) in Spain to US\$5,000 (11.2% GDP) in France, US\$5,600 (10.6% GDP) in Canada, US\$6,000 (8.5% GDP) in Australia, US\$8,600 (17% GDP) in the USA and US\$9,000 (8.9% GDP) in Norway.

In EU member states, 70-80% of expenditure is in the public sector, in Australia it is 68%, Canada 70% and in the USA 49%. Sweden, Canada, the UK, USA, Spain, Norway and Italy all have about 3 beds per 1,000 population whereas this rises to 6 beds in France, 8 in Germany and 13 in Japan. Japan also has a high average length of stay in acute care, at 18 days, compared to 8 in Canada or Germany, 7 in the UK and 5 in the USA, Australia and France.

Investment in devices differs markedly by country with just 6 MRIs per million population in the UK, 7.5 in France, 8.5 in Canada, 24 in Italy, 32 in the USA, and 47 in Japan. Per capita expenditure on pharmaceuticals and other non-durables ranges from US\$375 in the UK, to US\$487 in Italy, US\$536 in Spain, US\$587 in Australia, US\$633 in Germany, US\$641 in France, US\$652 in Japan, US\$752 in Canada and US\$995 in the USA.

In some countries the relatively high expenditure on health translates to higher life expectancy—83 years in Japan in 2010, but this is not always the case as shown by the life expectancy of 79 years in the USA, where it is also known that high inequalities exist.

### 4.2 Health System Organization and Funding

In a paper published in 2013, Light stated that 12 of 13 new cancer drugs approved in the last year were priced above US\$100,000 annually in the USA, with a 20% co-payment making them unaffordable even for well insured patients<sup>24</sup>. Meanwhile new medical devices, such as robotic surgery come with a high capital cost (circa £2 million) and annual servicing costs of £100,000.

However, it is not just the costs of health technologies that are straining the health system. Six years of financial austerity, an increasing aging population, greater consumer demand and limited increases in annual budgets have put strains on all health systems. Many have had to deliver major efficiency savings, increase co-payments, or worse implement substantial cuts. In systems where 70% of the expenditure is on staff that are often protected in employment and there is strong public support that prevents the closure of old healthcare institutions, technologies are often targeted for stringent review. Prescribers are increasingly incentivised to reduce their spending and medical technology purchasing is often carefully managed with sophisticated procurement systems.

Hence rationale, defensive decisions about which technologies to adopt and which to disinvest are crucial.

23 Institute of Health Economics. IHE in your pocket 2014. 2014. IHE: Canada.

24 Light D, Kantarjian H. Market spiral pricing of cancer drugs. Cancer. 2013; doi 10.1002/cncr.28321.

These discussions must be put in the framework of quality improvement and value that we have seen emerging in past few years, with recognition that even in the USA, there is a move from fee-for-service to performance-based reimbursement<sup>25</sup>, with recognition that healthcare delivery must focus on improving outcomes. Porter et al. discuss the need to track performance over time and compare with peers; not just adherence to guidelines and technical measures, but outcomes that are important to patients and are reported publicly.

Health systems often reorganise to attempt to improve quality, coverage and efficiency and there have been notable changes in the past few years in the USA and England. This can lead to important changes in the way decisions about health technologies are made and how budgets are allocated. For example, as a result of the increasing number of older people in the population, and the number of people living with long term conditions and a range of comorbidities, many systems are seeking to move from hospital to community to home based care, with better alignment of health and social services and joint budgets for health and social care. This is leading to new ways of budgeting and commissioning services. Furthermore, investigation of health care expenditure shows that there are “frequent flyers” in the health system, a small number of patients who consume a large part of the health and social care resource. Initiatives are being tried to support these patients and reduce expenditure and more emphasis is being placed upon preventative care and preventative spend. However, as Emergency Department attendance rates and hospital capacity figures show, demand keeps increasing and resources are slow to move into the community.

This presents a challenge because it has been recognised that successful HTA needs to link into decision making nodes. For pharmaceuticals the chain in decision making is clear. An HTA recommendation for use of a pharmaceutical in a particular population generally leads to reimbursement listing or statutory funding by commissioners or mandatory review by a formulary committee. However, for devices, there is greater uncertainty and so advice is often purely advisory and other issues are considered by hospitals or health service planners who consider organization and delivery of services. The different impacts of HTA on uptake of different technologies and return for HTA investment seem key to consideration of what is viable evidence generation.

## 5. Trends in Regulatory Approaches that Impact Evidence Generation for HTA

In 2008, the FDA established the Sentinel Initiative to find sustainable ways of combining a variety of healthcare data from administrative and insurance claims databases to enable it to actively monitor the safety of authorized drugs and devices in real-time (e.g. for orthopedic implants).

### 5.1 Drugs

#### 5.1.1 Clinical Trial Directive

In 2001, the European Clinical Trials Directive agreed to harmonise the conduct of clinical trials across the EU and provide greater protection to clinical trial participants. Since its inception there have been major concerns raised by private and public research funders about the administrative burdens that the Directive has created. These concerns were documented in a consultation in 2010. In June 2014, it was agreed that the Clinical Trial Directive should be repealed. This will come into force in May 2016 and so the implications of this are yet to be understood.

<sup>25</sup> Porter M, Lee T. The strategy that will fix health care. 2013. Harvard Business Review. <https://hbr.org/2013/10/the-strategy-that-will-fix-health-care/ar/1> Accessed 18 December 2014.

### 5.1.2 Early Evaluation

For many years regulators have had processes to fast-track review of drugs that could have substantial clinical benefits compared with available therapies, or if they treat conditions that are serious, life-threatening or have high unmet need. Such processes (e.g. conditional licensing and now Medicines Adaptive Pathways to Patients) often consider surrogate or biomarkers in phase II as sufficient. Such early regulatory evaluation leaves major uncertainties about longer term effects and the added value considered in HTA/coverage decisions.

In such circumstances, both regulators and HTA/coverage bodies require further evidence to reduce the uncertainty. So it is important to evaluate approaches for evidence development and generation pre and post marketing that have been developed in recent years to review their feasibility and consider how they can be optimized to make them more efficient and effective.

Since 2012 there has been substantial interest in the new designation of breakthrough therapies by the Food and Drug Administration (FDA). This process offers expedited review of drugs for serious or life-threatening conditions that have preliminary clinical evidence from phase I or II trials that demonstrate the drug may have substantial benefit compared with available therapies. In May 2014, the FDA published further guidance on these processes including explanation of a “serious condition” and “unmet medical need” with recommended study designs and consideration of what might constitute “substantial benefit” (see Appendix 1)<sup>26</sup>.

For the year from October 2012, there were 92 requests for breakthrough designation in FDA’s CDER branch, 31 of which were approved. Similarly for the following year 24/89 were approved for designation as breakthrough. For biologics 1/11 and 5/23 had breakthrough designation approved. None of these biologics have been approved yet, but as shown in Table 1 several of the drugs have been approved.

**Table 1. FDA CDER Breakthrough Therapy Approvals up to 8 September 2014**

Proprietary Name	Established Name	Indication
GAZYVA	OBINUTUZUMAB	Chronic lymphocytic leukaemia
IMBRUVICA	IBRUTINIB	Chronic lymphocytic leukaemia
SOVALDI	SOFOSBUVIR	Chronic hepatitis C
KALYDECO	IVACAFTOR	Cystic fibrosis
ARZERRA	OFATUMUMAB	Chronic lymphocytic leukaemia
ZYKADIA	CERITINIB	Lung cancer
ZYDELIG	IDELALISIB (GS-1101)	Chronic lymphocytic leukaemia
IMBRUVICA	IBRUTINIB (PCI-32765)	Chronic lymphocytic leukaemia
PROMACTA	ELTROMBOPAG	Chronic hepatitis C
KEYTRUDA	PEMBROLIZUMAB	Melanoma

One could say that such early regulatory approval is “disruptive” to the evidence generation process as it may inhibit later randomized controlled trials (RCTs).

Furthermore, 2014 has seen a range of interesting discussions about Solvadi given its use in a relatively common, chronic disease (hepatitis C) and the need to balance hopes that it will eradicate the disease, its effectiveness in different genotypes and sub-populations (naïve or pre-treated) and its price of US\$80,000 for a 12-week course of treatment.

26 [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf) Accessed 22 September 2014

### 5.1.3 Structured Benefit: Risk Assessment

Over the past few years there have been initiatives in Europe and the USA to create frameworks that present a structure delineating the key elements in the deliberative decision-making process of a benefit: risk evaluation. The aim of these initiatives is to create greater transparency and consistency.

The FDA has explained that its regulatory decisions about benefit: risk involve quantitative analyses and a subjective qualitative weighing of the evidence, but there has been a call for greater clarity to explain how this is performed. This has resulted in consultation on the implementation of the structured benefit: risk framework shown in the Figure 1, which presents the evidence/uncertainty and conclusions/reasons for each decision factor.<sup>27</sup>

Figure 1. FDA Benefit: Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusion and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		
<b>Benefit-Risk Summary Assessment</b>		

Meanwhile, the European Medicines Agency (EMA) benefit-risk methodology project has created four tools to provide greater transparency about benefit: risk assessment<sup>28</sup>:

- PrOACT-URL decision-making framework
- Effect table showing a range of outcomes, clustered into favourable and unfavourable effects, with uncertainties described
- Multi-criteria decision-analysis (MCDA) value map of the attributes of a product that are important to decision-makers in terms of assessing benefit and risk
- Visualisation tools, such as the Tornado plot.

It is interesting to consider whether these frameworks presenting different forms of evidence, their associated uncertainties and decision-making criteria, could be developed for HTA.

### 5.1.4 Patient Involvement

There is increasing recognition that the FDA structured benefit: risk assessment should be more patient-centered and use patient inputs to analyse the condition and current treatment options. As part of its implementation of the Prescription Drug User Fee Act (PDUFA), FDA will convene at least 20 meetings with patients to gather input from patients systematically on these areas. To date, this Patient Focussed Drug Development Initiative has led to "Voice of the Patient" reports for chronic fatigue syndrome, HIV, lung cancer, narcolepsy, sickle cell disease and fibromyalgia<sup>29</sup>.

27 FDA. Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making. Draft PDUFA V Implementation Plan. February 2013. Accessed 23 November 2014

28 [www.ema.europa.eu/ema/index.jsp?curl=pages/special\\_topics/document\\_listing/document\\_listing\\_000314.jsp&mid=WC0b01ac0580223ed6](http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000314.jsp&mid=WC0b01ac0580223ed6) Accessed 30 December 2014.

29 <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm>. Accessed 23 November 2014

In Europe, the iMi PROTECT project<sup>30</sup> has been evaluating quantitative approaches to elicit patient preferences for benefits and risks but challenges have been identified in communication of scenarios in plain language so that participants can understand the scenarios for which they are stating preferences.

Regulators continue to seek to develop meaningful interactions with patients and an interesting new case study from EMA has created a patient jury from their Patient and Consumer Working Party. The patients' jury built two MCDA models in a short time with minimal methodological guidance. This led to informative discussions about weights and positive feedback from patients about their involvement<sup>31</sup>.

## 5.2 Medical Devices/Diagnostics

### 5.2.1 The New EU Regulations

A suite of European device directives relating the medical devices and in-vitro diagnostics were created in the 1990s that outline how the quality, safety and performance of a medical device should be evaluated. Over the past five years, the adequacy of this legislation has been questioned given the various safety scandals with metal-on-metal hip implants, PiP breast implants and vaginal mesh for pelvic organ prolapse. Following extensive consultation, it has been agreed that these directives will be revised to create stronger device regulations.

The key elements of the regulations that might affect evidence collection include:

- Unique Device Identification system to enable better tracing of devices to enhance post-marketing safety of medical devices
- Stricter requirements for clinical evidence, to ensure patient and consumer safety
- Establishment of a database of key information about CE marked medical devices that can be accessed by patients, professionals and the public, allowing them to make better informed decisions
- Adaptation of the safety and performance evaluations to technological and scientific advances in healthcare, such as software and nanomaterials
- Better coordination between national surveillance authorities, to ensure that only safe devices are available on the European market.<sup>32</sup>

The UK MHRA expects these regulations to be adopted in the European Parliament in 2015 and to come into force in Members States in 2018-2020<sup>33</sup>. They will strengthen the clinical evaluation requirements of some medical devices.

<sup>30</sup> <http://www.imi-protect.eu/> Accessed 23 November 2014

<sup>31</sup> EMA, EUnetHTA. Final minutes of EMA/EUnetHTA meeting - 15 May 2014. EMA/2999386/2014. 11 July 2014.

<sup>32</sup> European Commission. Safe, more effective and innovative medical devices. EC Press Release. Brussels. 26 September 2012.

<sup>33</sup> <http://www.mhra.gov.uk/Howweregulate/Devices/Legislation/NewLegislationonMedicalDevices/>

## 6. Trends and Challenges in HTA/Coverage and Regulatory Interaction

### 6.1 WHO Resolution on HTA

In May 2014, the World Health Organization (WHO) restated its responsibilities in health research and its support for sustainable health financing structures and universal coverage, including rational use of medicines and devices. WHO recognises the importance of developing evidence-based health policy and that efficient use of resources is a crucial factor for sustainability in systems that seek to substantially increase access to essential medicines and other health care interventions. WHO acknowledges the critical role of independent HTA to achieve this, emphasizing that rigorous and structured research methodology and transparent and inclusive processes could help address the need for reliable information to guide rational policy and professional decisions and practices in developing countries, where capacity for assessment of technologies is inadequate. Hence it calls for strengthened national capacity and regional and international networking and collaboration on HTA to promote evidence based health policy in all Members States<sup>34</sup>.

### 6.2 EU HTA Network

In Europe, the implementation of the Cross-Border Healthcare Directive has led to the establishment of the HTA Network to support and facilitate (policy level) cooperation between Member State national authorities or bodies responsible for HTA. This is supported by scientific and technical cooperation on HTA, which is the responsibility of the European network for HTA (EUnetHTA) until the end of the Joint Action 2 period in December 2015. After this an appropriate mechanism of support for the scientific and technical cooperation is to be put in place by the European Commission and EUnetHTA may apply for this role.<sup>35</sup>

In October 2014, the HTA Network published its strategy that recognises the increased cooperation already achieved on EUnetHTA pilots, uptake of joint work in national assessment activities and the continuing exploration of synergies between regulators and payers along the life cycle of the technology<sup>36</sup>. Other work of the HTA Network includes discussions on conditions to facilitate uptake and reuse of joint work to produce their national HTA reports/guidance. This is a particular question because the appetite of the various HTA agency members for the joint assessment reports varies. Generally, small countries are more interested in these reports; some big countries with well-established ways to produce their HTA reports, including the initial assessment part, may be less keen to use this joint work, preferring their own processes, which may be available more rapidly.

In December 2014, the Council of the European Union invited the European Commission to support cooperation to implement the HTA Strategy through a third Joint Action, while exploring options for continued and sustainable financing<sup>37</sup>. The Council calls for measures to ensure the long-term sustainability of work on HTA including considerations about how to make the best use of existing bodies which could facilitate cooperation, efficiency gains and scientific synergies.

34 World Health Organization. Health intervention and technology assessment in support of universal health coverage. WHA67.23 24 May 2014.

35 <http://www.eunetha.eu/eunetha-and-hta-network>. Accessed 11 August 2014.

36 EU Health Technology Assessment Network. Strategy for EU Cooperation on Health Technology Assessment. Final Draft adopted on 29 October 2014.

37 Council of the European Union. Council conclusions on innovation for the benefit of patients. Brussels. 1 December 2014.

### 6.3 Regulatory/HTA Interaction

Previous Policy Forum papers have outlined the different legal bases, purposes and process of regulation, HTA and coverage as shown in Appendix 2. It is essential to keep these issues in mind as considerations about evidence generation are considered.

EUnetHTA has proposed to map the activities of HTA and regulation along the technology life-cycle to identify areas of commonality/interaction to identify areas for strengthened cooperation and collaboration with EMA.

### 6.4 EUnetHTA Methodological Developments

In Joint Action 2, EUnetHTA has continued to develop the HTA Core Model<sup>®</sup>, with an updated HTA Core Model<sup>®</sup> issued for consultation in November 2014 (featuring major changes in the legal domain). A revised model for Rapid Relative Effectiveness Assessment that seeks to reduce overlap in assessment elements is to be issued for public consultation in spring 2015. In terms of devices, two joint assessments are due to be published in December 2014 for balloon Eustachian tuboplasty and biodegradable stents for benign refractory oesophageal stenosis<sup>38</sup>. Also the draft industry submission template for medical devices will be issued for public consultation in spring 2015 and finalised in autumn 2015.

### 6.5 Other HTA Collaborative Projects

A range of other collaborative projects on HTA are funded by the FP7 Research stream in the European Commission.

**AdHopHTA** (Adopting Hospital based HTA) has performed a critical analysis of existing hospital based HTA initiatives and is now developing new methods, instruments and processes to support hospital based HTA (HB-HTA). An early result from the project has been a fully searchable database of HB-HTA projects to help avoid duplication in assessments. Principles to guide best practice for setting up or improving HB-HTA are being developed and a new tool to implement HB-HTA (mini HTA 2.0) is being created. To inform this work, the informational needs of hospital managers and heads of clinical departments were determined via a literature search and current mini HTA tools have been compared. These deliverables will be available in August 2015<sup>39</sup>.

Advance-HTA (Advancing and strengthening the methodological tools and practices relating to the application and implementation of HTA) has a range of different workstreams. Three workstreams focus on determining value—creating a taxonomy of the main factors affecting value for money HTA decisions in 10 countries, contrasting the factors driving different decisions in different countries and considering the specific case of determining value for orphan drugs. A framework has been developed that considers the reasons for differences in HTA decisions across the HTA process in terms of

- Evidence (preferences for different types of evidence)
- Interpretation of evidence (uncertainties, other considerations, stakeholder input)
- Recommendations<sup>40</sup>.

Other workstreams are more disparate. One will seek to elicit a new value set for a commonly used Quality of Life measure from patients and another has created taxonomy of medical devices and is documenting processes for medical device HTA. One workstream has reviewed the capacity for HTA in every Eastern European country and is currently doing the same in Latin America, with a view to determining needs and developing strategies to build HTA capacity in these regions<sup>41</sup>.

38 EUnetHTA Newsletter 6. July 2014.

39 Sampietro-Colom. Personal Communication and EUnetHTA 2014 conference poster.

40 Nicod E. Value assessments for orphan drugs. An analytical framework enabling the systematic comparison of HTA decision-making processes across countries. HTAi 2014 presentation.

41 Advance HTA. Rethinking the future of HTA. Poster for EUnetHTA 2014 conference.

**MedtechHTA** is aiming to improve the existing methodological framework of HTA for the assessment of medical devices, recognizing the special challenges that they raise. The project includes a review of country's approaches to medical device HTA and geographic variation in access to devices. A suite of methodological guidance documents for medical devices are being developed to cover comparative effectiveness, economic evaluation, uncertainty and value of information and organizational impact. These workstreams will be brought together in recommendations on HTA methods for medical devices in December 2015.

**INTEGRATE HTA** is developing concepts and methods to enable a patient-centred, comprehensive, integrated assessment of complex health technologies. By the end of 2015 it aims to publish methodological guidance on HTA of complex technologies, which will include assessment of socio-cultural, ethical and legal issues, patient preferences and patient specific moderators of treatments, context, setting and implementation issues alongside clinical and cost effectiveness. This model will be tested on the topic of palliative care.

## 6.6 Patient-centred HTA

The impetus to make HTA more patient-centred has been led by the HTAi Interest Sub-Group on Patient/Citizen Involvement in HTA (PCISG). PCISG promotes greater understanding of the perspectives of patients and their care-givers about what it's like to live with a disease, use of current treatments and experience/expectations of a new technology to inform HTA. Patient involvement in research and HTA, can elucidate outcomes of importance to patients, improve the quality and efficiency of research and help HTA decision-makers to better understand unmet needs and influence judgements about value.

PCISG recommends, not only good qualitative research to understand patients' perspectives, but also input from patient groups and involvement in the HTA process. The benefits and challenges of involving patients and their representatives in the HTA process were debated in a plenary session at HTAi 2014. This meeting also heralded the launch of the HTAi Values and Quality Standards for Patient Involvement in HTA<sup>42</sup> and Patient Group Submission Templates for Medicines' HTA<sup>43</sup>. These tools were developed with wide stakeholder involvement (patient groups and HTA agencies dominating the response) and input from all continents (including countries like Ghana and Mexico).

## 6.7 Collaborating to Promote Innovation

In the past few years there have been specific initiatives by governments to promote innovation and research, particularly in the health sector<sup>44</sup>. National HTA agencies are being drawn into these discussions to delineate their role in encouraging innovation.

### 6.7.1 A Pan-European Approach to Support Innovation

In December 2014, the Council of the European Union issued conclusions on innovation for the benefit of patients stating that healthcare can contribute to the health and well-being of citizens and patients through access to innovative products, services and treatments that have added value with regard to the existing ones and can lead to more effective ways to organize, manage and monitor work<sup>38</sup>. This referenced its earlier conclusions that modern, responsive and sustainable health systems advocate the need for cooperation on strategies to effectively manage expenditure on pharmaceuticals and medical devices, while ensuring equitable access to effective medicines.

42 [http://www.htai.org/fileadmin/HTAi\\_Files/ISG/PatientInvolvement/htaResources/valuesAndQualityStandards-FINAL.docx](http://www.htai.org/fileadmin/HTAi_Files/ISG/PatientInvolvement/htaResources/valuesAndQualityStandards-FINAL.docx) Accessed 18 December 2014.

43 [http://www.htai.org/fileadmin/HTAi\\_Files/Travel\\_Grant\\_applications/HTAi\\_Patient\\_Submission\\_Template\\_v1.doc](http://www.htai.org/fileadmin/HTAi_Files/Travel_Grant_applications/HTAi_Patient_Submission_Template_v1.doc) Accessed 18 December 2014

44 <http://www.scotland.gov.uk/Resource/0039/00396711.pdf> Accessed 18 December 2014.

It recognises that the development of innovative medicinal products is costly and time-consuming and includes risks, which may result in insufficient investment in research and development, making it particularly difficult for smaller companies to bring innovative products to market. It noted that to stimulate development there is a need to facilitate the translation of scientific advances into innovative medicinal products that meet regulatory standards, accelerate patients' access to innovative therapies with added value for patients and are affordable to EU Members States. However, due to very high prices of some innovative medicinal products in relation to their benefit to patients and to public health expenditure capacity, patients do not always have access to innovative treatments. European cooperation on HTA can promote more consistent approaches to HTA as a health policy tool to support evidence-based sustainable and equitable choices in healthcare and health technologies for the benefit of patients.

The European Council invited Member States to explore opportunities for cooperation on exchange of information for innovative medicinal products over the life cycle including early dialogue/scientific advice, pricing and reimbursement models, registries for monitoring the effectiveness of health technologies, appropriate reassessment and post-authorisation studies.

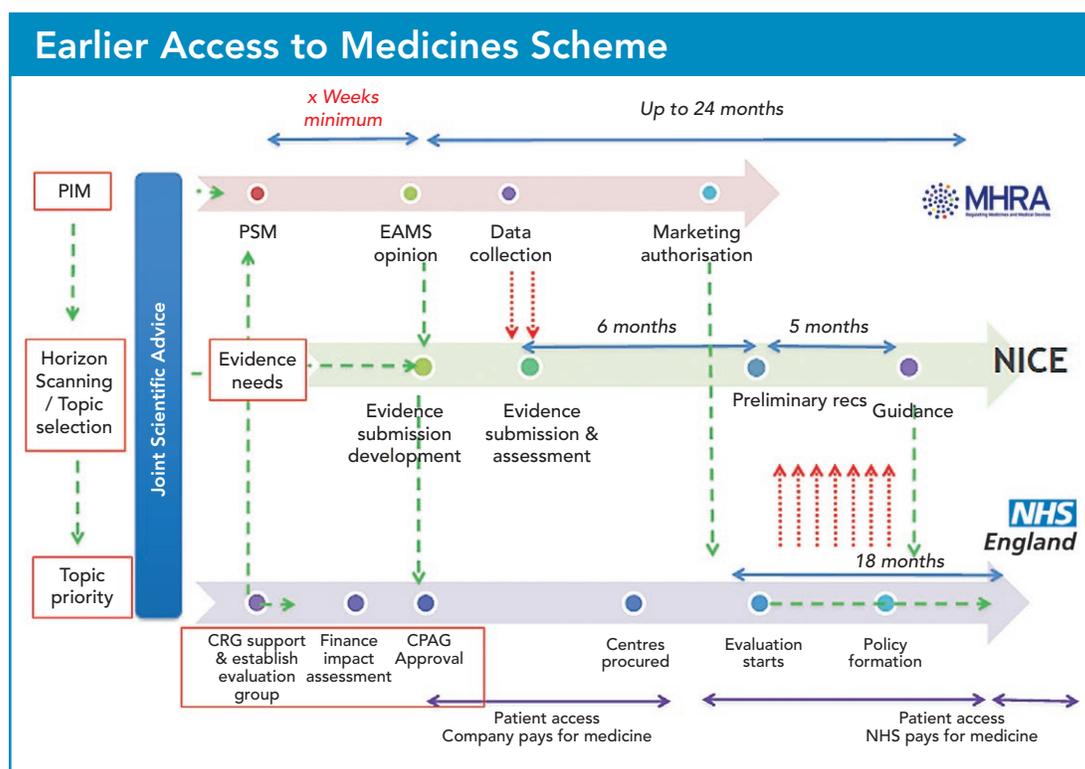
### **6.7.2 National Initiatives to Promote Innovation**

There are a range of initiatives underway nationally that seek to map the technology development life cycle and define the links that can be made with the health system, particularly for research and adoption. For example, in February 2014 the Health Innovation Procurement Portal was launched in Scotland as a resource to develop stronger partnerships with industry, providing information, guidance and support on how to develop ideas and innovations into products and technologies that may support the strategic aims of the NHS in Scotland, or to further develop established innovative products. This has been followed in July 2014 by the establishment of a national specialist hospital as a new innovation centre to test medical devices. At the same time a new process for primary submissions from manufacturers has been developed by the Scottish Health Technologies Group to provide overviews of published and unpublished information about promising technologies that are not yet adopted in NHSScotland to directly inform health system planners.

In England, the Department for Business Innovation and Skills has been a key player in the development of the Early Access to Medicines Scheme (EAMS). EAMS was launched in 2014 to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is clear unmet medical need (no treatment available or existing methods have serious limitations) and the product is likely to offer a major advantage. Companies can submit a product for a Promising Innovative Medicine (PIM) designation on the basis of Phase I/II or Phase II data and pre-clinical data and then the MHRA (the national regulatory agency) provides an opinion based on the data available about the benefit: risk. If the benefit: risk is considered positive, an EAMS Treatment Protocol will be created. The opinion lasts for one year and can be renewed. The EAMS submission requires a full Risk Management Plan, which is likely to include a drug registry including information on the condition, age, gender, dose and duration of treatment, comorbidities, concomitant medications and may include biomarker information if required to determine suitability of a patient for treatment. The first PIM designation was given to a cell therapy product for treatment of cancer in September 2014.

NICE has created an overview of the process as shown in Figure 2.

**Figure 2.** Reproduced with kind permission on Carole Longson, NICE



In Quebec, the Institut national d'excellence en santé et en services sociaux (INESSS) has established a multi-stakeholder Advisory Committee on HTA and Innovative Technologies to promote a common understanding of the challenges of introducing innovative technologies into the health system, and to identify possible solutions to ensure consistency in doing so, for the benefit of users<sup>45</sup>. It confirms the essential role of HTA and other forms of evaluation as part of an overall innovation ecosystem but stresses the need for a more dynamic assessment system better suited to the particularities of innovative technologies.

For technologies "with plausible promise" (greatest potential for positive impacts on patients and the health system), there is a need to optimize generation of knowledge in real-world settings, so-called progressive field evaluation. This evaluative research must involve relevant stakeholder groups in a public-private-users (including patients) research collaborative for which the principles of "living labs" are highly relevant in order to achieve greatest effectiveness, transparency and trust. "A living lab is a user-centric innovation environment, built on realistic activities and research where all relevant partners are involved in open processes, with objective to generate sustainable values for living lab partners and stakeholders."<sup>46</sup>

Essential to the process is a peer-reviewed research protocol that is flexible in design that yields open data and an innovation protocol that creates a social contract outlining the governance framework for the study, including stakeholder roles, timing of project and funding.

45 <http://www.inesss.qc.ca/en/networks-andpartnerships/bridging-mechanisms/advisory-committee-on-hta-and-innovative-technologies.html>. Accessed 18 December 2014.

46 Bergvall-Kåreborn, B, Ihlström Eriksson, C, Ståhlbröst, A et al. A Milieu for Innovation - Defining Living Labs. Presented at the 2nd ISPIM Innovation Symposium, New York, December 6-9 2009. [https://pure.ltu.se/portal/files/3517934/19706123\\_Paper.pdf](https://pure.ltu.se/portal/files/3517934/19706123_Paper.pdf)

See Appendix 3 for the logic model that supports this work. The hope is that this process will align the value proposal of an innovative technology with the needs of users, identify optimal conditions and adapt use of the technology accordingly, collect information about the effectiveness of a technology as well as contextual and organizational elements relevant to decision makers.

## 6.8 Coverage with Evidence Development/Managed Entry Agreements/ Additional Data Collection

HTA organizations may request additional evidence to resolve uncertainties. This can be mandatory (conditional coverage) or merely a recommendation. As an example, between 2004 and 2011, 165 of the 815 appraisals (20%) considered by HAS were requested to provide additional evidence. Additional evidence was requested on the population to be treated, clinical effectiveness and impact on healthcare organization, to inform reassessment within five years<sup>47</sup>.

The challenge for manufacturers is that they may receive several such requests, which may require real-world data specific to particular health systems alongside different regulatory benefit: risk data commitments that do not align with HTA evidence generation requirements.

A review of CED schemes<sup>48</sup> for medical devices found that Canada, the UK and the USA had most experience with the schemes, but that new procedures were in place in Germany and the Netherlands. The devices subject to CED ranged from implantable cardioverter defibrillators to spinal cord stimulators. It was noted that devices are viable candidates for CED given their unique characteristics and the uncertain evidence base which may be available at the time of coverage, but that some of the challenges in implementing CED schemes are:

- Establishing a clear framework for initiating, overseeing and stopping studies
- Identifying and applying appropriate study methods
- Funding and incentivising studies
- Using the new evidence to inform coverage decisions.

All these issues need to be addressed with greater stakeholder collaboration.

For orphan medicinal products, there has long been a call for a compulsory European-wide registry following authorization<sup>49</sup>, but this is difficult to achieve. A study by Morel, which accessed published and confidential databases, found that 42 MEAs had been implemented for 26 orphan medicinal products in Europe between 2006 and 2012<sup>50</sup>. Most were in Italy (15), then Netherlands (10), England/Wales (8), Sweden (5) and Belgium (4). Just over half the Agreements (55%) were performance-based (8 dependent on outcome, 15 listed as only in research), the remainder were financial-based. Nine of the products were subject to agreements in two or three different countries.

A presentation in 2013 on the experience of CVZ (now ZiN) with CED explained that all health technologies that required CED were given interim reimbursement listing with a requirement to resubmit a dossier after three or four years with outcome data. However, these dossiers yielded little useful information to inform economic evaluation and so were deemed more “coverage” than “evidence development”<sup>51</sup>. The learnings from CVZ were that four years is not sufficient for such studies and there is often insufficient support for such CED research in the real world. This may be because clinical pathways and treatment options change, which can lead to a smaller number of patients than anticipated, incomplete data, no quality of life (QOL) data and no comparator. They note that the more complex the design of the CED, the less successful the study was.

47 Meyer F. Additional data collection for drugs in Europe – HTA perspective. Presentation to ISPOR Europe, November 2013.

48 Sorenson C and Drummond M. Decision making under uncertainty: coverage with evidence development in the context of medical devices. ISPOR Europe Abstract. 5 November 2013.

49 Sheldon T. Dutch doctors call for EU evaluation of cost effectiveness of high cost orphan drugs. *BMJ*. 2012; 345:e5461.

50 Morel T, Aricx F, Beriffs G et al. Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries. *Orphanet Journal of Rare Diseases*. 2013; 8:198-213.

51 Graaf M. Sharing the burden in market access flexibilization. Presentation at NextLevel Pharma Market Access Leaders. October 2013.

So it is essential to define the essential elements that are required in a real-world study. One possibility may be to use a registry as an extension to a study protocol, rather than to setup a separate system. Another definite learning from a range of stakeholders is that registries should be established with clinical and patient buy-in and patient organizations or networks can often be the “honest broker” who can manage complex registries for CED data processes.

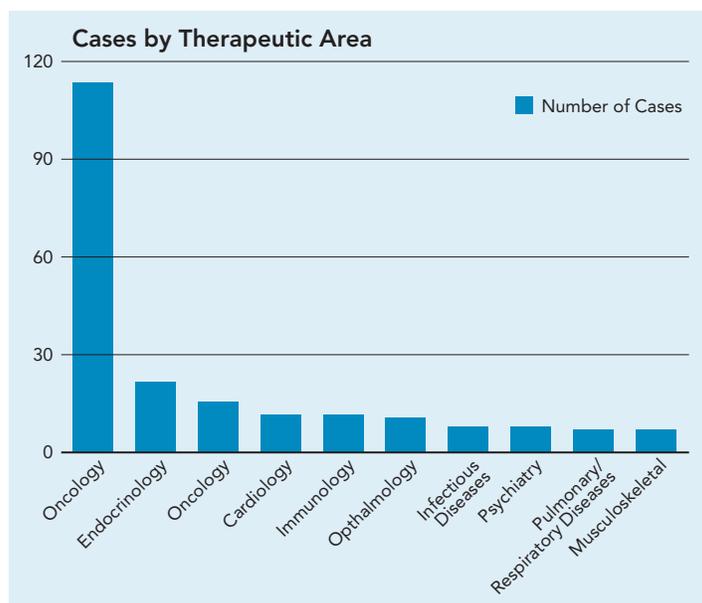
The study by Morel was too early to address outputs from the new AMNOG process in Germany, but it is interesting to see that many products assessed under this new Law have been reimbursed with stringent study requirements. These have been designed to resolve issues relating to the population to be treated, to study an alternative comparator, to provide additional information about outcomes, quality of life and safety, and resolve missing data issues<sup>52</sup>.

Another presentation outlined that in 2010-2013, 60 MEAs had been negotiated in Belgium and 15 of these were CED<sup>53</sup>. They noted that there were a range of challenges in designing appropriate studies and concerns about the value of new data over a short timeframe. Even when longer timeframes are planned for evaluation, the viability of such schemes is often questioned.

The University of Washington maintains a database of MEAs from 1995, with agreements categorized according to the taxonomy created by Carlson et al, discussed in the 2010 Policy Forum meeting. The database now contains 249 cases categorised by year of establishment, country, product, manufacturer, therapeutic area and type of agreement. In December 2014, the top 10 cases by therapeutic area are shown in Figure 3. This shows that the predominance of schemes is for oncology with 114, whereas the next highest is endocrinology with 22 schemes. Research using the database shows that European countries and the USA have the highest number of agreements, but there are also examples in Canada, Australia, Brazil and China<sup>54</sup>. This research noted that there has been a consistent movement towards arrangements that minimize administrative burden, particularly in the UK, where the last 17 “patient access schemes” were all simple confidential discounts.

**Figure 3. MEAs by therapeutic area – top 10 in University of Washington database**

Reproduced with kind permission of Josh Carlson at the University of Washington



52 Behring A. AMNOG is established. What are the next steps. Presentation at NextLevel Pharma Market Access Leaders. October 2013.

53 Knappenberg V. Risk-sharing and value-based pricing agreements: the Belgian experience. Presentation at NextLevel Pharma Market Access Leaders. October 2013.

54 Carlson J, Gries K, Yeung K et al. Current status and trends in performance-based risk-sharing arrangements between healthcare payers and medical product manufacturers. *Appl Health Econ Health Policy*. 2014; doi 10.1007/s402258-014-0093-x.

As the cost of evidence generation is high, we need some agreement on what additional evidence would be valuable and how it will impact not only decisions, but also uptake of technology. Empirical evidence about the impact of more information can be obtained through Value of Information models, but these are complex and rarely used to make decisions about the value of additional evidence generation.

EUnetHTA is seeking to overcome some of the problems of duplication that are apparent in evidence generation requests by piloting development and use of a common core protocol for evidence collection in cooperation with EMA and the European Network of Centres of Pharmacoepidemiology and Pharmacovigilance. In this work, they suggest the criteria for additional evidence collection shown in Figure 4<sup>48</sup>.

Figure 4

Additional Evidence Generation: <b>SELECTION/PRIORITIZATION CRITERIA</b>	
Primary criteria: eligibility for ADC?	Secondary criteria: further selection and prioritization
<ol style="list-style-type: none"> <li>1. Did you identify any critical evidence gaps during HTA? (yes, no)</li> <li>2. Is the research question explicitly defined? (yes, no)</li> <li>3. Is ADC feasible (especially in terms of timeframe, type of study, population and costs)? (yes, no)</li> <li>4. Is there a planned/ongoing similar study elsewhere?               <ol style="list-style-type: none"> <li>a) Yes, but there is an additional value of performing this one too (yes, no).</li> <li>b) No, thus this one is really necessary (yes).</li> </ol> </li> <li>5. Is there an added value of additional data for the subsequent HTA and decision making? (yes, no)</li> </ol> <p><b>One 'no' makes the technology not eligible!</b></p>	<ol style="list-style-type: none"> <li>1. Burden of target disease (mortality, morbidity prevalence, incidence, DALYs, QALYs)</li> <li>2. Expected benefit of the technology (on the burden of disease/on the management of disease/economical, organisational, social, ethical benefit)</li> <li>3. Potential of the technology to cover unmet health care needs or to substantially improve the healthcare system compared to existing alternatives</li> <li>4. Importance of ADC for confirming expected benefit and/or monitoring/optimizing the conditions of use.</li> </ol>

The EUnetHTA-EMA work plan also includes an item to “explore coordinated approaches on post-authorisation data collection, such as possible parallel advice, and explore the possibility of developing or testing methodologies for post-authorisation data collection that are relevant to support regulatory and HTA activities”. This will be important as the new Medicines Adaptive Pathways to Patients are developed, which stress the importance of post-authorisation data collection.

## 6.9 Explicit Modifications to Traditional HTA Decision-Making

Over the past few years, HTA organizations have clarified the flexibility of their decision making processes when the cost per QALY is relatively high and other factors/modifiers may be considered in specific situations, such as at end of life or for orphan products. For the Scottish Medicines Consortium (SMC), these modifiers include<sup>55</sup>:

- Evidence of a substantial improvement in life expectancy (e.g. median gain of three months) (with sufficient quality of life to make the extra survival desirable)
- Evidence of a substantial improvement in quality of life (with or without survival benefit)
- Evidence that a sub-group of patients may derive specific or extra benefit and that the medicine in question can, in practice, be targeted at this sub-group
- Absence of other therapeutic options of proven benefit for the disease in question and provided by the National Health Service
- Possible bridging to another definitive therapy (e.g. bone marrow transplantation or curative surgery) in a defined proportion of patients
- Emergence of a licensed medicine as an alternative to an unlicensed product that is established in clinical practice in NHS Scotland as the only therapeutic option for a specific indication.

NICE has similar modifiers.

Recently, three HTA organizations have developed new guidance to handle the uncertainty associated with very rare conditions.

SMC has launched the Patient And Clinician Engagement (PACE) process for end-of-life and very rare conditions. It rejects the idea of QALY adjustments to handle the uncertainty in these assessments. Instead, if an initial assessment does not recommend use in NHS Scotland, a mechanism is provided to enhance the deliberative decision making process by holding a special meeting with patients, clinicians and the manufacturer. This requires additional input from these stakeholders and a joint statement from the patients and clinicians is then reviewed by the SMC (appraisal committee)<sup>56</sup>. The first output from this process was available in November 2014.

NICE has consulted on its value based assessment process<sup>57</sup>. This proposed two new “value elements” that take account of the burden of illness as a proportional QALY shortfall and wider societal impact as an absolute QALY shortfall, but these have been rejected following public consultation. NICE has also launched its Highly Specialised Technologies programme for drugs for very rare conditions. The interim methods guidance for this programme states that it will consider the issues presented in Box 1 in its appraisal<sup>58</sup>:

55 [www.scottishmedicines.org.uk/About\\_SMC/Policy\\_Statements/SMC\\_Modifiers\\_used\\_in\\_Appraising\\_New\\_Medicines](http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/SMC_Modifiers_used_in_Appraising_New_Medicines) Accessed 22 September 2014

56 [https://www.scottishmedicines.org.uk/About\\_SMC/Latest\\_News/News\\_Articles/Patient\\_and\\_Clinician\\_Engagement\\_Factsheet](https://www.scottishmedicines.org.uk/About_SMC/Latest_News/News_Articles/Patient_and_Clinician_Engagement_Factsheet) Accessed 22 September 2014

57 [www.nice.org.uk/proxy/?sourceUrl=http%3a%2f%2fwww.nice.org.uk%2fmedia%2fFE2%2f2B%2fBA\\_TA\\_Methods\\_Guide\\_for\\_CONSULTATION\\_upload.pdf](http://www.nice.org.uk/proxy/?sourceUrl=http%3a%2f%2fwww.nice.org.uk%2fmedia%2fFE2%2f2B%2fBA_TA_Methods_Guide_for_CONSULTATION_upload.pdf) Accessed 22 September 2014

58 <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> Accessed 22 September 2014

**Box 1. NICE Issues for consideration for Highly Specialized Technologies****Nature of the Condition**

- Disease morbidity and patient clinical disability with current standard of care
- Impact of the disease on carers' quality of life
- Extent and nature of current treatment options

**Impact of the New Technology**

- Clinical effectiveness of the technology
- Overall magnitude of health benefits to patients and, when relevant, carers
- Heterogeneity of health benefits within the population
- Robustness of current evidence and the contribution the guidance might make to strengthen it
- Treatment continuation rules

**Cost to the NHS and Personal Social Services**

- Budget impact in the NHS and Personal Social Services
- Robustness of costing and budget impact information
- Patient access agreements

**Value for Money**

- Technical efficiency (incremental benefit of technology compared to current treatment)
- Productive efficiency (nature and extent of other resources needed to enable technology to be used)
- Allocative efficiency (impact of technology on budget available for specialized commissioning)

**Impact of the Technology Beyond Direct Health Benefits**

- Whether there are significant benefits other than health
- Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services
- The potential for long-term benefits to the NHS of research and innovation

**The Impact of the Technology on the Delivery of the Specialized Service**

- Staffing and infrastructure requirements, including training and planning for expertise.

The Ontario Public Drug Programme has developed a 7-step framework for the evaluation of treatments for rare diseases<sup>59</sup>, where each step is a prerequisite for the next step.

**1. Confirm the condition is truly “rare”**

As definitions of a rare disease were considered too liberal, rare was defined as an incidence of 1 out of 150,000 live births. In addition to the basic definition, mitigating factors are considered, such as vulnerability of population (e.g. early in life), severity of disease, potential impact of treatment on health outcomes (e.g. curative).

**2. Understand the disease**

Describe the pathophysiology, natural history and health effects of the condition to put the mechanism of action of the drug into context.

**3. Understand the potential value of the drug**

All relevant clinical data should be considered. Surrogate endpoints should be scrutinized for validity. In the 1960s, Bradford-Hill developed criteria for assessing causation between an exposure and a disease. These criteria have been modified to assess a treatment instead of an exposure, as shown in Table 2.

**Table 2. Bradford-Hill criteria for exposure causality modified for treatment effect assessment in uncontrolled trials**

Criteria	Example
Strength	Disease improvements strongly associated with drug exposure
Consistency	Disease improvements have been repeatedly associated with drug exposure despite variations in population, disease stage and therapy
Specificity	Benefit with the drug is specific to the disease mechanism
Temporality	Disease improvements occur after drug exposure
Biological gradient	Optimal disease improvements associated with optimal dose
Plausibility	Drug mechanism addresses underlying disease pathophysiology
Coherence	Observations of drug effects do not conflict with generally known facts of natural history and biology of the disease
Experiment	Experimental data confirm disease improvement with drug exposure
Analogy	Drugs of similar mechanism improve similar diseases.

This is not intended to be a checklist but to assist in answering if there is any other way of explaining the effects seen in patients other than the study drug. All candidate drugs should fulfil most of the criteria to be seen as potentially causal of tangible patient benefits.

**4. Model the potential clinical effectiveness of the drug**

**5. Evaluate cost implications (economic modelling and budget impact) and generate a funding recommendation**

**6. Review the drug evaluation with disease experts and stakeholders**

**7. Reassessment**

Continuously review and incorporate new information regarding disease incidence, natural history, effectiveness and cost of the therapy. If the new information has a potential impact on the clinical or cost effectiveness, this should trigger reanalysis.

59 Winquist E et al. An evaluation framework for funding drugs for rare diseases. *Value in Health*. 2012; 15: 982-6.

More generally, MCDA is being used to help describe in a clear framework how conflicting issues are balanced in the decision making process. The iMi PROTECT project has evaluated MCDA for regulatory benefit: risk assessment and there is increasing interest in its use in HTA. However, there are questions about the elicitation of the values used and the weighting applied.

## 7. Trends and Opportunities in Evidence Generation

### 7.1 Scientific Advice

Over the past few years scientific advice/early dialogue initiatives have been developed by HTA Agencies (NICE, HAS, GBA, etc) that provide confidential, non-binding, scientific advice about the design and analysis of Phase III studies that will suit the needs of HTA. This is available from individual Agencies, several agencies together or parallel HTA and regulatory advice with EMA.

An EFPIA survey of industry views on scientific advice obtained responses from 23 companies that had been involved in parallel scientific advice in the UK, Germany, Italy, Sweden, France, Netherlands, Spain, Belgium and Austria. All respondents felt there was a need for scientific advice and that a range of formats of advice is required depending on the questions to be asked.

EUnetHTA ran 10 pilot early dialogues on drugs and following feedback from participants, the Shaping European Early Dialogues (SEED) Consortium has been established. This involves 14 HTA Agencies with regulators, payers and patient representatives as observers. It has EC funding until August 2015<sup>60</sup> and so does not require fees from the manufacturer. Following an open call, 7 multi-agency HTA dialogues are underway (4 on drugs, 3 on devices) and 3 parallel with EMA on drugs. These are due to be completed by March 2015 and then a proposal for a permanent model for Early Dialogues in Europe is to be delivered by the end of August 2015. In SEED, advice can be given on relative effectiveness and/or economic issues, with the most popular topics relating to population, comparator, study design (duration and dosing), endpoints, statistical analysis and economic modelling (form of model, utilities, resource utilisation)<sup>61</sup>.

Health technology manufacturers generally create an initial plan for evidence generation prior to Phase II and it is locked in place prior to Phase III<sup>62</sup>. As Phase III may take about 3 years and regulatory review 1-2 years after that, the evidence requirements need to be known 4-7 years before launch. This is a particular challenge for HTA Advice, where issues such as comparators and pathways may change over the period. However, as suggested by Griffin, advice on aspects of “avoidable uncertainty” are valuable, as shown Table 3.

<sup>60</sup> [www.earlydialogues.eu](http://www.earlydialogues.eu) Accessed 21 September 2014

<sup>61</sup> Harousseau J-L. Early dialogues/scientific advice in European collaborative projects. Presentation to HTAi 2014.

<sup>62</sup> Griffin A. Establishing early dialogues/scientific advice between Industry and HTA Agencies. Presentation to HTAi 2014.

Table 3. Reducing Uncertainty in Evidence Development for HTA

Avoidable Uncertainty	Unavoidable Uncertainty
Generating Appropriate Evidence <ul style="list-style-type: none"> <li>• Meaningful end-points               <ul style="list-style-type: none"> <li>– Primary, secondary, surrogate</li> </ul> </li> <li>• Realistic trial duration</li> <li>• Appropriate comparators</li> <li>• Patient-Reported Outcomes/Quality of Life</li> <li>• Patient populations and sub-groups</li> <li>• Place in clinical practice</li> <li>• Model structure and inputs</li> <li>• Data extrapolation</li> </ul> <p><b>EARLY ADVICE HELPS HERE</b></p>	Unachievable Endpoints <ul style="list-style-type: none"> <li>• Overall survival at launch               <ul style="list-style-type: none"> <li>—diabetes, hepatitis C, indolent tumours</li> </ul> </li> <li>• Long-term follow-up of implants               <ul style="list-style-type: none"> <li>—orthopaedics</li> </ul> </li> <li>• Longer-term outcomes for earlier treatment of degenerative diseases               <ul style="list-style-type: none"> <li>—Alzheimer's, Multiple Sclerosis</li> </ul> </li> </ul>

When looking at Table 3, it would be helpful to understand whether we can agree on the list of elements under “avoidable uncertainty” that could be improved by better evidence generation. In particular how confirmatory trials need to change to suit the needs of HTA and additional endpoints that may be required, such as resource use.

One Policy Forum member outlined their experience with parallel scientific advice meetings (between EMA and several national HTA organizations in Europe) for five products in Phase II. In every case the Advice led to changes in the design of the phase III development programme or influenced strategy decisions (including product positioning in pathway, studies to undertake and gaining alignment on acceptable comparator). In addition the scientific advice process also influenced company culture, helping to align regulatory affairs, health economics and market access. This has led to ‘access issues’ and payer perspective and needs having a much greater influence on important development decisions, alongside clinical development influences. This view about the influence of the process on changing company culture is shared by other Forum members.

The EFPIA survey noted constraints with scientific advice including the lack of ownership of the process, timing (pre phase II advice helpful but some HTA agencies feel this is too early), lack of guidance on timelines and expectations of stakeholders, no process for bridging divergence of advice from different organizations and the need for a clear output from the advice process.

In addition to scientific advice about individual technologies, work continues on developing disease specific guidance for HTA evidence generation. EUnetHTA's first guideline to be developed is on osteoarthritis and the US Green Park Collaborative is developing disease specific guidelines for the USA.

Furthermore, EMA has requested that EUnetHTA be involved in the development of scientific advice about novel clinical endpoints, developing scales to define disease activity and progression in specific therapeutic areas. This was supported by EUnetHTA in principle recognising that it may overcome the challenge of new intermediate outcomes developed for regulation that are not useful in HTA. Also, where multiple scales exist, it would be helpful to identify those that are beneficial to both regulators and HTA<sup>32</sup>. However, there were some concerns about the ability to reach agreement and that the views of individual HTA organizations may be obtained (as in Scientific Advice), but it would not be a joint HTA community view.

## 7.2 Improving Surgical Data

The IDEAL Collaboration describes the stages of innovation in surgery as **Innovation**, **Development**, **Exploration**, **Assessment**, **Long-term study** and provides **recommendations** for each stage to improve the quality of evidence about surgical interventions<sup>63</sup> as shown in Figure 5.

**Figure 5. Stages of Surgical Innovation**<sup>64</sup> Reproduced with kind permission of P McCulloch.

	1 Idea	2a Development	2b Exploration	3 Assessment	4 Longterm
Purpose	Proof of concept	Development	Learning	Assessment	Surveillance
Number and types of patients	Single digit; highly selected	Few; selected	Many; may expand to mixed; broadening indication	Many; expanded indications (well defined)	All eligible
Number and types of surgeons	Very few; innovators	Few; innovators and some early adopters	Many; innovators, early adopters, early majority	Many; early majority	All eligible
Output	Description	Description	Measurement; comparison	Comparison; complete information for non-RCT participants	Description; audit, regional variation; quality assurance; risk adjustment
Intervention	Evolving; procedure inception	Evolving; procedure development	Evolving; procedure refinement; community learning	Stable	Stable
Method	Structured case reports	Prospective development studies	Research database; explanatory or feasibility RCT (efficacy trial); diseased-based (diagnostic)	RCT with or without additions/ modifications; alternative designs	Registry; routine database (eg, SCOAP, STS, NSQIP); rare-case reports
Outcomes	Proof of concept; technical achievement; disasters; dramatic successes	Mainly safety; technical and procedural success	Safety; clinical outcomes (specific and graded); short-term outcomes; patient-centred (reported) outcomes; feasibility outcomes	Clinical outcomes (specific and graded); middle-term and longterm outcomes; patient-centred (reported) outcomes; cost-effectiveness	Rare events; long-term outcomes; quality assurance
Ethical approval	Sometimes	Yes	Yes	Yes	No
Examples	NOTES video	Tissue engineered vessels	Italian D2 gastrectomy study	Swedish obese patients study	UK national adult cardiac surgical database

RCT=randomised controlled trial. SCOAP=Surgical Clinical Outcomes Assessment Programme. STS=Society of Thoracic Surgeons. NSQIP=National Surgical Quality Improvement Program. NOTES=natural orifice transluminal endoscopic surgery.

## 7.3 Real World Data

Over the past decade, HTA in many jurisdictions has gone beyond the traditional view of evidence hierarchies that assume RCTs as the gold standard to recognise that the questions which concern payers relate to real-world questions about which patients should be treated and for how long. This is particularly true for organizations that require complex economic models as part of the demonstration of added value, as these require context specific (real world) data about disease progression and management, often over long time periods.

One source of real-world data is through electronic health records. In countries where such records are kept and linkage is possible information about demography, disease characteristics, medications received and date of death can often be obtained.

A recent study has evaluated the feasibility of point-of-care randomised pragmatic trials, by evaluating two pilots in primary care in the UK. The pilots used routinely collected electronic health records (EHRs) with dedicated software to simplify identification of eligible patients and collection of data for end points<sup>65</sup>. The number of practices interested in participating dropped substantially with each stage of the complex governance process. From 459 eligible practices just 17 and 6 recruited patients in the two pilots. One trial comparing two statins recruited the planned 300 patients,

63 <http://www.ideal-collaboration.net/> Accessed 21 September 2014.

64 McCulloch P, Altman D, Campbell WB et al. No surgical innovation without evaluation: the IDEAL recommendations. *The Lancet*, 2009; 374: 1105-12. Original Text

65 van Staa TP, Dyson L, McCann G et al. The opportunities and challenges of pragmatic point-of-care randomised trials using routinely collected electronic records: evaluations of two exemplar trials. *HTA*. 2104; 18: Issue 43.

but another on the timing of antibiotics in chronic obstructive pulmonary disease was abandoned due to low recruitment of 31/150 patients. Another important challenge with the pilots was the heterogeneity of information in the EHR, including concerns about the validity of basic information such as diagnosis, which was based on the primary care consultation. This led to the recommendation that an algorithm was needed to cross check end points and validate them. This study suggests that the use of EHRs to support evidence generation for HTA will need to consider a number of fundamental operational issues related to their conduct.

One initiative that is gaining interest in the UK is that of the Systematic Anti-Cancer Therapy (SACT) chemotherapy dataset. This takes data from all the 147 NHS Trusts in England about the chemotherapy each patient has received and their immediate outcome, which can be linked to other data sources<sup>66</sup>. It currently has information on 153,000 patients.

The iMi GetReal consortium aims to improve the efficiency of the medicine development process by improving how outcomes relevant for relative effectiveness (RE) assessments are incorporated into drug development by<sup>67</sup>:

- Proposing innovative (and more pragmatic) trial designs and assessing the value of information
- Proposing and testing innovative analytical and predictive modelling approaches
- Assessing operational, ethical, regulatory issues and proposing and testing solutions
- Creating new decision making frameworks, and building open tools to allow for the evaluation of development programmes and use in the assessment of the value of new medicines.

The New Drug Development Paradigms (NEWDIGS) program brings together different stakeholders in a range of programs that use system engineering approaches and real case studies<sup>68</sup>. Their aim is to work collaboratively to find new ways of reliably and sustainably delivering new, better, affordable treatments to patients faster. Their initial work focussed on Medicines Adaptive Pathways to Patients (MAPPs) and has been discussing potential MAPP pilot case studies. The JANUS Program is now developing a set of linked simulation tools and processes to evaluate the implications of MAPPs based on each stakeholder's perspective. NICE is one of the partners co-developing JANUS, which will develop an agreed plan of work, undertake a pilot and then evaluate it to see what has been learnt. Another initiative undertaken by NEWDIGS is DIVALI, which will evaluate potential sources of real world data.

Schneeweiss recently identified the evidence challenges with Real World Data (RWD) as description of the problem (e.g. identifying true unmet need vs poor adherence), establishing causal association and predicting clinical outcomes. To overcome these challenges with RWD, bias must be reduced and quantified, and meaningfulness improved (representative of standard clinical practice, timely data collection and analysis and reproducible results). He particularly notes the time lag in data analysis and questions why rapid-cycle analytics cannot be used to inform our decision-making (like it is in banking)<sup>69</sup>.

66 [http://www.chemodataset.nhs.uk/about\\_sact/](http://www.chemodataset.nhs.uk/about_sact/)

67 <http://www.imi-getreal.eu/> Accessed 23 September 2014.

68 <http://cbi.mit.edu/research-overview/newdigshomepage/newdigs-activities/> Accessed 24 November 2014.

69 Schneeweiss S. Strategies to reduce bias and increase meaningfulness of finding from Real World Data. Presentation at ISPOR Europe 2014.

## 7.4 Methodological Developments

### 7.4.1 Guidance from Public Research Funders

In 2013, PCORI issued a methodology report that outlines its methods for research prioritization/translation and methodology for individual investigators<sup>70</sup>. Its prioritization processes consider:

- Disease incidence, prevalence, burden
- Gaps in evidence, variation, health inequalities
- Potential for new evidence to improve health, well-being and quality of care (e.g. using Value of Information)
- Effect on healthcare expenditure
- Patient needs, outcomes and preferences
- Relevance to patients and clinicians in making informed health decisions.

It states that for translation into health benefit, the appropriate study design, methods and analytic approaches must be used, balancing such factors as validity of resulting evidence, appropriate use of scarce research resources and timeliness of results. The methods guide is at a high level and covers basic issues such as defining research questions and analytical techniques, but also includes a section on patient centricity and specific sections on registries and data networks.

Another initiative in the USA is the development of the GRACE Principles, which provide high-level guidance to help evaluate the quality of non-randomized comparative effectiveness studies. The principles are outlined in Table 4 and are accompanied by sub-questions that help test the principles<sup>71</sup>.

**Table 4. GRACE Principles**

1. Were the study plans, including research questions, main comparisons, outcome, etc. specified in advance of conducting the study?	2. Was the study conducted and analysed in a manner consistent with good practices, and reported in enough details for evaluation and replication?	3. How valid is the interpretation of comparative effectiveness for the population of interest, assuming sound methodology and appropriate follow-up?
--	--	---

In the UK, work has been underway to formulate a clear framework to assess real world experimental studies. The Pragmatic Explanatory Continuum Indicator Summary tool has been recently extended to form the PRECIS-2 tool. Table 5 shows how a pragmatic trial could be assessed using the nine domains of PRECIS-2 tool<sup>72</sup>:

**Table 5. Application of PRECIS-2 Tool to a Pragmatic Study**

Eligibility criteria	Representative of population that would receive the treatment in usual care (e.g. older, comorbidities, on other therapies)
Recruitment	Involving no change to clinical routines
Setting	Usual care with ordinary oversight of clinical issues
Organization	Using typical health service resources
Fidelity	Flexible in applying protocol with clinical leeway
Adherence	Usual clinical encouragement to adherence
Follow-up intensity	According to clinical need, with as few visits as possible (e.g. baseline and endpoint, using routine data)
Outcomes	Direct relevance to patients, clinical outcomes, PROMs
Analysis	Always intention to treat

70 PCORI (Patient-Centered Outcomes Research Institute) Methodology Committee. 2013. "The PCORI Methodology Report." [pcori.org/research-we-support/research-methodology-standards](http://pcori.org/research-we-support/research-methodology-standards). Accessed 24 November 2014

71 [http://www.graceprinciples.org/doc/GRACE\\_Principles\\_10April2010.pdf](http://www.graceprinciples.org/doc/GRACE_Principles_10April2010.pdf) Accessed 22 September 2014

72 Pinnock H. Pills, people and preferences: evaluating real-life practice in pragmatic trials. ISPOR Europe 2014 Presentation.

The UK Medical Research Council is seeking to develop innovative methods to identify, synthesize and interpret observational data and consider how it can be combined with data from other sources and study designs such as Randomized Controlled Trials (RCTs)<sup>73</sup>. It is particularly keen to focus on:

- New approaches for deriving estimates of effectiveness from databases
- Determining and characterizing exposures, outcomes and potential confounders from routine databases where data may be complex and/or incomplete
- Approaches to be able to identify, assess, quantify, control and adjust for biases and confounding in observational data
- Evaluation of the strengths and weaknesses of randomized and observational studies in different settings so as to define the types of questions for which each approach is to be preferred
- Methods to inform the use of the data for systematic reviews, meta-analysis, decision analysis and health economics.

#### 7.4.2 Guidance from Regulators and HTA-funded Bodies

For the past two decades, regulatory agencies have provided guidance on clinical trial methodology and appropriate study designs for specific conditions that is based on wide consultation with regulators, clinical experts and now patients<sup>74, 75</sup>.

HTA organizations publish their own guidance and ISPOR provides a helpful repository to compare different pharmacoeconomic guidelines<sup>76</sup>. A number of HTA organizations have links with academia and methods have been developed to support more complex analytical and modelling approaches that are made possible by increased computing power. There have been major developments in the last decade in relation to network meta-analysis for indirect treatment comparisons and a range of issues related to economic modelling. NICE's Decision Support Unit has this year published reports on issues related to value based assessment (and the QALY adjustments), cost effectiveness modelling using patient level simulation and adjusting survival estimates in the presence of treatment switching<sup>77</sup>.

#### 7.4.3 2020 Vision for CER/RE

Mohr, Towse et al.<sup>78</sup> have conducted an intensive modified-Delphi process with 90 payers, regulators, patient representatives, senior executives in industry and other thought leaders to present a vision of the demand for and capacity to produce evidence for CER/RE in 2020. They note that adaptive designs, sequential cohort studies and large simple trials will play a much larger role in 2020. Their 2020 visions for evidence generation in the USA and EU are to be published in a paper in 2015 and have been presented to the HTAi Policy Forum in confidence.

73 <http://www.mrc.ac.uk/funding/how-we-fund-research/highlight-notice/methods-research-observational-data/> Accessed 21 November 2014.

74 [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000085.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000085.jsp) Accessed 24 November 2014

75 <http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/> Accessed 24 November 2014

76 <http://www.ispor.org/PEguidelines/index.asp>

77 <http://www.nicedsu.org.uk/> Accessed 23 September 2014

78 Mohr P, Towse A, Dutta T et al. A new drug development paradigm for the year 2020: Responding to the challenge of comparative or relative effectiveness research in the United States and Europe. In preparation. 2014.

## 8. Summary of Issues for Consideration by the HTAi Policy Forum

---

This paper identifies new issues that impact on health technology evidence production and HTA, or initiatives that are seeking to understand the implications of this ever changing landscape on HTA and coverage decisions. A key challenge for HTA is the call for earlier access to innovative/breakthrough treatments in areas of unmet need. This leads to a smaller evidence base for coverage decision making and more uncertainty. The key challenge for industry is the increasing demands for more evidence pre and post marketing and lack of coordination of evidence requests from different organizations.

We need to understand the forms of uncertainty that occur over the life cycle of the technology and how they can be managed, how we can better coordinate data requirements, what trade-offs we are willing to bear (e.g. uncertainty vs timeliness) and what incentives or sanctions could be brought to bear on evidence collection. The concept of a network of evidence that evolves over the life cycle of the technology with quantitative and qualitative methods for linking and adapting it, could be a useful one.

These issues can be helped by greater collaboration among HTA and regulatory agencies to provide advice to manufacturers on evidentiary requirements pre and post marketing, by coordination among HTA organizations and by continuing to improve transparency of coverage decision making. New real world data sources and methodologies may also be helpful. However, none of this is enough. We need to consider how collaboration amongst all stakeholders can be improved to ensure that throughout the life cycle of the technology evidence generation is focussed on regulatory, HTA, patients and clinicians needs and that best use is made of all available evidence sources to improve the efficiency and effectiveness of evidence production. These issues will be discussed at the HTAi Policy Forum meeting.

## 9. Outputs and Outcomes of the Policy Forum Meeting

The outputs of the February 2015 HTAi Policy Forum discussion will include:

- Note of the meeting by end of February 2015
- Suite of papers in the International Journal of Technology Assessment in Health Care
- PowerPoint presentation for Policy Forum members to use in their organisations and networks
- A panel session at HTAi 2015 with meeting report
- 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 (e.g. infographics).

Intended outcomes from the 2015 Policy Forum meeting include:

- Improved understanding of main challenges and opportunities for evidence generation from the perspective of different stakeholders
- In the light of these challenges and opportunities, proposals for improvements to the process for health technology evidence generation to make it more effective and efficient, stress-tested against some of the most significant pressures the system currently is currently experiencing.

For:

- Meeting attendees and their organisations and networks
- All stakeholders in the wider HTA community.

Karen Facey  
HTAi Policy Forum Scientific Secretary  
6 January 2015

## Appendix 1

---

Trial design and analysis guidance for breakthrough therapies

Extracted from Guidance for Industry Expedited Programs for Serious Conditions—Drugs and Biologics. FDA, Washington. May 2014.

### Substantial Improvement

The determination of whether the improvement over available therapy is substantial is a matter of judgment and depends on both the magnitude of the drug's effect on a clinically significant endpoint (which could include duration of the effect) and the importance of the observed effect to the treatment of the serious condition or serious aspect of the condition. In general, the preliminary clinical evidence should show a clear advantage over available therapy.

#### Approaches to Demonstrating Substantial Improvement:

- Direct comparison of the new drug to available therapy shows a much greater or more important response (e.g. complete responses where the control treatment generally results only in partial responses). Such a trial could be conducted in treatment-naïve patients or in those whose disease failed to respond to available therapies, either as a comparison with the failed therapy (if ethically acceptable) or as a no-treatment controlled study.
- If there is no available therapy, the new drug shows a substantial and clinically meaningful effect on an important outcome when compared with a placebo or a well-documented historical control.
- The new drug added to available therapy results in a much greater or more important response compared to available therapy in a controlled study or to a well-documented historical control. This trial also could be conducted in treatment-naïve patients or in those whose disease failed to respond to available therapies.
- The new drug has a substantial and clinically meaningful effect on the underlying cause of the disease, in contrast to available therapies that treat only symptoms of the disease, and preliminary clinical evidence indicates that the drug is likely to have a disease-modifying effect in the long term (e.g. a sustained clinical benefit compared with a temporary clinical benefit provided by available therapies).
- The new drug reverses or inhibits disease progression, in contrast to available therapies that only provide symptomatic improvement.
- The new drug has an important safety advantage that relates to serious adverse reactions (e.g. those that may result in treatment interruption) compared with available therapies and has similar efficacy.

## Clinically Significant Endpoint

For purposes of breakthrough therapy designation, FDA considers *clinically significant endpoint* generally to refer to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease. It can also refer to findings that suggest an effect on IMM or serious symptoms, including:

- An effect on an established surrogate endpoint that typically would be used to support traditional approval
- An effect on a surrogate endpoint or intermediate clinical endpoint (see section VII.B.2.) considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard)
- A significantly improved safety profile compared with available therapy (e.g. less dose-limiting toxicity for an oncology agent), with evidence of similar efficacy.

In a breakthrough therapy designation request, a sponsor should provide justification for why the endpoint or other findings should be considered clinically significant.

In rare cases, a pharmacodynamic (PD) biomarker may be considered a clinically significant endpoint if it strongly suggests the potential for a clinically meaningful effect on the underlying disease. In such cases, a sponsor should provide evidence supporting the use of the PD biomarker. Such evidence should include, for example, (1) the extent of understanding of the disease pathophysiology, (2) whether the biomarker is on a causal pathway of the disease process, and (3) the time course of the drug's effect on the biomarker (e.g. the biomarker can be measured earlier than a surrogate endpoint used for accelerated approval). In addition, strong evidence of the drug's effect on the PD biomarker generally is expected. FDA is more likely to rely on a PD biomarker for breakthrough therapy designation in a disease setting in which there is no available therapy, if the evidence supports such use.

### (Study Design Advice)

FDA will seek to ensure that a sponsor of a product designated as a breakthrough therapy receives timely advice and interactive communications to help the sponsor design and conduct a drug development program as efficiently as possible. During these interactions, the Agency may suggest, or a sponsor may propose, alternative clinical trial designs (e.g. adaptive designs, an enrichment strategy, crossover or N-of-1 design, use of historical controls) or use of an interim analysis by a data monitoring committee. These trial designs may result in smaller trials or more efficient trials that require less time to complete and may help minimize the number of patients exposed to a potentially less efficacious treatment (i.e., the control group treated with available therapy). Such approaches may be especially useful in studies in rare diseases. For example, single-arm trials may be an important option in rare diseases with well-understood pathophysiology and a well-defined disease course.

## Appendix 2. Comparisons of Regulatory, HTA and Coverage Processes<sup>79</sup>

**Table 1. Regulatory approval, HTA and coverage processes**

	Regulatory approval	Health Technology Assessment (HTA)	Coverage
Legal authority	Generally defined in national public health legislation, with regulatory bodies accountable to the government in their jurisdiction.	HTA may be undertaken by a group within and accountable to a coverage body itself, and/or by groups within and accountable to a government department, university, hospital, research institute or industry	Generally defined within the rules and regulations of the health care system in which decisions are being made, with coverage bodies generally being accountable to the health care system within which they operate. In some health care systems the role and responsibilities of a coverage decision making body may be defined in legislation and such a body may be accountable to government
Role	To decide on market authorization for a product in the relevant jurisdictions on the basis of assessments of safety, quality, efficacy and benefit-risk profile.  Regulatory bodies often also have a role to promote or support the development of new treatments addressing important unmet health needs	To provide the best evidence available to inform decisions about coverage, and decisions about use by patients and clinicians and/or tools to support those decisions, such as clinical practice guidelines	To decide whether a product should be covered, paid for and/or reimbursed within a particular healthcare system, on the basis of assessments of relative effectiveness, cost and in some systems affordability and/or value for money, given current practice, funding, priorities and social values within the system
Decision	Does the product do more good than harm for patients with defined indications in this jurisdiction?	HTA seeks to support decisions on whether an intervention offers useful, appropriate and affordable benefits for patients in a particular health care system	Will the product offer useful, appropriate (and affordable) benefits for some or all eligible patients in this health care system?
Evidence considered	Pre-launch, typically evidence on efficacy from randomized controlled trials (RCTs), usually placebo-controlled, though active controls may be required particularly when placebo control would not be ethical. Post-launch, evidence on relative efficacy, effectiveness and/or relative effectiveness may also be considered when reviewing a product's ongoing benefit-risk profile.	Such evidence on relative effectiveness/efficacy (and costs and opportunity costs across the system) as can be assembled from all relevant trials (of the product and alternatives) with placebo or active controls, and where necessary other study designs and/or analytic techniques such as modeling	Initially, such evidence on relative effectiveness (and costs and opportunity costs) as can be assembled from all relevant trials (of the product and alternatives) with placebo or active controls, and where necessary other study designs and/or analytic techniques. Coverage or ongoing coverage may sometimes be made conditional on the collection and review of further evidence post-launch or initial/provisional coverage.  Evidence considered may or may not be in the form of an HTA

<sup>79</sup> Henshall C, Mardhani-Bayne L, Fronsdal K, Klemp M. Interactions between health technology assessment, coverage, and regulatory processes: emerging issues, goals, and opportunities. *IJTAHC*. 2011; 27:253–60

**Table 2: Goals and challenges along the product lifecycle**

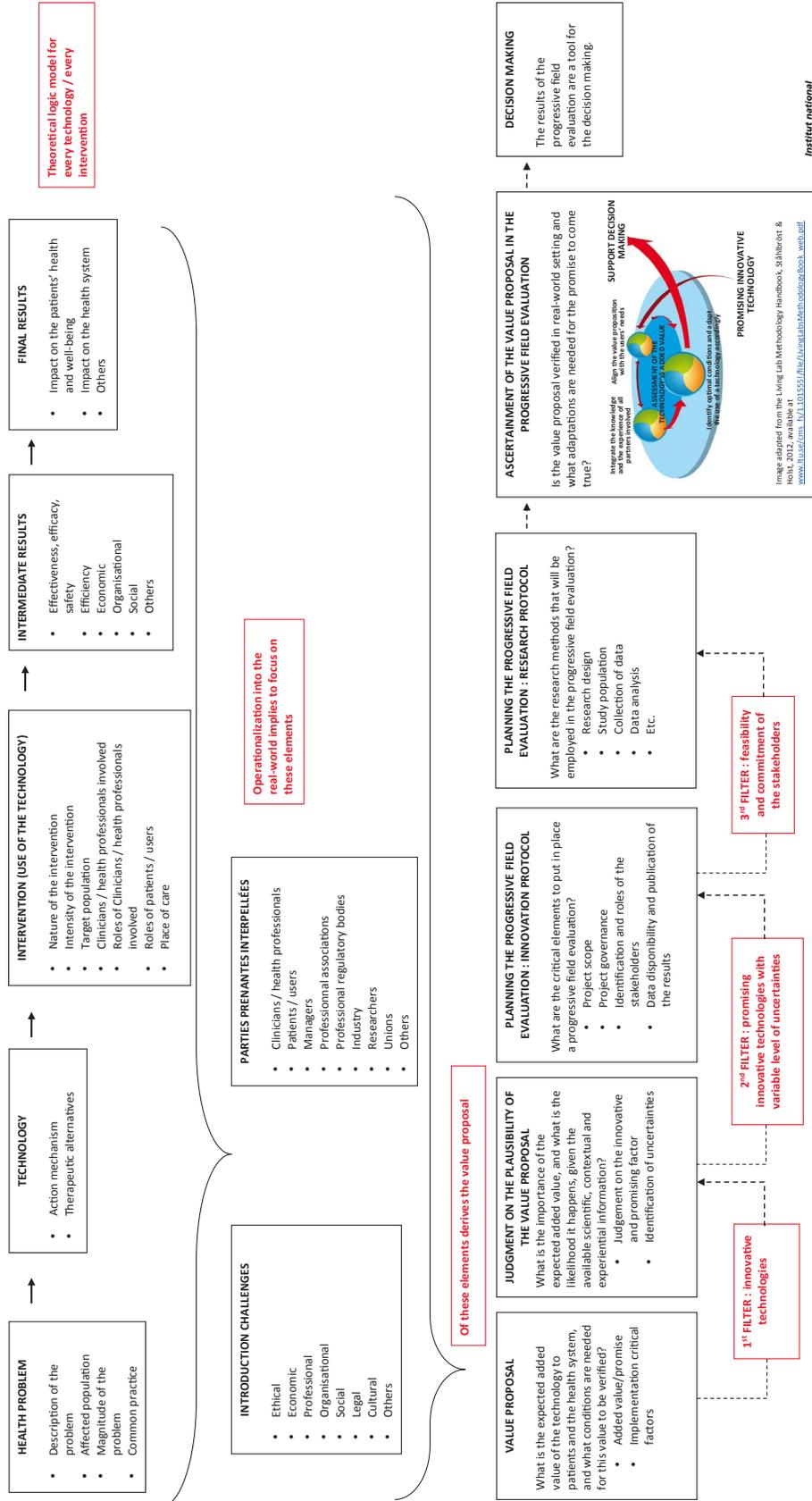
	Readily achievable goals	More ambitious goals	Challenges and barriers
R&D investment decisions	Joint discussions between coverage bodies, regulators and industry about unmet health needs and the development and reimbursement of products to address them	Include health ministries and public biomedical research funders in these discussions Improve incentive structures for the development of new affordable products for unmet health needs	Identifying the right geographical level to work at (i.e., country, region or international) Identifying the right people to engage from health ministries and public research funders Engaging clinicians, patients and the public more actively in the discussions Some coverage bodies may not see discussions about new products as a priority
Design of pre-market evaluations (phase 2 and 3 trials)	Coordinated or joint scientific advice from regulatory and coverage/HTA bodies for industry on design of pre-market evaluations (phase 2 and 3 trials) of specific products	Coordinated or joint guidance from regulatory and HTA and coverage bodies for industry on data requirements for products for specific conditions (e.g. relevant outcome measures, comparators) Joint guidance for industry from regulatory and payer/HTA bodies on key general aspects of trial design (to be developed in parallel with guidance for specific conditions, identifying the methodological issues that are common across conditions) Harmonization of pre-marketing data requirements	Identifying the right geographical level to work at (i.e., country, region or international) Engaging clinicians and patients more actively in the discussions Progress on harmonization of data requirements will depend on progress on challenging methodological issues around comparative efficacy and effectiveness, and on the relative roles of regulatory and HTA and coverage bodies in these areas
Initial reviews by regulatory, HTA and coverage bodies	Coordination of administrative procedures of regulatory and HTA and coverage bodies (e.g. points and format of submission) Coordination of review and decision timetables of regulatory and HTA and coverage bodies Communication between HTA, coverage and regulatory bodies prior to market approval to allow timely coverage decisions	Sharing of industry data between regulatory and HTA and coverage bodies	HTA and coverage bodies will need to guarantee that proprietary data will be treated in absolute confidence; and the public and politicians will have to accept that some data underlying HTAs and coverage decisions may not be publicly available Industry will need to accept that HTA and coverage bodies want access to all relevant data submitted to regulatory bodies

Table 2: Goals and challenges along the product lifecycle (CONTINUED)

	Readily achievable goals	More ambitious goals	Challenges and barriers
Post-marketing data collection, analysis and review	Coordinated or joint scientific advice from regulatory and HTA and coverage bodies for industry and public sector research funders on design of post-marketing data collection for specific products	<p>Coordinated or joint guidance from regulatory and HTA and coverage bodies for industry and public sector research funders on key methods for post-marketing data collection and analysis</p> <p>Harmonization of data requirements for, and/or active collaborations on, post-marketing surveillance between regulators, HTA and coverage bodies and industry, to increase the value of the information collected and avoid unnecessary duplication</p>	<p>Identifying the right geographical level to work at (i.e., country, region or international);</p> <p>Engaging clinicians and patients actively in the discussions</p> <p>Progress on harmonization of data requirements will depend on progress on methodological issues around comparative efficacy, effectiveness and safety, and on the relative roles of regulatory and HTA and coverage bodies in these areas</p>

## Appendix 3

### Logic model of the Progressive Field Evaluation



Based on the current work of the Advisory Committee on HTA and Innovative Technologies. For further information : [genevieve.plamondon@INESSS.QC.CA](mailto:genevieve.plamondon@INESSS.QC.CA) or [reiner.banken@INESSS.QC.CA](mailto:reiner.banken@INESSS.QC.CA)





**Health Technology  
Assessment international**

1200, 10405 Jasper Avenue,  
Edmonton, Alberta, Canada T5J 3N4  
Tel: 780.448.4881 Fax: 780.448.0018

E-mail: [info@htai.org](mailto:info@htai.org)

Twitter [@HTAiOrg](https://twitter.com/HTAiOrg)

Facebook [HTAiOrg](https://www.facebook.com/HTAiOrg)

[www.HTAi.org](http://www.HTAi.org)