HTA 2025 AND BEYOND: LIFECYCLE APPROACHES TO PROMOTE ENGAGEMENT AND EFFICIENCY IN HEALTH TECHNOLOGY ASSESSMENT

HTAi Global Policy Forum 2022 Background Paper

Contents

Introduction

The purpose of this background paper is to inform discussions at the HTAi Global Policy Forum (GPF) meeting being held in Vancouver, BC, Canada on the 26th to 28th March, 2022. The topic is "HTA 2025 and Beyond: Lifecycle Approaches to Promote Engagement and Efficiency in Health Technology Assessment". The topic was chosen and refined through engagement with the GPF membership in 2021.

A major factor influencing the choice of the topic for the 2022 GPF was a recurrent theme that emerged during discussions at the February 2021 virtual GPF. The prior topic was "Considering and Communicating Uncertainty in HTA", and while the discussions were wide ranging, a frequent suggestion for reducing and managing the inherent uncertainty in HTA processes was to consider a "lifecycle approach" with increased use of HTA processes and principles throughout the lifecycle of technologies to promote robust evidence generation and transparent communication across all stakeholders. This concept is also gaining traction internationally and "the lifecycle approach to HTA" will be the theme of the HTAi Annual Meeting in 2022, with a focus on priority setting, improving patient and public confidence in HTA activities and outputs, and fostering international collaboration, both across HTA bodies and sectors (e.g., regulators, clinical societies); see Appendix for the plenary session descriptions.

While the lifecycle concept is gaining popularity within HTA circles, what it means to implement such an approach, how realistic it is to apply HTA activities to all aspects of a technology lifecycle, and what improvements might be realized by doing so remain relatively unclear. Therefore, this paper presents an overview of key lifecycle approaches as well as important considerations for a lifecycle view. Information available in the published literature was gleaned from a structured literature review conducted in collaboration with the Institute of Health Economics (https://www.ihe.ca/). This was supplemented by the concerns identified by HTA users, producers and other stakeholders as well as those identified by GPF members, which were elicited during 10 expert informant interviews, including previous GPF Chairs, HTAi Interest Group chairs and others, conducted by the GPF Scientific Secretary, Chair, and HTAi Manager of Scientific Initiatives. We also interviewed representatives of HTA agencies from 14 countries (both members and non-members of the GPF for a global perspective on the issue); see the Acknowledgements for further details. A patient representative (Neil Bertelsen) also provided guidance and input on the development of the background paper and additional support to the HTAi project team. A survey of the current for-profit members of the GPF was conducted to determine what activities are currently undertaken or being planned in the context of stakeholder engagement and lifecycle approaches, as well as the challenges and barriers faced from an industry perspective. A total of 5 responses from for-profit member organizations were received (out of a possible 18 organizations). Finally, review and further input from the HTAi GPF Organizing Committee, the wider HTAi GPF membership, and members of the HTAi Board were also considered during the development of this background paper.

The main aim of the 2022 GPF will be to discuss how engagement and information-sharing between and within stakeholders throughout the HTA lifecycle can be enhanced and made more efficient. And while lifecycle considerations are certainly present during the process of conducting and deliberating on a given assessment, the greatest potential for alignment across the GPF membership is likely to be found in discussing 'pre-assessment' activities as well as 'post-assessment' monitoring. These activities do not represent two ends of a single timeline but rather two phases of a cycle which is continual/iterative and

will likely evolve over time. For example, learning from post-assessment activities may inform HTA activities and deliberations during a subsequent pre-assessment phase for a similar technology or in the same clinical field.

To provide the most value from the GPF, clear next steps will need to be developed for HTA agencies, industry and other stakeholders regarding expectations in considering lifecycle approaches and how these can be best utilized for improved efficiency. The intention is that the focus of the GPF discussions remain policy-oriented, rather than at a detailed operational or methodological level. Outputs from the GPF will include a post-meeting report, a journal article, and a panel discussion at the 2022 HTAi Annual Meeting. Additional efforts may include: development of white paper(s) and position statements, as well as other actions such as the launching of a topic-focused task force, as was the case with the 2020 GPF deliberative process topic.

Background

The definition of Health Technology Assessment (HTA) was updated in 2020 and defines HTA as "a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points *in its lifecycle*". Within this, the different points in the lifecycle of a health technology are "pre-market, during market approval, post-market, through to the disinvestment" (1).

HTA has been traditionally utilized as a basis for determining the clinical benefits, risks, and cost-effectiveness of technologies that then inform decisions about the reimbursement of the technology within a health system. This is typically, and increasingly, conducted as close to product launch as possible (the point at which the technology receives regulatory approval). However, in taking a lifecycle view, as described in the new definition of HTA and as illustrated, for example, by Gutierrez-Ibarluzea in 2017 (2), there are multiple points at which the potential benefits, risks, economic impact, patient burden, implementation issues, environment (context) and equity issues surrounding a new technology can be considered and discussed. These multiple interactions may include but not be limited to: early scientific advice and/or dialogue, early awareness (horizon scanning), HTA [for reimbursement], post-HTA observation, monitoring of managed entry agreements, HTA reviews (health technology re-assessment), implementation and clinical practice considerations, and disinvestment decisions (see Figure 1).

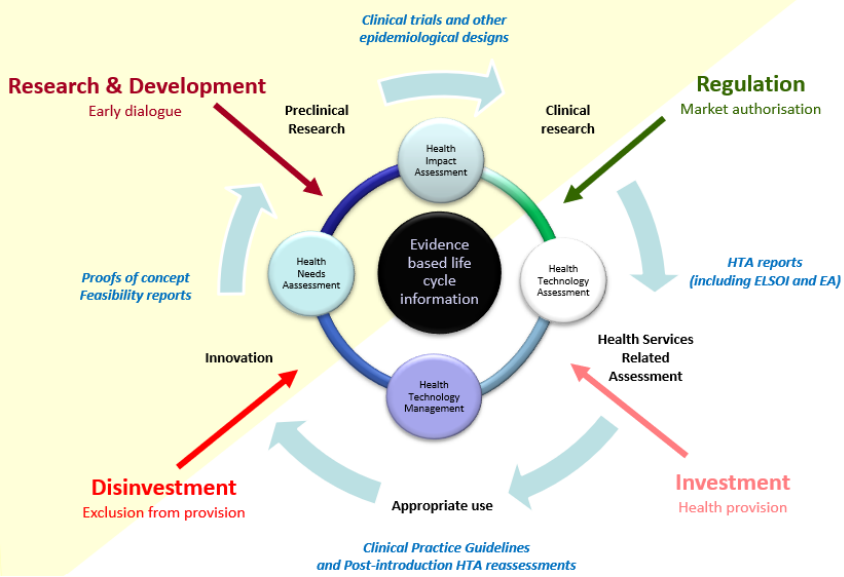

*Figure 1 The life cycle of health technologies concept. Taken from 'The Life Cycle of Health Technologies. Challenges and Ways Forward', I. Guttierz-Ibarluzea, M. Chiumente, H. Dauben, Front. Pharmacol., 24 January 2017 | https://doi.org/10.3389/fphar.2017.0001. *ELSOI= Ethical, Legal, Social, Organizational Issues; EA = Economic Analysis.*

While full lifecycle management of a technology (from pre-clinical to post-authorization and beyond) may be an intriguing idea, this may be infeasible for some HTA bodies given budgetary (funds that can be allocated to different lifecycle activities) and resourcing (deploying, hiring, and retaining individuals skilled in different lifecycle roles) constraints and may be completely outside the remit of some agencies. Whether a HTA body is applicant (submission) driven and/or whether if it can fully set its own workplan also plays a role in dictating the ability, capacity and willingness of HTA agencies to embrace the lifecycle approach. Additionally, the influence of HTA on payers is likely to be determined by a combination of policy and legislative or other mandates, administrative arrangements, and organizational structures. HTA bodies may have reporting obligations to a governance entity which may in turn determine the relevant activities, including the types of technologies to be considered, the stakeholders to include, and the opportunities to engage with them. Importantly, the role in which a HTA body plays in informing, negotiating and setting/guiding prices of technologies varies widely across the world. The links with payer entities (i.e. those bodies with ultimate decision-making authority on funding) also vary, as do the policy tools that payers employ (such as ability to negotiate and publish prices and enter into managed entry agreements [MEAs]). How HTA advice interacts with the policy tools available and is actually used within each jurisdiction is a key concept, and working more closely with payers may facilitate, influence and even expand the policy options available. The increasing use of mechanisms such as payment for performance or value-based contracting was also noted.

The additional investment required to conduct lifecycle activities in HTA only makes sense if such activities ultimately make the health system more efficient and add value. Lifecycle approaches can validate early data and measure appropriateness of recommendations and technology usage, and HTA agencies can act as a neutral broker bringing the relevant parties together (payers may be considered as too finance oriented, patients may have personal biases that are perceived as conflicts, and so on).

Terminology

For the purposes of this paper and the GPF discussion, the following definitions and terms will be used:

Technology lifecycle is the term used to describe the way that a technology is developed, introduced, matures and eventually becomes obsolete. It applies to both health and non-health technologies, with the most common depiction in the form of 'S-curves' with 4 distinct phases: research and development; ascent (implementation); maturity (diffusion); decline (disinvestment/obsolescence):

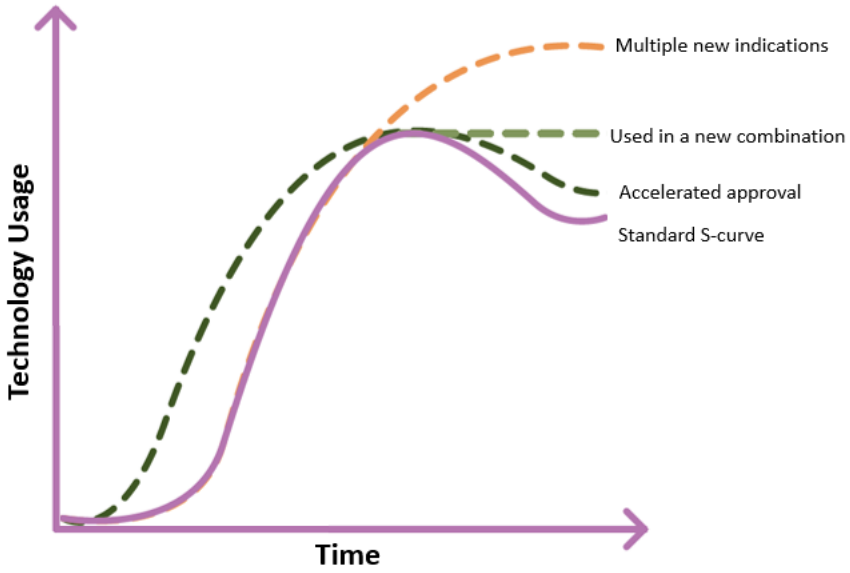

Figure 2-depiction of some key possible Technology S-curves, adapted from EuroScan (REF)

While the same 'S-curve' pattern holds for most health technologies, two critical elements have the potential to make health technology lifecycles especially complex. First, health technologies do not exist in isolation from one another; while many technologies (particularly so for pharmaceuticals) may be developed and possibly introduced as single technologies, they are given within a treatment pathway and increasingly in combination with other existing or new technologies (e.g., multi-modal cancer therapies). This has the potential to change the shape and time scale of the curve. For example, the maturity component of a technology can be extended if it is introduced as a monotherapy but then is given in combination with a newer technology or as an earlier line of treatment. Similarly, patient populations (and therefore the maturity phase) may be increased with the advent of a new companion diagnostic; although in this case the R&D and implementation phases may also be lengthened while the companion diagnostic test is developed and evidence generated. This is further complicated by technologies having multiple indications; the lifecycle of the technology can be altered as additional indications receive regulatory approval.

Second, the lengths of the S-curves of health technologies are not consistent and uniform. This has been noted for many years, particularly for medical devices where new versions and adaptations of devices are rapidly released; in some cases, the maturity timeline can be considerably shortened if a new device emerges before the older device has reached full diffusion (3) and technologies such as mobile Health that often develop iteratively and flexibly (4). In cases such as these, it can be challenging to determine what phase a technology is in and at what stage a new technology (rather than a new version) emerges. The advent of accelerated regulatory approvals for drugs (5) may also shorten R&D phases within the S-curves and disrupt the diffusion of other technologies more rapidly; these interdependencies between

health technologies and the challenges with accelerated approvals may increase the potential for reduced predictability and information loss.

Lifecycle activities refers to HTA activities that occur along the various timepoints of a health technology lifecycle. Table 1 below contains descriptions of the most conducted types of lifecycle activities; it should be noted that for different activities, different elements of HTA may be applied. Traditionally, these types of activities have occurred somewhat in isolation from each other and also for single technologies (except perhaps in the case of development of clinical guidelines which tends to be more condition, rather than technology, specific):

Table 1- Key HTA Lifecycle Activities

Activity	Definition
Early HTA	There currently is no accepted definition or framework for early HTA. However, Ijzerman et al. (6) suggested that it informs industry and other stakeholders about the potential value of new medical products in development, including methods to quantify and manage uncertainty; this means the role of early HTA can be extended to inform "[target] product profile development, research and development decisions, research decisions and uncertainty management" (7).
Horizon scanning	The systematic identification of health technologies that are new, emerging or becoming obsolete and that have the potential to effect health, health services and/or society (HTA Glossary)
Early dialogue/ Scientific advice	Scientific advice (or early dialogue process) is offered by regulators and/or HTA agencies to companies developing medicines and increasingly devices and diagnostics. In some countries it is conducted as a fee-for-service (8)
Monitoring implementation	Obtaining data to track the uptake of HTA recommendations within a health system, including reimbursement (or not) or technologies having undergone a HTA and particularly in the context of a managed entry agreement (which can be performance/outcome or financially based) (9)
Health Technology Reassessment	A structured, evidence-based assessment of the clinical, social, ethical, and economic effects of a technology, currently used in the health care system, to inform the optimal use of that technology in comparison with alternatives (10)
Disinvestment	The deliberate and systematic reduction of (government) funding for a health technology of questionable or comparatively low clinical and/or economic value (HTA Glossary)
Optimization	Optimization involves assessment or re-assessment of a technology, a decision on optimal use, and decision on implementation (11)

Lifecycle Approach refers to the concept of developing and using technologies in a continual and iterative process. There is no universally accepted definition of the term "lifecycle approach", some people consider the term to be synonymous or synergistic with "Health Technology Management (HTM)" (12). However, there are key differences between the perspectives (typically societal versus health facility), methods (systematic review and cost-effectiveness analysis versus project management) and criteria (clinical and cost-effectiveness versus needs analysis) of HTA compared with HTM (13). Some experts consulted in the development of this paper considered that a lifecycle approach simply means that key HTA concepts (such as comparative evidence considered in context with costs) are applied to multiple points of the technology lifecycle rather than conducting full HTA activities per se.

HTA is primarily established as a tool to help health systems determine the best use of finite health resources. Similarly, there is no capacity for HTA agencies to conduct a HTA for every technology and certainly not to conduct 'additional' lifecycle activities for every technology. For the purposes of this paper, the GPF discussions and beyond, a flexible and adaptive mindset with prioritisation of activities is therefore necessary. The context for the GPF will be on how this conceptual approach can be used to increase efficiencies in the HTA process, with a focus on how information can be shared and evidence bases developed throughout the lifecycle of health technologies. Importantly it will include how stakeholders (particularly patients but also clinicians and health system stakeholders) can contribute along the way without cumbersome burden on them and their time. It is important to note that elements of a lifecycle approach already exist within the current HTA framework, where multiple submissions for the same technology (e.g., at various lines of therapy, or in combination with other technologies, or for subsequent indications, or with development of new versions in the case of devices) require translation across assessments, consideration of whether clinical practice has changed, identification of what data can be re-used, and whether the evidence base is therefore reflective of current practice. This is potentially an area for significant efficiency gains across HTA agencies.

Key Issues Related to Lifecycle Approaches

The Current Context

Recent years have seen a rapid influx of innovative and disruptive health technologies (14). New approaches to treatment, including cellular and regenerative therapies, mRNA vaccines, genetically-based tests and treatments, nanotechnology, new methods of transmitting health information (such as with digital health and machine learning) are altering everything from the regulatory landscape to the drivers of clinical practice. This has been illustrated multiple times in our pandemic setting, where rapid and emergency usage of medicines and vaccine development became almost routine, sometimes with non-clinical trial data. These advances pose unique challenges to global health care systems from a sustainable funding perspective, particularly as care is shifting more and more towards a patient-centred approach (15). With the advent of genetic profiling and more targeted technologies, health care is becoming more personalized and care is shifting from the clinical setting to home, with patients becoming increasingly empowered. This creates additional challenges in generating comparative evidence bases in a rapid timeframe.

Fostering Innovation

As a result of technological advances and innovations there comes a pressure to pay for the newest technologies; HTA is seen by some as a hurdle to innovation, and can sometimes lack political backing in the face of pressures from manufacturers and patient groups who want access to new technologies quickly. Adopting a lifecycle approach to HTA can be a way to facilitate faster access to promising, cost-effective technologies at an earlier stage, primarily through early HTA approaches, managed entry agreements and through optimizing/disinvesting in older technologies to make funds available. Rapid access should not merely equate to the idea that positive HTA recommendations are produced in close alignment with regulatory decisions; there still remains a need for HTA to take all aspects of its remit as gatekeeper into account. Responding quickly to and being flexible in the face of technological innovations and implementing recommendations in a dynamic way can also be challenging; particularly in large organisations (such as complex health systems). Change generally doesn't happen in a quick or uniform way and this can create pockets of inequity, where there are areas that are better resourced

and able to adapt to change more quickly; for example, in the space of digital health and wearable technologies that typically incur out-of-pocket expenses and are therefore used more by people in higher income areas. Sustainability of funding for health systems to afford innovative technologies is critical. Iterative and condition-related assessments rather than the more traditional approach of single assessments of single technologies may offer an opportunity to more fully encompass consideration of changes to the health system (for example diagnostics or new technologies that may disrupt the system) and have a more holistic view of the implementation of innovative technologies.

There are a number of examples of large-scale public investments in making development of health technologies more efficient. Horizon 2020 is the largest EU Research and Innovation programme, with nearly €80 billion of funding invested (and additional private funds leveraged) dedicated to increasing the pace of life sciences development, from laboratory to market. Other examples of public-private partnerships include MIT's **NEW** Drug **D**evelopment Parad**IG**m**S** (NEWDIGS) program, an initiative that takes a systems approach to designing, evaluating and catalyzing important clinical advancements. With initiatives such as these and others, there is a growing traction for the concept of 'responsible innovation in health', which suggests that health technologies could be designed with more dynamic and reflective processes that ultimately better support health systems and are responsive to shifting health needs. This approach emphasizes the importance of inclusive design processes to gather the needs of diverse stakeholders; solutions that are responsive to system-level challenges and consideration of the level and intensity of care required for the innovation to be used safely and effectively (16). Evidence-based and systematic approaches such as this could be synergistic with developments in the early HTA space.

In line with the push towards greater innovation, early HTA may have a role. Early HTA is conducted early enough in the technology lifecycle (i.e. in the pre-regulatory space) so that decisions that are made that result in changes to the development of the technology. This would be followed by (multiple) iterative HTAs to continually review the evidence being generated, with refinement of plans and subsequent recommendations. Aims of early HTA could include agreement on key endpoints, development of historical databases for comparative data, and it is increasingly forming part of a manufacturer's 'go/no-go' decision making process if early HTA principles are used by manufacturers themselves. As with horizon scanning, finding the right time to engage in early HTA is key, as activities conducted too early can lead to wasted resources (as many technologies inevitably are not progressed) and with little evidence to inform decisions; too late and the full value of early HTA (i.e. the ability to change the technology and/or evidence generation plans) is lost.

Accelerated Regulatory Approvals

With the increased investment in innovation, there is also an increasing interest in accelerated regulatory approvals and adaptive (flexible) licensing including "rolling reviews", mainly due to: growing patient demand for timely access to promising therapies; emerging science leading to evidence of differing effects in treatment populations; rising payer influence on product accessibility and pressure to ensure sustainability of health systems (17).

There are several schemes, which (particularly in the COVID era) are designed to promote faster routes to regulatory approval. The Early Access to Medicines Scheme in the UK provides patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorization when there is a clear unmet medical need through the Medicines and Healthcare

Regulatory Agency (MHRA). Other recent developments within the regulatory landscape are collaborations such as Project Orbis, which provides a framework for concurrent submission and review of oncology products among international partners. This may be expanded outside of oncology in the near future. The European Medicines Agency (EMA) have also introduced schemes such as EMA PRIME, which offers manufacturers early and proactive support to optimize the generation of robust data and enable accelerated assessment of medicine applications.

Efforts such as these, while providing accelerated regulatory approval for certain technologies, create potential issues for the HTA community. Faster regulatory approval typically means lower-quality evidence (that is smaller sample sizes, shorter follow up, use of surrogate outcomes, and other concerns) and inevitably increased input uncertainty for HTA agencies. In addition to this, the number of novel active substances receiving regulatory approval increases every year, adding to the workload for regulatory and HTA agencies. CADTH and Health Canada are exploring agile licensing approaches designed to be more flexible, particularly in the face of future drug developments. There are arguments for closer alignment between regulatory and HTA agencies, though some are concerned that closer alignment could result in a dilution of the purpose of HTA as compared with regulatory authorities, or that HTA will be seen as a barrier to access (see Figure 3).

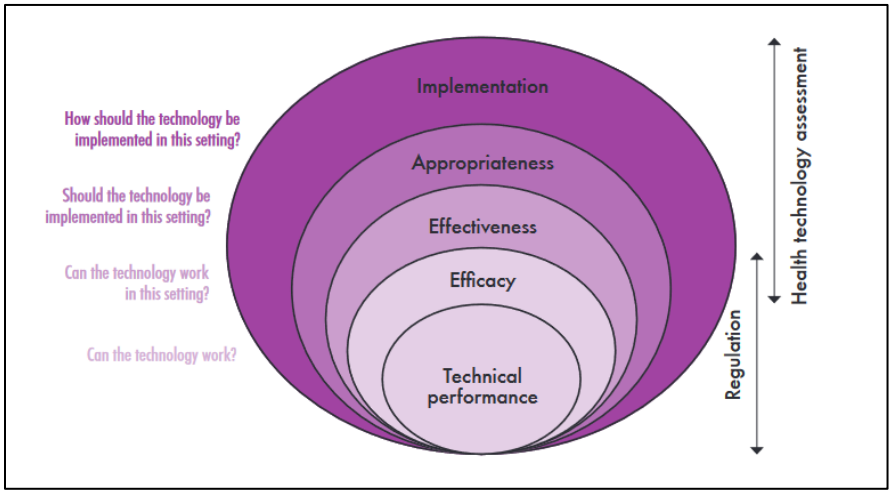

Figure 3-Layers of questions in healthcare; taken from WHO report (18)

Literature Review Results

Despite the current proliferation of the term and others, lifecycle activities are not a new concept and HTA has always been adapted and applied to other points of the technology lifecycle to aid decision making. In 1990, Banta and Thacker argued that "assessment of health care technologies should be an iterative process" (19), and Mowatt et al concluded that that HTA should be conducted early in the technology lifecycle and then repeated throughout (20). The results of our literature review highlighted limitations of the literature pertaining to the lifecycle approach. The literature review found a total of 218 articles, but only 55 discussed concepts and aspects related to lifecycle approaches rather than individual lifecycle activities.

Much of the literature that does exist on holistic lifecycle approaches pertains to medical devices, likely due to the issues germane to this area such as device-user interaction, incremental (and rapid) nature of innovation, and the broader organisational impact that is possible with devices (21). The MedtecHTA

collaboration recently recommended that aligning regulatory processes, harmonising HTA evaluation frameworks, and processes for conditional coverage with further evidence generation should be undertaken (22). While the literature is mainly device-focused, a PhD dissertation on "HTA throughout the Drug Lifecycle" was recently published (23). In the thesis, three key messages are summarised with accompanying policy and research recommendations (see Table 2 below).

Table 2- Key Messages by Vreman on Drug Lifecycles

Key Message	Policy recommendations	Research recommendations
Evidence inevitably comes with uncertainty	-HTA agencies should actively steer evidence development -Stakeholders should think prospectively about evidence requirements and be explicit about the evidence and evaluation	-Evidence generation and reimbursement decisions should be analyzed -Regulatory and HTA agencies can facilitate evidence generation and drug and policy development so that stakeholders are prepared.
What one stakeholder does has an effect on others	-Stakeholders should be aware of the policies of others and should consider how new policies will be perceived -Regulatory and HTA alignments should continue and regional coalitions of countries should be encouraged -Stakeholders should systematically publish their assessment reports. -HTA agencies could consider if a full HTA is needed where the regulatory evaluation is similar (orphan drugs first)	-Areas for closer coordination on stakeholder assessments should be identified. Appropriate involvement of manufacturers and patients in these processes needs further research -The effects of new policies (including international coherence) should be monitored -Research on HTA recommendations can benefit from international good practice guidelines and from the development of methods to automatically extract data from stakeholder reports.
Timing is crucial	National HTA agencies should develop a process that informs which lifecycle activities for which drugs are worthwhile; including developing a cyclic approach to (re)assessments and conditions for early advice and HTA. These processes can be developed nationally but aligned internationally.	The methods and models for HTA throughout the drug lifecycle should be further developed. Particularly, how (cost-)effectiveness models can accommodate the integration of a changing extent of uncertainty in pricing and reimbursement decision-making throughout the drug lifecycle, and how they can be embedded in existing and future policy structures.

Current Lifecycle Activities within HTA

It is important to reflect on what lifecycle activities are being conducted by various HTA agencies across the world, what benefits are being realized, and where the major challenges lie. We interviewed representatives from 17 HTA agencies from 14 countries and supplemented these with website reviews. The HTA agencies were selected from the GPF membership with additional agencies for a global perspective.

All of the agencies were conducting at least some lifecycle activities in addition to HTA for reimbursement recommendations. Most of these activities were in the "pre-assessment" phase with most agencies undertaking, and manufacturers involved in, horizon scanning and scientific advice (increasingly with regulatory authorities present). There was less consensus around the "post-assessment" phases, with variable approaches to post-decision monitoring and health technology

reassessment (HTR). Many agencies have moved from routine reassessment to only considering HTR if there are significant changes to the evidence base expected; however, some agencies do consolidate multiple HTAs across disease areas into clinical guidelines (and update recommendations where necessary). None of the agencies are now routinely conducting active and explicit disinvestment activities. There are some historical examples of disinvestment reviews (for example the Medicare Benefits Schedule review in Australia) or some HTR resulting in "do not do" recommendations.

The sections below are organized by pre- and post-assessment lifecycle activities, and highlight the major opportunities and challenges associated with each. In addition, a detailed table outlining current lifecycle activities is included in the Appendix.

"Pre-Assessment" phases

Early HTA Early HTA has yet to be widely accepted as a cost-effective use of HTA resources, and is not routinely conducted by the HTA agencies interviewed. This may be in part due to HTA not having a strong mandate in some countries (and therefore the incentive for manufacturers to participate is low) coupled with resourcing constraints and a lack of a sustainable payment model. To date, the potential of early HTA has been evaluated using retrospective case studies (i.e. what value could early HTA have brought) (7). Industry members reported, however, that the principles of early HTA are used with increasing frequency for internal company decision-making on technology development and clinical trial design.

For early HTA to be successful, teams conducting early HTA need experience in HTA (for example with reimbursement recommendations) to understand the nuances of the system and should work with a wide range of relevant stakeholders. Early HTA could also incorporate value of information analyses to guide the future research. According to a paper by Wang et al (7), there are three main benefits of conducting early HTA:

1. Financial – can eliminate technologies from the development process at an early stage. This can save the manufacturer money in development costs (although the cost to the HTA body was noted)
2. Time – facilitates the HTA process overall and accelerates HTA for reimbursement (e.g. COVID vaccines), shortening the overall technology development timeframe
3. Targets - can help identify a more targeted (clinically and cost-effective) population that the technology is appropriate for. Starting in one population and working through HTAs, possibly with additional trials to find the most appropriate target population, can take a long time and cost a lot of money to manufacturers and the health system more broadly.

There are also some examples of a "co-creation" approach in the hospital setting, where clinicians work with a technology developer and/or an academic or research institute to progress an initial idea. HTA methods and concepts (not necessarily undertaken by HTA agencies but other health system stakeholders) can be a useful tool to assess the adequacy and feasibility of these initial ideas. The value to patients and clinicians in participating needs to be carefully considered (24). For example, the Idea, Development, Exploration, Assessment, Long-term study (IDEAL) framework aims to better understand the data steps necessary to bring an idea from routine practice to further marketing, approval and monitoring (25), (26). The VALIDATE-EU program (VALIDATE – VALIDATE project website (validatehta.eu)) also outlines some of the issues and could be applied to earlier stages with shaping

through iterative assessments. As noted at the 2021 GPF, greater exploration of resolvable and unresolvable uncertainties at an earlier stage in the lifecycle may be beneficial, in particular for technologies for rare diseases. This could result in alternative HTA processes or timelines for assessment being triggered. A systematic pilot study to assess the true benefits of conducting early HTA may happen in Singapore in the near future with a tool for scoring candidates for early HTA (for example, precision medicines are likely to be a good target for such a process). ***If successful, this approach, learnings and even possibly information could be shared across countries; is early HTA an area worthy of active exploration and development, or would it have matured already if there were value in HTA agencies being involved in the approach? What is the value for stakeholders such as clinicians and patients to be involved in such an early stage and how can any conflicts of interest be managed? If conducted, what is the best resourcing model for early HTA?***

Horizon Scanning

Most of the agencies interviewed conduct horizon scanning either by themselves or as part of an international consortium. One of the major concerns pertaining to horizon scanning, and indeed to all lifecycle activities, is that of timing. Determining how early in the technology lifecycle horizon scanning can add value is a contentious topic (27). Too early may mean potentially wasted resources, reviewing evidence on technologies that will not come to market or may have completely different treatment paradigms by the time they are launched. Too late, and the value of horizon scanning is unlikely to be maximised. Typically, the agencies interviewed that are conducting horizon scanning are doing so up to two years prior to product launch and for internal work planning. Some countries also have health boards that conduct horizon scanning mainly for financial planning/budgeting purposes.

During interviews, it was raised that horizon scanning could perhaps add more value to the HTA process if it were used to flag where resolvable or unresolvable uncertainties may lie; for example, identifying where technologies are likely to come to market with weak evidence bases but with large patient demand, (28). In these situations, linking the horizon scanning with early scientific advice activities could result in more proactive outputs such as collection of historical data, with patient relevant outcomes, that could help develop a true baseline understanding of standard of care *before* the technologies start to be introduced and diffuse into the health system. Once technologies are available within a health system, it may be unethical to withhold them, and for disease-modifying technologies this can result in particular challenges in determining their comparative effectiveness to standard of care. HTA agencies may even be able to prepare for the subsequent evidence submission by determining the most appropriate methodologies in advance. Linking horizon scanning through to the post-HTA space can also result in better system preparedness with logistical issues identified ahead of time (such as being able to prepare for a new technology that requires a PET scan for diagnosing the condition).

The argument as to whether horizon scanning could be done in a more proactive manner is also longstanding (i.e. rather than simply critiquing what is provided, can HTA methods or concepts be used or promoted to better identify clinical unmet need across disease areas and drive research and development of new technologies)? It can be challenging to find patients and clinicians at a very early stage of technology development that are not perceived to have conflicts of interest (through early experience of the technology and potentially close links with the technology manufacturer). The boundary between horizon scanning and early HTA (and even early scientific advice) can also become blurred, with some arguing that this flexible and open approach can be beneficial to all stakeholders (although potentially time and resource consuming). ***What is the ongoing value of horizon scanning;***

can it be used as more than a work planning tool for HTA agencies; how can it be made more proactive and effective in readying the health system for disruptive change? Can more common criteria be developed globally, including both HTA agencies and technology manufacturers and others, to identify which technologies should be prioritized for HTA?

Scientific Advice

An area of significant development in recent years is that of informal early dialogues and formal scientific advice, both directly between HTA agencies and technology manufacturers but also increasingly with regulatory authorities in attendance. Most of the agencies interviewed are conducting some form of early advice; a "bottleneck" of demand for scientific advice compared with supply was noted during interviews and in survey responses; similarly, industry responses noted challenges in identifying the right time for seeking scientific advice to ensure that the advice is early enough in product development but at a mature enough stage that the product shows sufficient potential. Collaboration on scientific advice between agencies is also underway; CADTH and NICE began offering parallel advice in early 2019. CADTH is undertaking further exploration on how it could build on its established processes to inform RWE generation, particularly for conditions where there are likely to be greater uncertainties.

Another very recent example is the Innovative Licensing and Access Pathway (ILAP) in the UK that is a collaborative effort between NICE, the Scottish Medicines Consortium (SMC), All Wales Therapeutics and Toxicology Centre, and the MHRA with support from the National Health Service and National Institute for Health Research. It aims to "accelerate the time to market, facilitating patient access to medicines" with a Steering Group and patient representatives designating "Innovation Passports" according to the criteria in Table 3.

Table 3 - Criteria for ILAP eligibility

Criteria 1	-The condition is life-threatening or seriously debilitating -There is significant patient or public health need
Criteria 2	-An ATMP or new chemical, biological entity or drug combination -Clinically significant new indication for an approved medicine -Medicines for rare disease and/or other special populations such as neonates and children, elderly and pregnant women -Development aligning with the objectives for UK public health priorities
Criteria 3	-The medicinal product has the potential to offer benefits to patients

For those who meet the criteria, a Target Development Profile is developed based on the product's characteristics that will define key regulatory and development features, identify potential pitfalls and create a road map for delivering early patient access. The program will also include access to a toolkit for applicants (technology manufacturers) to support all stages of the design, development and approvals.

The intention of ILAP is to provide safe, early and financially sustainable patient access to important treatments. While the program is still in its relative infancy, there is a lot of inter-agency support within the UK for it. Establishing such a program is resource intensive (particularly in developing the toolkits

and meeting with technology manufacturers) but the hope is that the workload and the ability to staff teams appropriately will become more manageable with a cost-recovery model proposed. Interest in the program has reportedly been high so far with genuine collaboration and commitment from all stakeholders to date. It is not envisaged that ILAP would remove the need for scientific advice directly between the HTA body and manufacturer at a later timepoint (closer to product launch). While there is no formal mechanism envisioned for allowing the flow of information from ILAP to the relevant HTA deliberative committees, the hope is that the program will result in "better" HTA submissions, meaning fewer unanswered questions for the appraisal committees with reduced uncertainty about the clinical and cost-effectiveness of the technology in that setting. The Innovative Devices Access Program (IDAP) for medical devices takes a similar approach, and is currently being developed in partnership by HTA bodies across the UK and the MHRA.

There is also closer collaboration between HTA agencies and regulators globally, for example ADAPT-SMART, a multi-stakeholder consortium that aims to prospectively plan medicine development with multi-stakeholder dialogue (including HTA agencies) (29). While the benefits of this include greater alignment on study endpoints, including patient relevant outcomes, there is a perceived risk that the role of HTA may be tempered with a desire for faster access to all new technologies.

The process of restricting information flow between the teams providing early scientific advice and the teams conducting the HTA, for example with "firewalls" (that is, deliberate restriction of the flow of information pertaining to scientific advice between advice and assessment teams) was highlighted by most HTA agencies that currently conduct scientific advice. Concerns around confidentiality of technologies in the pre-competitive environment (with commercially sensitive data) have had a chilling effect on the sharing of input, knowledge, advice or recommendations across and between HTA agencies. These firewalls often extend to keeping the very fact that a manufacturer has engaged in an early advice process confidential from the HTA stakeholders (for example the appraisal committee, within and across HTA agencies). In most systems, there is no way to know what advice was provided and whether the manufacturer acted upon the advice, and why they did or did not choose to do so. It was noted, however, that scientific advice itself does "belong" to the manufacturer and there is nothing to stop the manufacturer from sharing the advice internally and learning from the advice provided. However, it is important to consider that from the manufacturer perspective, there are multiple competing country markets and a global evidence package cannot be finely tailored to suit each one; because of this, not all advice from each country can be taken on board. The upcoming EU HTA Regulation (see Collaboration section) and the joint scientific consultation that will be undertaken may go some way to addressing this issue.

The level of confidentiality that currently exists around many early advice processes also means that patients and clinicians (if they are involved at this early stage) do not know how their input was used and what value they added to the process; this can be disincentivising and can also result in duplication where the same questions may be asked multiple times. ***Are there specific (non-commercially sensitive) aspects that are discussed in early dialogue that could be shared both within a HTA body and across jurisdictions (like an 'FAQ' for disease areas)? Could patient input be shared within and across jurisdictions? Would greater transparency in whether advice results in changes to clinical development plans allow HTA agencies to better evaluate the value of providing it?***

"Post-Assessment" Phases

Monitoring Implementation (including Managed Entry Agreements and Dynamic Pricing)

After recommendations have been made on the use and efficacy of a technology in a health system, monitoring the usage and effectiveness in practice is one activity some agencies undertake (with some countries undertaking this activity but through different divisions or organisations). Risk sharing agreements (RSA) or managed entry agreements (MEA) are becoming more commonplace, particularly as regulatory approvals are being accelerated across a spectrum of drugs and devices, with consequent reductions in the amount of evidence available at initial assessment and uncertainties in budget impact (30), (31).

In theory, such an approach could be factored into a dynamic pricing model; this would allow for both fluctuation in prices from external forces (e.g., pharmaceuticals lose exclusivity and reduce in price and medical device prices naturally fluctuate over time (21)) as well as price increases or decreases resulting from updated estimates of clinical benefit and safety as new evidence emerges. Research indicates that using the expected lifetime prices of technologies within a HTA (that is, incorporating lower costs of drugs when they lose market exclusivity) may reduce cost-effectiveness estimates (i.e., make them more favorable) compared with using a static costs (32). Some of the manufacturers who were consulted in the development of this paper highlighted the importance of such an approach to account for the fact that the price at launch is likely the highest price that the technology could demand, even if new indications are added. Using dynamic pricing is more common for HTA of medical devices, and Daubner-Bendes et al recommended that average expected payments rather than actual costs should be used for medical device HTAs (33). Factors such as the timing of the comparator's loss of exclusivity, whether patent extension strategies will be attempted, and other factors such as MEAs (that may include outcome-based agreements) could be taken into account if contemplating dynamic pricing (34). This is also controversial, as some feel that the savings that accrue from genericization (90% of prescriptions filed in the US are for generic drugs, but this makes up only 23% of the total costs) represent society's "surplus" rather than industry's (35). In addition, a recent report by IQVIA published in October 2021 suggests that the majority of countries are converging to a position where they spend approximately 15% of their total health budget on pharmaceuticals, indicating the impact of biosimilars, generics and reference pricing is in effect (36). Regarding MEA implementation however, the administrative burden on collecting data and monitoring uptake to inform the conditions that may accompany an MEA are such that changes to the usage or pricing of a technology are the exception rather than the rule (37). Some agencies argue that the maximal value may lie in more appropriately directing the use of technology initially (either through restricting access or finding a cost-effective population subgroup) rather than investing heavily in pricing negotiations and overly complex MEAs. A new concept gaining some traction is whether a new technology could be introduced with a "certainty bonus" or "uncertainty discount" according to the robustness of the evidence base; this was also highlighted at the 2021 GPF.

One recent example dynamic pricing in action is with the real-world monitoring of immunotherapies for cancer in Taiwan. Two pathways were announced for high-cost medicines; MEAs or a set of general rules for reimbursement submissions that allows an access period for patients while real-world data (RWD) are collected. Through this latter pathway, the list price was paid for 3 immunotherapies (atezolizumab, pembrolizumab and nivolumab covering 8 diseases/10 indications) and data on progression free and overall survival was collected through a patient registry that was established (38). The prices are now

being negotiated based on the comparison of real-world to clinical trial results, with significant price reductions possible.

Some formalised systems do exist for post-assessment monitoring, such as the Cancer Drugs Fund in the UK and the soon to be launched Innovative Medicines Fund (IMF) for non-cancer drugs. The IMF will be a fixed budget that will aim to allow for additional studies/data generation to resolve clinical uncertainty in a relatively short timeframe. Given the criteria for ILAP (see Table 3), it is conceivable that this will be a route that many ILAP technologies end up taking. Other countries, such as Germany (with its "testing trials" for medical devices) and, in the interviews, it was reported that the Netherlands and South Korea are establishing systems where public funds can be used to set up registries, studies or trials for certain technologies that require ongoing monitoring and additional evidence generation following a HTA. Many HTA agencies also reported closer working relationships with (academic) research institutes; providing more direct links for answering research questions that arise during HTA to institutes that may be able to answer them in a non-conflicted way. Challenges however with defining clinical outcomes and aligning the differing remits, perspectives and funding models for academic institutes remain to ensure that the questions that payers and health systems need answering are explored.

One example of HTA agencies becoming more involved in this space is the Post-Market Drug Evaluation (PMDE) Program that CADTH will launch in September 2022. The program will build upon the previous Drug Safety and Effectiveness Network (DSEN) program and leverage CADTH's knowledge of the pharmaceutical life cycle and relationships with federal, provincial and territorial decision-makers. The PMDE program will establish a network of Canada's expert applied researchers, methodologists, and data analysts to deliver credible and timely evidence to meet the post-market drug safety and effectiveness needs of Canada's decision-makers. Finally, consideration is being given to whether MEAs can be discussed much earlier in the HTA process (for example during an early dialogue phase) to "ready the system" and ensure that studies are planned well ahead of time rather than designed hastily at the post-HTA pricing/negotiation stage. If earlier MEA negotiation could be incorporated into HTA discussions and recommendations, it could enable more feasible MEAs, potentially reducing the time to patient access. ***Pricing has not historically changed based on post-HTA assessment activities; however, are there learnings or considerations (such as with the Taiwanese immunotherapy example) that could still be developed and shared across these settings? Could the details of data collection within an MEA (rather than the pricing itself) be disclosed and discussed earlier to aid global collaboration and data sharing?***

Health Technology Reassessment

There is currently little consistency globally with respect to the use and timing of HTR. Some countries conduct formal HTR at set time points (although this seems to be less common) and an increasing number conduct HTR if 'triggered' either proactively through forecasting and monitoring of treatment paradigms or reactively through experience or events (39). Flexibility in the approach to HTR with clearly defined objectives was mentioned during the interviews as being a critical component. For example, HTR might be relevant in the case of new comparators, changes to the treatment landscape (for example a new combination) or move from use of technology as a second line treatment to primarily a first line treatment, through to changes in treatment duration and emerging knowledge about adverse effects. Questions about how the technology is used in practice (and by whom) compared with what was expected in the HTA is critical for HTR and as such administrative data and pricing information are often needed (40). From the responses gathered through interviews, most HTR occurs when a significant

change; particularly a broadening of the patient population is expected. The possibility of using HTR as a mechanism to also conduct quality improvement for HTA agencies themselves was also raised; that is, using HTRs as a way of reflecting on the HTA processes and methods that were used to determine if anything could have been conducted more effectively and efficiently.

As mentioned, HTR of individual technologies becomes complex and intertwined (for example in oncology there are multiple lines of individual and combination therapies, surgical and other approaches) and as noted in previous GPF conclusions, development of clinical guidelines covering treatment pathways with broader disease lenses may be more practical than HTR of individual technologies. These clinical guidelines could be developed as "living" documents that promote the concept of a learning healthcare system informing the appropriateness, affordability and accountability of health technologies. Methodological advances in disease modelling, as well as approaches to combining randomised controlled trial (RCT) information and RWD are also happening in parallel; for example, the online Covid-NMA initiative between the World Health Organization and Cochrane (https://covid-nma.com) that is an open, real-time, centralized curation of clinical data, combining international data from RCTs with RWD. Additionally, techniques such as value of information analyses (currently used to inform where more research could be of value following an initial HTA) could theoretically be used to direct where a HTR or additional research would be warranted. To date, however, no agencies have reported using this type of analysis in this way.

Given that there is little consensus about the concept of HTR, there is unsurprisingly no agreement on how frequently HTR should be conducted. In some countries (such as Italy), technologies can be reviewed multiple times over their lifecycle until the HTA body and/or the manufacturer request that it be removed from future HTRs. There currently is little clarity on the point at which the value of a technology has stabilized such that a HTR would not be warranted. Theoretically, HTR could be possible until a technology becomes either passively or actively disinvested from a health service. ***Given the resources required to conduct HTR, can more be done to collaborate with other jurisdictions to share data, learnings and findings about technology use in practice? Can HTR be better linked with initial HTAs in the same clinical area (perhaps in different countries)?***

Disinvestment/Optimization

None of the agencies interviewed routinely conduct active disinvestment activities, with negative connotations highlighted and concerns around the language often employed such as cost savings and withdrawal of services. There are some countries (such as Malaysia) are considering exploring it in the future and there are some historical examples of disinvestment activities (41), (42). Some agencies, by law, cannot conduct active disinvestment (for example in Germany, direct evidence of harm is required to disinvest in a technology, which would be unethical to obtain in a randomized way if harm is suspected). Most agencies instead refer to the "optimization" of existing technologies (restricted use to a very targeted subgroup of the candidate patient population) without removing the technology from the health system completely. All agencies agreed, however, that in any HTR or possible disinvestment activities, involving key stakeholders (such as patients, clinicians and payers) was critical and some industry responses suggested that optimization of technologies and redundancy of older technologies happens naturally in clinical practice, as evidence and clinical guidelines emerge. It was noted that early access is freely discussed and encouraged but there is very little discussion around early or managed exits of technologies from health systems. Entry evidence requirements seem to be reducing but the bar for exit from the market continues to be set higher, with it seemingly almost impossible to actively

disinvest in some countries due to public resistance or legal restraints. There of course will be natural attrition from older technologies as new technologies are brought to market, and there are some national initiatives looking at appropriate care and reducing harms and variation in practice. However there appears to be little formalization, standardization and monitoring of this end of the technology lifecycle at present.

The conundrum of paying for more innovative and increasingly expensive new technologies without active disinvestment was highlighted. This is a particularly acute "pain point" for the payers within a healthcare system who have to balance the needs of patients wanting the "best" new technologies coupled with access to all possible choices of treatment. There are a range of examples of mechanisms to effect disinvestment in cost-ineffective technologies from health-related fields (although not specifically HTA). Organizations such as the Lown Institute in the United States publish reports on the most cost-efficient hospitals in America (https://lowninstitute.org/), and the international 'Choosing Wisely' initiative aims to identify low value care and facilitate open conversations between patients and their doctors. Implementation is challenging, however, and alignment with HTA recommendations and clinical guidelines is variable.

One promising avenue for HTA comes from Knowledge translation (KT), an evolving field that is defined as a dynamic and iterative process that includes the synthesis, dissemination, exchange and ethically-sound application of knowledge to improve population health, bridging the gap between "what we should be doing" and "what we are actually doing" (13). It has been suggested that KT frameworks could also provide guidance to improve the uptake of evidence-informed policies and recommendations resulting from the process of HTR (43). ***The role of HTA agencies in this space is also a key question; where does the remit of HTA agencies end and that of the health system begin? In resource-constrained environments is active disinvestment by HTA agencies possible or is passive disinvestment and reduced pricing sufficient to make funding available for new technologies?***

Key Related Themes Discussed by the GPF

Many previous HTAi GPF meetings have discussed elements of lifecycle activities and approaches. Reviewing the previous conclusions (see Table 5 of the Appendix), supplemented with the literature review and stakeholder interviews, the following key themes have been identified: collaboration; data generation; frameworks/criteria; resourcing; stakeholder engagement; transparency/predictability. While each of these key issues are highlighted in turn below, it is acknowledged that the themes should not be considered as "stand alone" issues but in relation to each other during meeting discussions.

Collaboration

Collaboration can be considered in multiple ways, such as within and between HTA agencies and between HTA agencies and other health system stakeholders (including but not limited to regulators, patients, clinicians, payers, manufacturers, policy and health systems). Criticisms of collaborations are that they can be slow and ineffective, however there are several international multi-stakeholder initiatives that have recently launched.

One of the most important to note is the EU HTA Regulation, which follows the initial voluntary EuNetHTA initiative. Announced in 2018, with the text finalized in December 2021, the Regulation will apply a centralized HTA process from January 2025. Pharmaceuticals for oncology and ATMPs will be

brought in first with non-pharmaceuticals through a topic selection process initially. The following activities will eventually be conducted:

1. Mapping on emerging health technologies
2. Scientific consultations on the development of new products
3. Joint clinical assessments (pharmaceuticals and medical devices)
4. Voluntary contribution on non-clinical topics (e.g. economical, ethical, organisational aspects)

Alignment in the post-assessment space is less clear. However, it is expected that any country will be able to trigger a HTR. Examples of collaboration between other countries outside of the EU (such as between HTA agencies in Australia, the UK and Canada) are also becoming more common.

While there is a push for greater sharing across jurisdictions (for example on lessons learnt, processes, and clinical data), this is difficult with resource constrained organizations, and also problematic when the remits and decision-making processes as well as treatment paradigms differ across countries. Confidentiality is also a major potential barrier to collaboration, although development of codes of ethics and memorandums of understanding between jurisdictions are becoming more commonplace.

One possible area for collaboration could be around whether there can be better sharing of data/issues across countries that have staggered access/introduction of technologies. Greater collaboration in this space could enable jurisdictions to see effects of change within treatment landscapes (for example observing where first line treatment has shifted in one country) or where post-marketing monitoring in one country could help provide data to inform horizon scanning/early HTA in another country.

Data Generation

Lifecycle approaches, by their nature, require continuous data generation. Therefore, how data are collected is a key consideration. There have been well documented efforts to standardize outcomes (such as the development of core outcome sets for specific conditions and the subsequent Core Outcome Measures in Effectiveness Trials, COMET Initiative that brings together people interested in such development). The overarching intention of producing core outcome sets is to make it easier for studies to be compared, contrasted and combined as appropriate; and this is typically done prospectively (with defining common outcomes more challenging after evidence generation has commenced). This is particularly pertinent in the case of rare diseases, where evidence generation is challenging and combining data from multiple sources may be necessary and indeed beneficial. Methodological developments are also continually evolving, which can enable exploration of new approaches; such as the use of external control arms in a rigorous way (44). Evidence generation for emerging innovations in health care will be a priority topic for the Patient-Centered Outcomes Research Institute, for example (PCORI, personal communication).

The ethical context of what can be reasonably expected from patients once a technology becomes available within a healthcare setting (rather than in the context of clinical trial only) is important to consider (45). Once a technology becomes available/reimbursed in a health system, then enrolling patients into a clinical trial to receive the technology (which will necessitate multiple follow up timepoints with sampling and so on) becomes more challenging. This will most likely result in the use of observational studies, administrative data and registries as the main sources for obtaining data for HTR.

The use of RWD and RWE in HTA is also increasing generally (46) and as discussed in detail at the 2019 GPF on RWD and RWE (47), there is still ongoing debate about the use and appropriateness of RWD and RWE for decision making (48). Considering what the right research question is and whether there are opportunities for greater cross-country collaboration is important. Additionally, the role of digital health to gather data (perhaps in a way that will be less cumbersome for patients) is being explored, alongside the use of machine learning and artificial intelligence to gather and analyse data. Consideration of information tracked in these datasets is critical, as they may not have been designed to capture patient-centric outcomes. Separate capture of patient-reported outcomes will therefore grow in importance (49), (50).

Good data systems that enable data linkage across health systems are needed to facilitate lifecycle approaches. There are increasing numbers of countries where good registry and public health datasets exist (for example Canada and Israel were highlighted). Development of data lakes (huge storage repositories that can rapidly ingest large amounts of raw data) during the pandemic may have ongoing benefits if data are still collected, the systems and stakeholders (including patients) become used to the concept and better mechanisms for sharing data across stakeholders within and between jurisdictions are further developed. Privacy issues and access to data and data sharing however are likely to remain challenges in the context of lifecycle approaches.

Frameworks

Development of specific frameworks or criteria may be useful and could help facilitate and streamline the use of lifecycle approaches. For example, discussion around the following areas may have merit:

- acceptable evidence standards for HTA
- incorporation of patient and other stakeholder views and data
- formalised approaches to the use of RWE and disease models
- criteria for MEA implementation and monitoring
- understanding the pace of technology adoption
- triggers for HTR

As an example, the Green Park and CMTP Initiative on Alzheimer's disease (51) set some standards around what was acceptable and what the evidence requirements for HTA were; the major barriers to implementation of the standards were the data systems and lack of administrative capacity to support the recommendations; for example, around data collection on healthcare utilization and care partner outcomes (see case study in the Appendix). Non-profit organizations, independent of industry and HTA agencies may still play a major role in data sharing and development of frameworks.

Resourcing

Many HTA agencies face resourcing constraints not only in budgets but also through staff shortages and skills gaps, noting that different skills may be required to undertake activities at different stages of the lifecycle. In the post-COVID era, many HTA agencies are facing even more budget cuts and efficiency is critical. Conducting 'additional' activities is resource intensive and careful consideration should be given to whether these activities can be prioritized (for example, can they be focused on particularly innovative technologies or new methods of action?) During the interviews it was made clear that the HTA agencies do not want to do continuous evaluations of the same technologies at the detriment to assessing innovative technologies.

One option for resourcing lifecycle activities in a sustainable way is through a cost recovery model; whereby typically the manufacturer pays to cover the costs of staffing the activity. While this is in place across some agencies for some activities, others expressed concerns at the perceived or actual conflicts of interest that such a funding model could create. Other options suggested included greater collaboration and sharing of data and economic models, even "crowdsourcing" the ability to review the changes to cost-effectiveness estimates as data are generated (ICER communication). A new initiative called the Assess Project (The ASSESS Project) launching mid-2022 will take a similar approach with "an online, decentralized early HTA ecosystem powered by the token economy". Moving to more active disinvestment to ensure money is available for newer innovative technologies but also to pay for the lifecycle activities to support their introduction to health systems could also be theoretically possible. It was highlighted that during the COVID pandemic, teams had to "pivot" and rapidly produce evidence syntheses and HTA reports; are there lessons of efficiency related to resourcing that could be gleaned from this and transferred into "business as usual" as we transition to a post pandemic normal?

Stakeholder Engagement

Stakeholder engagement should be diverse and conducted early and iteratively (52), (53). However, alongside this is a need to reduce the burden on patients and other stakeholders to ensure that stakeholder input is structured, methodologically robust, relevant and not unnecessarily duplicated (54). Support for stakeholders is also required to ensure they can participate fully, but also as highlighted at the 2021 GPF, care must be taken to ensure communications around HTA are understandable to all (55). Early clarification of the role and remit of stakeholders may enhance input and engagement, coupled with shared practices on training and including stakeholders across jurisdictions (56). Many patients are not aware they have a voice until after the technology has come to market; better inclusion of patients in the development of technologies (identifying unmet needs and addressing what outcomes matter most to patients) and ensuring that their contributions are appropriately recognized are needed for robust patient engagement (57), (58).

There are also additional stakeholders that could be considered, such as lawyers (e.g., for patent or anti-trust waivers in certain circumstances), data stewards, registry administrators and citizens representing a societal perspective (59). In the future, key stakeholders may come from outside health altogether, with technology stakeholders (such as Google and Amazon) becoming more involved in the delivery of healthcare. For patients it is important to acknowledge that lifecycle approaches may mean that patients will have to sometimes wait while sufficient evidence is gathered or that technologies may be removed from health systems to make way for newer products. Inclusivity of stakeholders, however, can be met with hesitancy if the processes are unclear or previous outcomes have been deemed unfavorable; trust and confidentiality are therefore required to facilitate participation (60). Many health systems are very complex or decentralized with multiple invested stakeholders (61). This can result in resourcing constraints, additional time required and the need to carefully consider conflicts of interest (perceived or actual). There may also be a requirement for advanced skills in synthesizing numerous perspectives and data sources.

Transparency and Predictability

Transparency is a key principle for HTA, and there needs to be informal avenues for open discussions and building trust, through to more formalized opportunities. The Agency of Health Quality and Assessment of Catalonia (AQuAS) have set up an agreement on what is deemed confidential and the

discussions are guided by an ethical code that manufacturers sign up to. However, there is an abundance of caution in many countries, particularly those with less mature HTA systems, about perceived conflicts of interest and preferential treatment of manufacturers with whom you have the best working relationships.

There are clear challenges regarding anti-competition laws and commercially sensitive issues that make disclosing pricing agreements difficult, but it may be easier to come to agreement on disclosure of clinical data. This is an area that has not been explored by many HTA agencies to date; often the time to listing is the priority (with as close to product launch as possible determined in many jurisdictions); this will necessarily come at the detriment to being able to disclose and publish clinical data (which is likely still academic-in-confidence). In Australia however, the Pharmaceutical Benefits Advisory Committee (PBAC) have recently announced that clinical data submitted to and relied on by PBAC will not be redacted in public documents unless limited criteria are met. Other examples of transparency are in Germany where core elements of trials are agreed upon and published on the website (however data in study reports remains confidential).

Summary of Key Challenges and Opportunities

The key issues highlighted by the literature review, stakeholder interviews and previous GPF discussions relevant to a lifecycle approach to HTA are summarised in Table 4 below.

Table 4-Summary of key challenges and opportunities related to a lifecycle approach to HTA

Thematic Area	Key Policy Issues	Possible opportunities
Collaboration	-Resource constraints -Confidentiality concerns -Different jurisdictional contexts and remits	-Can collaboration be effectively targeted for priority areas and/or for technologies with multiple indications? -Monitor ongoing collaborations and share lessons learnt
Data Generation	-Assessing the quality of RWD -Ensuring the data are fit to answer the research questions -Ability to link and share data, particularly on rarer diseases (note privacy concerns) -Data generation and monitoring is administratively burdensome	-How can the data lakes and linkage projects/learnings from COVID be maximized? -Methodological advances -CORE outcome sets -Leveraging existing datasets and enhancements for quality
Frameworks	-Consensus building is challenging -Flexibility is often paramount	-Stronger role for independent not-for-profits in developing frameworks?
Resourcing	-Funding all lifecycle activities is not possible -HTA agencies often have to prioritize new technologies, close to launch -Skills and staff shortages	-‘Crowdsourcing’; i.e. using the public to update models -Exploration of industry funding (and management of conflicts of interest) -Explore public funding sources
Stakeholder Engagement	-Conflicts of interest (perceived or actual) -Burden on patients, clinicians to participate (and value for them) -Synthesising multiple viewpoints	-Increased communication between all stakeholders -Use of integrated knowledge translation frameworks and approaches

	-Negative connotations of disinvestment	
Transparency	-Commercial sensitivities from manufacturer perspective leading to limited data in public domain -Firewalls between advice and assessment teams (resource intensive) -Privacy concerns from patients	-Share data/patient input across disease areas (not specific technologies; develop FAQs) -Develop ethical codes of practice

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782 Two case studies are outlined in the Appendix to provide further context to the key issues highlighted.
783 The first is of the treatments for Alzheimer's Disease and the challenges experienced in older HTAs, as
784 well as the current debate around the recently-approved drug aducanumab. The second is of advanced
785 therapy medicinal products (ATMPs) with a focus on the possible impact on complementary evidence
786 collected pre-assessment, dynamic pricing, post-assessment monitoring, and other lifecycle activities in
787 HTA.

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Appendix

HTAi Annual Meeting 2022; Plenary Descriptions.

Plenary One

Adopting a Lifecycle Approach in HTA: Consequences for Priority-Setting and International Collaboration

HTA has recently been defined as

"a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system" (O'Rourke, Oortwijn and Schuller, Int J Technol Assess Health Care 2020; 36: 187 – 190).

Adopting such a lifecycle approach in HTA has a number of potentially far-reaching consequences. Rather than a one-off exercise to critically appraise and synthesize the best available evidence to support market access and coverage decisions, it involves several tasks and requirements which continuously need attention. Central, but not exclusive, is the careful monitoring of novel technological developments, the anticipation of their potential impact, and keeping track of their evolution, especially in terms of gaining or losing value as the result of (parallel) technological, epidemiological, economic, organizational and cultural developments. Hence, rather than focusing on individual technologies, a health system's perspective will be needed. Consistent consideration of the lifecycle will change the way research and policy interact and inform each other and affect the tasks of HTA agencies, both quantitatively and qualitatively. Diversification of methods will be needed, as well as a re-thinking of what constitute relevant data and how these may be obtained (e.g., is organizing continuous data collection combined with AI-supported analysis the key?). Appropriate scientific development and capacity building will be required and, because of an increased workload for HTA agencies, setting priorities and international collaboration and coordination will be needed more urgently. What could be the best path to follow winding through these challenges and opportunities associated with the adoption of lifecycle approach in HTA? Do adequate priority-setting and international collaboration and coordination help? This plenary will try to find out.

Plenary Two

Public Confidence in Healthcare Decision-Making

The legitimacy of healthcare decision-making has never been so fiercely debated as in the COVID19 pandemic. The pandemic has highlighted significant differences between public worldviews, including populations who are skeptical of science and distrust governments and health systems. Within this climate, HTA depends on public confidence for its funding and the implementation of its recommendations or advice. For its credibility and legitimacy, its processes should be seen as fair and transparent. But HTA is typically only seen by a small subsection of the population who have an interest in its assessments. Even among the many stakeholders who may experience consequences from HTAs, the process may not be visible resulting in misunderstandings or distrust about whose interests and values are being considered or prioritized.

Integrating stakeholders' perspectives in HTA – either through evidence or participation – may play a role in improving public confidence in HTA by fostering openness and transparency and increasing the

relevance of HTA recommendations by ensuring they are informed by stakeholders. Despite many years of research to develop the field, in most jurisdictions its use and impact in HTA is unclear, and its relationship to scientific rigor is unresolved. The task remains challenging. How should stakeholders' perspectives be integrated transparently? How can competing needs and claims be managed? Which types of stakeholders are not included and what are the consequences of this lack of inclusivity? What does public confidence look like, how should it be measured and to what extent can it be achieved?

A lifecycle approach promises opportunities to address the disconnect between stakeholders, but may also increase the number and diversity of stakeholders and their perspectives as HTA collaboration crosses jurisdictions and assesses and reassesses value in different settings and cultures. Amongst this potentially increased diversity of world views, can shared values be found to support public confidence? What processes can support the continuous dialogue imagined among stakeholders in a lifecycle approach? Will processes to integrate stakeholder perspectives support wider confidence in procedural justice? Who will agree the priorities? How will power differences be managed?

Since its conception, HTA has invested heavily in developing robust processes that can stand the test of scientific scrutiny and peer review. But the pandemic has highlighted that scientific rigor is not synonymous with public confidence. Elements of the public, including some stakeholders, may have no awareness or connection to the scientific principles, processes, methods and institutions esteemed in the HTA community. HTA may be able to determine the value of health technologies from pre-market approval to disinvestment, but can it find the shared values necessary to foster and maintain public confidence?

This plenary will explore the nature of public confidence and how it might influence how we reconceptualize HTA's place in the lifecycle and our societies. It will elicit different stakeholders' experiences of integrating perspectives in HTA and challenge the community to take a critical view of HTA's contribution to public confidence in health and science.

Plenary Three

Running Around in Circles; Time for Real Collaboration between Regulators, HTA Bodies and Clinicians.

Regulators, HTA bodies/payers but also clinicians and their guideline organizations, may provide recommendations regarding (cost-)effectiveness of health technologies that have a large influence on the access to these technologies. Their recommendations may not always closely align which might lead to hampered and delayed access to these health technologies and uncertainty for patients. However, the remit of those organizations may vary to a large extent over the lifecycle of a health technology. To what extent do we wish for more alignment of their recommendations, for instance, if the same data are used to evaluate clinical effectiveness? Or do we value the different roles of those stakeholders to ensure a cautious balance between quality, affordability, and accessibility of healthcare? How do innovators that develop new health technologies experience these different roles of those stakeholders and see their differences as barriers or enablers for their innovations to come to patients?

This plenary will also include a discussion on the role of clinical practice data to improve our knowledge on the effectiveness and cost-effectiveness of health technologies, such as pharmaceuticals, medical devices, and digital health (including AI) and how different types of data and evidence can be efficiently collected, used, and shared between those stakeholders at the different stages of the lifecycle. In the

plenary, specific disease areas in which the collaboration on the collection and analyzing of data may be flourishing such as cardiology, oncology (ATMPs such as CAR-T) and rare diseases, maybe highlighted. Further, emphasis may be placed on therapies approved through accelerated regulatory processes or with coverage with evidence development requirements.

The following topics will be specifically addressed in the plenary:

How are different types of effectiveness evidence perceived by regulators, HTA bodies/payers and clinicians over the lifecycle of health technologies?

What are experiences in terms of interaction between regulators, HTA bodies/payers and clinicians and how could these be implemented for different types of health technologies such as medical devices and pharmaceuticals?

How do other stakeholders such as innovators and patients perceive this interaction between regulators, HTA bodies/payers and clinicians, what is in it for them in different settings around the globe?

This third plenary will explore the impact of regulators, HTA bodies and clinicians on the quality and efficiency of healthcare by focusing on their clearly laid out roles, their interaction and alignment of their processes. It will use the experiences of innovators and patients to assess this impact and the interaction of these regulators, HTA bodies and clinicians.

Lifecycle Activities Currently Conducted by HTA Bodies and Supporting Organizations

HTA Body, country (focus)	Horizon Scanning	Early Advice (+/- regulators)	Monitoring (including MEAs)	Reassessments	Disinvestment	Comments
AIFA, Italy, (pharma)	Yes – horizon scanning office within the regulatory approval department. They collect information fro m the authorization process and other sources. Knowledge about new drugs (not full reports) can be shared within AIFA easily without confidentiality concerns.	AIFA were one of the first European agencies to conduct HTA joint scientific advice with the EMA in 2010 however national HTA activities have stopped since COVID. Scoping phase on optimising the evidence dossier with manufacturer introduced by law in 2020 (not yet implemented).	A monitoring registry system is in place for any technologies that have clinical or financial uncertainty surrounding their usage. Manufacturers participate in the registries for a fee.	AIFA and the manufacturer agree on conditions of usage which is valid for 24 months (shorter by exception). Reviews conducted periodically, in particular for drugs with MEA in place or that are on the monitoring registry system.	Optimization rather than disinvestment (though have had some examples of disinvestment due to poor efficacy).	AIFA has adopted a lifecycle approach since it was founded in 2004. AIFA is responsible for all pharmaceuticals for human use in the Italian health system; this includes regulatory authority in Italy, HTA through to post-HTA monitoring. There is a link between regulation and HTA with the same clinical experts responsible for the regulatory dossier and the clinical components of the HTA.
CADTH, Canada (pharma and devices)	The CADTH horizon scanning program identifies new and emerging health technologies	Yes – CADTH has offered early scientific advice services on study design since 2015. Service offerings include CADTH-only	CADTH is positioning itself to launch a post-marketing drug evaluation program with a pan-Canadian data network for Sept 2022. The network will respond to queries by generating	Medical Devices: Both proactive and reactive reassessments are conducted. Topics are prioritized if there is pan Canadian potential	Medical Devices: Yes, with a focus on optimization rather than disinvestment. Disinvestment is passive, through recommendations	CADTH formally adopted a lifecycle approach to HTA as one of the three pillars in its strategic plan for 2019-2021 This included a commitment to initiatives across the health technology life cycle that will

	likely to have a significant impact on health care in Canada. CADTH scans and monitors various health information sources to identify promising technologies – devices, procedures, diagnostics, and other health interventions – that are within one to three years from being licensed in Canada or in the early days of use in Canada.	advice or parallel scientific advice with Health Canada or with NICE.	evidence for federal and provincial decision makers. CADTH also has an active drug HTA program which responds to jurisdictional queries and examining topics such as comparative clinical effectiveness, utilization, and health policy	for impact and ability to influence patient important outcomes, and/or equitable access to care. Drugs: CADTH has a suite of reassessment processes that are tailored to address the complexity of the decision problem: (1) single drug reassessments evaluate potential changes to reimbursement criteria based on new evidence and/or changes in contextual factors; and (2) multiple drug reviews are undertaken when there is a need to reassess the place in therapy and/or reimbursement criteria based on new comparative	to enhance uptake of other comparable technologies. Drugs: A recommendation to disinvest is one potential outcome of the CADTH reassessment processes. Renegotiation of reimbursement criteria would be a more common result of the reassessment process.	improve access, appropriate use, and affordability.

				effectiveness and cost-effectiveness information.		
HIQA, Ireland (devices)	Topics are suggested annually by the Department of Health and the Health Service Executive (national health and social care provider). Scoping documents are developed and topics prioritized informed by advice from a prioritization group which includes policy, service and patient representation, Topics may be prioritized for either full or rapid HTA.	Planning to do some early engagement type activities next year with the Department of Health to better educate policy makers about the process and benefits of HTA.	No.	Conducts follow-up HTA where the population may warrant expansion (for example where an age bracket for cancer screening is widened).	Disinvestment is passive; typically technologies are naturally phased out as they are superseded by new technologies.	HIQA assess non-pharmaceuticals, including vaccines, surgical procedures and public health programs (including programs that have ethical and organisational implications).Medicines may be included e.g. review of smoking cessation interventions; HTAs for reimbursement decision making are not undertaken by HIQA.

National Centre for Pharmacoeconomics (NCPE), Ireland (drugs)	Yes - acts mainly as work planning function.	The NCPE have a face-to-face meeting with drug manufacturers before they submit evidence dossier to explain what they would like to see presented.	Use of drugs is monitored by the Medicines Management Centre (a linked, but separate, team) and may issue refined guidance on best usage. MEAs are not common in Ireland.	This may happen if the company wishes to submit new evidence.	Disinvestment is passive; typically technologies are naturally phased out as they are superseded by new technologies.	Pharmaceuticals, and occasionally vaccines and diagnostics are considered by the National Centre for Pharmacoeconomics for reimbursement. Both the NCPE and HIQA work closely together.
Scottish Health Technologies Group (SHTG), health Improvement Scotland (HIS), Scotland, UK (devices)	Not routinely – SHTG used to undertake a horizon scanning function, but less so now and relies on partnership working in Scotland to identify key technologies.	Yes, SHTG is involved in the IDAP pilot with NICE, Wales and MHRA. SHTG produces innovation overviews, and seeking to move further into the 'early HTA advice' stage of the pathway.	No – currently seeking to explore the utilization of Scottish patient data for monitoring.	Not routinely (see also the comments). There are a few examples where devices have been looked at more than once (e.g. TAVI)	Not routinely (see comments)	SHTG is a small team and so relies on a referral process to consider topics on a case-by-case basis and according to priorities in Scotland. The process is open to reassessments and disinvestment-related questions which are considered alongside competing priorities. SHTG has developed a process for adapting HTA guidance to reduce the burden of evidence gathering.
Scottish Medicines Consortium (SMC), Healthcare Improvement Scotland, Scotland, UK (pharma)	Yes; SMC have conducted horizon scanning for many years (member of UK PharmaScan)	Yes- partner in the ILAP with NICE, Wales and the MHRA.	Not typically; once advice issued then SMC do not monitor or re-visit. For medicines in the ultra-orphan pathway, SMC makes an initial assessment then there is use within the system	Reassessments will take place for medicines in the ultra-orphan pathway and or medicines accepted using the interim acceptance decision option (conditional marketing	No	As above

			with a 3-year data collection plan.	authorization or ILAP/EAMS). Medicines not recommended by SMC can resubmit for reassessment.		
Health Intervention and Technology Assessment Program (HITAP), Thailand (drugs, devices and public health)	No- all topics to be evaluated by HITAP are nominated by relevant stakeholders through a systematic and transparent process organised by decision making bodies such as the national drug committee or the Universal Health Coverage (UHC) benefit package committee.	HITAP is working with Thailand Science Research and Innovation (which manages all public research budgets) to set priority for health R&D using early HTA. HITAP gives advice to the Thai FDA upon request on product registration (the past examples include HPV vaccines, HIV oral test).	HITAP conducts real-world safety and effectiveness studies for products conditionally approved to be part of the Thai UHC benefit package using HTA (approval with evidence development condition). See example https://pubmed.ncbi.nlm.nih.gov/30069864/ https://pubmed.ncbi.nlm.nih.gov/30922350/	HITAP carry out reassessment of products with good potential (to be part of the public health plan) but not be approved for reimbursement. However, there is no formal criterion for reassessment. Relevant stakeholders can submit the topics for reassessment through the process mentioned in the first column	Disinvestment is always part of HTA conducted by HITAP. Most recommendations on new technologies will offer recommendations on whether to disinvest in the current/existing technology/intervention. There are a few studies focusing on disinvestment in the past.	HITAP has adopted a lifecycle approach since it was founded in 2007 with the more emphasis on the late stage of technology lifecycle i.e. policy implementation at the beginning of HITAP's establishment and now moving toward the beginning of technology lifecycle i.e. early HTA. This is partly because the Thai government is investing on health R&D. Moreover, HITAP is supporting HTA capacity building for other LIMCs and that our approach may influence other HTA systems in the region (see example https://pubmed.ncbi.nlm.nih.gov/29333249/.
Health Technology Wales (HTW), Wales, UK (non-pharma)	Yes – early identification of technologies is within the remit of HTW. Co-located with and works closely with	Yes – involved in IDAP with NICE, Scotland and MHRA. Offers a scientific advice service to technology developers to	Yes – status of guidance is "adopt or justify" with an expectation that the guidance is implemented. An annual adoption audit is undertaken on	Yes – review of extant guidance every 3 years with reassessment undertaken if requested and if new evidence is available that is likely to	In remit however no explicit disinvestment topics undertaken to date. Currently exploring	HTW was established in 2017 to provide a strategic and nationally coordinated approach for the identification, appraisal and adoption of medical technologies across Wales.

	Welsh life sciences industry and associations. HTW also accesses the GB wide HealthTech Connect platform www.healthtechconnect.org.uk that encourages innovators to register their products and receive support from GB HTA agencies.	assist them to develop their value propositions and evidence case for adoption.	agreed metrics with each local health board (n=7) with results reported to the Minister of Health.	materially alter the national guidance	potential for a disinvestment call in partnership with key bodies – e.g. the Welsh Value in Health Centre.	
Institute for Clinical and Economic Review (ICER), United States (drugs and devices)	Yes – have two staff members that conduct horizon scanning and ICER conduct internal meetings for topic selection and broader horizon scanning.	No, but have developed guides for manufacturers available online	Yes, and have ICER analytics that enable members of the public to make changes to economic models based on updated pricing/treatment effects	"Lean team" involved in HTR; the primary focus of ICER is to influence technology pricing at the time of product launch	Active disinvestment not undertaken, though opportunities during scoping for stakeholders to comment on areas for disinvestment that could be included as part of the normal	Given the role and remit of ICER and the American health system, there are currently limited opportunities for ICER to conduct lifecycle activities (particularly from a resourcing perspective). The team are looking for ways in which some of these activities may be possible in a "crowd-sourced" model with academia and the public.

					assessment process.	
IQWIG, Germany (pharma and non-pharma)	IQWiG has no role in horizon scanning (some of this is done by the G-BA)	IQWiG has no role in scientific advice (this is done by the G-BA)	i) Comparative observational data collection by the manufacturer can be mandated for specific drugs (orphan drugs and those with con-ditional approval or approval under exceptional circumstances). ii) Trials on non-drug interventions can be publicly funded to answer key research questions post HTA ("testing trials").	Re-assessment when i) data collection on drug or ii) trial on non-drug intervention is completed.	No (but candidate topics may be selected by the G-BA); by law need active evidence that the treatment is not working and/or harmful. This would likely necessitate a trial to prove this which would not be considered ethical.	Involve patients from the beginning of the HTA; very few exceptions due to commercial sensitivities, e.g. when assessing manufacturers' applications for "testing trials"
MAHTAS, Malaysia (pharma)	Yes; have been conducting horizon scanning since 2014 (pilot) and launched 2017. Priority is local innovation and to identify expensive technologies.	New "sandbox" for emerging technologies; facilitate regulatory approval. Not large scale advice with manufacturers; case-by-case basis on request from manufacturer or researcher.	Monitoring of uptake and MEA is done by the Pharma Services Division (a separate unit within the Department of Health)	Conduct reassessment if requested by clinicians or policy makers; the pharmacovigilance monitoring data collected by the Pharmaceutical Regulatory Agency will be reviewed.	Currently strengthening the reassessment team and plan to explore active disinvestment in the near future	MAHTAS also develop clinical practice guidelines that contain "do not do" recommendations. Patients not typically involve ed in the pre-assessment activities; clinicians and health system and payers are. Patients are involved at the HTA and clinical guideline development stages.

National Evidence-based Healthcare Collaborating Agency (NECA), South Korea (Medical procedures with devices and pharma, clinical guidelines)	Yes – member of EuroScan since 2013; new "special track" HTA process for innovative devices and procedures and horizon scanning is now linked to this too.	Yes – Early advice between NECA, Korean FDA and HIRA (payers) for device manufacturers. Companies choose if they take the advice.	NHIS (insurer) and HIRA (review & assessment agency) do manage RSA for pharmaceuticals. Ongoing discussion about RWD/RWE for NHI decision making in HIRA. Support evidence development through CER with public funding if there is a clinical unmet need.	HTR program has been tried for several medical procedures in National Health Insurance. There is a process for assessing "preliminary coverage" between NECA-HIRA; a kind of Coverage with Evidence Development approach.	No	Korean FDA want to set up more proactive post-marketing surveillance with RWE in collaboration with academia (CDMs are under development). National insurance have claims (utilisation) data; not as much data on patient outcomes. A trial is underway to build up national health data system (My healthway) connect clinical data with claims data but are working through privacy concerns.
National Institute for Health and Care Excellence (NICE), England (pharma and devices)	Yes – NICE works with the NIHR Innovation Observatory, is a member of UK PharmaScan and has Healthtech Connect for devices.	Yes – NICE has offered scientific advice services since 2010. Services include joint scientific advice with partners including the UK MHRA and other HTA agencies.	Yes – working with the NHS, NICE monitors MEA activities for several products, including those in the Cancer Drugs Fund. Similar activities are expected in the anticipated Innovative Medicines Fund.	Yes – NICE prioritizes reassessment where there is a likelihood of new clinical and/or economic evidence changing the recommendations.	No	As a partner in the UK ILAP, lifecycle activities are likely to become more important to NICE.
Pharmaceutical Benefits Advisory Committee (PBAC)/Medicare Services	Yes – but currently not done in a systematic way.	Yes, but advice given to applicants largely at the pre-submission stage (rather than study design phase).	Yes – listings on the pharmaceutical benefits scheme (PBS) and Medicare Benefits Schedule (MBS) are routinely monitored for actual	Yes. There is a formal "post-market review" process for all listings. The main drivers for reassessments are the committee	Technologies can be disinvested if this is determined by reassessments.	A broad range of technologies are considered by the committees PBAC and MSAC with support from the Department of Health.

Advisory Committee (MSAC)/Department of Health (pharma and devices), Australia		Details for applicants are available on the websites.	utilization versus predicted. Monitoring for any other purpose is on an as-needs basis.	request and/or evidence of differing actual utilization than was predicted.		
Dental and Pharmaceutical Benefits Agency (TLV), Sweden (drugs)	Horizon Scanning in Sweden is made by the Regions (especially the four biggest ones).	Yes (but with limited resources)	Sweden has a number of registries and national data sets used for monitoring. MEAs can be found between the regions and the companies but not by TLV.	HTR has been part of TLV's remit by law since 2002. Since 2010 they are mainly done in drug classes with more than one off patent treatment option but still without competition.	No	Evidence generation is increasingly important for TLV and the Swedish regions (payers) and can potentially contribute to better evidence both at first assessment (historical data sets etc) and in later phases (RWD studies etc)
The National Health Care Institute (ZIN), The Netherlands (drugs and devices)	Yes; also involved in European horizon scanning efforts	Yes (limited numbers) direct with manufacturer	A trial of publicly funded trials to address specific research questions is underway.	Yes; used to be time-based trigger (e.g. after 4 years) but considering a more flexible approach	No	ZIN have stated (not yet public) they want to develop lifecycle approaches. The responses obtained were mainly in relation to pharmaceuticals but they are actively considering how to apply the same principles/activities in the devices space. ZIN believe that flexibility is critical.

Previous Policy Fora Recommendations/Conclusions

As mentioned, the GPF have previously considered elements of lifecycle activities during past meetings. The key conclusions from relevant GPF meetings conducted since 2007 are included in the Appendix. Within this summary, it is clear that many recurrent themes during the lifecycle have been raised (as highlighted in the table in yellow). A word cloud of the most commonly repeated terms has been generated (see Figure 5)

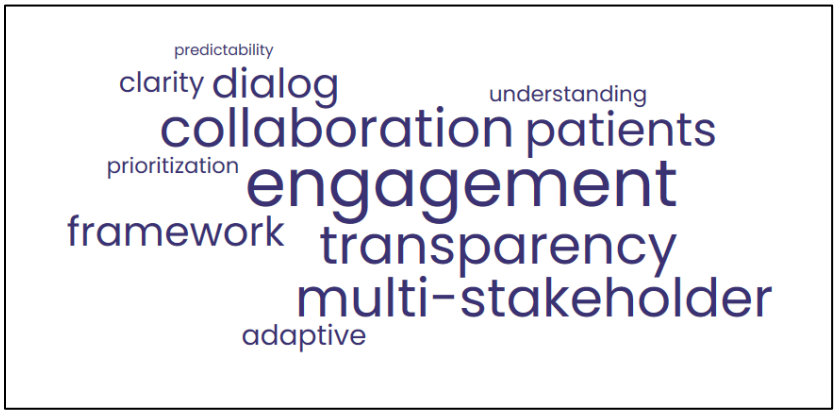

Figure 4- Word Cloud generated from Key Themes from Previous Policy Fora

The intention is to not repeat and return to any of these topics in detail during the 2022 GPF discussions but for GPF members to draw on these resources as required.

Table 5- Summary of Previous GPF conclusions

Topic, Year	**Key Recommendations/Conclusions suggested (from IJTAHC article)**
Considering and Communicating Uncertainty in HTA	-Utilisation of a life cycle/HTA management approach helps manage uncertainty -Genuine stakeholder input and engagement (and not just consultation) can clarify uncertainty - Tolerance of risk, the relationship of risk to uncertainty, and the context in which uncertainty is considered is critical -Transparent and early dialogues could be increased to further reduce the uncertainty during HTA -Communicating uncertainty in HTA outputs is critical.
Deliberative processes, 2020	-Transparency; there should be sufficient information and guidance available prior to and following the deliberative process to allow any interested person to understand the decision and all factors. -Inclusivity: committees are composed of enough people so that they have the relevant knowledge and skills and character required; the process of selecting committee members is clearly described; stakeholders are supported to make robust decisions and included; views of stakeholders are genuinely considered and responded to; deliberative environment is facilitated to avoid power differences; interactions are respectful; deliberations are made as public as possible. -Impartiality: All people involved understand role and responsibility; clear description of CoI and declaration format; chair manages the discussion to achieve equitable input and prevent undue influence of their own opinions

Real-world evidence, 2019	-Create a common understanding regarding the types of HTA questions RWE is appropriate to answer -Develop common data models and quality standards for RWD/RWE -require full transparency of stakeholders in the process of generating and analyzing RWD -increase collaboration with organizations that are capturing and analyzing RWD, including groups outside the traditional HTA community and health sector -Develop good practice on multi-stakeholder data ownership and management -define what data can be shared between HTA agencies and regulators -Create a global directory of accredited sources -establish an ethical framework for collecting and using RWD -develop an international cross-country (governance) framework, sharing PICOTS and conducting multi-country pilots -define meaningful patient related outcomes to allow replication and cross-validation -promote data collection in clinical settings -Engage with relevant stakeholders, especially clinicians and patients -develop capacity and methods to analyze RWD and RWE -HTA to act as information brokers; create effective collaboration between industry, payers and other relevant stakeholders in the development and use of RWE -HTA community to become influencers; instruct technology developers as to what data is needed
Horizon scanning, 2018	-The end user(s), their needs, the time horizon, purpose and scope of horizon scanning needs to be more clearly defined -horizon scanning systems need to identify unmet needs in order to drive innovation -horizon scanning systems should focus on disease and/or care pathways (instead of individual technologies) -horizon scanning needs to include all relevant stakeholders at an early stage -use of smart data systems and international collaboration can improve the efficiency of horizon scanning
Value frameworks, 2017	-create clarity between what constitutes value of health technology versus values of the decision-making process -Define the core components of a value framework for assessing the value of a health technology, using the HTA Core Model as a starting point -Use both quantitative and qualitative methodologies to appropriately address different diseases and/or health technologies -Value frameworks should adhere to the principles of transparency, predictability, broad stakeholder involvement and accountability along with being forward looking, explicit and consistent across decisions -decision makers have a responsibility to clearly state the rationale and detail behind the application of value frameworks to make a decision.
Changing HTA paradigms, 2016	-Five broad areas of change (engagement, scientific dialogue, research prioritization, adaptive approaches, and real world data) were identified. -re-thinking scientific dialogue and multi-stakeholder engagement -re-thinking value, affordability, and access

	-Earlier and ongoing engagement to steer the innovation process and help achieve appropriate use across the technology lifecycle was perceived as important but would be resource intensive and would require priority setting. -Patients need to be involved throughout, and particularly at the early stages. -Further discussion is needed on the type of body best suited to convening the dialogue required. -Enhanced horizon scanning could play an important role in preparing for significant future investments. -Questions remain as to the most appropriate role for HTA bodies.
Evidence production, 2015	-HTA must be independent and objective, but it needs to develop more agile and adaptive processes that help to broker alignment among technology developers and health systems (including healthcare professionals and patients). -HTA needs to innovate and be prepared to play a more active role to influence evidence production and help facilitate dialogue among stakeholders to optimize technology development and use (HTA 2.0). -HTA needs to help facilitate dialogue among stakeholders over the life cycle of the technology to develop a shared understanding of evidence requirements to demonstrate value and enable rapid decisions about use of technologies. -Technology developers can improve dialogue by explaining the scientific rationale underpinning the creation of a technology, providing a clear overview of information available, and posing clear questions to HTA and coverage bodies about future evidence requirements and approaches to value determination. -Those involved in the wider health system such as patients, clinicians, and managers should be encouraged to contribute to this dialogue to help clarify unmet needs, quantify risks, determine value, and ensure rapid adoption of effective technologies. -All stakeholders need to engage in a discussion about the development of this new collaborative approach to health innovation.
Adaptive approaches to licensing, 2014	-need to define the goals of and to set priorities for adaptive approaches -examine evidence collection approaches; to clarify the roles and responsibilities of stakeholders; -to understand the implications of adaptive approaches on current legal and ethical standards -determine costs of such approaches and how they will be met -identify differences in applying adaptive approaches to drugs versus medical devices. -importance of recognizing and including a full range of stakeholders as contributors to a shared decision-making model implicit in adaptive pathways in future discussions on, and implementation of, adaptive approaches.
Value-based decision making and innovation, 2013	-development of a general framework for the definition and assessment of value -development by HTA/coverage bodies and regulators of disease-specific guidance and further joint scientific advice for industry on demonstrating value -development of a framework for progressive licensing, usage, and reimbursement -promoting work to better adapt HTA, coverage, and procurement approaches to medical devices.

"Disinvestment", 2012	-*Health system leaders, politicians, clinicians, HTA bodies, organizations, and experts, and industry* should work together to explain to patients and the public the importance of reassessment and optimization -*Health system leaders* should: ensure they have processes and incentives in place for ongoing reassessment and optimization, with clear and transparent governance arrangements and appropriate stakeholder involvement; resource appropriate HTA systems; draw on HTA expertise and advice when conducting ad hoc reviews of technology use in response to budgetary pressures. -*HTA systems and bodies* should: work with clinicians, patients, the public and industry in work to reassess and promote optimization of technologies in routine use; Work with decision makers to identify candidate technologies for reassessment and optimization using explicit criteria; where possible, anticipate requests for advice on technology optimization; strike an appropriate balance between rigor and speed, taking account of the specific challenges described above; work with decision makers to develop a coherent and robust approach to identifying technologies for reassessment -*HTAi and other international and national HTA organizations s*hould: promote, support, and disseminate work to improve methods and tools for reassessment, evidence-based decision making and implementation strategies; promote the value of HTA across the full technology lifecycle; develop an inventory of practical approaches in systems around the world for prioritization, reassessment, decision making, and implementation of technology optimization; develop a library of reassessment reports and recommendations, optimization decisions, implementation strategies, and outcomes from systems around the world.
Interactions between HTA, coverage and regulatory, 2011	-Continue Dialogue to Promote Understanding and Interaction -Align Scientific Advice on Design of Pre- and Post-market Evaluations (Particularly Phase 2, 3, and 4 Studies for Pharmaceuticals) -Extend Dialog Better to Address Unmet Need -effort must be well directed and focused on the areas of most importance
Managed Entry Agreements, 2010	-stakeholder involvement (patients and clinicians), transparency (the final MEA should be clearly published), clear description of the basis for review and appeal, and assertive leadership, including acceptance of accountability. -Collaborative work is needed to improve the evidence that is available; requires early engagement on technology development plans and better interaction with regulators and payers/providers
HTA to optimize health technology utilization: using implementation initiatives and monitoring processes, 2009	-Improved technology utilization can be achieved by high quality, relevant, timely HTA advice; funding for the technology; coherent decision-making systems; professional engagement; sufficient infrastructure; and patient participation. -more effective engagement of all stakeholders throughout the HTA process -"Intelligent dissemination" needed -Monitoring must be scientifically robust, feasible and fundable; "minimum data sets" informed by VoI? (greater partnership is needed) -HTA requires clear policy receptor functions; more initiatives that drive decision maker or provider behaviours
Harmonization of evidence requirements, 2008	-Harmonization of HTA should not aim to produce a single decision on reimbursement and utilization of a technology; harmonizing on clinical evidence most potential -Transparency is essential

Coverage with evidence development, 2007	-Greater collaboration with regulators (divergent evidence requirements) -Better inclusion of patient views and data/inputs to CED

Case Studies

Alzheimer's Disease

One example of a disease that embodies many of the issues highlighted within this paper is that of Alzheimer's Disease and the pharmaceutical treatments available. Alzheimer's Disease is a progressive neurodegenerative disorder that causes loss of cognitive function, changes in behavior and interference with daily functioning. It is the leading cause of dementia around the world with an estimated 50 million cases, placing significant burden on healthcare systems and also the families and carers of people living with the disease (62). Alzheimer's Disease typically has a slow onset and can be challenging to diagnose in a timely and accurate manner. Before the early 2000s, the only way to definitely diagnose Alzheimer's Disease was at autopsy, however advances in imaging mean that a formal diagnosis can now be obtained with a CT Scan, MRI or PET Scan. However, logistical challenges and limited capacity and access to these technologies across the world mean that some people still have a delayed diagnosis of Alzheimer's Disease, which may alter treatment effectiveness and determine treatment pathways. In addition, the benefit of advanced screening has been debated, given that available treatments are of questionable effectiveness (see below). Horizon scanning efforts and preparing the health system for an increase in this type of imaging has been noted as challenging (interview communication).

In 2006, the drugs donepezil, galantamine, rivastigmine and memantine were licensed for the treatment of mild, moderate and severe Alzheimer's Disease. The HTAs of these drugs were globally controversial, with some countries initially recommending that the drugs did not demonstrate clinical effectiveness and that they should not be used for mild disease but rather they would only be cost-effective if used for moderate disease. Patient groups and the technology manufacturers appealed these recommendations. As a result, and as previously mentioned in this paper, efforts were made by the Green Park and CMTP to try and set some standards on how progression and outcomes in Alzheimer's Disease should be measured in the future to avoid situations such as this again. However, it appears that the concerns remain, and both challenges in outcome measurement and the importance of including relevant stakeholders in determining value was reiterated by Bauer et al in 2020 (63), who conducted a literature review of Alzheimer's Disease HTAs in England, Germany and the Netherlands. The authors found that outcomes measured using clinical scales dominated the decision making and did not always allow for the inclusion of outcomes relevant to people living with Alzheimer's Disease or their families and carers. Methodological work in this space is ongoing.

Horizon scanning shows that there are many new technologies in development for Alzheimer's Disease. While there have been a number of other promising technologies, most have not received regulatory approval. In June 2021 however, the FDA approved aducanumab (Aduhelm™) for the treatment of Alzheimer's Disease. This is the first drug to receive regulatory approval that works by targeting amyloid plaques in the brain that are the underlying cause of the disease. However, evidence of plaque removal was not accompanied by material improvements in cognition or slowing of disease progression. The approval was therefore highly controversial. This has been followed by the US Centers for Medicare and Medicaid Services releasing the proposal to cover the FDA-approved treatment through a coverage with evidence development model. This means that the drug will only be reimbursed by Medicare if it is provided in the context of a qualifying clinical trial. This has also been controversial, and depicts in sharp relief the challenges associated with accelerated approvals that carry limited evidence. Conversely, in December 2021, the EMA adopted a negative opinion citing that "although Aduhelm reduces amyloid beta in the brain, the link between this effect and clinical improvement has not been established…In

addition, the studies did not show the medicine was sufficiently safe as images […] showed abnormalities suggestive of swelling or bleeding which could potentially cause harm" Aduhelm: Pending EC decision | European Medicines Agency (europa.eu).

Advanced Therapy Medicinal Products (ATMPs); lifecycles of the future

Advanced Therapy Medicinal Products (ATMPs) are medicines for human use that are based on genes, tissues or cells and offer groundbreaking new opportunities for treatment of disease and injury (64). ATMPs are classified into three main types: gene therapy medicines; somatic-cell therapy medicines; tissue-engineered medicines. In addition, ATMPs may contain one or more medical devices as an integral part of the medicine.

ATMPs have the potential to offer curative or regenerative options for treating diseases that were previously incurable and/or required lifelong medical interventions. This has a huge possible value to patients and health systems with some "one-shot" style treatments being developed. There are a few examples already considered by HTA bodies and the uncertainty created with the relatively small studies, lack of control groups, surrogate endpoints, and short-term follow up has proved challenging to mitigate. Additional complexities came from the poorly defined subgroups which created inconsistencies throughout the world in how the technologies were evaluated. Discrepancies in the economic modelling across HTA bodies was noted in a recent review of gene therapy HTAs (65).

In addition, these therapies typically come with a high price tag; Zolgensma, a gene therapy for use in spinal muscular atrophy, is the most expensive drug in the world at $2.1 million USD. To date, all ATMPs considered by HTA bodies have been recommended for use only when a MEA is also in place. The challenges with monitoring these and following patients up for a sufficiently long period has been highlighted previously (55) and there is a linked increase in use of RWD to support and monitor the use of ATMPs in practice that becomes more important as these technologies are introduced. Whether these technologies will lose exclusivity and naturally reduce in price, evolve as versions or be displaced by new technologies remains to be seen. Dynamic pricing (if feasible) and discounting become key issues in the assessment of these technologies.

The effect of ATMPs on the broader spectrum of the technology lifecycle has yet to be fully determined. It is possible that if these technologies offer true innovation and benefits to patients as yet previously unseen, they will become the dominant technology type for all diseases they are developed for. This may actually simplify the management of diseases with fewer technologies for each disease area. Patient variability, choice and ultimate deterioration of ATMP effect must be expected though with a continued requirement for more traditional technologies post-ATMP treatment; there will inevitably again be challenges in developing evidence bases for these patients who have experience of ATMPs followed by other technology types. How individual ATMPs and their lifecycles may evolve over time is still to be observed given the relative infancy of these technologies; how and whether health systems can disinvest from these technologies over time, and still ensure continued patient care is likely to be a challenging issue to tackle.

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