Project Title: Next Generation Health Technology Assessment to support patient-centred, societally oriented, real-time decision-making on access and reimbursement for health technologies throughout Europe

Grant Agreement Number: 825162

Deliverable Title: Review on the outcomes of synergies between regulatory agencies and HTA agencies

Deliverable Nº 4.2	Version: 01
Date: 31 May 2020	Lead Beneficiary: University of Copenhagen
Nature: Report	Diss Level: Confidential

TABLE OF CONTENTS

DOCUMENT INFORMATION

Grant Agreement Number	825162	Acronym	HTx
Full title	Next Generation Health Technology Assessment to support patient-centred, societally oriented, real-time decision-making on access and reimbursement for health technologies throughout Europe		
Project URL	www.htx-h2020.eu		
EU Project officer	Leslie Pibouleau (Leslie.PIBOULEAU@ec.europa.eu)		

Deliverable	Number	D4.2	Title	Review on the outcomes of synergies between regulatory agencies and HTA agencies (M12)
Work package	Number	4	Title	Implementation into Systems and Processes

Delivery date	Contractual	31/05/2020		Actual	29/05/2020
Status		Version:		Draft ☐ Final ☑	
Nature		Report ☑ Prototype ☐ Other ☐			
Dissemination Level		Public ☐ Confidential ☑			

Authors (Partner)	Copenhagen Centre for Regulatory Science (CORS)			
Responsible partner			Email	cors@sund.ku.dk
	Partner		Phone	+4535330818

Description of the deliverable	A systematic review and cross-sectional survey on harmonization between HTA and regulatory agencies
Key words	HTA, regulatory, synergy

DOCUMENT HISTORY

NAME	DATE	VERSION	DESCRIPTION
D4.2 Report Synergy	28/05/2020	1	Final

EXECUTIVE SUMMARY

The need to improve drug development and facilitate faster access for patients have ignited discussions around the importance of building synergies between health technology assessment (HTA) bodies and regulatory agencies. In this study, we conducted a systematic review to examine processes, progress, outcomes, and challenges of harmonization initiatives between HTA and regulatory bodies. Medline, EMBASE, and the International Pharmaceutical Abstracts database were searched from their inception until 21 October 2019. Searches for grey literature (working papers, commissioned reports, policy documents, etc.) were performed via google scholar and several institutional websites. An online cross-sectional survey was also conducted among HTA (n=22) and regulatory agencies (n=6) across Europe to supplement the systematic review. Overall, we found that while there are areas of divergence, there has been progress over time in narrowing the gap in evidentiary requirements for HTA and regulatory agencies. Most regulatory agencies (4/6; 67%) and half (11/22, 50%) of the HTA bodies reported having a formal link for 'collaborating' with the other. Several mechanisms such as early tripartite dialogues, parallel submission (review), adaptive pathways to licensing, and post-authorisation data generation have been explored as avenues for improving collaboration. A number of pilot initiatives have shown positive effects of these models to reduce the time between regulatory and HTA decisions, which may translate into faster patients' access to life-saving therapies. However, data on long-term impacts are limited. Several barriers including legal, organizational, and resource-related factors were also evident and these need to be addressed to achieve greater alignment in the current regulatory and reimbursement landscape.

TITLE:

Improving Synergies Between HTA and Regulatory Agencies: A Systematic Review and Cross-sectional Survey on Processes, Progress, Outcomes, and Challenges

INTRODUCTION

The transition of a product from benchside to clinical use involves several stages and engagements with different stakeholders.[1] The first interaction is often with regulators who provide marketing authorization following satisfactory review of the product's risk-benefit profile (i.e, evaluation of safety, efficacy, and quality). Here, emphasis is usually placed on evidence generated from well-controlled studies (those with high internal validity), such as randomized controlled trials (RCTs).[2.] Moreover, relative efficacy against an active comparator is often not a requirement and placebo comparators are considered to provide simpler statistical and clinical interpretation.[3,4]

Once a product has gained marketing authorization, market access is further dictated by the particular healthcare system's financing mechanisms.[5] Usually, payers relying on the assistance of health technology assessment (HTA) agencies, decide whether to reimburse a product based on its relative value under current clinical practice scenarios.[6] The value assessment usually focus on relative performance (such as relative safety, relative effectiveness, and cost-effectiveness) of a technology against currently available clinical options. Unlike regulators who may accept short-term or surrogate outcomes, payers usually prefer long-term clinical outcomes.[3,7] Moreover, their assessment may involve a broader perspective such as the consideration of the potential social, legal, ethical, and political impacts of adopting the new technology.[8,9]

Given the differences in decision mandates of HTA/reimbursement bodies and regulatory agencies, their activities have been distinct from each other (Table 1). However, there are growing interests in the harmonization of the activities of these agencies.[10,11] These interests in harmonization/collaboration stem from criticisms that the current 'silo-based model' is ill-equipped to drive innovation, that it hinders the

rapid adoption of evolving clinical evidence, as well as delay timely patient access to life-saving technologies.[3,11] As an example, among all new medicines approved by the European Medicines Agency (EMA) between March 2000 and March 2018, just 56% were recommended by the United Kingdom (UK)'s National Institute for Health and Care Excellence (NICE) for reimbursement.[12] Moreover, less than half of new cancer medications assessed during 2013-2017 across 20 countries, received positive reimbursement recommendations.[13] Hence, it is anticipated that greater collaboration between different stakeholders could improve efficiency in the drug development processes and increase the availability and access to innovative therapies to improve patient outcomes.[14]

To date, limited reviews have examined the experiences across different markets regarding harmonization initiatives between regulatory and HTA/reimbursement agencies or their impacts and challenges.[3] Such an exercise is needed to improve understanding of the current landscape, identify learning opportunities, and develop insight into areas requiring improvement for effective harmonization. Thus, in the present report, we aimed to provide a synthesis of the literature regarding opportunities and outcomes of synergy initiatives between HTA and regulatory agencies. The systematic literature review was supplemented by a cross-sectional survey among European HTA and regulatory agencies to provide further insight into current trends.

METHODS

A systematic review of the literature was performed in Medline, EMBASE, and the International Pharmaceutical Abstracts database from their inception until 21 October 2019. We used two sequential search strategies to identify relevant information. In the first search strategy (Strategy A), we looked for papers related to either HTA (using terms such as "health technology assessment" or "cost-effectiveness" or "economic evaluation" or "economic analysis" or "cost-benefit analysis" or "cost-utility analysis") or regulatory (using terms such as "drug approval" or "pharmaceutical regulation" or "drug legislation" or "pharmaceutical administration" or "European medicines agency (EMA)" or "food and drug administration (FDA)") decision-making processes (Supplementary Tables S1). In the second strategy (Search B), we combined the keywords in Search A with "synergy" or "collaboration" or "alignment" or "partnership" "harmonization" or "scientific advice" or "parallel consultation" (Supplementary Tables S2). Citations from different databases were combined in Endnote X9 (Clarivate analytics®) and duplicates were removed. Subsequently, titles and abstracts were screened and those deemed likely to be eligible were subjected to full text assessment. Once the relevant articles were selected, additional articles were identified by exploring their bibliographies.

We also searched for grey literature (working papers, commissioned reports, policy documents, etc.) via google scholar and several national and multinational institutional websites including those of the EMA, US FDA, and the European Network for Health Technology Assessment (EUnetHTA) (Supplementary Tables S3-S5). We started with general searches on websites and reviewed the hits to identify relevant materials. We then followed up to search their references and ascertain specific case examples.

Only studies published in English at the time of this review were included. Moreover, to be eligible for selection, a report had to describe in whole or in part assessments on harmonization of HTA

(reimbursement) and regulatory approval, focusing on mechanisms, implementation models, outcomes, or challenges. Our review centered mainly on pharmaceuticals, although in some respects insights from medical devices were considered. Furthermore, the review focused on reports from Europe, North America, Australia/New Zealand, and Asia. However, with the exception of Europe in which we decided *a priori* to include all relevant data regardless of country, for all others, only information from high-income countries (HICs) were targeted. An HIC was defined as per the criteria used by the World Bank to include any country with a gross national income per capita of US$12,376 or more in 2019.[15] The articles' screening was performed by one author (RO). However, a second author (MLDB) provided a rapid perusal of the appropriateness of inclusion of documents in the final report.

We undertook a narrative synthesis that was largely inductive in nature — i.e., centered on themes that were described or highlighted in detail in the literature.[16] However, we also applied a deductive method by synthesizing specific information such as those related to alignment of evidentiary requirements, stakeholder involvement and perspectives, program implementation challenges and successes. The key papers selected were those that had information to help develop the main themes for the report. However, references were also made to other papers outside those informing the themes to allow for broader contextualization.

An online cross-sectional survey among European HTA bodies and regulatory agencies was conducted using LimeSurvey® Pi (v3.1.4). The same set of questions seeking insight into HTA-regulatory interactions were sent to both agencies (Table S6). The survey was conducted between January and April 2020. Information originating from the survey was used to corroborate the findings from the systematic review.

RESULTS

Literature search results

The bibliographic search identified 30,110 citations from which 4354 were duplicates. Following titles and abstract screening 104 articles were selected for full-text assessment of which 16 articles were retained. An additional six articles were identified by reference screening and 38 more resources were retrieved via the grey literature search particularly from institutional websites. Figure 1 summarizes the flowchart of the reports' screening steps. The description of the key reports included in this review are provided in Supplementary Table S7.

Survey response

The online survey received responses from 22 HTA bodies and 6 regulatory agencies. Response rates were 18% (6/34) and 61% (22/36) for regulatory agencies and HTA bodies, respectively. Of the regulatory agencies, one was from Western Europe, two from Northern Europe, two from Central and Eastern Europe, and a representative from the EMA. Among the HTA bodies, nine were from Western Europe, seven from Central and Eastern Europe, four from Northern Europe, and two from Southern Europe.

What is HTA/regulatory harmonization — is it necessary?

Harmonization is broadly considered to encompass the streamlining of regulatory and reimbursement processes.[17] It is also deemed process-oriented and centered on reducing the time between regulatory and reimbursement decisions, and minimizing duplication of work.[18,19] Such an approach is viewed to have potential positive implications for the healthcare system in terms of improving patient care, innovation, and system sustainability.[3,7,14] Regardless, there are divergent views as to whether harmonization between HTA and regulatory agencies is needed, and if at all desirable. Proponents of harmonization initiatives posit that it presents an opportunity to develop economies of scale particularly with respect to

evidentiary requirements and/or alignment of a product's lifecycle.[20,21] Critics on the other hand, have highlighted that such mechanisms may have some unintended adverse impacts. In particular, separate regulatory and reimbursement functions is seen to allow health technologies to undergo robust quality assurance processes while being available on a free market.[3] Thus, harmonization is recognized by some to potentially trigger overregulation that hinders the abilities for markets to function thereby leading to market failures.[3] Moreover, cross-border harmonization mechanisms are also viewed by some as having the potential to diminish local decision-making power that could lead to the adoption of methods and standards that may not be well suited to the local context.[22]

Types of harmonization/interactions

From the survey, 67% (4/6) of regulatory agencies reported that they have an established formal link for interacting with HTA bodies whilst the remaining 33% (2/6) indicated that their engagement is informal. Among the 22 HTA bodies that responded to the survey, half (11/22) indicated having a formal link of collaborating with regulatory agencies. Ten out of 22 indicated that their engagement with regulators is only informal or sporadic, whereas one HTA body reported no interactions at all.

The interactions between regulatory and HTA agencies can be viewed across all the three phases of the product life cycle: a) the pre-marketing phase, b) the phase of actual market entry and c) the post-launch phase.[17] While this distinction is useful, a continuous link between the different phases is assumed. Moreover, current harmonization models or approaches can broadly be considered along the broader spectrum of evidentiary needs and those focusing on specific processes and timeframes (Figure 2).[3] In the subsequent sections, we will discuss key issues identified from the literature and survey pertaining to harmonization mechanisms with an emphasis on alignment of evidentiary requirements, tripartite

dialogues, parallel submissions (reviews), adaptive licensing pathways, and post-marketing collaborations, and highlight their implementation challenges and successes.

Alignment of evidentiary requirements

One overarching theme that transcended across the literature and survey is the need to align evidentiary requirements for HTA and regulatory agencies.[2,7,19,21,23] In general, while there are distinct data needs for HTA and regulatory agencies, there is considerable scope to minimize the gap in their evidentiary requirements through improved alignment.[24,25] In particular, subject to demographic, epidemiological, and other factors, clinical data are generally regarded as transferable across geographical and social boundaries.[22] In this context, most discussion have centered on "safety" and "clinical outcomes" as these requirements are common to both regulators and HTA agencies.[2] The discussions in the literature have given a significant boost to comparative-effectiveness research (CER) and relative efficacy.[26-28] Relative efficacy can be defined as the extent to which an intervention does more good than harm, under ideal circumstances, compared with one or more intervention alternatives in achieving the desired results.[26,29]

The information obtained from relative efficacy studies has the potential to meet the evidentiary requirements of both HTA and regulatory agencies.[2,30] For example, relative efficacy studies can provide the comparative clinical data necessary to support health economic modelling or cost-effectiveness analysis. Nonetheless, while it is generally viewed that relative efficacy of a health technology will be consistent across difference settings, very few studies have examined that assumption.[31] In the RE-LY trial for example, the relative efficacy of dabigatran — a new oral direct thrombin inhibitor varied between countries even under RCT conditions, depending on the efficiency of warfarin management.[32] Thus, relative efficacy can differ between different settings (countries) when healthcare practice varies. This raises additional challenge of the acceptability of evidence generated from relative efficacy studies by HTA

agencies given their preference for evidence derived in their local clinical context — i.e, real world settings.[31,33] Moreover, to fully meet the needs of both regulators and HTA agencies, a number of methodological issues need to be addressed. These include study design (e.g., will consideration be given to indirect comparison, or will head-to-head clinical trials between the new product and its comparator be required?),[3] endpoints (e.g., will HTA bodies consider surrogate endpoints or will they accept only clinical endpoints?), comparator (e.g., will it be the standard of care or any suitable therapeutic alternative?),[25] and target patient population (as relative efficacy varies across patient subpopulations, what will be the optimal patient population?).[2,34]

There is increasing recognition that CER (which is very similar to relative effectiveness) can be integrated into the existing two-stage assessment framework of regulatory and HTA agencies.[2,3] However, historically, the adoption of active-comparator relative efficacy studies to support regulatory approval has been slow, as enabling laws such as the US Food Drug and Cosmetic Act of 1938, as subsequently amended in 1962 do not require assessment of comparative effectiveness.[35] Regardless, in the US, recent developments such as the establishment of the Patient-Centered Outcomes Research Institute, as part of the Affordable Care Act, has embodied a need for CER.[36,37] The most prominent drivers of CER appear to be “cost pressure” or a “search for value”.[38]

From the survey, one respondent indicated that in 2018, a proposal from their government suggested that the regulatory agency should make the evaluations on relative efficacy proactively to inform the reimbursement decisions by the national HTA agency. It was noted that several objections were raised to this proposal, and that this suggestion has not yet become a formal regulated duty of the regulatory agency. Regardless, the summaries of new drugs published nationally by the regulatory agency have since then been slightly modified to include more relative efficacy information.

In general, a standard methodology for compiling comparative data is yet to be developed.[39] Thus, there exist ambiguity as to how CER will be appropriately designed to reflect regulators, HTA bodies (payers), patients, and clinicians' perspectives. As opined by Woodcock,[36] from a regulator's perspective, "the tolerance for (and recognition of the probability of) error is probably the greatest divide separating the CER enterprise and the current framework for medical product regulation".

Global initiatives such as the Green Park Collaborative is exploring the scientific feasibility of developing methodological guidance relative to evidence generation that meets the needs of different stakeholders.[40] In Europe, following the publication of the conclusions of the Pharmaceutical forum in 2008, the European commission gave the EMA the political mandate to interact with HTA bodies with the aim to improve the availability and best use of data relevant to HTA.[41] The primary objective of this joint project of regulators and HTA bodies was to examine how information in the European Public Assessment Reports (EPARs) can contribute to relative effectiveness assessment by EU Member States' HTA organizations (EUnetHTA). The collaboration between the EMA and EUnetHTA on EPARs started in February 2010 and lasted for more than 2 years. An evaluation of the EPAR pilot program suggested that it demonstrated the opportunity to engage in discussions about better exchange of data and information.[42] It was further noted that the parallel review of EPARs has been useful for each of the organizations to not only critically review the end-product "assessment report" using a predefined methodology but also mutually identify areas for future improvement.[42] Consequently, the EMA's Road Map to 2015 identified the need for further improvement of EPARs given their use for HTAs.[10] A joint EMA-EUnetHTA three-year work plan 2013-2015 was further instituted to build on this work.[43] A report of this three-year work plan was published in March 2016, which suggested that it facilitated the identification of areas for possible synergies as well as helping to improve understanding of the differences between individual agencies' procedures.[44]

Overall, there is some recognition that the gap in evidentiary requirements between regulatory and HTA agencies has narrowed over the past few years.[25,45,46] For example, Dekker et al.,[46] recently examined the similarities and differences in evidentiary requirements of regulatory and HTA bodies (NICE) with respect to Alzheimer's disease approved products. They found a large overlap in the inclusion of phase III RCTs in regulatory and HTA assessments, although the focus on specific outcomes slightly differed.[46] Moreover, a 2016 survey revealed close alignment of the perspectives of HTA bodies and regulators on several evidentiary blocks (Figure 3) including the use of patient reported outcomes (PROs), whereas greater disagreements in areas such as the inclusion of secondary efficacy parameters were documented.[25]

Tripartite early dialogues

In several markets, systems exist for pharmaceutical manufacturers to seek advice from regulators during the design of their clinical development programs.[47,48] Although the advice provided is usually not legally binding,[48] adherence to the recommendations can minimize the risk that regulators will later raise objections during assessment of the corresponding market authorization applications. For example, an analysis by Hofer et al. revealed that from 2008 to 2012, 85% of applications that received and followed early scientific advice by the EMA were ultimately granted marketing authorization compared to only 41% that did not.[49] The concept of early dialogue with HTA agencies is rather relatively new.[50] Regardless, this form of engagement offers manufacturers an opportunity to obtain early insight regarding the evidence needs (e.g., safety, efficacy/effectiveness, cost-effectiveness, budgetary impact) and how this should be communicated to reduce bottlenecks during product launch. From the perspectives of the regulatory and HTA agencies, early engagement with developers has the potential to improve the efficiency of the decision-making process.[20,51]

Harmonizing this process via tripartite "early dialogue" meetings consisting of regulators, manufacturers, and HTA agencies can increase collaboration and improve understanding among the different parties. Regulatory and HTA bodies can offer joint (parallel) advice (in areas such as defining unmet medical need, analysis methodology, acceptable primary endpoints etc.),[25] discuss divergent data needs with the aim of minimizing discrepancies and identifying trade-offs, whereas manufacturers can have a single forum to discuss any potential claims or concerns.[52] The opportunity to incorporate patients and clinicians' perspectives in these discussions could further enrich the data needs.[20,53]

Tripartite advisory models have been implemented in different jurisdictions (Table 2). In 2010, the EMA commenced a pilot on Parallel Scientific Advice (PSA) together with HTA-bodies.[44] Moreover, in May 2014 the EMA released a "Best Practice guidance for Pilot EMA-HTA Parallel Scientific Advice procedures" for public consultation,[54] and the EMA-HTA PSA was formalized in 2015. Some of the issues specified in the guidance document were that; 1) all medicinal products are eligible irrespective of their eligibility for the central procedure; 2) it is the applicant´s choice which HTA-bodies could participate (usually the number of HTA-bodies participating should not exceed 5); 3) The invited HTA-bodies are not obliged to participate; 4) A common briefing document is used; 5) Advice is not legally binding (however, the EMA views scientific advice to be scientifically binding when regulators give scientific advice based on the current state-of-the-art in medicine development. Thus, while they recognize that due to evolving scientific knowledge, an alternative approach to that advice may be appropriate, where companies choose not to apply the advice, they are requested to justify clearly their position in any subsequent marketing authorisation application);[52] 6) The process is confidential, and 7) The Administrative work is done by the EMA.[54] By the end of December 2015, the overall number of completed procedures for the EMA-HTA scientific advice was 63.[44] An analysis of 43 PSA procedures showed that the most frequently represented HTA bodies were NICE (involved in 90% of all parallel advice procedures), followed by the German Federal Joint

Committee (65%), Italian Medicines Agency (45%), Dental and Pharmaceutical Benefits Agency (Sweden) (35%), National Authority for Health (France) (19%), Main Association of Austrian Social Security Institutions (10%), Catalan Agency for Health Quality and Assessment (10%), and National Institute for Sickness and Invalidity Insurance (Belgium) (3%).[45]

An analysis of the first 11 EMA-HTA PSAs also showed that most of the questions posed by developers related to the design of clinical studies such as endpoint and comparators (Supplementary **Figure S1**),[55] a trend which is largely expected. Moreover, analysis of 518 answers provided by regulators and HTA assessors in 31 PSAs conducted during 2010-2015, revealed that full agreements, partial agreements, disagreements were reached in 61%, 23% and 16% of responses, respectively.[45] In particular, the occurrence of divergence in recommendations provided were seen to be lowest for the study patient population and highest regarding selection of comparator.[45] Where divergence in recommendations have occurred, notable cases of successful compromises in product development have also been reported from parallel EMA-HTA PSAs. For example, in one instance, a company preparing to launch a novel therapy for chronic obstructive pulmonary disease (COPD) proposed utilizing a licensed comparator in its pivotal trial. The EMA agreed with this proposal; however, an HTA representative who was present requested a different comparator not licensed for use, yet routinely used. The solution was to introduce a new arm of the pivotal study to include both comparators, meeting the recommendations from both advisors.[56] In another case, a pharmaceutical company had developed a novel therapeutic as a first-in-class treatment for a rare oncological disease. With no other product previously licensed for this indication, the company proposed standard of care as its comparator and the EMA agreed. However, HTA bodies requested the use of an off-label drug.[53]

When Tafuri and colleagues[57] analyzed the uptake of the comparator recommendations at the time of 31 PSAs (during 2010-2015) in the actual development, they found that manufacturers implemented comparators to address both the needs of regulators and of at least one HTA body in 12 out of 21 studies (almost 60%). Studies for which manufacturers followed the regulators' and >50% of the HTA bodies' advice were 8/21 (38%), while those following exclusively the regulatory advice were 7/21 (about 30%). Only in two studies did the manufacturer implement recommendations, neither from the regulators nor from the HTA advice. Moreover, it was found that changes were never implemented solely based on the HTA advice. For the primary endpoint in all included studies (23 out of 23) manufacturers implemented both the requests of the regulators and at least one HTA body. In 15 studies out of those 23 the manufacturer complied with the advice of both the regulators and >50% of the HTA bodies. These data suggest to some extent that manufacturers seem to be more inclined to satisfy the regulatory advice.[57] In 2017, the EMA-HTA PSA was replaced with the EMA-HTA Parallel Consultation (PC) process the key update being the incorporation of the European Network for Health Technology Assessment (EUnetHTA) and Early Dialogue Working Party (EDWP), although all other aspects of the PSA remained largely unchanged.[23]

Overall, regulators and HTA bodies have expressed positive views about tripartite dialogues.[20,51,52] Moreover, pharmaceutical manufacturers have identified several benefits with the process including reducing development program risk and creating common multi-stakeholder understanding of unmet medical need and acceptability criteria for innovative study design approaches.[53] Nonetheless, the value of any dialogue is dependent on the stability of the advice or when it is provided. Thus, to derive maximum benefit, planning is critical. For example, if advice is sought too early, issues that may arise after the clinical trials have commenced may not be addressed or it would be costly to revise and collect new information.[56] On the other hand, if sought too late, there may be insufficient time to complete the clinical trials before

the target market date. For a potential product that is not a strong candidate for an early access pathway, it is suggested that the ideal time for a sponsor to initiate the dialogue is during phase II evaluation, or just after achieving proof of concept, and at least 6 months prior to planned phase III initiation.[53] Regardless, earlier consideration of strategic advice in the phase I setting may be necessary to discuss assumptions and concepts for potential accelerated development opportunities before data generation. Overall, increased confidence in the PSA dialogue process is likely to be achieved via provision of formal (e.g., written) feedback.[3] However, projects have tended to adopt different approaches. For example, whereas, NICE-MHRA PSA Program[58] and the Tapestry Network pilots[59] provide formal written post-consultation reports, in the case of the Swedish authorities, the responsibility for documenting any discussions lies with the applicants themselves.[3] It is also useful for manufacturers pursuing tripartite dialogue to recognize that any advice provided is contextualized within existing knowledge and this may evolve as scientific and clinical understanding progresses.

Despite, the potential benefits of early tripartite dialogues, some perceived cons of the process include the fact that there are no formal mechanisms for addressing divergence between the actors. Moreover, the desire to achieve one consolidated position from HTA and regulatory agencies has been opposed in some settings as this is viewed to limit the rights of individual agencies to develop and express their own independent views.[60] Another potential setback with tripartite meetings is that they may present additional financial hurdles for pharmaceutical companies as these dialogues are usually provided as a fee-for-service.[23,58] Regulatory capture could also be seen to present a conflict of interest as early interactions can imply that regulatory and HTA bodies are potentially engaged in co-development of medicines.[56] Furthermore, there are concerns that the role of HTA agencies as final gatekeepers may be compromised through early involvement with developers. However, according to McAuslane et al., if the current challenges with early dialogue are properly addressed it “is the process that will likely provide the

greatest return on investment of time and effort to identify, develop, review, and recommend important new medicines, especially those that address an unmet medical need".[61]

Parallel submission (review)

Parallel submissions seek to reduce the time between regulatory and reimbursement decisions by aligning their review processes. In Australia, as part of a Memorandum of Understanding, a parallel process of regulatory (TGA) and reimbursement (PBAC) submission has been implemented since 2011 (Table 2).[62] While a product must still be listed on the Australian Register of Therapeutic Goods before it is listed on the Pharmaceutical Benefits Scheme (PBS), the Australian Drug Evaluation Committee (ADEC) and Pharmaceutical Benefits Advisory Committee (PBAC) can now receive submissions for a product in parallel. A PBS listing cannot occur prior to the product being listed on the Australian Register of Therapeutic Goods for the relevant indication. Moreover, if the final TGA approval for a product is received before a PBAC recommendation has been made, the PBAC secretariat will check that any proposed PBS listing is fully consistent with the final TGA registration.[63] If there are any discrepancies, the PBAC reconsiders its evaluation. By 2012, five products (linagliptin, testosterone solution, ivabradine, mycophenalate sodium and rifaximin) had their PBAC decisions deferred until ADEC recommendations were made.[64] Analysis of regulatory and HTA review found that when TGA took a longer than average time to review products, those products typically received a negative recommendation from PBAC, although, it was unclear whether similar issues were raised by both agencies.[65] The usefulness of parallel submission has been highlighted in one case study involving pembrolizumab – a medicine used to treat melanoma that has spread or cannot be removed by surgery (advanced melanoma) or to prevent post-surgery relapse. The manufacturer put the medicine through parallel review. This resulted in the listing of pembrolizumab on the PBS, only 4.5 months after TGA approval.[66] Ordinarily, when perused sequentially, the median time between a positive TGA

recommendation and PBS listing has been found to exceed 30 months.[64] An analysis by the Centre for innovation in regulatory science (CIRS) of drug-appraisals during 2015 suggested that the TGA/PBAC parallel process may have been instrumental in the shorter time between regulatory approval to HTA decision in Australia (n=46; median=44 days) compared to Canada (n=38; median=269 days), France (n=57; median=230 days), England (n=27; median=314), Germany (n=51; median=139 days), Poland (n=32; median=444 days), Scotland (n=47; median=260 days), and Sweden (n=48; median=184 days).[65]

In Canada, a manufacturer can submit for a CADTH Common Drug Review before a Health Canada Notice of Compliance (NOC) is issued. For the Health Canada/CADTH parallel review process the submission to CADTH can occur 180 days before the date of anticipated NOC from Health Canada.[67] This accelerates the process since the Canadian Drug Expert Committee can release its reimbursement recommendation to CDR immediately following the regulatory decision. A review of 56 New Active Substance (NASs) appraised by CADTH from 2014 to 2016 showed that Parallel review reduced the time from regulatory approval to HTA recommendation. The median time from Health Canada approval to CADTH recommendation was 158 days for drugs undergoing parallel review (n=22) compared to 377 days for drugs undergoing sequential review (n=34).[68] However, this was an unmatched analysis, thus prone to influence by other factors.

In 2010, the US Food and Drug Administration (FDA) and Centers for Medicare and Medicaid Services (CMS) announced the FDA-CMS Parallel Review pilot program for medical devices.[69] Through the program, manufacturers can request initiation of a CMS national coverage determination (NCD) while the product is still under FDA review. After five years, the program's impact was deemed to have been minimal and interest among manufacturers remained low.[70] In particular, only one device (Exact Sciences' Cologuard test, a multitarget stool DNA test developed for noninvasive screening for colorectal cancer) was approved

through the process. The time from premarket approval submission to the final NCD was 489 days compared to an average of 612 days for other NCDs issued in 2013.[71] While this suggested that parallel-review process could shorten the expected interval from regulatory approval to coverage determination, the experience with Cologuard was only one case. The only other product known to have undergone the pilot parallel review was Medtronic's Symplicity renal denervation system. However, the process was not completed as the device's phase III trial (SYMPLICITY HTN-3) failed to meet its primary efficacy endpoint.[72] In 2016, the FDA-CMS Parallel Review was fully implemented and extended indefinitely.[73] Since then, increased interest in the parallel review program among developers has been reported, and in 2017, Foundation Medicine's FoundationOne CDx next generation sequencing (NGS) based test was approved under the scheme.[74]

In May 2019, the Medicines Evaluation Board (MEB) and the Netherlands Healthcare Institute (ZIN) launched their pilot 'Parallel Procedures MEB-ZIN'. The stated objective is to "shorten the time from registration to reimbursement of a medicine".[75] The 'Parallel Procedures MEB-ZIN' will commence in Mid-2020. However, by March 2020, two manufacturers (Insmed BV for their amikacin liposomal inhalation suspension (ALIS) (Arikayce®) and Novo Nordisk BV for their oral dosage form of Semaglutide (Rybelsus®)) had registered their products to undergo the parallel review process.[75]

Overall, one major challenge with parallel review is that if a product fails to obtain regulatory approval, it renders the work of HTA bodies redundant and a waste of time and resources. In Australia, if regulatory approval is not granted for a product that goes through parallel review, the sponsor company is made to pay a cost-recovery fee to compensate for the resource used for HTA evaluation.[65] This may not be ideal for developers. Thus, to minimize such an occurrence, it may be useful that the HTA's initial review centers on the less resource-intensive components so that the time between assessments remains shortened

while at the same time not committing too much resources in the event of negative regulatory outcome. Moreover, the institution of a mechanism to select technologies that are most likely to secure regulatory approval to undergo parallel review might also be essential. Regardless, without the requisite data to meet the evidentiary needs of regulators and HTA bodies, parallel submission may not always lead to earlier market access, as an unfavorable review outcome could still occur.[3] Hence, a strategy of combining alignment of evidentiary data needs and early dialogue may be necessary to ensure that trials are designed in such a way that the data necessary to meet the needs of both agencies are collected. One such initiative is the EXCITE Programme by The MaRS Excellence in Clinical Innovation and Technology Evaluation which brings together a broad spectrum of research under one harmonized platform based on relationships brokered with academic health research facilities across the Ontario province in Canada. Through EXCITE, medical devices undergo a combination of clinical testing and HTA in order to obtain the evidence needed for both federal licensing and provincial health system adoption.[76]

Adaptive pathways

Since the emergence of drug regulation, approval mechanisms have been challenged by the need to achieve a balance between ensuring timely access for patients without compromising safety.[77,78] The traditional regulatory paradigm is characterized by well-defined structures and rigid processes that require several years of research, development, and authorization for a medicine to reach the market.[79] However, this mechanism is criticized as outdated and that it ignores the complexities of health technologies, as well as the diversity in population features and disease progression.[3] Hence, there has been a push for a shift from the traditional approach, which relies on extensive testing and the marketing authorization for large groups of patients (with a single decision point focus) to a procedure that employs periodic or staged assessment and re-assessment using an evolving evidence base.[79,80] While there have been a number of proposals (Supplementary Table S8) advocating for planned adaptive approaches to

drug licensing using terms such as “staggered entry”, “adaptive approval” and “progressive authorization”, much of the conceptual framework of adaptive licensing emanated from the New Drug Development Paradigms (NEWDIGS) collaboration that started in 2010 as an initiative of the Massachusetts Institute of Technology (MIT) and was hosted by the MIT Center for Biomedical Innovation.[79] The concept has however been renamed to “adaptive pathways (APs)” to better reflect a focus on the development and managed introduction of medicines rather than a new way of regulating and authorizing medicines.[81] Moreover, over the past years, regulators in different jurisdictions have had several mechanisms in place to facilitate an earlier access of new promising medicines especially in areas of high unmet medical needs and for orphan diseases.[82] In Europe, the EMA early access and registration tools include Priority Medicine (PRIME),[83] conditional marketing and authorization and approval under exceptional circumstances,[84] as well as compassionate use exist.[85] Hence, the concept of AP is not necessarily a new licensing pathway but a way of getting clinical data in order to design a smart development program to meet the evidentiary needs.[80,81]

In 2014, the EMA launched the AP pilot program inviting participation from companies that had candidate products that were early in clinical development.[86] The AP is based on key principles such as the need for early dialogue (collaboration) with multiple stakeholders (regulators, HTA agencies, and patient and healthcare professional representatives) to identify a subset of patients expected to present a favorable benefit–risk profile as well as significant emphasis on the use of real‐world data to supplement clinical trial data. Other criteria for the selection of products for the APs pilot was an iterative development plan. The iterative development plan can follow two registration scenarios: 1) starting with a marketing authorization for a well-defined subpopulation, expanding the population and finally achieving full authorization (‘widening of the indication’ scenario) or 2) obtaining a Conditional Marketing Authorization, whether based on surrogate endpoints or not, and conducting confirmatory studies

afterwards ('prospectively planned reduction of uncertainty' scenario) (Supplementary Figure S2).[87] In the AP pilot project, EMA received 62 applications out of which seven progressed to a formal scientific advice (one) or parallel regulatory-HTA scientific advice (six). The reasons for non-acceptance into the pilot included: 1) development programmes that did not have scope for expansion and iteration; 2) proposals for areas without unmet need; and 3) late stage development programmes (where no changes to the plan could be effected).[86]

In general, the 'safe harbour' environment of APs is intended to foster an increasing willingness to share information, data, and expertise, thereby improving collaboration between the different agencies.[81,87] For example, actual and modelled clinical development and licensing programs of three case studies as part of the Janus initiative concluded that the adaptive licensing approach increases stakeholder commitment.[88] Regardless, to achieve the intended acceleration in patients access, the adaptive pathways need to identify ways to reduce the time lag between marketing authorization and reimbursement. This further reinforces the importance of early dialogue with HTA and regulatory agencies as well as alignment of evidentiary needs.[53] To facilitate such interactions, the Innovative Medicines Initiative (IMI) through the ADAPT‐SMART initiative assembled together stakeholders to develop better ways to achieve APs.[89]

To ensure efficient adoption of APs, appropriate legal structures need to be in place.[78] For example, a report by Oye et al. indicated that attorneys from the US FDA, EMA, and the Singapore Health Sciences Agency found that existing statutes in their jurisdictions provided authority for adaptive licensing, although gaps were noted in the Canadian legislation.[90] Moreover, the success of APs requires a more "system-wide" approach including for example the willingness of patients to participate in clinical research to evaluate benefit/risk and determine if new medicines were effective and how different stakeholder perspectives are reflected in the decision-making process.[88] As highlighted by Schulthess et

al,[91] the bigger challenge facing the adoption of APs borders on how to incorporate different decision-making processes into AP methodologies "to ensure the appropriate balance is struck between earlier access to new medicines, a given regulator's willingness to facilitate that to occur, a healthcare provider's willingness to accept more focused data before prescribing a new medicine, as well as the provider's correlating willingness to restrict their off-label prescribing practices and to participate in real-world clinical research to progressively reduce uncertainties, a given payer's willingness to purchase such medicines, and having strong multifaceted postauthorization systems in place to facilitate all of this in as safe and dependable a manner as possible".

Post-authorisation data generation

At the time of marketing authorisation, the available information relating to a medicine may not yet be sufficient to fully assess the benefit/risk profile to the desired degree of certainty.[92,93] Therefore, regulatory agencies may require the generation of additional data, e.g. in the form of clinical studies after authorization. Nonetheless, there is considerable opportunity for HTA and regulatory agencies to collaborate towards providing guidance on the design of post-approval studies that can fulfil both of their needs.[17,25] This would be necessary to avoid developers' duplication of efforts in the post-launch evidence generation phase for example with respect to the planning and execution of post-authorisation efficacy studies (PAESs) and post-authorisation safety studies (PASS).[44] In this context, a collaboration between EMA and EUnetHTA on post-authorisation data collection commenced in March 2011. The discussions began from collaboration on two projects: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), under leadership of EMA, and the EVIDENT database — a database containing evidence information on new technologies. Through, this collaboration, reports on the feasibility of conducting post-approval studies in Europe were produced as well as guidelines on the necessary methodological standards to execute such studies.[94,95] In 2016, the EMA instituted the Scientific

Advice Working Party (SAWP)/The Pharmacovigilance Risk Assessment Committee *(*PRAC) joint scientific advice for the PASS/PAES studies.[96]

There are additional opportunities for HTA and regulatory agencies engagement around optimization of real-world data (RWD) generation such as use of patient registries, or the opportunity to share periodic benefit-risk assessment reports and therapeutic value re-assessments. This would include alignment on key areas such as outlining the definition of data to be collected (i.e. minimum dataset) in registries.[17] In this context, the EMA launched an initiative with EUnetHTA representation in 2015 to facilitate the establishment of patient registries as well as introducing and supporting a systematic and standardized approach to their contribution to serve regulatory and HTA needs.[97] There is also opportunity for collaboration regarding the use of additional sources for the collection of RWD, such as data derived from electronic patient records. Within this space, the IMI GetReal project (2013-2016) was a multi-stakeholder initiative, involving regulators, HTA agencies, patient organisations, academics and industry that sought to propose and create tools to support new robust methods of RWE synthesis for use in medicine development and decision making throughout the product-cycle including the initial regulatory and post-approval phases. Whiles this project has ended, the work continues via the IMI GetReal initiative launched in 2018.[98]

Barriers and challenges to harmonization

Despite the increasing interest and potential for synergies between HTA and regulatory agencies, several barriers, hurdles, and challenges were identified via the survey and systematic review. Some survey respondents indicated that the intensity of cooperation is low as there is no institutional framework for cooperation and it all comes down to individual initiatives. Moreover, there is a need to build trust and understanding between all relevant stakeholders including HTA bodies, regulatory agencies, payers,

manufactures, clinicians, and patients through effective communication and transparency.[20,51] In particular, mechanisms for continuous open dialogue is important to foster the development of stronger relationships and minimize misconceptions. For example, some manufacturers have expressed misgivings about harmonization initiatives for fear that HTA/payers might be able to influence market authorization decisions and vice versa.[51] Improved knowledge of each other's functions, roles and remits may also reduce misunderstandings that may lead to unintended policy consequences that can create misalignment.[99]

Furthermore, greater understanding of each agency's remits and processes provides a medium for conveying realistic expectations about the extent of coordination and agreement that is achievable. An HTA agency responded in the survey that it is sometimes "difficult to separate evidence review from policy issues and financial consideration" when engaging with regulators. There are also practical differences in areas such as evidentiary requirements that need to be acknowledged. For example, HTA agencies may be hesitant to accept trials using placebo control when an active comparative exists although this may be acceptable to regulators.[2,3,25] On the other hand, it is conceivable that payers and HTA agencies may agree to some of the clinical outcomes specified by regulators, whilst also highlighting the need for additional data such as those related to quality-of-life and long-term effects.[46] These potential differences need to be anticipated, so that efforts can be channeled into areas with greatest potential for harmonization. Furthermore, it is also important to establish leadership and clearly defined roles and responsibilities to minimize a culture of blame if the intended outcomes of harmonization are not attained.[99] For example, regarding the use of CER and relative efficacy studies, it is critical to outline how this should be implemented, who will be responsible, how will such research be funded (and by whom) and how will the data generated be disseminated. It must be anticipated that allocation of responsibilities, can be a

sensitive area as different agencies may seek to fiercely guard their existing responsibilities and operations.[60,99]

Harmonization is also likely to introduce changes to the current regulatory and reimbursement pathways that would only be possible with the implementation of new supportive structures and, if required, legislations.[78] For example, in some cases, legislative amendments may be needed since the roles of regulators are specifically defined in law or by their governments and HTA agencies may or may not be fully established in law. Indeed, one survey respondent indicated that within their jurisdiction, "HTA assessment is not mandatory and regulators are not obligate to cooperate with us". In general, there are also concerns that regulatory structures need revamping as they were instituted when no formal reimbursement mechanisms were in place.[12] Existing laws may hinder cooperation between the respective agencies as one survey respondent indicated that in their country "social laws does not provide many opportunities to do so". Moreover, the sharing of confidential information between different stakeholders may be limited by law. One respondent indicated that "although there are potential synergies there is limited scope for joint operations. Horizon scanning was explored but it was not possible for the regulatory agency to share this information". There are also concerns among companies about how proprietary information may be handled by the different agencies given their unique working styles.[99] In particular, regulators are usually bound by strict confidentiality codes,[100] whereas payers have varied frameworks that center around transparency in decision-making.[101] Thus, to support harmonization initiatives, a system is needed that offers inter-agency exchange of information to allow each to learn how the other is using available data to inform decision-making. For example, a central component of APs is the need for continuous data collection. In this context, information related to appropriate usage (compliance) as well as those related to effectiveness and safety collected by payers may be relevant to regulators to inform periodic regulatory assessment.[3] To facilitate the sharing of data, some pilot

programs have been tested as part of the EMA's 'Road Map to 2015'.[10] An optional information sharing process has also been established to permit Health Canada and CADTH to exchange information regarding a drug under review, for submissions filed with CADTH on a pre-NOC basis. Sponsors are encouraged to agree to this data sharing mechanism to facilitate the parallel review process.[102] The FDA-CMS Parallel Review also has an inbuilt mechanism for cross-sharing relevant data.[69]

Another challenge to broader harmonization is the availability of resources required for regular cooperation between the agencies. For example, one survey respondent indicated that "we are not in the same city, so face-to-face meetings need resources", and others hinted that resources for joint training is limited. In this context, several initiatives have relied on user fees (e.g. scientific advice) and alternative funding models may be needed to ensure their sustainability.[23,58] Moreover, a balance needs to be struck in the pursuit of national/regional collaborations as opposed to international harmonization initiatives. This is because whilst initiatives with an international scope (e.g., Green Park Collaboration) may offer high value to industry because their outputs could apply across multiple markets, and may reduce duplication of similar efforts in multiple jurisdictions, they are likely to face jurisdictional challenges as well as issues related to context-specific disparities (e.g., differences in standard of care and relevant comparators, economic and political priorities, and healthcare delivery systems).

DISCUSSION

Improvements in health technology raise hopes for better patient outcomes and a more efficient delivery of health care. However, the processes of diffusion and implementation of new health technologies require a series of steps and engagement with different stakeholders, and most healthcare systems continue to struggle with finding ways to ensure access to safe and efficacious healthcare products for their patients. A large part of this challenge has been ascribed to the two sequential processes of

regulatory and reimbursement decision making which is deemed to be ill‐suited to facilitate timely, well‐informed patient access, stimulate drug development, and simultaneously ensure routine collection and evaluation of all relevant information on benefits and risks.[81] Against this background, the alignment of regulatory and HTA processes has been proposed as a means to remedy the situation towards increasing the effectiveness of decision-making, mitigating the disconnect between different agencies and their stakeholders as well as promoting public trust in the review processes.

In this systematic review and cross-sectional survey of HTA and regulatory agencies, we found that there has been progress over time in narrowing the gap in evidentiary requirements between HTA and regulatory agencies. Different models and approaches aimed at fostering closer interactions between agencies were also identified. The initiatives described often require organizations to work outside of their traditional remits, to engage with different stakeholders, and in some instances to modify their processes. Regardless, the expected level of change necessary to adopt different models, or the practicalities (time and resources needed) of their implementation varies. Broadly, we have considered five key areas: early dialogues, alignment of evidentiary needs, parallel submissions (reviews), adaptive licensing, and post-marketing data generation. However, these mechanisms must feedback into each other and they should not be viewed as mutually exclusive.

Concerns over potential merger of regulatory and reimbursement functions to have adverse impacts on quality assurance processes as well as distorting the free market dynamics may explain some of the hesitance to greater collaboration between these agencies.[22] Despite this, there is considerable scope to develop economies of scale particularly with respect to evidence generation. Harmonization of evidentiary requirements is likely to be feasible and most effective when targeted at common requirements that are assessed by both HTA agencies and regulators (i.e., clinical outcomes). However,

greater friction is expected in areas that are more specific to each agency (e.g., economic, budgetary impact). Thus, in promoting harmonization, it is important to include outcome measures within trials that satisfy both agencies' needs. For example, regulators must ensure acceptable choice of surrogate endpoints, particularly those that have demonstrated good correlation with hard outcomes (such as mortality). Since, most HTA-regulator discussions are related to specific trial design and the selection of appropriate comparators and outcomes, a focus on product-level harmonization appears appealing to foster closer evidentiary alignment. Regardless, emphasis on initiatives addressing the evidentiary expectations of HTA and regulatory bodies at the level of therapeutic areas may offer greater return at maximizing the efficient use of scarce organizational resources and for generating outputs that are of wider importance. Furthermore, significant efficiencies for both companies and the reviewing agencies may be gained via development of condition specific as well as general methodological guidance at the international level.

Models such as APs although still in early development and largely applied to pharmaceuticals, have potential to be adopted for medical devices as well. For example, the continued reassessment characteristics of adaptive licensing would thus align well in assessing the impact of incremental innovation and real-life usage of the medical device. Some results of parallel submission programs suggest that such mechanisms may reduce time between regulatory approval and reimbursement decisions. Moreover, some analyses have revealed the positive effect of tripartite dialogues on clinical development programs,[57] although, mechanisms for addressing divergence needs to be clarified. Moreover, the long-term impacts of such measures are yet to be evaluated. The increasing desire for the use of real-world evidence to supplement RCT data also provides further opportunities for increased alignment between HTA and regulatory agencies throughout the product-cycle, but methods and standards require further refinement with time.

A number of practical enablers, challenges and barriers were also identified in the literature and survey which require attention to improve harmonization between HTA and regulatory agencies. In particular, the need to build trust and buy-in from all stakeholders is important. Moreover, greater understanding of each institution's processes as well as objective characterization of each agencies' needs, responsibilities and resources is important to building collaboration. Regardless, mechanisms need to be better developed on how to secure the exchange of confidential data between different agencies. Further consideration of resources available should inform models and approaches that are pursued. It is expected that each approach to harmonization will provide different benefits and challenges. Thus, in deciding on a harmonization approach, reflection on local contextual factors including healthcare system, political factors and resource availability are important. While a desire for international harmonization initiatives is understandable due to their potential to generate outputs that could apply across different markets, their inherent limitation such as likelihood of lacking context-specific focus need to be recognized.[22]

This study has several limitations. Firstly, while inferences were made to specific cases, the evidence synthesis was largely qualitative and descriptive in nature thereby amenable to interpretation bias. The included reports were mainly reviewed by a single author given the available resources and time constraints. It is possible that some reports may have been missed. However, we do not think that further major themes outside of what has been discussed would have emerged. In particular, most of the themes identified from the literature were further highlighted in the survey. A number of deliberations such as PSAs are usually treated as confidential.[23,58] Thus, the information extracted from published literature may not be entirely reflective of the processes and outcomes. Thus, to gain further insight, a symposium has been planned for October 2020 to engage both HTA and regulatory agencies on the matter of harmonization. Furthermore, as the systematic review was limited to articles published in the English

language, this may limit the generalizability of the findings. In the survey, the response rate from the regulatory agencies was low (<20%). However, the final number of included regulatory agencies (n=6), is comparable to that from a 2016 survey by Wang et al (n=7).[25] Lastly, the survey respondents were mainly from Europe and their experiences may not be generalizable to other jurisdictions.

CONCLUSIONS

There has been progress over time in narrowing the gap in evidentiary requirements for HTA and regulatory agencies. In many European countries, a formal link of collaboration between HTA and regulatory bodies has been instituted. Several mechanisms such as early tripartite dialogues, parallel submission (review), adaptive pathways to licensing, and post-authorisation data generation have been explored as avenues for improving collaboration. A number of pilot initiatives have also shown positive effects of these models to reduce the time between regulatory and HTA decisions, which may translate into faster patients' access to life-saving therapies. However, data on long-term impacts are limited. Several barriers including legal, organizational, and resource-related factors were also evident and these need to be addressed to achieve greater alignment in the current regulatory and reimbursement landscape.

Table 1: Characteristics of different agencies[2,19,20]

	Regulatory approval	HTA assessment (to inform reimbursement decisions)
Legal mandate	Usually defined within national public health legislation, with regulatory bodies accountable to the government in their jurisdiction.	HTA may be undertaken by a group within and accountable to a payer, and/or by groups within and accountable to a government department, university, hospital, research institute, or industry. The coverage body (payer) is usually specified within the rules and regulations of the healthcare system in which decisions are being made and are usually accountable to the healthcare system within which they operate. In some healthcare systems, the role and responsibilities of a coverage decision-making body may be defined in legislation with accountability to government.
Primary role	Provide market authorization within the mandated jurisdiction on the basis of an assessment of safety, quality, efficacy, and risk–benefit profile	Support for clinical and coverage decisions within a particular healthcare system on the basis of assessment of relative effectiveness, costs and, in some, system affordability, value for money, and values within the system
Decision	Evaluates whether the clinical benefits for patients outweigh the risks? Should this technology be available?	Assess whether the product offers useful, appropriate (and affordable) benefits for all or a select subgroup of patients in the particular healthcare system compared to what is most commonly used in the disease area?
Assessment focus	Efficacy, safety, quality (e.g., GMP)	Effectiveness, safety, quality of life, economics, budgetary impact, social, ethical, legal, organizational
Strength of Evidence	Pre-launch: Efficacy and safety from RCTs (usually placebo-controlled) Post-launch: Relative efficacy or effectiveness may be considered when reviewing product's ongoing risk– benefit profile	Pragmatic RCT*, observational studies, decision-analytic techniques (modelling)
Characteristics of studies they prioritize		
Validity	Internal validity	External validity
Comparator	Placebo	Active control, ideally standard of care
Endpoints	Laboratory findings and surrogate endpoints	Quality of life; final clinical 'hard' outcomes such as death
Time horizon	Trial duration	Lifetime or at minimum the time needed to capture all risks and benefits of therapy

RCT=randomized controlled trials; GMP=good manufacturing practices; *Not always used

Figure 1: Schematic process of the review

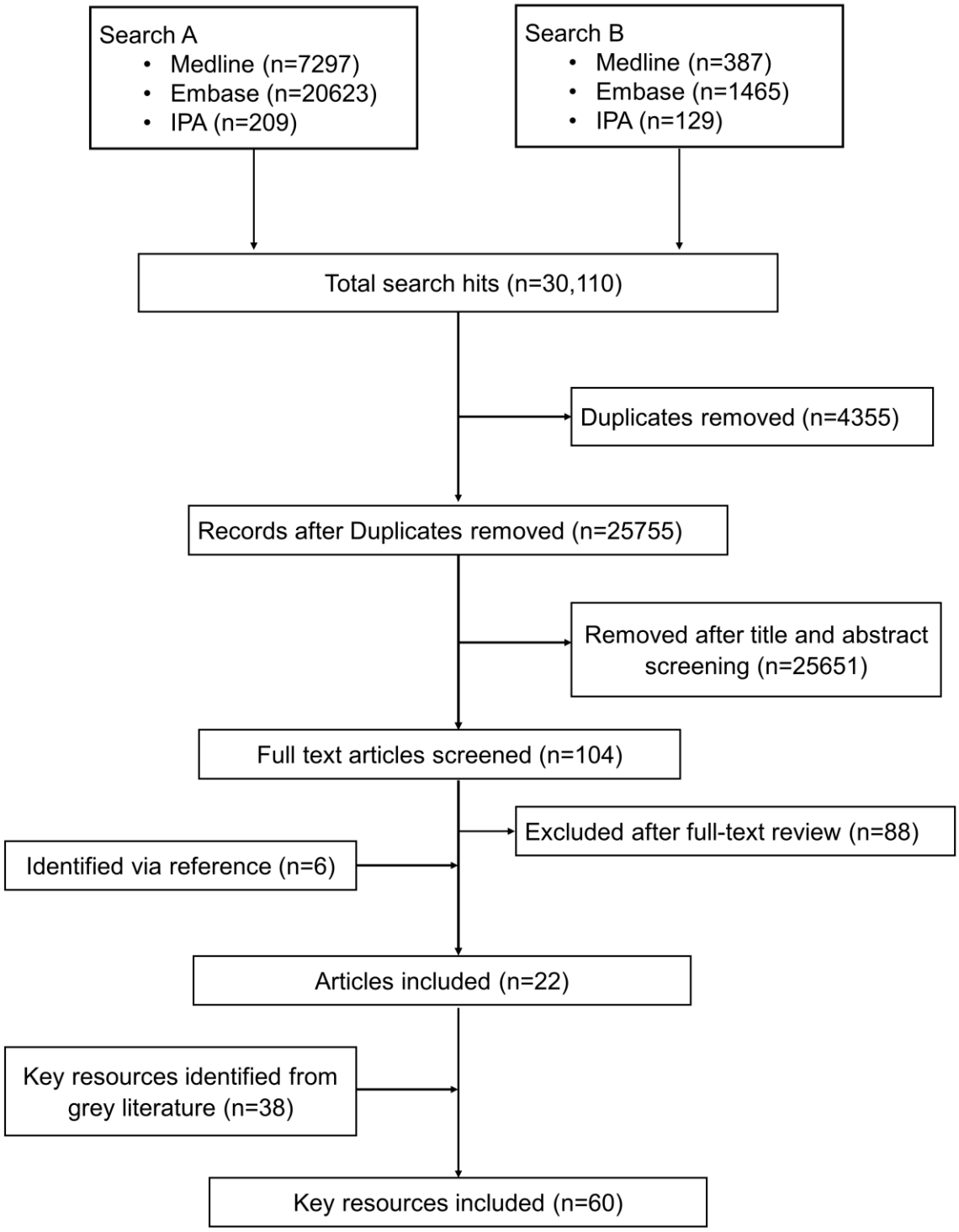


Figure 2: Conceptual display of the key avenues for HTA-regulatory harmonization of which alignment of evidentiary requirement is a central theme

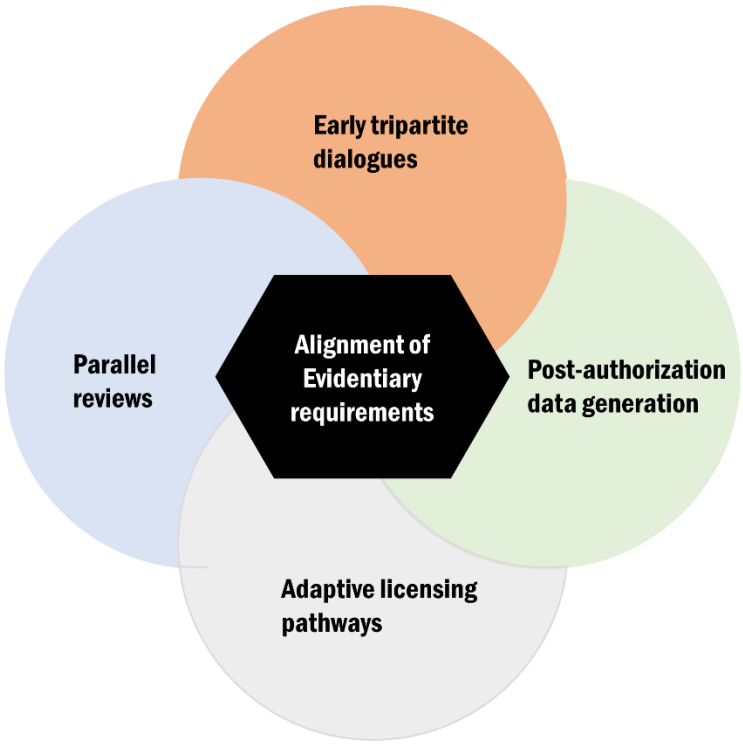
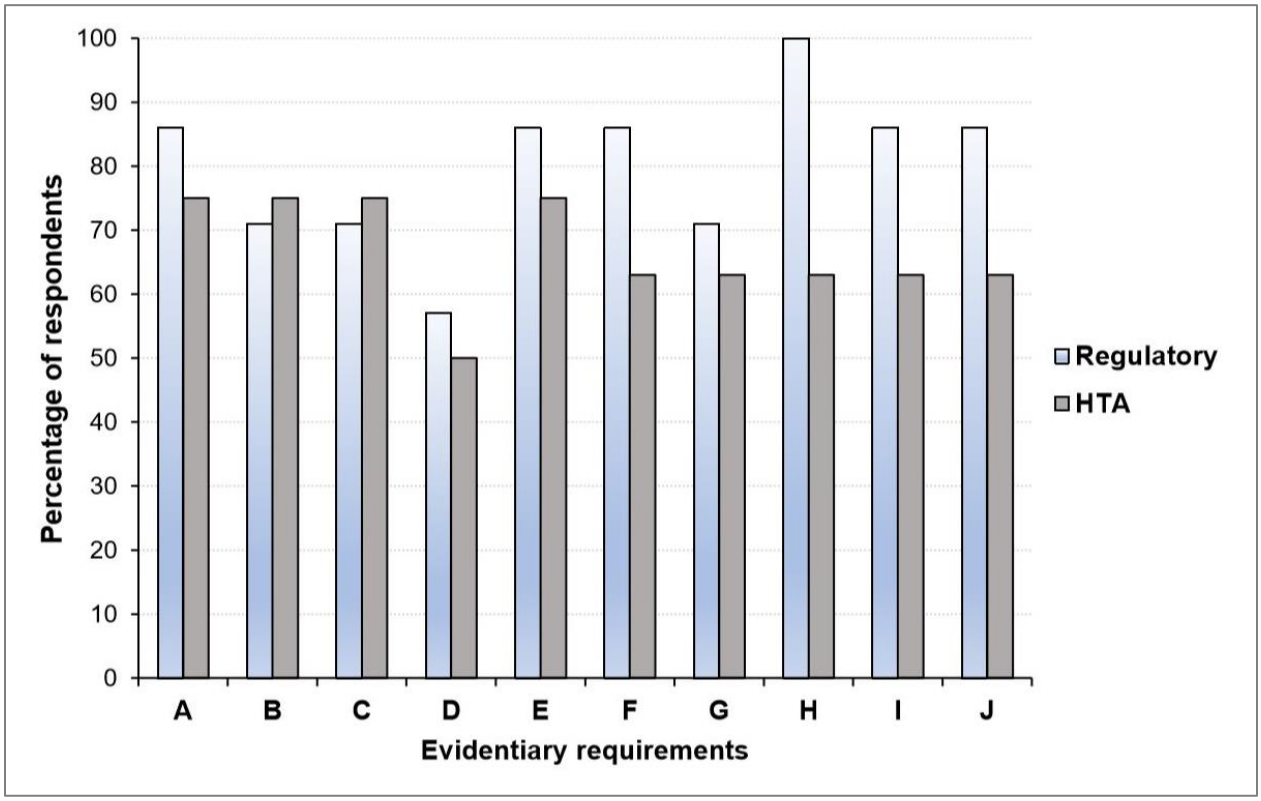


Figure 3: Perspective of HTA assessors and regulators regarding areas where alignment in evidentiary requirement could occur*



A = Acceptable primary end point; **B** = Inclusion of active comparator arm in the trial; **C** = Use of patient reported outcomes; **D** = use of health-related quality of life measures; **E** = Choice and use of surrogate measures; **F** = Criteria considered in choice of comparator: therapeutic; **G** = Use of subgroup analyses; **H** = Inclusion and choice of secondary efficacy parameters; **I** = Definition of unmet medical need; **J** = Use of biomarkers to monitor patient outcomes. HTA= health technology assessment; *Graph produced by author using data from Wang et al.[25] in which a questionnaire-based survey was conducted among regulators (n=7) and HTA agencies (n=8) between August and September 2016.

Table 2: Overview of early tripartite dialogues and parallel submission interactions

Region/country	Stakeholders	Name of program
Australia	TGA (Regulator) PBS (Payer)	Scientific advice on development (Pilot)[60]
Australia	TGA (Regulator) PBAC (Payer)	Parallel submission/review[63]
Canada	Health Canada (Regulator) CADTH (Payer)	Parallel submission/review[67]
UK	MHRA (regulator) NICE (Payer)	NICE Scientific Advice Programme[58]
Sweden	MPA (regulator) TLV (Payer)	Scientific advice on development[103]
Netherlands	MEB (regulator) ZIN (payer)	Parallel submission/review (Pilot)[75]
Europe	EMA (regulator) EUnetHTA (multinational HTA network)	Parallel consultation[23]
Europe	Multiple stakeholders, including EMA, MHRA, MPA, BfArM, AFSSAPS, AIFA (regulators) NICE, TLV, G-BA, CEPS, AIFA (payers) EUNetHTA (as observer) FDA (as liaison)	Tapestry Network (Scientific advice on development)[59]
US	FDA (regulator) CMS (payer)	Parallel submission/review[69,73]
Global	Multiple stakeholders	Green park collaboration (scientific advice on development)[40]

TGA = Therapeutic goods administration; PBS=pharmaceutical benefits scheme; PBAC = Pharmaceutical Benefits Advisory Committee; CADTH = Canadian Agency for Drugs and Technologies in Health; MHRA = Medicines and Healthcare products Regulatory Agency; NICE= The National Institute for Health and Care Excellence; MPA = Medical Products Agency; TLV = The Swedish Dental and Pharmaceutical Benefits Agency; MEB = medicines evaluation board; ZIN= The National Health Care Institute; EMA =European Medicines Agency; FDA= Food and Drug Administration; AIFA= Italian Medicines Agency; BfArM =The Federal Institute for Drugs and Medical Devices; CMS = Centers for Medicare & Medicaid Services

REFERENCE

1. Clark D, Dean G, Bolton S, Beeson B. Bench to bedside: The technology adoption pathway in healthcare. *Health and Technology.* 2019.
2. Eichler HG, Bloechl-Daum B, Abadie E, Barnett D, Konig F, Pearson S. Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers. *Nat Rev Drug Discov.* 2010;9(4):277-291.
3. Tsoi B, Masucci L, Campbell K, Drummond M, O'Reilly D, Goeree R. Harmonization of reimbursement and regulatory approval processes: a systematic review of international experiences. *Expert Rev Pharmacoecon Outcomes Res.* 2013;13(4):497-511.
4. Katz R. FDA: evidentiary standards for drug development and approval. *NeuroRx.* 2004;1(3):307-316.
5. Panteli D, Edwards S. Ensuring access to medicines: How to stimulate innovation to meet patients' needs? 2018; http://www.euro.who.int/__data/assets/pdf_file/0009/379701/PB29_AUSTRIA_web_13082018.pdf. Accessed Accessed March 30, 2020.
6. Goodman C. *HTA 101: Introduction to Health Technology Assessment.* Bethesda, MD: National Library of Medicine (US); 2014.
7. Angelis A, Lange A, Kanavos P. Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. *Eur J Health Econ.* 2018;19(1):123-152.
8. Iskrov G, Dermendzhiev S, Miteva-Katrandzhieva T, Stefanov R. Health Economic Data in Reimbursement of New Medical Technologies: Importance of the Socio-Economic Burden as a Decision-Making Criterion. *Front Pharmacol.* 2016;7:252-252.
9. Panzitta M, Bruno G, Giovagnoli S, Mendicino FR, Ricci M. Drug delivery system innovation and Health Technology Assessment: Upgrading from Clinical to Technological Assessment. *Int J Pharm.* 2015;495(2):1005-1018.
10. European Medicines Agency. *Road map to 2015: The European Medicines Agency's contribution to science, medicines and health.* London: EMA; 2011.
11. Mossialos E, Mrazek M, Walley T. *Regulating pharmaceuticals in Europe: striving for efficiency, equity and quality. .* Copenhagen: European Observatory on Health Systems and Polices; 2004.
12. Grignolo A, Siu A. Improving Drug Development and Patient Access With the Right People, Processes, and Culture: What Needs to Happen Right Now to Bring Better Medicines to the Patients Who Need Them. *Ther Innov Regul Sci.* 2019;53(3):398-402.
13. IQVIA Institute for Human Data Science. Global Oncology Trends 2018: Innovation, Expansion and Disruption. 2018; www.iqvia.com/institute/reports/global-oncology-trends-2018. Accessed January 20, 2020.
14. OECD. *New Health Technologies: Managing Access, Value and Sustainbility.* Paris: OECD Publishing; 2017.
15. The World Bank. New country classifications by income level: 2019-2020. 2019; https://blogs.worldbank.org/opendata/new-country-classifications-income-level-2019-2020. Accessed January 02, 2020.
16. Bradley EH, Curry LA, Devers KJ. Qualitative data analysis for health services research: developing taxonomy, themes, and theory. *Health Serv Res.* 2007;42(4):1758-1772.
17. Commission E. HTA network reflection paper on "synergies between regulatory and hta issues on pharmaceuticals. 2016; https://ec.europa.eu/health/sites/health/files/technology_assessment/docs/ev_20161110_co06_en.pdf. Accessed March 30, 2020, European Commission.

18. Enzmann H. New trends and challenges in the European regulation of innovative medicines. *Regul Toxicol Pharmacol.* 2016;80:314-320.
19. Liberti L, Pichler F, Walker S. Preparing for regulator review and reimbursement decisions- a case for cooperation between regulatory authorities, sponsors and health technology assessment agencies. . *Pharm Med* 2009;23:263-267.
20. Henshall C, Mardhani-Bayne L, Fronsdal KB, Klemp M. Interactions between health technology assessment, coverage, and regulatory processes: emerging issues, goals, and opportunities. *Int J Technol Assess Health Care.* 2011;27(3):253-260.
21. Office of Health Economics (OHE). Workshop on HTA and Regulatory Review. 2010; https://www.ohe.org/news/workshop-hta-and-regulatory-review. Accessed January 15 2020.
22. Hutton J, Trueman P, Facey K. Harmonization of evidence requirements for health technology assessment in reimbursement decision making. *Int J Technol Assess Health Care.* 2008;24(4):511-517.
23. European Medicines Agency. Parallel consultation with regulators and health technology assessment bodies. 2019; https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/parallel-consultation-regulators-health-technology-assessment-bodies. Accessed January 15 2020.
24. Balaisyte L, Joos A, Hiligsmann M. Early Dialogue in Europe: Perspectives on Value, Challenges, and Continuing Evolution. *Int J Technol Assess Health Care.* 2018;34(5):514-518.
25. Wang T, McAuslane N, Liberti L, Leufkens H, Hovels A. Building Synergy between Regulatory and HTA Agencies beyond Processes and Procedures-Can We Effectively Align the Evidentiary Requirements? A Survey of Stakeholder Perceptions. *Value Health.* 2018;21(6):707-714.
26. Messner DA, Towse A, Mohr P, Garau M. The future of comparative effectiveness and relative efficacy of drugs: an international perspective. *J Comp Eff Res.* 2015;4(4):419-427.
27. Institute of Medicine Committee on Comparative Effectiveness Research Prioritization. *Initial National Priorities for Comparative Effectiveness Research.* Washington, DC, USA: The National Academies Press; 2009.
28. Jonsson B. Relative effectiveness and the European pharmaceutical market. *Eur J Health Econ.* 2011;12(2):97-102.
29. Eichler HG, Abadie E, Breckenridge A, et al. Bridging the efficacy-effectiveness gap: a regulator's perspective on addressing variability of drug response. *Nat Rev Drug Discov.* 2011;10(7):495-506.
30. Wildson T, A S. *A comparative analysis of the role and impact of Health Technology Assessment* Charles River Associates; 2011.
31. Towse A, Jonsson B, McGrath C, et al. UNDERSTANDING VARIATIONS IN RELATIVE EFFECTIVENESS: A HEALTH PRODUCTION APPROACH. *International journal of technology assessment in health care.* 2015;31(6):363-370.
32. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361(12):1139-1151.
33. Garber AM, Sox HC. The role of costs in comparative effectiveness research. *Health Aff (Millwood).* 2010;29(10):1805-1811.
34. Myshko D. Addressing Reimbursement During Development. 2012; https://www.pharmavoice.com/article/2012-05-addressing-reimbursement-during-development/. Accessed January 12 2020.
35. Miller HI. A proposal for FDA reform. *Nat Rev Drug Discov.* 2002;1(8):642-648.
36. Woodcock J. Comparative effectiveness research and the regulation of drugs, biologics and devices. *J Comp Eff Res.* 2013;2(2):95-97.
37. Patient Protection and Affordable Care Act. Public Law 111–148. www.gpo.gov/fdsys/pkg/BILLS-111hr3590enr/pdf/BILLS-111hr3590enr.pdf. Accessed January 08, 2020.

38. Messner DA, Mohr P, Towse A. Futurescapes: evidence expectations in the USA for comparative effectiveness research for drugs in 2020. *J Comp Eff Res.* 2015;4(4):385-400.
39. Blackstone EA, Fuhr JP, Jr., Ziernicki D. Will comparative effectiveness research finally succeed? *Biotechnol Healthc.* 2012;9(3):22-26.
40. CTMP. Green Park Collaborative. 2020; http://www.cmtpnet.org/green-park-collaborative/. Accessed January 12, 2020.
41. European Commission. High level pharmaceutical forum 2005-2008 conclusions and recommendations. 2008; https://op.europa.eu/en/publication-detail/-/publication/4fddf639-47cc-4f90-9964-142757d2515a. Accessed Februray 03, 2020.
42. Berntgen M, Gourvil A, Pavlovic M, Goettsch W, Eichler HG, Kristensen FB. Improving the contribution of regulatory assessment reports to health technology assessments--a collaboration between the European Medicines Agency and the European network for Health Technology Assessment. *Value Health.* 2014;17(5):634-641.
43. European Medicines Agency. EMA-EUnetHTA three-year work plan. 2013; https://www.ema.europa.eu/en/documents/other/european-medicines-agency-eunethta-three-year-work-plan_en.pdf. Accessed January 09, 2020.
44. Tafuri G, Pagnini M, Moseley J, et al. How aligned are the perspectives of EU regulators and HTA bodies? A comparative analysis of regulatory-HTA parallel scientific advice. *Br J Clin Pharmacol.* 2016;82(4):965-973.
45. Dekker M, Bouvy JC, O'Rourke D, et al. Alignment of European Regulatory and Health Technology Assessments: A Review of Licensed Products for Alzheimer's Disease. *Front Med (Lausanne).* 2019;6:73.
46. U.S. Department of Health and Human Services Food and Drug Administration. Best Practices for Communication Between IND Sponsors and FDA During Drug Development Guidance for Industry and Review Staff Good Review Practice 2017; https://www.fda.gov/media/94850/download. Accessed March 25, 2019.
47. European Medicines Agency. *European Medicines Agency guidance for applicants seeking scientific advice and protocol assistance* London: EMA; 2017.
48. Hofer MP, Jakobsson C, Zafiropoulos N, et al. Regulatory watch: Impact of scientific advice from the European Medicines Agency. *Nat Rev Drug Discov.* 2015;14(5):302-303.
49. Backhouse ME, Wonder M, Hornby E, Kilburg A, Drummond M, Mayer FK. Early dialogue between the developers of new technologies and pricing and reimbursement agencies: a pilot study. *Value Health.* 2011;14(4):608-615.
50. Fronsdal K, Pichler F, Mardhani-Bayne L, et al. Interaction initiatives between regulatory, health technology assessment and coverage bodies, and industry. *Int J Technol Assess Health Care.* 2012;28(4):374-381.
51. European Medicines Agency. *EMA-HTA workshop Bringing together stakeholders for early dialogue in medicines development:Report from the public workshop hosted by the European Medicines Agency (EMA) in London on 26 November 2013.* London: EMA; 2013.
52. Khan S, Carter M. European Medicines Agency-Health Technology Assessment Parallel Consultation Platform: An Industry Perspective. *Clin Pharmacol Ther.* 2019;105(4):822-825.
53. European Medicines Agency. Report on the implementation of the EMA-EUnetHTA threeyear work plan 2012-2015. 2016; https://www.ema.europa.eu/en/documents/report/report-implementation-european-medicines-agency-european-network-health-technology-assessment_en.pdf. Accessed January 23, 2020.
54. European Medicines Agency. Best Practice guidance for Pilot EMA HTA Parallel Scientific Advice procedures. 2014; https://www.ema.europa.eu/en/documents/regulatory-procedural-

guideline/draft-best-practice-guidance-pilot-european-medicines-agency-health-technology-assessment-parallel_en.pdf. Accessed January 15, 2020.
55. Tschank D. *The Impact of the EMA-EUnetHTA Collaboration on Drug Development*: der Mathematisch-Naturwissenschaftlichen Fakultät, Friedrich-Wilhelms-Universität Bonn; 2014.
56. Bramley T, Spackman E, Hebborn A, Ho LK, Parcher B, McLaughlin T. To Seek or Not to Seek Parallel European Medicine Agency and Health Technology Assessment Scientific Advice? *Value & Outcomes Spotlight* 2017(March/April):12-15.
57. Tafuri G, Lucas I, Estevao S, et al. The impact of parallel regulatory-health technology assessment scientific advice on clinical development. Assessing the uptake of regulatory and health technology assessment recommendations. *Br J Clin Pharmacol.* 2018;84(5):1013-1019.
58. NICE. Scientific Advice. 2020; https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice. Accessed January 03, 2020.
59. Trapestry Network. Pilots of multi-country, multi-stakeholder consultations in drug development: from proof of concept to tangible benefits. 2012; https://www.tapestrynetworks.com/sites/default/files/publication_pdf/Pilots-of-multi-stakeholder-consultations-in-drug-development-6-June-2012.pdf. Accessed February 05, 2020.
60. Wonder M, Backhouse ME, Hornby E. Early scientific advice obtained simultaneously from regulators and payers: findings from a pilot study in Australia. *Value Health.* 2013;16(6):1067-1073.
61. McAuslane N, Liberti L, Connelly P. The Confluence of Accelerated Regulatory and Health Technology Assessment Access Pathways. *Clin Pharmacol Ther.* 2019;105(4):935-942.
62. Australian Government. Memorandum of Understanding 2010; http://www.pbs.gov.au/industry/useful-resources/memorandum/MOU-MA-Sep2010.pdf. Accessed January 12, 2020.
63. Department of Health. TGA and PBAC Parallel Process and Requirements. 2018; http://www.pbs.gov.au/info/publication/factsheets/shared/tga-pbac-parallel-process. Accessed March 25, 2020.
64. Pearce A, van Gool K, Haywood P, Haas M. Delays in access to affordable medicines: putting policy into perspective. *Aust Health Rev.* 2012;36(4):412-418.
65. Centre for Innovation in Regulatory Science (CIRS). *Review of HTA outcomes and timelines in Australia, Canada and Europe 2014-2015.* London: CRIS; 2017.
66. GlaxoSmithKline Australia Pty Ltd, ViiV Healthcare Pty Ltd. The Pharmaceutical Benefi ts Scheme in Australia: An explainer on system components. 2018; https://au.gsk.com/media/421635/gsk-viiv-the-pbs-in-australia-feb-2018.pdf. Accessed January 21, 2020.
67. CADTH. CADTH Common Drug Review Will Accept Submissions Up to Six Months Pre-Notice of Compliance (NOC). 2018; https://cadth.ca/news/cadth-common-drug-review-will-accept-submissions-six-months-pre-notice-compliance-noc. Accessed January 15, 2020.
68. Liberti L. Will parallel regulatory and HTA review processes reduce access time for patients in Canada? 2018; https://www.cadth.ca/sites/default/files/symp-2018/presentations/april16-2018/Concurrent-Session-B1-Lawrence-Liberti.pdf. Accessed January 12, 2020.
69. Federal Register. Parallel Review of Medical Products. 2010; https://www.federalregister.gov/documents/2010/09/17/2010-23252/parallel-review-of-medical-products. Accessed February 12, 2020.
70. Podemska-Mikluch M. *FDA-CMS Parallel Review: A Failed Attempt at Spurring Innovation.* Arlington, VA: Mercatus Center at George Mason University, ; 2016.
71. Ridge JR, Statz S. Exact Sciences' experience with the FDA and CMS parallel review program. *Expert Rev Mol Diagn.* 2015;15(9):1117-1124.

72. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med.* 2014;370(15):1393-1401.
73. Register F. Program for Parallel Review of Medical Devices. 2016; https://www.federalregister.gov/documents/2016/10/24/2016-25659/program-for-parallel-review-of-medical-devices. Accessed January 11, 2020.
74. Mezher M. FDA, CMS: Second Parallel Review Decision Ever for NGS Test. 2017; https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/12/fda,-cms-second-parallel-review-decision-ever-for-ngs-test. Accessed January 23, 2020.
75. Netherlands Healthcare Institute Pilot 'Parallel Procedures MEB-ZIN'. 2020; https://www.zorginstituutnederland.nl/werkagenda/parallelle-procedures-cbg-zin. Accessed April 25, 2020.
76. MaRS Discovery District. Why the medical device industry is shifting focus to early health technology assessment. 2020; https://www.marsdd.com/news/why-the-medical-device-industry-is-shifting-focus-to-early-health-technology-assessment/. Accessed January 15, 2020.
77. Bouvy JC, Jonsson P, Longson C, Crabb N, Garner S. Health Technology Assessment in the Context of Adaptive Pathways for Medicines in Europe: Challenges and Opportunities. *Clin Pharmacol Ther.* 2016;100(6):594-597.
78. Brownsword R, Scotford E, Yeung K. *The Oxford Handbook of Law, Regulation, and Technology.* Oxford, UK: Oxford University Press; 2017.
79. Eichler HG, Oye K, Baird LG, et al. Adaptive licensing: taking the next step in the evolution of drug approval. *Clin Pharmacol Ther.* 2012;91(3):426-437.
80. Nicotera G, Sferrazza G, Serafino A, Pierimarchi P. The Iterative Development of Medicines Through the European Medicine Agency's Adaptive Pathway Approach. *Front Med (Lausanne).* 2019;6:148.
81. Eichler HG, Baird LG, Barker R, et al. From adaptive licensing to adaptive pathways: delivering a flexible life-span approach to bring new drugs to patients. *Clinical pharmacology and therapeutics.* 2015;97(3):234-246.
82. Stein D, Soni M. Early Access Programs Opportunities and Challenges for Real-World Data Collection. 2018; https://www.evidera.com/wp-content/uploads/2018/05/Early-Access-Programs-Real-World-Data.pdf. Accessed January 12, 2020.
83. European Medicines Agency. PRIME: priority medicines 2020; https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines. Accessed March 22, 2020.
84. European Medicines Agency. Conditional marketing authorisation 2020; https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation. Accessed April 02, 2020.
85. European Medicines Agency. Compassionate use 2020; https://www.ema.europa.eu/en/human-regulatory/research-development/compassionate-use. Accessed January 12, 2020.
86. European Medicines Agency. Final report on the adaptive pathways pilot. 2020; https://www.ema.europa.eu/en/documents/report/final-report-adaptive-pathways-pilot_en.pdf. Accessed February 16, 2020.
87. National Institute for Public Health and the Environment. *The adaptive pathways process: benefits and potential hurdles from a Dutch perspective.* Bilthoven, The Netherlands: RIVM; 2016.
88. Baird LG, Trusheim MR, Eichler HG, Berndt ER, Hirsch G. Comparison of Stakeholder Metrics for Traditional and Adaptive Development and Licensing Approaches to Drug Development. *Ther Innov Regul Sci.* 2013;47(4):474-483.

89. Innovative Medicines Initiative. ADAPTSMART. 2020; http://adaptsmart.eu/adapt-smart-kick-off-meeting-the-innovative-medicines-initiatives-adapt-smart-laying-the-foundations-and-building-consensus-to-make-mapps-work-for-all/. Accessed March 15, 2020.
90. Oye K, Baird LG, Chia A, et al. Legal foundations of adaptive licensing. *Clin Pharmacol Ther.* 2013;94(3):309-311.
91. Schulthess D, Baird LG, Trusheim M, et al. Medicines Adaptive Pathways to Patients (MAPPs): A Story of International Collaboration Leading to Implementation. *Ther Innov Regul Sci.* 2016;50(3):347-354.
92. European Medicines Agency. European Medicines Agency post-authorisation procedural advice for users of the centralised procedure 2019; https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-post-authorisation-procedural-advice-users-centralised-procedure_en.pdf. Accessed March 12, 2020.
93. Food and Drug Administration. Postmarketing Studies and Clinical Trials - Implementation of section 505(o)(3) of the Federal Court Food, Drug and Cosmetic Act. 2011. 2011; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf. Accessed March 13, 2020.
94. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. ENCePP Guide on Methodological Standards in Pharmacoepidemiology. 2018; http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml. Accessed January 12, 2020.
95. Blake K, Kurz X, Toussi M, al e. ENCePP-HTA Working Group 2014 survey of members' experience in conducting research to support HTA. 2014; http://www.encepp.eu/publications/documents/ENCePP_HTA_Poster_ICPE2014.pdf. Accessed January 13, 2020.
96. Tavridou A, Sarinic V. PRAC interaction with SAWP PASS pilot and other consultations. 2016; https://www.ema.europa.eu/en/documents/presentation/presentation-prac-interaction-sawp-anna-tavridou_en.pdf. Accessed April 25, 2020.
97. European Medicines Agency. Patient Registries. 2018; https://www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries. Accessed January 15, 2020.
98. Get Real. Overall objectives. 2020; https://www.imi-getreal.eu/About-GetReal/Overall-objectives. Accessed January 16, 2020.
99. Tsoi B, O'Reilly D, Masucci L, Drummond M, Goeree R. Harmonization of HTA--based reimbursement and regulatory approval activities: a qualitative study. *J Popul Ther Clin Pharmacol.* 2015;22(1):e78-89.
100. Kesselheim AS, Mello MM. Confidentiality laws and secrecy in medical research: improving public access to data on drug safety. *Health Aff (Millwood).* 2007;26(2):483-491.
101. Hailey D. Toward transparency in health technology assessment: a checklist for HTA reports. *Int J Technol Assess Health Care.* 2003;19(1):1-7.
102. CADTH. Procedures for the CADTH Common Drug Review and Interim Plasma Protein Product Review. 2020; https://cadth.ca/sites/default/files/cdr/process/Procedure_and_Guidelines_for_CADTH_CDR.pdf. Accessed March 25, 2020.
103. Swedish Medical Products Agency. Scientific Advice. 2019; https://www.lakemedelsverket.se/en/permission-approval-and-control/advisory/scientific-advice. Accessed January, 15, 2020.

Supplementary materials

Table S1: Search strategy for decision making processes for HTA and regulatory agencies

1. Decision mak*.mp. OR decision-mak*.mp. OR decision process*.mp. OR decision technique*.mp. OR (decision-making).m_titl OR (decision-making process).m_titl. OR (decision making).m_titl. OR decision-making approach OR exp decision making/ OR (decision techniques).m_titl. OR (decision-making strategies).m_titl.

2. (Health technology assessment).mp. OR exp technology assessment, biomedical/ OR (health technology assessment).m_titl. OR HTA.mp. OR HTA.m_titl. OR cost-effectiveness analysis.mp. or exp Cost-Benefit Analysis/ OR (cost-effectiveness analysis).m_titl. OR (cost-benefit analysis).m_titl. OR cost-benefit analys* OR economic evaluation*.mp. OR (economic evaluation).m_titl. OR cost-utility analys*.mp. OR (cost-utility analysis).m_titl. OR health economic evaluation*.mp. OR (health economic evaluation).m_titl. OR cost-benefit evaluation*.mp. OR (cost-benefit evaluation).m_titl OR technology assessment*.mp. OR (technology assessment).m_titl. OR economic analys*.mp. OR (economic analysis).m_titl.

3. Exp drug approval/ OR (drug approval).mp. OR (drug approval).m_titl. OR (pharmaceutical approval).mp. OR (pharmaceutical approval).m_titl. OR (drug regulation).mp. OR (drug regulation).m_titl. OR (pharmaceutical regulation).mp. OR (pharmaceutical regulation).m_titl. OR exp legislation, Drug/ OR (drug legislation).mp. OR (drug legislation).m_titl. OR (pharmaceutical legislation).mp. OR (pharmaceutical legislation).m_titl. OR government regulation* OR (pharmaceutical administration).mp. OR (pharmaceutical administration).m_titl. OR exp government regulation/ OR (government regulation).m_titl. OR (government regulation).mp. OR exp drug industry/ OR (drug industry).mp. OR (drug industry).m_titl. OR (drug industry legislation).mp. OR (drug industry legislation).m_titl. OR (drug standards).mp. OR (drug standards).m_titl. OR (pharmaceutical standards).mp. OR (pharmaceutical standards).m_titl. OR (pharmaceutical approval).mp. OR (pharmaceutical approval).m_titl. OR (Drug Industry jurisprudence).mp. OR (Drug Industry jurisprudence).m_titl. OR exp "United States Food and Drug Administration"/ OR FDA.m_titl. OR (Food and drug administration).m_titl. Or EMA OR (European medicines agency).m_titl.

4. 2 OR 3

5. 1 AND 4

6. Limit 5 to (English language and humans)
7. Limit 7 to English language

Table S2: Search strategy for synergies between HTA and regulatory agencies

1.	(Health technology assessment).mp. OR exp technology assessment, biomedical/ OR (health technology assessment).m_titl. OR HTA.mp. OR HTA.m_titl. OR cost-effectiveness analysis.mp. or exp Cost-Benefit Analysis/ OR (cost-effectiveness analysis).m_titl. OR (cost-benefit analysis).m_titl. OR cost-benefit analys* OR economic evaluation*.mp. OR (economic evaluation).m_titl. OR cost-utility analys*.mp. OR (cost-utility analysis).m_titl. OR health economic evaluation*.mp. OR (health economic evaluation).m_titl. OR cost-benefit evaluation*.mp. OR (cost-benefit evaluation).m_titl OR technology assessment*.mp. OR (technology assessment).m_titl. OR economic analys*.mp. OR (economic analysis).m_titl.
2.	Exp drug approval/ OR (drug approval).mp. OR (drug approval).m_titl. OR (pharmaceutical approval).mp. OR (pharmaceutical approval).m_titl. OR (drug regulation).mp. OR (drug regulation).m_titl. OR (pharmaceutical regulation).mp. OR (pharmaceutical regulation).m_titl. OR exp legislation, Drug/ OR (drug legislation).mp. OR (drug legislation).m_titl. OR (pharmaceutical legislation).mp. OR (pharmaceutical legislation).m_titl. OR government regulation* OR (pharmaceutical administration).mp. OR (pharmaceutical administration).m_titl. OR exp government regulation/ OR (government regulation).m_titl. OR (government regulation).mp. OR exp drug industry/ OR (drug industry).mp. OR (drug industry).m_titl. OR (drug industry legislation).mp. OR (drug industry legislation).m_titl. OR (drug standards).mp. OR (drug standards).m_titl. OR (pharmaceutical standards).mp. OR (pharmaceutical standards).m_titl. OR (pharmaceutical approval).mp. OR (pharmaceutical approval).m_titl. OR (Drug Industry jurisprudence).mp. OR (Drug Industry jurisprudence).m_titl. OR exp "United States Food and Drug Administration"/ OR FDA.m_titl. OR (Food and drug administration).m_titl. Or EMA OR (European medicines agency).m_titl.
3.	1 AND 2
4.	Synerg*.mp. OR synerg.mp. OR synergy.m_titl. OR synergies.m_titl. OR align*.mp. OR alignment.m_titl. OR alignments.m_titl. OR collaborat*.mp. OR collaborate.m_titl. OR collaboration.m_titl. OR engage*.mp. OR engage.m_titl. OR engagement.m_titl. OR agree* OR agreement.m_titl. OR disagree*.mp. OR disagreement.m_titl. OR alliance* OR alliance.m_titl. OR partner*.mp. OR partnership.m_titl. OR harmon*.mp. OR hamony.m_titl. OR hamonisation.m_titl. OR harmonization.m_titl. OR confluence*.mp. OR confluence.m_titl. OR collision*.mp. OR collision.m_titl. OR standard*.mp. OR standardisation.m_titl. OR standardization.m_titl. OR cooperate*.mp. OR cooperation.m_titl. OR interact*.mp. OR interaction.m_titl. OR parallel scientific advice.mp. OR (parallel scientific advice).m_titl. OR (Parallel Regulatory-HTA Scientific Advice).m_titl. OR scientific advice.mp. OR (scientific advice).m_titl. OR parallel consultation*.mp. OR (parallel consultation).m_titl.
5.	3 AND 4
6	Limit 5 to (English language and humans)

Table S3: List of HTA bodies and websites

Country	HTA body (formal)	Other HTA bodies	Website
Europe	n/a	EUnetHTA: European Network for Health Technology Assessment Health Evidence Network (HEN) EuroScan - The European Information Network on New and Changing Health Technologies EURONHEED Database – Health economics Central and Eastern European Society for TA in Health Care (CEESTAHC)	http://www.eunethta.net/ http://www.euro.who.int/hen http://www.euroscan.bham.ac.uk/ http://infodoc.inserm.fr/euronheed/Publication.nsf
International	n/a	INAHTA - The International Network of Agencies for Health Technology Assessment Health Technology Assessment International (HTAi) ISPOR global health care system roadmap WHO Essential Health Technologies (EHT)	
Albania	n/a	MoH, Dept of General Policy Planning and Health Pharmaceutical Directorate	n/a
Armenia	n/a	n/a	n/a
Australia	Pharmaceutical Benefit Advisory Committee (PBAC)/ Medical Services Advisory Committee (MSAC)	National Health and Medical Research Council Australia Victorian Policy Advisory Committee on Clinical Practice and Technology Centre for Health Program Evaluation (Monash University) The Centre for Clinical Effectiveness (CCE) Adelaide Health Technology Assessment (Committee) (AHTA) Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) Centre for Health Economics Research and Evaluation (CHERE) Australia and New Zeland Horizon Scanning Network (ANZHSN) Social and Public Health Economics Research Group (SPHERE) University for Health Sciences, Medical Informatics and Technology	http://www.msac.gov.au/ http://www.nhmrc.gov.au/ http://www.health.vic.gov.au/newtech/committee.htm http://www.buseco.monash.edu.au/centres/che/ http://www.mihsr.monash.org/cce/ http://www.adelaide.edu.au/ahta/ http://www.surgeons.org/asernip-s/ http://www.chere.uts.edu.au/ http://www.horizonscanning.gov.au/ http://sphere.curtin.edu.au/
Austria	Austrian Federal Institute for Health Care (ÖBIG) / Austrian Institute of Technology Assessment	Gesundheit Osterreich GmBH, Austrian Health Institute (GoG) Ludwig Boltzmann Institute of Health Technology Assessment (LBI for HTA) Institute for Pharmaeconomic Research (IPF) University for Health Sciences, Medical computer science and engineering Institute of Public Health, Medical Decision Making and HTA Department for Evidence-Based Medicine and Clinical Epidemiology , Danube University Krems	http://www.oeaw.ac.at/ita/welcome.htm http://hta.lbg.ac.at/de/index.php http://www.ipf-ac.at http://www.umit.at/page.cfm?vpath=departments/public_health
Belgium	Belgian Health Care Knowledge Centre (KCE)	Centre for Health Services Research Katholieke Univesiteit Leuven Research and Development	http://www.kce.fgov.be/Index.aspx?SGREF=3232 https://www.inami.fgov.be/fr/Pages/default.aspx

Country	HTA body (formal)	Other HTA bodies	Website
	National institute for Health and Disability Insurance		
Bosnia and Herzegovina	HTA board by MoH (recently established)	n/a	http://www.alims.gov.ba/index.html www.farmakoekonomika.ba
Bulgaria	n/a	Committee for the Positive Drug List National Centre of Public Health Protection (NCPHP)	
Canada	Canadian Agency for Drugs and Technologies in Health (CADTH)	Institut National d'Excellence en Sante et Services Sociaux (INESS) Alberta Heritage Foundation for Medical Research (AHFMR) British Columbia Centre for Health Services and Policy Research (CHSPR) Institute for Clinical Evaluative Sciences (ICES) Institute of Health Economics (IHE) Centre for Health Economics and Policy Research (CHEPA) Centre for Health Services and Policy Research (CHSPR) Calgary Institute for Population and Public Health (CIPPH) Toronto Health Economics and Technology Assessment (THETA) Centre for Health Evaluation and Outcome Sciences (CHEOS) Centre Hospitalier de l'Université de Montréal (CHUM) Canadian Task Force on Preventive Health Care (CTFPHC) Health Quality Council (HQC) Technology Assessment Unit of the McGill University Health Centre (MUHC) Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care (MAS) Ontario Health Technology Advisory Committee (OHTAC) Programs for Assessment of Technology in Health, McMaster University (PATH)	http://www.inesss.qc.ca/ http://www.ahfmr.ab.ca/ http://www.chspr.ubc.ca/ http://path-hta.ca/report.htm http://www.cadth.ca/index.php/en/home http://www.ices.on.ca/webpage.cfm http://www.ihe.ca/ http://www.chepa.org/Home.aspx http://www.chspr.ubc.ca/ http://www.ucalgary.ca/cipph/ http://theta.utoronto.ca/ http://www.cheos.ubc.ca/ http://www.chumtl.qc.ca/notre-equipe/directions/detmis.fr.html http://www.ctfphc.org/ http://healthcouncilcanada.ca/en/index.php http://www.mcgill.ca/tau/ http://www.health.gov.on.ca/english/providers/program/mas/mas_mn.html
China (Hong Kong)	n/a	School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong	
Croatia	Agency for Quality and Accreditation in Health Care, Croatia Department for Development, Research and HTA	n/a	http://www.aaz.hr/main.php?ID=4
Cyprus	n/a	n/a	http://www.moh.gov.cy/moh/moh.nsf/dmlhealth_en/dmlhealth_en?OpenDocument

Country	HTA body (formal)	Other HTA bodies	Website
Czech Republic	National Reference Centre/Drug Categorization Committee	n/a	http://www.nrc.cz/
Democratic People's Republic of Korea	n/a	n/a	n/a
Denmark	Danish Centre for Evaluation and HTA (DACEHTA)	Centre for Applied Health Services Research and Technology Assessment (CAST) Danish Institute for Health Services Research and Development (DSI) Odense Universitetshospital, Department of Quality and Research, Health Technology Assessment Centre for Applied Health Services Research and Technology Assessment (CAST) Centre for Public Health, MTV og Sundhedstjeneste- forskning National Board of Health (NBoH) Institute for Rational Pharmacotherapy (IRF)	http://www.sst.dk/Planlaegning_og_behandling/Medicinsk_teknologivurdering.aspx?lang=en http://www.dsi.dk/ http://www.ouh.dk/wm134768 http://www.sdu.dk/om_sdu/institutter_centre/cast http://www.centerforfolkesundhed.dk/om+centret/in+english
Estonia	n/a	Pharmaceutical Committee and State Agency of Medicines Estonian Health Insurance Fund (EHIF) University of Tartu-Department of Public Health (UTA)	http://www.haigekassa.ee/kindlustatule/soodusravimid/hindamine/
Finland	Finnish Office for Health Technology Assessment (FinOHTA)	n/a	http://finohta.stakes.fi/EN/index.htm
France	Agence Nationale d'Accreditation et d'Evaluation en Santé et Haute Autorité de Santé (ANAES and HAS)	Agence Nationale pour le Developpement de l'Evaluation Medicale (ANDEM) Comité d'Evaluation et de Diffusion des Innovations Technologiques Assistance Publique Hôpitaux de Paris, France (CEDIT) Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS) REES - Reseau d'Evaluation en Economie de la Sante	http://www.has-sante.fr/portail/display.jsp?id=j_5 http://upml.fr/andem/andem.htm http://cedit.aphp.fr/ http://www.rees-france.com/
Germany	The Institute for Quality and Efficiency in Health Care (IQWiG)	German Institute for Medical Documentation and Information (DIMDI) Hannover Medical School, Medizinische Hochschule Hannover (MHH) Institute for Public Health and Nursing Research, IPP Bremen Department of Health Services Research, Faculty for Human Sciences and Health Sciences, The University of Bremen German Health Care System and the Federal Joint Committee (G-ba)	http://www.dimdi.de/static/en/index.html http://www.iqwig.de/ http://www.mh-hannover.de/ http://www.g-ba.de
Greece	National Organisation for Medicines (EOF)	Center for Health Services Management and Evaluation, University of Athens National School of Public Health (NSPH/ESDY)	http://www.eof.gr/ http://chesme.nurs.uoa.gr/eng/ http://www.nsph.gr/default.aspx?page=home

Country	HTA body (formal)	Other HTA bodies	Website
Hungary	Health Economics and Technology Assessment Research Centre (HunHTA)	Technology Appraisal Committee (TAC) Office of HTA (OHTA) Hungarian Coordination Office for HTA (HCOHTA) National Institute for Quality and Organizational Development in Healthcare and Medicines (GYEMSZI)	http://hecon.uni-corvinus.hu/ http://www.medinfo.hu/new3/technologia_en/technologia_en.php http://gyemszi.hu/
Iceland	n/a	n/a	http://www.velferdarraduneyti.is/raduneyti/um-raduneytid/
Ireland	Health Information and Quality Authority (HIQA)	Health Economics Association of Ireland (HEAI) Medicines Board National Centre for Pharmacoeconomics (NCPE)	http://www.dohc.ie/ http://www.hiqa.ie/publications.asp http://www.ncpe.ie/index.php
Israel	Israel Center for Technology Assessment in Health Care (ICTAHC)	n/a	http://www.gertnerinst.org.il/e/health_policy_e/technology/ http://www.health.gov.il/english/
Italy	L'Agenzia nazionale per I servizi sanitari regionali, the Agency for Regional Healthcare (Age.Na.S)	HTA Unit in A. Gemelli Teaching Hospital (UVT) OSMED Coordination Office and the activities of HTA Laziosanita, Agenzia di Sanita Pubblica, Regione Lazio Reglom-DGSAN, Regione Lombardia Direzione Generale Sanita Regione Emilia Romagna, Agenzia Sanitaria e Sociale Regione Emilia Romagna (ASSR) Regione Veneto, Direzione Piani e Programmi Socio Sanitari	http://www.assr.it/ http://www.policlinicogemelli.it/area/?s=206 http://asr.regione.emilia-romagna.it/
Japan	Institute of Healthcare Technology Assessment, Shomachi/ Department of Technology Assessment and Biostatistics	Technology Assessment & Decision Science Unit College of Life Sciences, Ritsumeikan University Department of Health Economics and Epidemiology Research, University of Tokyo	http://www.niph.go.jp/English/research/01techno/index.html
Latvia	Health Statistics and Medical Technology State Agency (VSMTA)	State Medicines Pricing and Reimbursement Agency Centre for Health Economics (VEC)	http://www.vm.gov.lv/index.php?setlang=en http://vec.gov.lv/en
Leichtenstein	n/a	n/a	http://www.llv.li/amtsstellen/llv-ag-home.htm
Lithuania	State Health Care Accreditation Agency under the MoH (VASPVT)	Pharmaceutical Reimbursement Committee	http://www.vaspvt.gov.lt/en

Country	HTA body (formal)	Other HTA bodies	Website
Luxembourg	n/a	Cellule d'Expertise Medicale (CEM) Centre de Recherche Public de la Sante (CRP-Sante)	http://www.ms.public.lu/fr/index.html
Malta	Pharmaceutical HTA Unit	Ministry for Social Policy/Strategy and Sustainability Division (SSD/MSOC)	https://ehealth.gov.mt/HealthPortal/strategy_policy/pharm_pol_mon/pharm_hta_unit.aspx
Monaco	n/a	n/a	http://www.gouv.mc/devwww/wwwnew.nsf/
Netherlands	National Health Care Institute		https://english.zorginstituutnederland.nl/about-us
New Zealand	Pharmacology and Therapeutics Advisory Committee (PTAC)/ New Zealand Health Technology Assessment (NZHTA)	Core Services Committee Health Services Assessment Collaboration (HSAC)	http://www.healthsac.net/index.htm http://nzhta.chmeds.ac.nz/
Norway	Norwegian Knowledge Centre for the Health Services (NOKC)	Health Services Research Unit Institute of Community Medicine SINTEF-UNIMED	http://www.kunnskapssenteret.no/
Poland	Agencja Oceny Technologii Medycznych, Agency for Health Technology Assessment in Poland (AHTAPol)	Association for Quality Promotion (TPJ) Centre for Farmacoeconomics Polish Society for Pharmacoeconomics Central and Eastern European Society for Technology Assessment in Health Care (CEESTAHC)	http://www.tpj.pl/hta.php http://www.farmakoekonomika.edu.pl/ http://www.aotm.gov.pl/ http://www.farmakoekonomika.pl/
Portugal	National Institute of Pharmacy and Medicines (INFARMED)	n/a	http://www.infarmed.pt/portal/page/portal/INFARMED/ENGLISH
Republic of Korea (South)	Health Insurance Review and Assessment Agency (HIRA)	National Evidence-based Healthcare Collaborating Agency (NECA) Korea Association of HTA (KAHTA) Committee for New Health Technology Assessment (CNHTA)	http://www.hira.or.kr/cms/rb/rbb_english/index.html?pgmid=HIRAB960000000000 www.neca.re.kr http://www.kahta.or.kr/
Romania	n/a	National School of Public Health, Management and Professional Development (SNSPMS)	
Serbia	n/a	Medicines and Medical Devices Agency of Serbia (ALIMS) Quality Unit, Ministry of Health Serbia	http://www.alims.gov.rs/

Country	HTA body (formal)	Other HTA bodies	Website
Singapore	Research and TA Department	n/a	http://www.singhealth.com.sg/Research/HealthServicesResearch/OurServices/HealthTechnologyAssessment/Pages/Home.aspx http://www.moh.gov.sg/mohcorp/publications.aspx?id=92
Slovakia (Slovak Republic)	Slovak Agency for HTA (SLOVATHA)	n/a	http://www.health.gov.sk/ http://www.farmako-ekonomika.sk/main.php?skok=60&idnew=353
Slovenia	Agency for medicinal products and medical devices of the republic of slovenia (JAZMP)	Health Insurance Institute Institute of Public Health of the Republic of Slovenia (NIPH-RS) Institute for Economic Research (IER), Ministry of Health, Slovenia	http://www.jazmp.si/index.php?id=1
Spain	Agencia de Evaluación de Tecnologías Sanitarias (Instituto de Salud Carlos III) (AETS)	Catalan Agency for Health Information, Assessment, and Quality (CAHIAQ formely CAHTA) Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) Basque Office for Health Technology Assessment (OSTEBA) Agencia de Evaluación de Tecnologías Sanitarias de Galicia (AVALIA-T) Agencia de Evaluación de Tecnologías Sanitarias de Canarias Agencia de Evaluación de Tecnologías Lain Entralgo, also host of Unidad de Evaluacion de Tecnologias Sanitarias (UETS) Ministry of Health and Social Policy	http://www.isciii.es/htdocs/index.jsp http://www.gencat.net/salut/depsan/units/aatrm/html/en/dir394/index.html http://www.juntadeandalucia.es/salud/orgdep/aetsa/ http://www.osasun.ejgv.euskadi.net/r52-2536/es/ http://www.sergas.es/MostrarContidos_Portais.aspx?IdPaxina=60538&Idioma=es http://www.gobiernodecanarias.org/sanidad/sescs/ http://www.madrid.org/cs/Satellite?c=CM_Actuaciones_FA&cid=1142402651366&idConsejeria=1109266187266&idListConsj=1109265444710&idOrganismo=1109266228196&language=es&pagename=ComunidadMadrid%2FEstructura&pid=1109265444699&sm=1109266100977
Sweden	Swedish Council on Technology Assessment in Health Care (SBU)/Dental and Pharmaceutical Benefits Agency (TLV)	Center for Medical Technology Assessment, Linköping University (CMT) Center for evidence-based medicine and health technology assessment in Örebro County Council (OCC) HTA Center Western Götlandsregionen (CWG) The Swedish Institute for Health Economics (IHE) Centre for evidence-based medicine and evaluation of medical training in the Örebro County Council (CAMTO)	http://www.sbu.se/en/ http://www.cmt.liu.se/ http://www.orebroll.se/uso/page____2834.aspx http://www.sahlgrenska.se/sv/SU/Forskning/HTA-centrum/Hogerkolumn/Genomforda-mini-HTA/ http://www.ihe.se/ http://www.orebroll.se/sv/uso/Forskning/Forskningsenheter/CAMTO/
Switzerland	Swiss Centre for Technology Assessment (TA-SWISS)/ Medical Technology Unit - Swiss Federal Office of Public Health (MTU-SFOPH)	Swiss Network for Health Technology Assessment (SNHTA) Federal Office of Public Health Medical Advisors Section	http://www.ta-swiss.ch/en/ http://www.snhta.ch/home/portal.php http://www.bag.admin.ch/

Country	HTA body (formal)	Other HTA bodies	Website
Ukraine	n/a	n/a	
United Kingdom (England)	National Institute for Health and Care Excellence (NICE)	n/a	http://www.nice.org.uk/
United Kingdom (Scotland)	Scottish Medicines Consortium (SMC)	n/a	http://www.sign.ac.uk/
United Kingdom (Wales)	All Wales Medicines Strategy Group (AWMSG)	n/a	http://www.awmsg.org/

Country	HTA body (formal)	Other HTA bodies	Website
United States of America	Agency for Healthcare Research and Quality (AHRQ) Centre for Medical Technology Policy (CMTP)	American health care provider (AETNA) Academy of Managed Care Pharmacy (AMCP) Foundation of Managed Care Pharmacy (FMCP) Health Services/Technology Assessment Text, NLM (HSTAT database) National Information Center on Health Services Research and Health Care Technology (NICHSR) Centre for Drug Evaluation and Research (CDER) *drugs only ECRI (formerly Emergency Care Research Institute)* free access through MDT elibrary Health Technology Advisory Committee, Minnesota Department of Health (HTAC) HAYES Inc – an independent health technology assessment organization University Health System Consortium (UHC) The Institute for Clinical Systems Improvement (ICSI) Medical Technology and Practice Patterns Institute (MTPPI) National Guidelines Clearinghouse (NGC) VA Technology Assessment Program (VATAP)	http://www.aetna.com/cpb/cpb_menu.html http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat http://www.nlm.nih.gov/nichsr/nichsr.html http://www.fda.gov/AboutFDA/CentersOffices/CDER/default.htm http://www.ecri.org/Pages/default.aspx http://www.health.state.mn.us/htac/ http://www.hayesinc.com/ http://www.uhc.edu/ http://www.icsi.org/index.aspx http://www.mtppi.org/frameset.asp?Pg=/&MI=1 http://www.guideline.gov/ http://www.va.gov/vatap

Table S4: List of regulatory agencies

Country	Agencies	Websites
Multi-national	World Health Organization International organization for standardization International conference on harmonization	https://www.who.int/ https://www.iso.org/home.html https://www.ich.org/home.html
Americas	Pan American Health Organization	https://www.paho.org/hq/index.php?lang=en
Europe	European medicines Agency	https://www.ema.europa.eu/en
Australia	Therapeutics goods administration	https://www.tga.gov.au/
China	State Food and Drug administration	http://sfda.com/
Denmark	Danish Medicines Agency	https://laegemiddelstyrelsen.dk/en/Borgere/
Estonia	State Agency of Medicines	https://ravimiamet.ee/en
Finland	National agency for medicines	https://www.fimea.fi/web/en
France	National agency for the safety of medicine and health products	http://www.ansm.sante.fr/
Germany	Federal Institute for Drugs and Medical Devices	http://www.bfarm.de/
Greece	National organization for Medicines	http://www.eof.gr/
Hong Kong	Department of Health, Pharmaceutical sciences	https://www.dh.gov.hk/
Hungary	National Institute of pharmacy and nutrition	http://www.ogyei.gov.hu/
Iceland	Icelandic medicines agency	http://www.ima.is/
Ireland	Health Products Regulatory Authority	https://www.hpra.ie/
Latvia	State agency of medicines	http://www.zva.gov.lv/
Liechtenstein	Office of health/ Department of pharmaceuticals	https://www.llv.li/
Lithuania	State medicine control agency	http://www.vvkt.lt/
Luxembourg	Ministry of Health	http://www.ms.etat.lu/
Malta	Medicines authority	http://www.ms.etat.lu/
Israel	Ministry of Health	https://www.health.gov.il/English/Pages/HomePage.aspx
Italy	Italian Medicines Agency	https://www.aifa.gov.it/
Japan	Pharmaceutical and Medical devices agency	http://www.pmda.go.jp/english/index.html
Netherlands	Medicines Evaluation Board Healthcare inspectorate	https://english.cbg-meb.nl/ http://www.igz.nl/
New Zealand	Medicines and Medical devices safety authority	https://www.medsafe.govt.nz/
Norway	Ministry of Health and Care Services	https://www.regjeringen.no/en/dep/hod/id421/
Poland	Office for registration of medicinal products, medical devices and biocidal products Chief pharmaceutical inspectorate	http://www.urpl.gov.pl/ http://www.gif.gov.pl/
Portugal	National authority of medicines and health products	http://www.infarmed.pt/
Romania	National authority of medicines and medical devices	http://www.anm.ro/
Slovakia	State institute for drug control	http://www.sukl.sk/
Slovenia	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia	http://www.jazmp.si/
Russia	Public health institute	https://public-health.ru/en
Serbia	Ministry of Health	https://www.zdravlje.gov.rs/
South Korea	Ministry of food and drug safety	https://www.mfds.go.kr/eng/index.do
Spain	Spain agency for medicines and health products	http://www.aemps.gob.es/
Sweden	Medical Products Agency	http://www.lakemedelsverket.se/
Switzerland	Swiss Agency for therapeutic products	https://www.swissmedic.ch/swissmedic/en/home/about-us/swissmedic--swiss-agency-for-therapeutic-products.html
Turkey	Ministry of Health	https://www.saglik.gov.tr/?_Dil=2
Ukraine	Ministry of Health	https://en.moz.gov.ua/
UK	Medicines and healthcare products regulatory agency	https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
USA	Food and drug administration	https://www.fda.gov/

Table S5: Examples of large EU funded projects that were reviewed for relevant information

Project	**Link**
EUnetHTA Joint action 1,2, 3: Collaboration of all HTA bodies in Europe	https://www.eunethta.eu/category/activities/eunethta-joint-action-3-2016-2020/ ; https://ec.europa.eu/health/technology_assessment/joint_actions_en https://www.eunethta.eu/ja1-archive/ https://www.eunethta.eu/ja2-archive/
IMI Project PREFER – patient preferences in benefit-risk assessments: Studies how to determine and include patient-preference in decision making during the drug life cycle.	https://www.imi-prefer.eu/ https://www.imi.europa.eu/
IMI BigDATA HARMONY: Public-private partnership aiming to improve the outcomes of patients with hematological malignancies via the sharing of big data among all stakeholders.	https://www.imi.europa.eu/news-events/events/big-data-health-imis-harmony-project https://www.harmony-alliance.eu/
H2020 IMPACT HTA (improved methods and actionable tools for enhancing HTA): proposes new and improved methods, tools and guidance for decision-making across in the context of HTA and health system performance measures.	https://www.impact-hta.eu/
H2020 COMED: Pushing the boundaries of cost and outcome analysis of medical technology	http://www.comedh2020.eu/wps/wcm/connect/Site/COMED/Home https://cordis.europa.eu/project/rcn/213046/factsheet/en
IMI GetReal Initiative (Real life data in drug development): Aims to show robust new methods for collecting and synthesizing real world data that can contribute to pharmaceutical R&D and healthcare decision making.	https://www.imi-getreal.eu/ https://www.imi.europa.eu/projects-results/project-factsheets/getreal-initiative

Table S6: Short online survey sent to HTA bodies*

Q1: What is your name? **Q2:** Is there a formal link between your agency and HTA bodies? Yes/No **Q3a:** Have there been any collaborative initiatives between your organisation and HTA bodies? Yes/No **Q3b:** If yes, what are the key areas of collaboration? **Q4:** What have been the key outcomes, challenges and learning points from synergy initiatives with HTA bodies? **Q5:** Is there anything else you want to report regarding collaborative efforts with HTA bodies? **Q6a:** Do you think some of your operations can be jointly performed with HTA agencies? **Q6b:** If yes to the above question, which ones?

*The wording was reversed for regulatory agencies

Table S7: Overview of key publications informing key themes for the report

Reference	Type of document	Key highlight
Eichler et al[2]	Journal article	Discusses the methodology of relative efficacy and effectiveness
Katz[4]	Journal article	Good overview of evidentiary standards for drug approval
Liberti et al[19]	Journal article	Commentary on cooperation between regulatory agencies, sponsors and HTA bodies
Tsoi et al[3]	Journal article	In-depth review of harmonization of reimbursement and regulatory processes
Tsoi et al[99]	Journal article	Presents results of interview among Canadian HTA assessors and regulators concerning synergies
Henshall et al[20]	Journal article	Summaries discussion in an HTA assessors of their views about synergy with regulatory
Fronsdal et al[51]	Journal article	Good overview of initiatives of HTA regulatory synergy
Wang et al[25]	Journal article	Explores potential areas of synergy via questionnaire
Hutton et al[22]	Journal article	Discussions on harmonization of evidence requirements for HTA
Berntgen et al[42]	Journal article	A report on the contribution of regulatory reports to HTA
Tafuri et al[57]	Journal article	Examines the impact of HTA-regulatory parallel advice on clinical development programs
Tafuri et al[45]	Journal article	Examines the evidentiary alignment of HTA and regulatory during early dialogue
Khan et al[53]	Journal article	Commentary on industry perspectives of parallel consultation
Dekker et al[46]	Journal article	Assesses the evidentiary alignment of HTA and regulatory agencies relative to dementia medicines
Wonder et al[60]	Journal article	Describes pilot scientific program in Australia
Backhouse et al[50]	Journal article	Describes HTA early dialogue
Ridge et al[71]	Journal article	Describes an experience with the US FDA-CMS parallel submission program
Eichler et al[81]	Journal article	Discusses concept of adaptive licensing
Eichler et al[79]	Journal article	Discusses concept of adaptive pathways to medicine access
Bouvy et al[77]	Journal article	Discusses HTA within adaptive pathways
Pearce et al[64]	Journal article	Examines timelines of PBAC decisions after TGA approval in Australia
McAuslane et al[61]	Journal article	Presents findings from a workshop discussion on HTA and regulatory harmonization
Bramley et al[56]	ISPOR policy perspective	Discusses industry dilemma whether to seek scientific advice

Tschank[55]	Master's thesis	Examines the role of EMA-HTA engagement on drug development
EMA[17]	Report	Reflection paper on synergies between HTA and regulatory agencies
EMA[10]	Report	Road map to 2015, which discusses EMA's contribution to science, Medicine and Health
Panteli et al[5]	Policy brief	Discusses important concepts around patient access
GSK[66]	Report	Provides extensive overview of the PBS in Australia
Brownsword et al[78]	Book	Provides useful chapter on adaptive licensing
CRIS[65]	Report	Reviews HTA timeliness and outcomes in Australia, Canada and Europe during 2014-2015
Podemska-Mikluch[70]	Working paper	Discusses some of the challenges of the FDA-CMUS parallel review
EMA[48]	Policy Document	Provides guidance for applicants seeking scientific advice
National Institute for Public Health and the Environment[87]	Report	Discusses adaptive pathways within the Dutch context
Liberti[68]	Presentation	Provides overview on the impact of HTA-regulatory parallel review in Canada
National Institute of Medicine[27]	Book	Discusses priorities of CER within US
Innovative Medicines Initiative[89]	Website	ADAPT-SMART initiative
Stein et al.[82]	Report	Provides overview of early access programs
EMA[23]	Website	Provides information on parallel consultation process
Office of Health Economics (OHE)[21]	Website	Provides some comments on HTA-regulatory harmonization from a workshop
CTMP[40]	Website	Green Park Collaboration
European Commission[41]	Report	Conclusions of 2008 Pharmaceutical forum
EMA[43]	Report	EMA-EUnetHTA three-year work plan, 2013
EMA[52]	Report	Report from a workshop on EMA-HTA early dialogue
EMA[44]	Report	implementation of the EMA-EUnetHTA threeyear work plan 2012-2015
EMA[54]	Report	Best practice guidance for PSA
NICE[58]	Website	Scientific advice
Trapestry Network[59]	Report	Consultation on multi-stakeholder involvement in drug development

Australian government[62]	Website	Memorandum of understanding for parallel review
Department of Health, Australia[63]	Website	TGA-PBAC parallel review process
CADTH[67]	Website	CADTH common drug review
US Federal register[69]	Website	FDA-CMS parallel review, 2010
US Federal register[73]	Website	FDA-CMS parallel review, 2016
Netherlands Healthcare Institute[75]	Website	Parallel Procedures MEB-ZIN
MaRS Discovery District[76]	Website	MaRS project
EMA[86]	Report	Final report on adaptive pathways pilot
EMA[92]	Advisory document	post-authorisation procedural advice
US FDA[93]	Guidance document	Post marketing studies guidance
EMA[97]	Website	Patient registries
GET Real[98]	Website	GET real project
Swedish Medical Products Agency[103]	Website	Scientific advice MPA-TLV

Figure S1: Thematic clusters of questions submitted for Parallel Scientific Advice by the EMA and HTA-bodies[55]

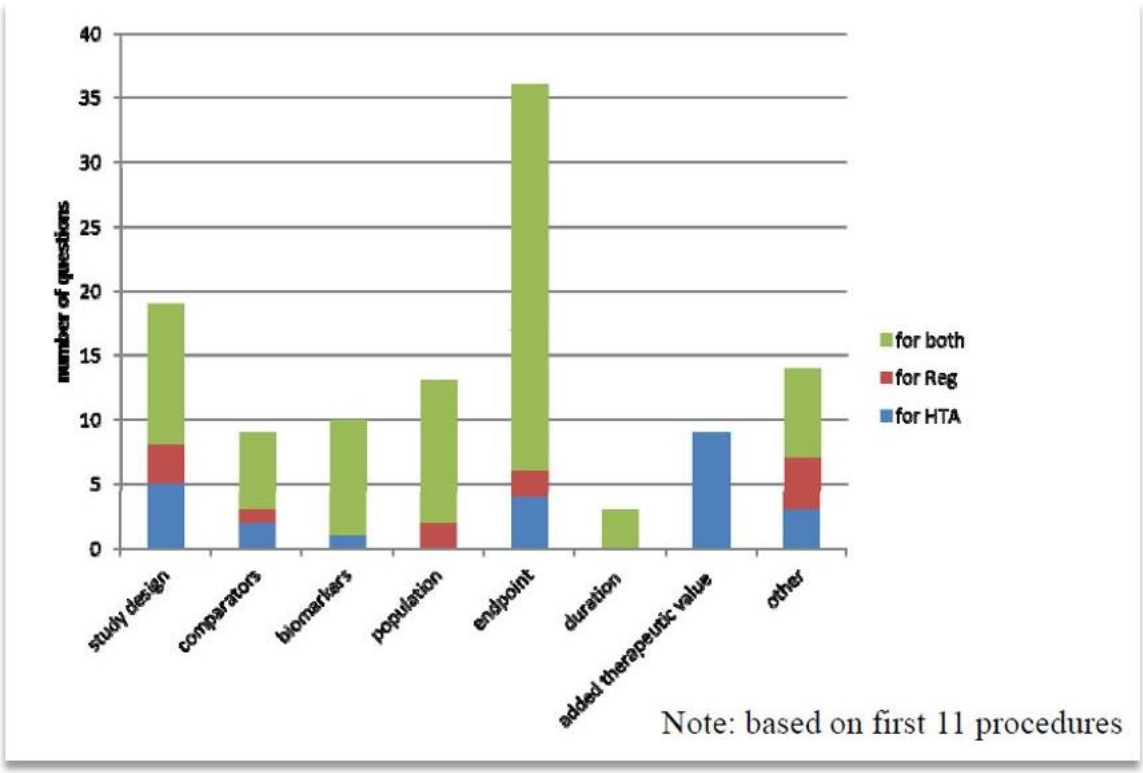


Table S8: Summary of proposals for adaptive licensing approach[79]

Initiative	Details
Health Canada Progressive Licensing Project (2005-present)	Life cycle evidence-based strategy to drug licensing. The proposed legislation expired in 2008 but regulatory modernization efforts continue
US institute of Medicine, Future of drug safety (2006)	Recognizes the impossibility of understanding the effects of drugs at time of market entry and endorses (i) aggressive assessment of drug effects through life cycle; (ii) public-private funding of post market assessment (iii) overhaul of adverse events reporting (iv) investments in pharmacoepidemiology and (v) FDA to demand postmarketing reports and conduct full 5-year reviews of new molecular entities.
European Medicines Agency, Road Map to 2015	Outlines staggered approval approach for situations not covered by conditional marketing authorizations, with initial focus on restricted population of good responders, followed by modification as data from real world settings become available.
Singapore health services authority (2011)	Expressed commitment to explore adaptive licensing for selected drugs. May enable patients and providers to have faster access to novel drugs without compromising safety through proactively accumulating clinical data via active surveillance to better understand heterogenous response to new therapies
UK athenaeum group (2010-present)	Multi stakeholder group that examines the limits of the current model of drug licensing and argues for flexibility in licensing, enabling in appropriate cases early access by patients while evidence continue to be collected.

Figure S2: Adaptive pathways approaches[87]

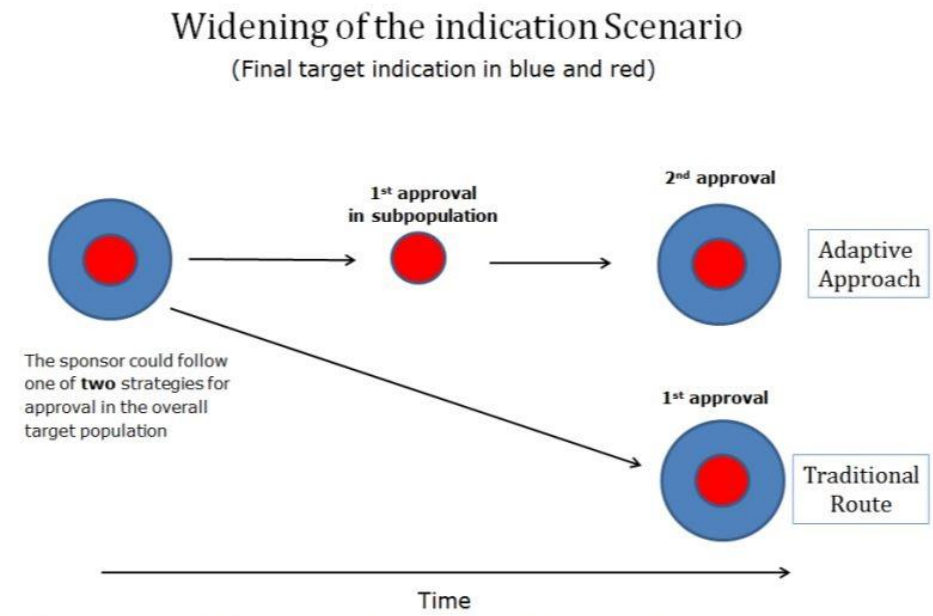


Figure 1. Adaptive pathway registration scenario 1: widening of the indication

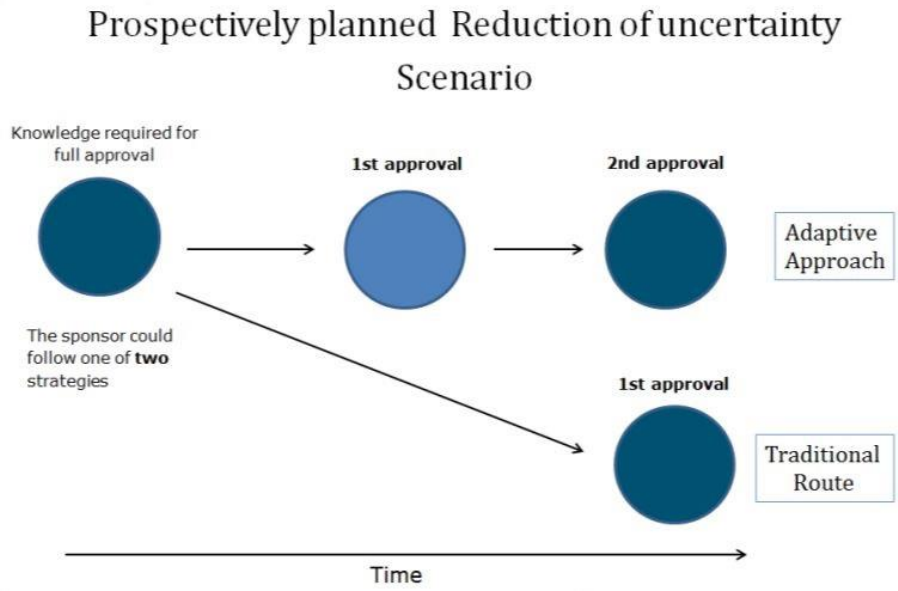


Figure 2. Adaptive pathway registration scenario 2: Conditional approval and confirmatory studies