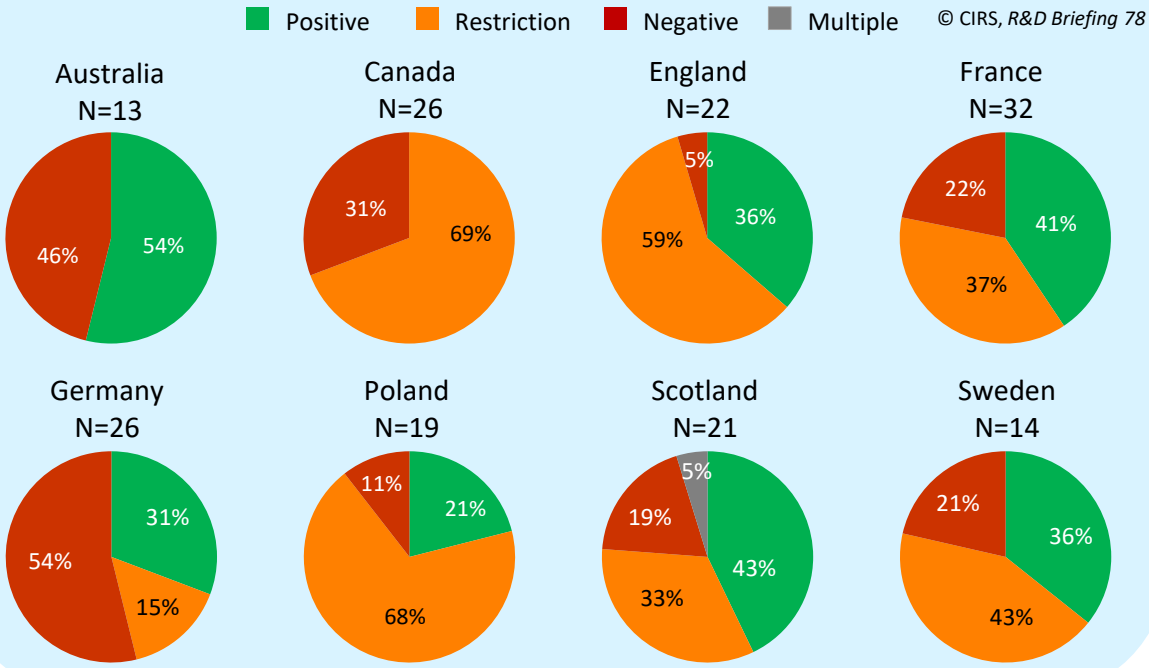
Review of HTA outcomes and timelines in Australia, Canada and Europe 2015-2019

Figure 1: First HTA recommendations: comparisons across key jurisdictions in 2019



Contents

SUMMARY

Introduction

Timely recommendation for drug reimbursement by health technology assessment (HTA) agencies is critical to ensure that patient access to medicines of therapeutic value is not delayed. As part of an ongoing study to monitor regulatory and HTA performance, CIRS has been collecting data on new active substances (NASs) appraised between 2015 and 2019 by eight health technology assessment (HTA) agencies, analysing synchronisation between the regulatory decision and first HTA recommendation in timing and outcome.

Recommendations were collected from the Australian Pharmaceutical Benefits Advisory Committee (PBAC), Canadian Agency for Drugs and Technologies in Health (CADTH; both Common Drug Review [CDR] and pan-Canadian Oncology Drug Review [pCODR]), English National Institute for Health and Care Excellence (NICE), French Haute Autorité de Santé (HAS), German Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), Polish Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT), Scottish Medicines Consortium (SMC) and Swedish Tandvårds- & läkemedelsförmånsverket (TLV), for NASs approved 2012-2019 by the respective jurisdictional regulatory agencies, the Australian Therapeutic Goods Administration (TGA), Health Canada and European Medicines Association (EMA).

Using a methodology outlined on page 13, the HTA recommendations in this report have been classified as *positive, positive with restrictions* or *negative*. Figure 32 illustrates how the specific recommendations by the eight HTA systems are captured within this trichotomous categorisation. In cases in which more than one HTA dossier was submitted by a company for the same drug based on different sub-indications within an approved regulatory label and the final HTA outcome for these individual sub-indications differed, the outcome was classified as *multiple*.

Observations

- In 2019, 46% to 95% of NASs approved by regulatory agencies received a positive or positive with restrictions first recommendation by HTA agencies across all of the studied jurisdictions. England had the highest proportion of positive/positive with restrictions recommendations for NASs appraised by HTA agencies.
- Of all studied HTA agencies, Germany had the highest proportion of products recommended within one year of regulatory approval (92% in 2019).
- Australia had the shortest median time between regulatory approval and HTA recommendation (24 days) in 2015-2019, followed by Germany (132 days).
- CIRS analysed NASs rolled out to seven jurisdictions, excluding Poland due to variation, and identified 37 NASs that received a recommendation by all HTA agencies during the period of 2015-2019. Germany provided the highest number of recommendations as the first country of appraisal (30%), followed by Australia (24%). England and Scotland had the highest congruence (73%) of first HTA recommendations.

In Australia, more than 60% of NASs were listed in the PBS list in 2015-2019 after receiving a positive or positive with restrictions first recommendation.

Of 103 drugs with PBAC recommendations in Australia from 2015-2019, 63 were listed in the PBS list. Of those drugs in the PBS list, 38% took more than one cycle to receive a positive/ positive with restrictions PBAC recommendation.

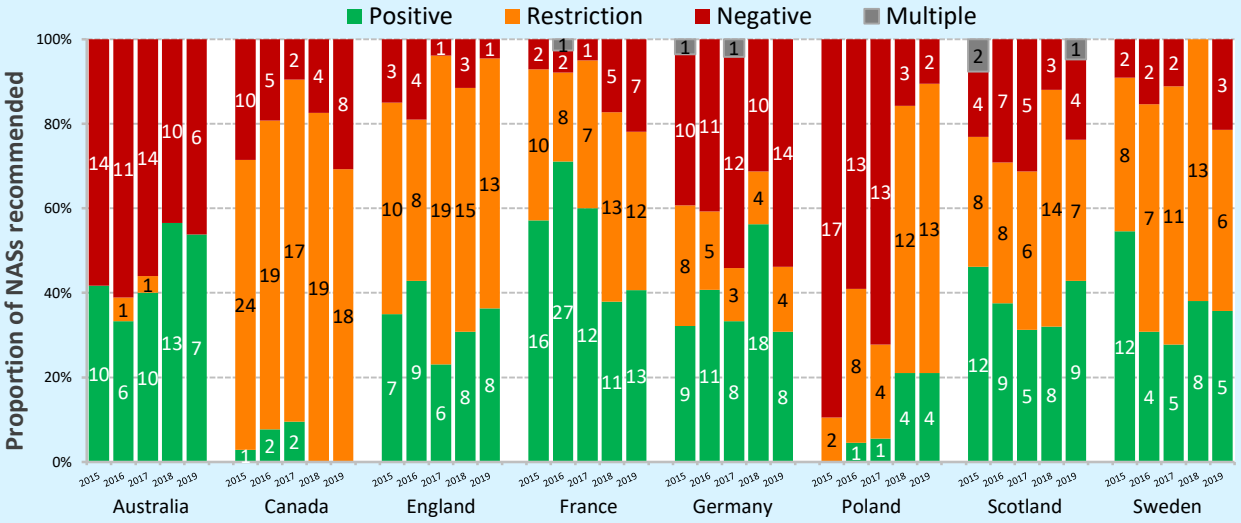
In Canada, the HC/CADTH parallel process reduced the time from regulatory approval to HTA recommendation.

Approximately half of the NASs submitted for HTA recommendation underwent the Health Canada/ CADTH parallel review process. The parallel review process was a success in reducing the time taken to reach the first HTA recommendation. In 2018-2019, the median time taken from regulatory approval to HTA recommendation was reduced by using the parallel process (144 days), compared to the sequential process (426 days).

In Europe, the lag between EMA approval and HTA recommendations varied across the European jurisdictions, from 132 median days in Germany to 538 median days in Poland.

In the studied European jurisdictions, the time from EMA approval to HTA recommendation was generally longer for those NASs that received a negative HTA outcome. Among 39 commonly appraised NASs approved by EMA, drugs with accelerated regulatory approval generally had the fastest median time from regulatory approval to HTA recommendation.

Figure 2: First HTA recommendation comparison across key jurisdictions by year of HTA recommendation Between 2015-2019



N= Number of NASs

In 2019, England had the highest proportion (95%) of positive/positive with restrictions recommendations for NASs appraised by HTA agencies (Figure 1).

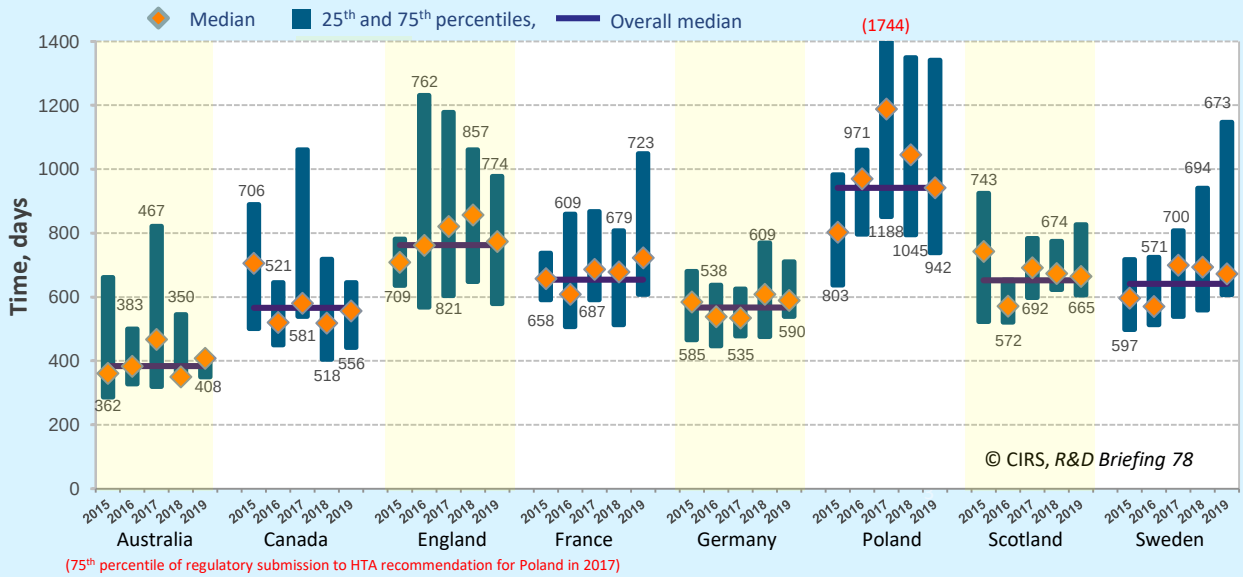
Within this cohort, France appraised the highest number of NASs in 2019 (32 NASs), while Australia appraised the fewest (13 NASs) (Figure 1). In 2019, three Australian PBAC recommendations obtained TGA approval in 2020 and were outside of the criteria of this briefing. The year-on-year variation in the number of recommendations is due to a number of reasons, including the number of regulatory approvals, the company submission strategy and the review time by the HTA agencies.

More than 45% of NASs approved by relevant regulatory agencies received a positive or positive with restrictions recommendation by HTA agencies in all of the studied jurisdictions in 2019 (Figure 2). Over these five years, Australia and Poland had a gradual increase in the proportion of positive or positive with restrictions recommendations (increase from 42% in 2015 to 54% in Australia and increase from 11% in 2015 to 89% in Poland).

Australia had the fastest median rollout time from regulatory submission to first HTA recommendation in 2019 (408 days), followed by Canada (556 days). There were less variation in rollout time in these two countries in 2019 compared with 2018, which indicated an improved consistency (Figure 3).

The median rollout time has been relatively constant in 2015-2019 across all jurisdictions with the exception of England and Poland, which showed a decrease of 83 and 103 median days respectively from 2018 to 2019. In Poland, a decrease in 246 median days was observed over the last 3 years, from 1188 days in 2016 to 942 days in 2019. However, it still took the longest time for products to roll out in Poland compared with other jurisdictions.

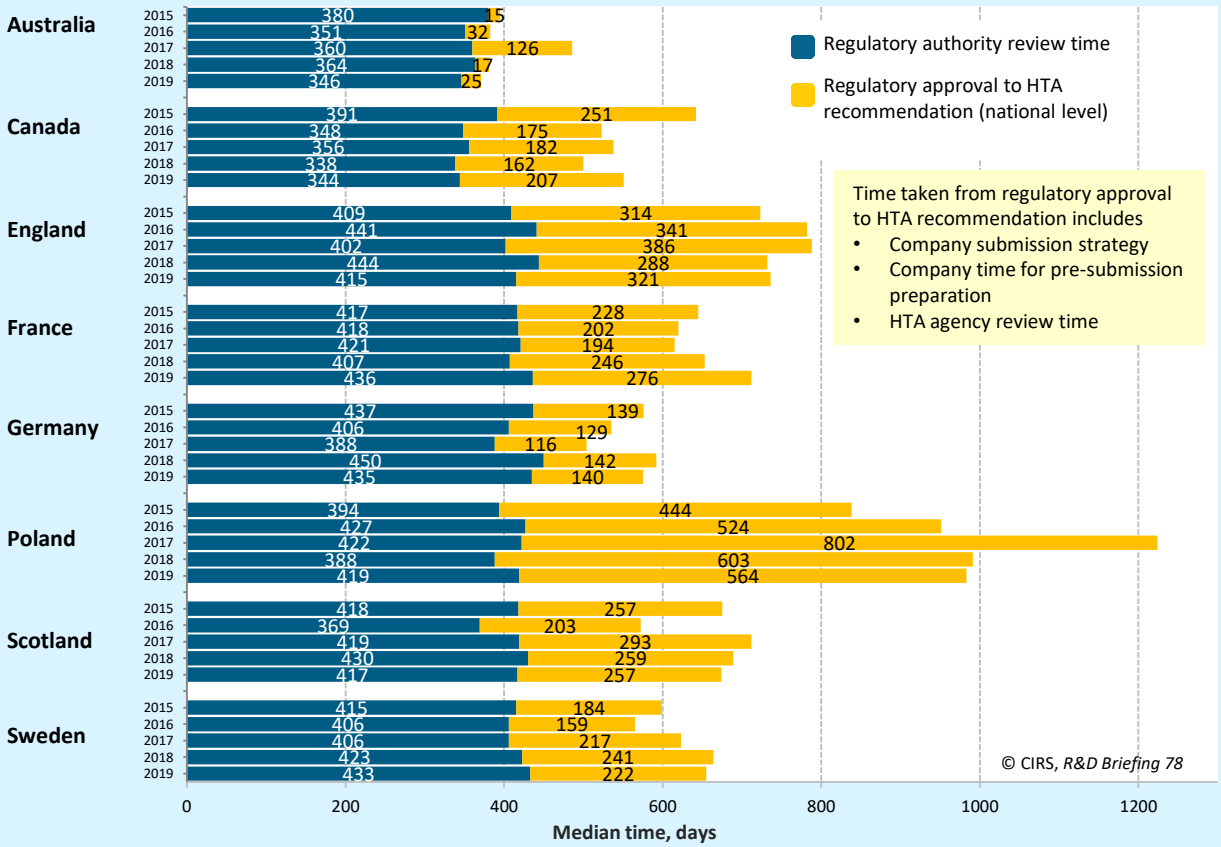
Figure 3: Rollout time from regulatory submission to HTA recommendation by year of HTA recommendation



(75th percentile of regulatory submission to HTA recommendation for Poland in 2017)

SYNCHRONISATION OF REGULATORY AND HTA RECOMMENDATIONS

Figure 4: Breakdown of rollout time across all jurisdictions in 2015-2019

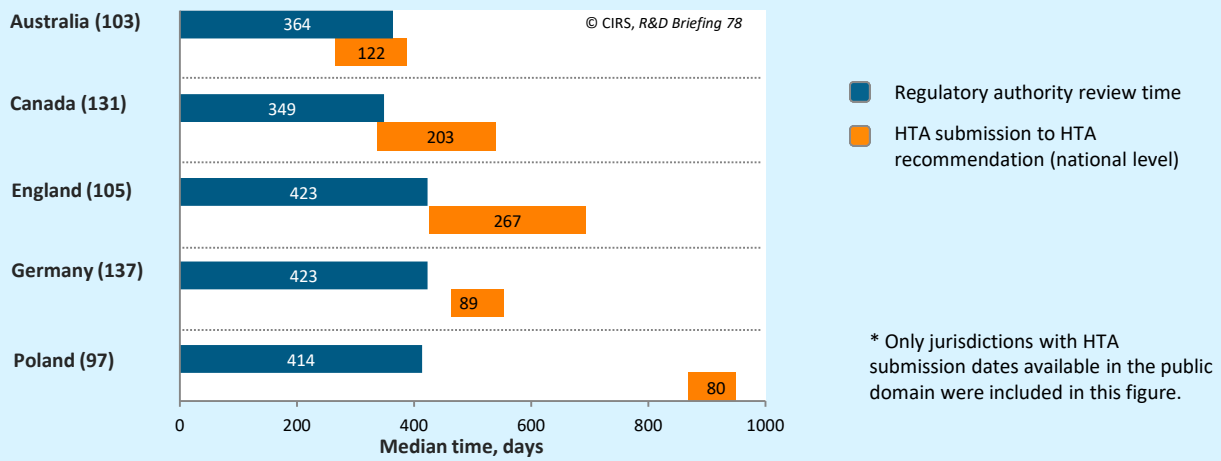


Australia had the shortest median time between regulatory approval and HTA recommendation of 24 days in 2015-2019 (Figure 4).

PBAC had the shortest overall median time between regulatory approval and HTA recommendation, suggesting the proactive approach within Australia to move toward synchronising the timing of HTA and regulatory recommendation is achieving its purpose. The time taken from regulatory approval to HTA recommendation can be attributed to company submission strategy, company time for pre-submission preparation and HTA agency review time.

Among these eight jurisdictions, HTA submission dates are only provided in Australia, Canada, England, Germany and Poland (Figure 5). The parallel review mechanism in Australia and Canada has shortened the time from regulatory approval to HTA submission. In Germany, companies can set their drug prices freely at market entry but they must submit a HTA dossier to G-BA (Federal Joint Committee, *Gemeinsamer Bundesausschuss*) who then request IQWiG to assess the added therapeutic benefit of the drug over the appropriated comparator within 3 months. Although Poland had a shorter HTA appraisal time (80 days), it took a longer time for the product to reach patients due to the gap between regulatory approval and HTA submission.

Figure 5: Breakdown of rollout time in jurisdictions where HTA submission date is provided 2015-2019*



37 NASs APPRAISED BY SEVEN JURISDICTIONS IN 2015-2019

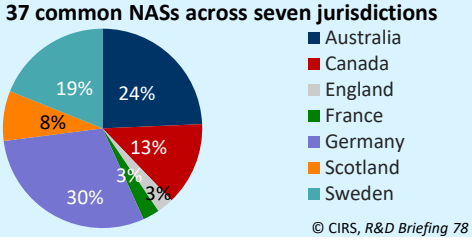
Figure 6: First HTA recommendation comparison for 37 common NASs across seven jurisdictions

Positive | Restriction | Negative | Multiple

n = Date order of the first HTA recommendation

Country	AUS	CAN	ENG	FRA	GER	SCO	SWE
abemaciclib	4	7	3	1	2	5	6
alectinib hydrochloride	2	1	7	5	3	6	4
alirocumab	7	5	3	2	1	4	6
apremilast	1	5	6	7	3	2	4
baricitinib	6	7	5	2	3	4	1
benralizumab	1	4	6	5	2	7	3
brigatinib	7	5	2	6	3	4	1
ceritinib	7	4	6	2	1	3	5
daratumumab	4	2	7	5	1	3	6
dupilumab	5	3	6	4	1	7	2
elbasvir + grazoprevir	2	1	5	4	7	6	3
eliglustat tartrate	2	6	5	3	1	7	4
evolocumab	1	5	7	3	2	6	4
glecaprevir / pibrentasvir	4	6	7	5	3	2	1
guselkumab	4	2	6	7	3	5	1
ibrutinib	5	2	7	4	1	6	3
ixekizumab	1	4	6	3	7	5	2
ledipasvir; sofosbuvir	5	6	7	4	3	1	2
lenvatinib	4	5	7	2	1	6	3
lumacaftor	2	6	5	4	1	3	7
mepolizumab	1	5	7	6	2	3	4
midostaurin	1	2	6	6	3	5	4
migalastat hydrochloride	6	7	5	4	1	2	3
nintedanib	2	7	6	5	3	1	4
olaparib	6	7	5	2	4	3	1
ombitasivr; paritaprevir; ritonavir	6	5	7	2	3	4	1
osimertinib mesylate	7	5	3	2	1	4	6
palbociclib	3	1	7	4	2	6	5
ribociclib succinate	1	7	3	5	2	6	4
risankizumab	3	1	4	7	5	6	2
sacubitril / valsartan	2	3	6	7	4	1	5
sarilumab	7	1	2	5	3	6	4
secukinumab	1	6	4	7	5	2	3
sofosbuvir / velpatasvir	6	5	7	4	3	2	1
tofacitinib citrate	1	2	6	5	4	7	3
trifluridine/tipiracil hydrochloride	5	7	1	3	4	6	2
venetoclax	4	6	5	2	1	3	7

Figure 7: First agency to obtain HTA recommendation for 37 common NASs across seven jurisdictions



France had the highest proportion of positive recommendations for 37 NASs appraised by all seven HTA agencies (51%), with Canada showed the lowest proportion (3%).

CIRS analysed NASs rolled out to seven jurisdictions, excluding Poland due to variation, and identified 37 NASs that had been approved between 2012 and 2019 and that had also received a first HTA recommendation between 2015 and 2019 by all seven HTA agencies. Figure 6 shows a traffic light system to compare the different HTA outcome across jurisdictions in 2015-2019, reflecting the diverse perception on the value of these NASs across the agencies. The recommendation dates for each product were compared across all seven agencies and the order of first HTA recommendation was ranked accordingly.

In England and France, the majority of NAS received a positive/ positive with restrictions recommendation (95% and 92% respectively). In comparison, in Australia and Germany the first HTA recommendation were mostly negative (54% and 46% of the NASs review respectively). NASs were mostly likely to receive a restrictive recommendation in Canada (73% of the 37 products). In this cohort, none of the NASs had the same first HTA recommendation but 7 NASs received positive/ positive with restrictions outcome from all seven jurisdictions.

Germany provided the highest number of recommendations as the first country of appraisal (30%), followed by Australia (24%) (Figure 7).

In England, 57% of the NASs received a NICE recommendation as the 6th or 7th country among all jurisdictions (Figure 7). England and Scotland had the highest congruence (73%) of first HTA recommendations, where identical HTA outcomes were provided based on the trichotomous categories of HTA recommendation (Figure 8).

Germany had the shortest median time (523 days) from first world-wide regulatory submission to jurisdictional HTA recommendation, followed by Australia (578 days) (Figure 9).

Figure 8: Congruence of first HTA recommendations for 37 common NASs across seven jurisdictions

	AUS	CAN	ENG	FRA	GER	SCO
CAN	19%					
ENG	22%	57%				
FRA	30%	32%	35%			
GER	22%	32%	24%	41%		
SCO	27%	51%	73%	43%	35%	
SWE	19%	54%	57%	49%	38%	57%

≥ 50% and <75% congruence | 75% congruence

Figure 9: Breakdown of rollout time (days) across 7 jurisdictions for 37 common NASs in 2015-2019

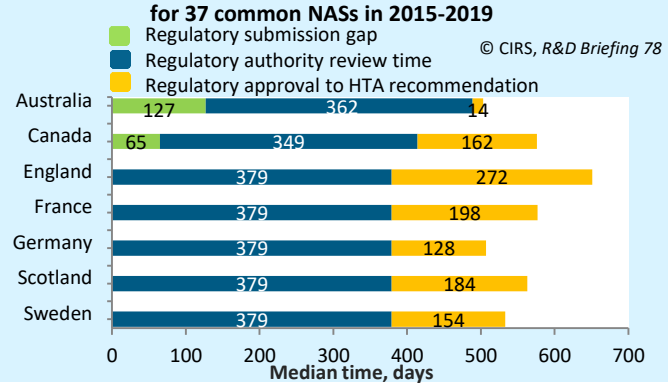


Figure 10: Breakdown of rollout time by regulatory orphan designation in 2015-2019

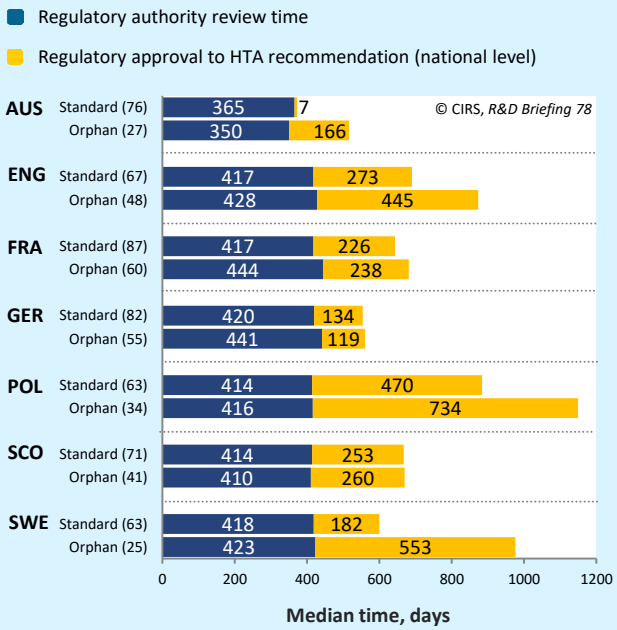
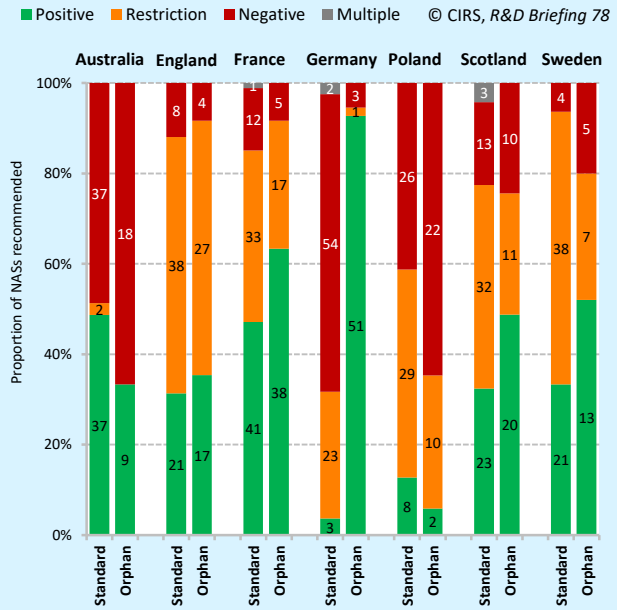


Figure 11: First HTA recommendation comparison across key jurisdictions by regulatory orphan designation in 2015-2019

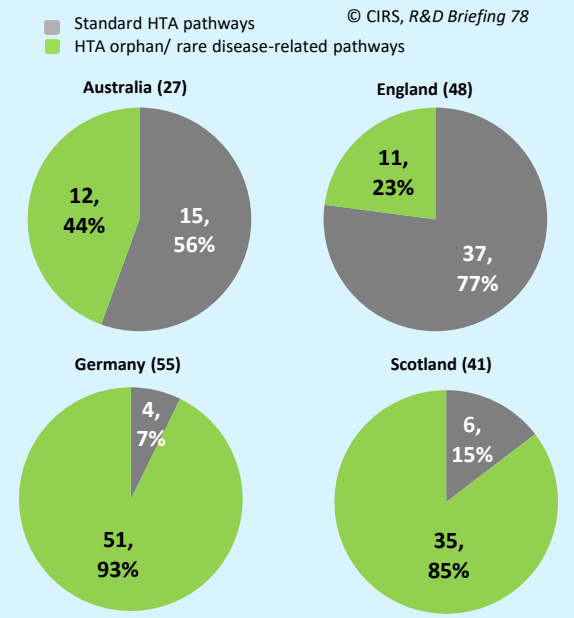


The regulatory orphan designation lengthened the overall time to HTA recommendation (Figure 10) but did not have a considerable effect on the type of HTA recommendation in all jurisdictions except Germany (Figure 11).

In an effort to expedite the approval of drugs treating serious illness or addressing unmet medical need, orphan designations has been used in several regulatory agencies (TGA in Australia and EMA in Europe). The effects of regulatory orphan designation was explored in terms of time to first HTA recommendation and HTA outcome.

NAS with regulatory orphan designation had a longer time post-regulatory process (time from regulatory approval to HTA recommendation) in all jurisdictions except Germany (Figure 10). Interestingly, there is little time difference in regulatory approval between standard and orphan drugs, indicating that the increase in overall time was driven post-regulatory. The time taken from regulatory approval to HTA recommendation includes company strategy and HTA review time. In addition, the regulatory orphan designation do not have a considerable effect on HTA recommendation with the exception of Germany (Figure 11). In this briefing, IQWiG recommendations for orphan drugs are considered as positive as additional therapeutic benefit is considered to be proved at marketing authorisation. The assessment of orphan drugs are conducted by G-BA and the assessment report outcome was out of scope of this briefing.

Figure 12: Proportion of regulatory orphan designations with HTA orphan/rare disease-related Pathways



The list of HTA orphan/rare disease-related pathways across all jurisdictions are elaborated in the Appendix (HTA orphan/rare disease-related pathway, Figure 34).

Not all NAS that received a regulatory orphan designation undergo a HTA orphan/rare disease-related pathway (Figure 12).

In Germany and Scotland, the majority of the NAS that received a regulatory orphan designation underwent a HTA orphan/ rare disease-related pathway (93% and 85% respectively) while in Australia and England, less than half of the NAS that received a regulatory orphan designation went on to a HTA orphan/ rare disease-related pathway.

In England and Germany, all the NAS that underwent a HTA orphan/ rare disease-related pathway received a regulatory orphan designation. In these countries, the EMA orphan designation criteria is used in the HTA orphan/ rare disease-related pathways (Figure 34). However, in Australia and Scotland, a fewer proportion of NAS that underwent a HTA orphan/ rare disease-related pathway received a regulatory orphan designation (55% and 69% respectively). In Australia, the HTA orphan/ rare disease-related pathways identified do not apply to only orphan drugs and thus, there is less congruence in the orphan-related criteria between regulatory and HTA.

FOCUS ON ATMP

Advanced therapy medical products (ATMPs) have the potential to address high unmet medical need but their complexity and novelty present challenges to patient access. Ten ATMPs were approved in Australia, Canada and Europe in 2015-2019. Data on the regulatory and HTA landscape of ATMPs were collected up to June 2020 (Figure 13).

Figure 13: Regulatory and HTA landscape of ATMPs

		Regulatory				HTA							
Type	**Brand Name**	**EMA FRP**	**EMA Orphan**	**EMA approval year**	**Regulatory approval**	**AUS**	**CAN**	**ENG**	**FRA**	**GER**	**SCO**	**SWE**	**POL**
Cell therapies	Alofisel		Y	2018							Orphan		
	Zalmoxis	Conditional	Y	2016									
Gene therapies	Imlygic		N	2015	AUS (2015)			PAS				HE	
	Kymriah	PRIME	Y	2018	AUS (2018), CAN (2018)			MAA	MEA		Ultra-Orphan; PAS	HE	
	Luxturna		Y	2018				HST; PAS				HE	
	Strimvelis		Y	2016				HST					
	Yescarta	PRIME	Y	2018	AUS (2020), CAN (2019)	2020		MAA	MEA		Ultra-Orphan; PAS	HE (2020)	
	Zynteglo	PRIME, Accelerated	Y	2019					MEA (2020)	2020			
Tissue-based therapies	Holoclar	Conditional	Y	2015	AUS (2015)			PAS					
	Spherox		N	2017									

First HTA recommendations: Positive Restriction Negative Different HTA committee

PAS: Patient Access Schemes; MAA: Managed Access Agreement; HST: Highly-Specialised Technologies; HE: Health Economic Assessments

ATMPs can be assessed through a different HTA assessment procedure (e.g. medical devices), undergo a HTA-related orphan drug pathway and be provided Managed Entry Agreements (MEAs) to address its uncertainty.

HTA agencies have various ways of dealing with this uncertainty (Figure 13), in terms of:

1) HTA assessment procedure. ATMPs may be assessed as a health technology by a different HTA committee in Australia (Medical Services Advisory Committee, MSAC) and Canada (Health Technology Expert Review Panel, HTERP). In Sweden, health economic assessments (HE) are conducted for ATMPs and TLV is investigating the payment models for ATMP.

2) Orphan drug pathways. 80% of ATMPs with EMA approval are classified as orphan drugs and HTA orphan/ rare disease-related pathways can be applied to these ATMPs. In Scotland, all 3 ATMPs assessed were considered for a PACE meeting.

3) Managed Entry Agreements (MEAs). Financial MEAs through Patient Access Schemes (PAS) in NICE and SMC and performance-based MEA such as Managed Access Agreement (MAA) in NICE can be used.

Kymriah is the first ATMP to receive a HTA recommendation in all key jurisdictions excluding Poland and Sweden, followed by Yescarta. The time from regulatory approval to HTA recommendation across these jurisdictions for Kymriah is relatively similar (117 median days), with France and Germany having the fastest time to HTA recommendation (Figure 14). Yescarta took a longer time to HTA recommendation and more variation in time between the jurisdictions is observed.

Figure 14: Breakdown of rollout time (days) across key jurisdictions for Kymriah and Yescarta

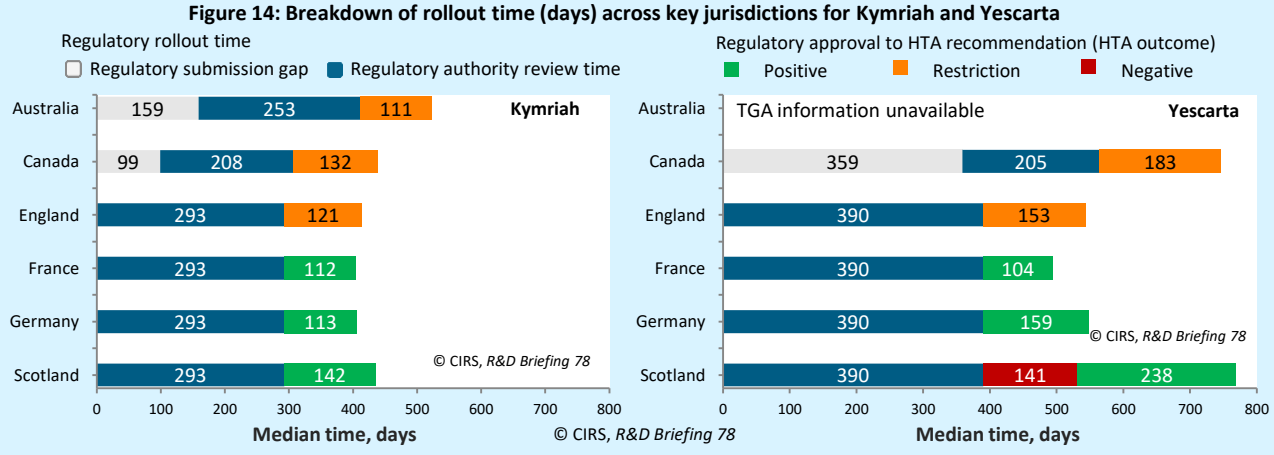
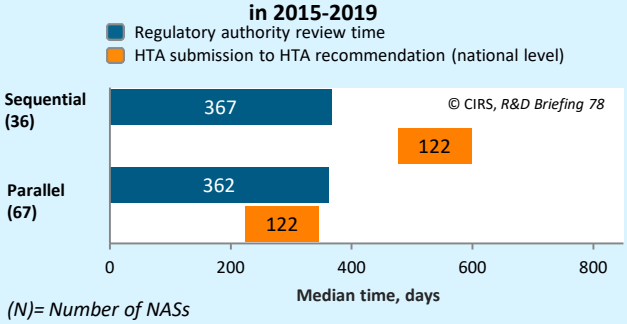


Figure 15: Breakdown of rollout time by type of sequence in 2015-2019



(N)= Number of NASs

Figure 16: Number of cycles to first positive/ positive with restrictions HTA recommendation in PBS list in 2015-2019

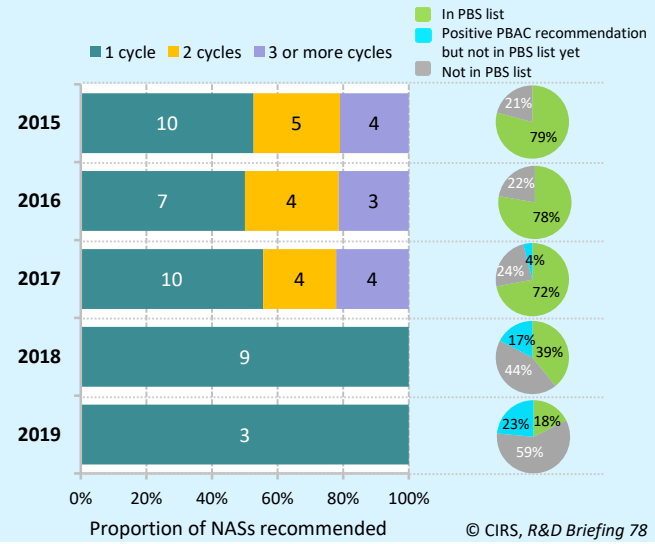
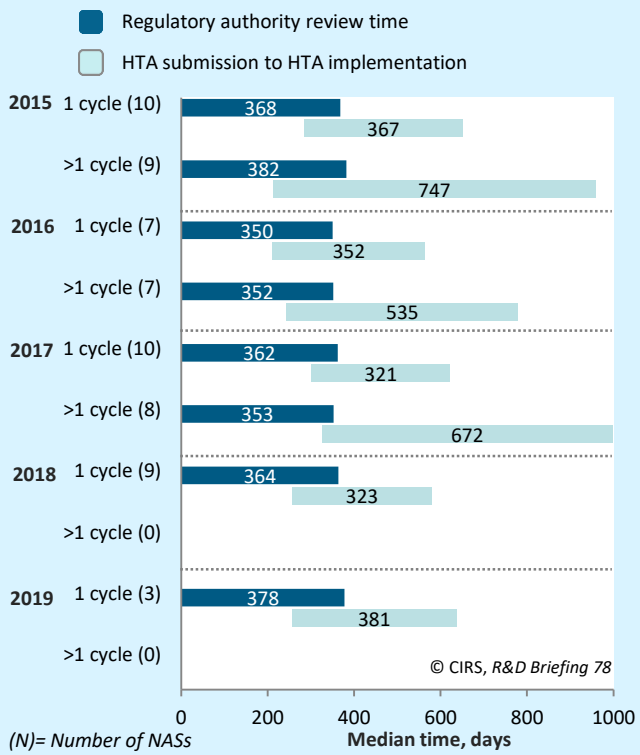


Figure 17: Breakdown of rollout time for PBS-listed drugs in Australia in 2015-2019



(N)= Number of NASs

Companies have taken advantage of the parallel review mechanism in Australia, with 65% products undergoing this process and submitted to PBAC approximately 4 months before TGA approval (Figure 15).

Under the TGA/PBAC parallel process, the TGA delegate's overview is informative to PBAC consideration to appraise a drug and companies can submit the regulatory delegate overview up to a week prior to the PBAC meeting. Median submission to PBAC was 138 days prior to TGA approval for products that went through parallel review, compared with a 110-day delay in HTA submission with sequential review.

61% of drugs with PBAC recommendations in 2015-2019 were listed in the PBS list in Australia, of which 38% appraised by PBAC took more than one cycle to be listed in the PBS in this cohort (Figure 16).

PBAC makes HTA recommendations for listing of medicines on the Pharmaceutical Benefits Scheme (PBS) list that are non-binding and require Ministerial approval. For pharmaceuticals with a projected annual cost of less than AUD$20 million, the Minister of Health (or a delegate) is the decision maker for listing new drugs onto the PBS. For pharmaceuticals with a projected annual cost of greater than AUD$20 million, Cabinet consideration is required. These decisions follow the completion of negotiations with the sponsor by officers from the Australian Government Department of Health based on the advice from PBAC.

In Australia, drugs cannot be listed on the PBS without a PBAC recommendation to do so. When the first HTA recommendation does not support listing, companies can re-submit an application with an improved dossier. Consequently, a number of review cycles may take place until a positive/positive with restriction recommendation is achieved to support listing. The proportion of drugs that had a regulatory approval, HTA recommendation and was listed with one-cycle review was higher in 2018-2019 (all 12 products in PBS list) compared with 2015-2017 (53%). However, the proportion of drugs not listed in the PBS list was higher in 2018-2019 compared to previous years as drugs may not be listed yet or have not gone through a re-submission. Multiple review cycles increase the time from HTA submission to HTA implementation/ publication in the PBS list (732 median days in 2015-2017, Figure 17). The Department of Health and Medicines Australia have been working since 2017 to deliver on commitments under *clause 10 of the Strategic Agreement* to streamline medicines listing processes, including a target of 50% reduction in the number of resubmissions to the PBAC and reduction in time from PBAC recommendation to listing by an average of two months.

In 2016-2019, anti-infectives took the shortest time from regulatory approval to HTA recommendation (Figure 18).

The top four therapeutic groups from the 96 NASs assessed by CADTH in 2016-2019 were anti-cancer & immunomodulators (40%), alimentary & metabolism (21%), anti-infectives (10%) and nervous system (5%). Looking at the overall median time taken from regulatory approval to HTA recommendation, anti-infectives were fastest, followed by anti-cancer & immunomodulators (Figure 18). In addition, all anti-infectives and nervous system products appraised in 2016-2019 received a positive or positive with restrictions CADTH recommendation (Figure 19).

In 2016-2019, 21 anti-cancer & immunomodulators were submitted under the pan-Canadian Oncology Drug Review (pCODR), which evaluates oncology drugs and makes recommendations and guides the drug funding recommendations of provinces. Established in 2010, pCODR enables all provinces and cancer agencies to take a single approach to cancer drug evaluation; pCODR moved to CADTH in 2014. In 2018-2019, anti-cancer & immunomodulators that underwent the pCODR evaluation were faster from regulatory approval to HTA recommendation than in 2016-2017. In general, pCODR timelines were longer than those that underwent CDR (Figure 18).

The Health Canada/CADTH parallel process shortened the overall time taken from regulatory approval to HTA recommendation (Figure 20).

The Health Canada/CADTH parallel review process, which allows for a submission to CADTH within 90 days before the date of anticipated Notice of Compliance (NOC) from Health Canada, has been available for companies since 2012. However, on 2 April 2018, CADTH submission criteria were changed to within 180 days before the anticipated NOC from Health Canada. In 2016-2019, 58% of the NASs submitted for HTA recommendation underwent the Health Canada/CADTH parallel review process. In the last two-year cohort, an increased proportion of NASs were submitted through the parallel process: 55% in 2016-2017 to 61% in 2018-2019. Assessed in two-year cohorts, products that underwent the parallel review process in 2018-2019, had faster regulatory review time and time from regulatory approval to HTA submission (24 median days) than in 2016-2017. In 2018-2019, the median time taken from regulatory approval to HTA recommendation for the parallel process was a median 282 days faster that the sequential process.

A higher proportion of NASs submitted to the Health Canada/CADTH parallel process underwent pCODR review compared with CDR review (Figure 21). Thus, the rollout time from regulatory submission to HTA recommendation for NASs submitted for pCODR review was shorter than those submitted for CDR review. In 2018-2019, NASs submitted to pCODR had a faster time to HTA recommendation than CDR, which was mainly driven by shorter review time by Health Canada.

Figure 18: Time from regulatory approval to HTA recommendation by therapeutic area

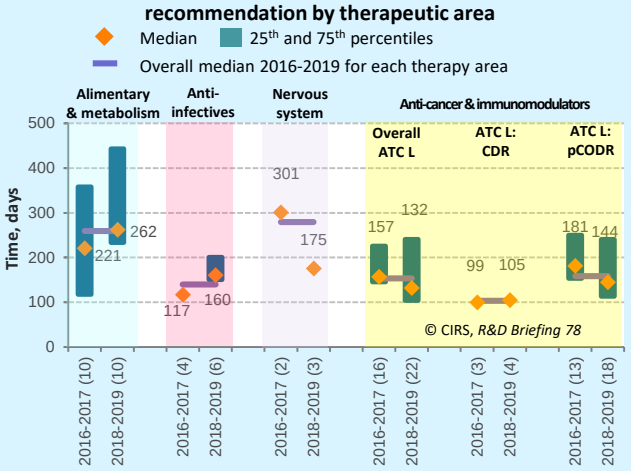


Figure 19: HTA outcome by therapeutic area

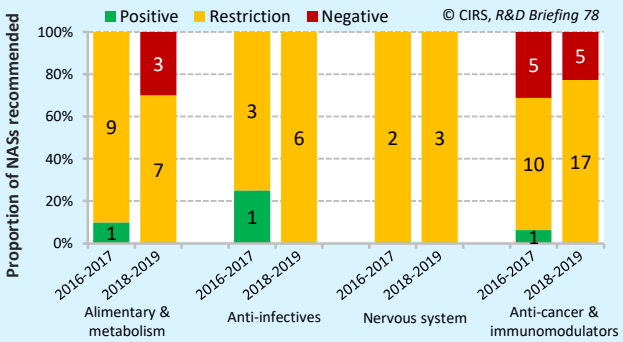


Figure 20: Breakdown of rollout time by type of sequence

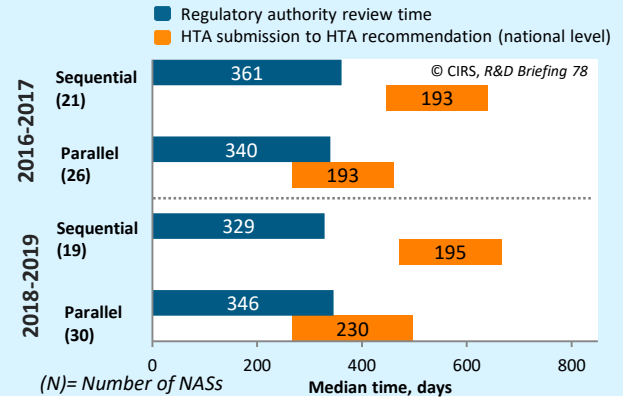


Figure 21: Time taken from regulatory approval to HTA recommendation by review type

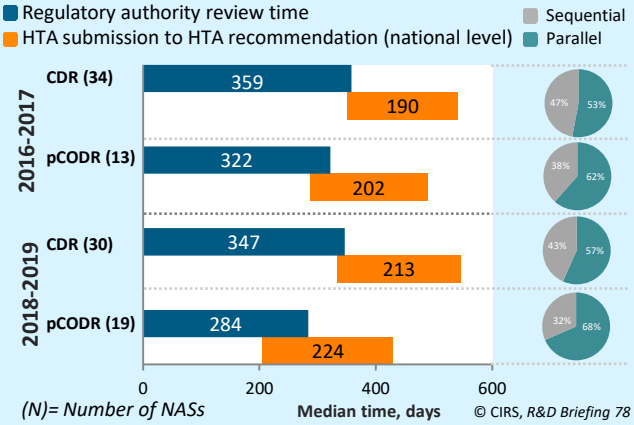
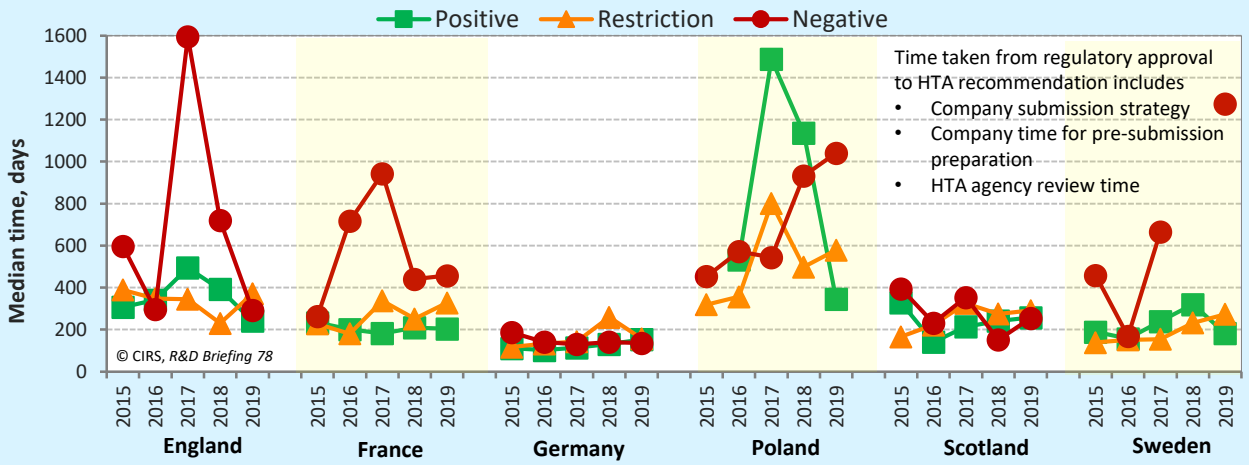


Figure 22: Time taken from regulatory approval to HTA recommendation by HTA outcome

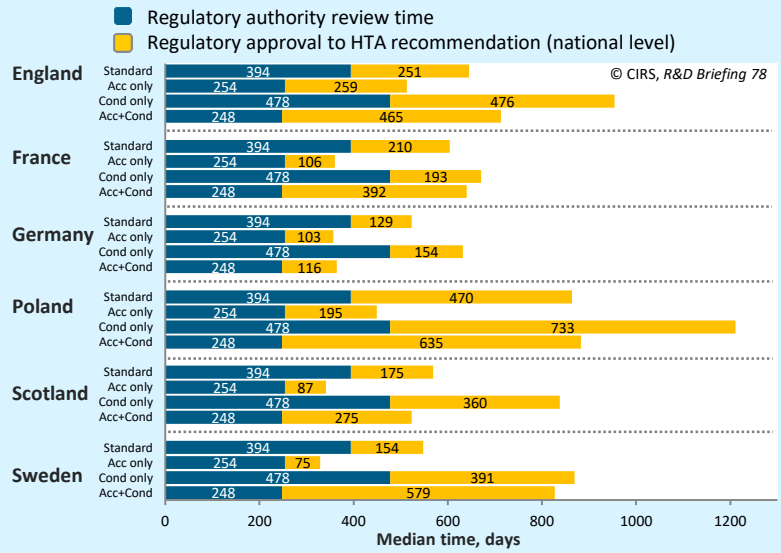


* NASs with multiple outcome were excluded from the analysis due to low numbers

Generally, NASs that received a negative recommendation took longer to receive that HTA recommendation from the time of EMA approval (Figure 22).

Despite the fact that new drugs were approved at the centralised level, Figure 22 shows divergent timing from regulatory approval to HTA recommendation across the jurisdictions. The shortest time from regulatory approval to HTA recommendation for NASs that received a positive recommendation occurred in Germany, at a median of 132 days in 2015-2019.

Figure 23: Breakdown of rollout time (days) by EMA approval type for 39 common NASs



Number of Standard = 27; Number of Accelerated = 6; Number of Cond only = 4; Number of Acc+Cond = 2

In 2015-2019, 39 NASs approved by EMA have been appraised by all six EMA jurisdictions, of which 23 were anti-cancer products and 6 were anti-infectives.

Among the 39 commonly appraised NASs, six were approved as accelerated approval by EMA, four were conditional approvals and two were accelerated and conditional approvals. Accelerated products had the fastest median time from regulatory approval to HTA recommendation in all jurisdictions. In particular, in Poland, the median time was nearly half of the standard approvals. (Figure 23). In general, anti-infective NASs showed the fastest median time from regulatory approval to HTA recommendation and the highest proportion of positive or positive with restrictions HTA recommendation (Figure 24 and 25).

Figure 24: Time taken from regulatory approval to HTA recommendation by therapeutic area in for 39 common NASs

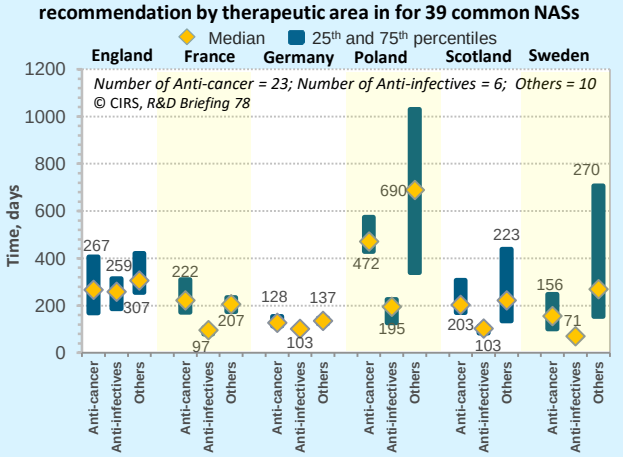


Figure 25: First HTA recommendation comparison for 39 common NASs by therapeutic area

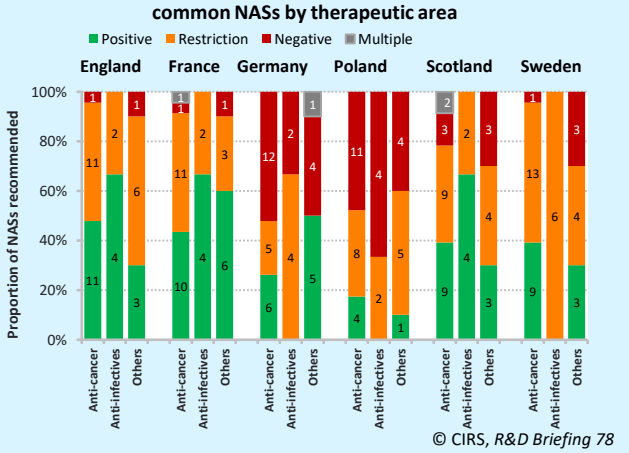
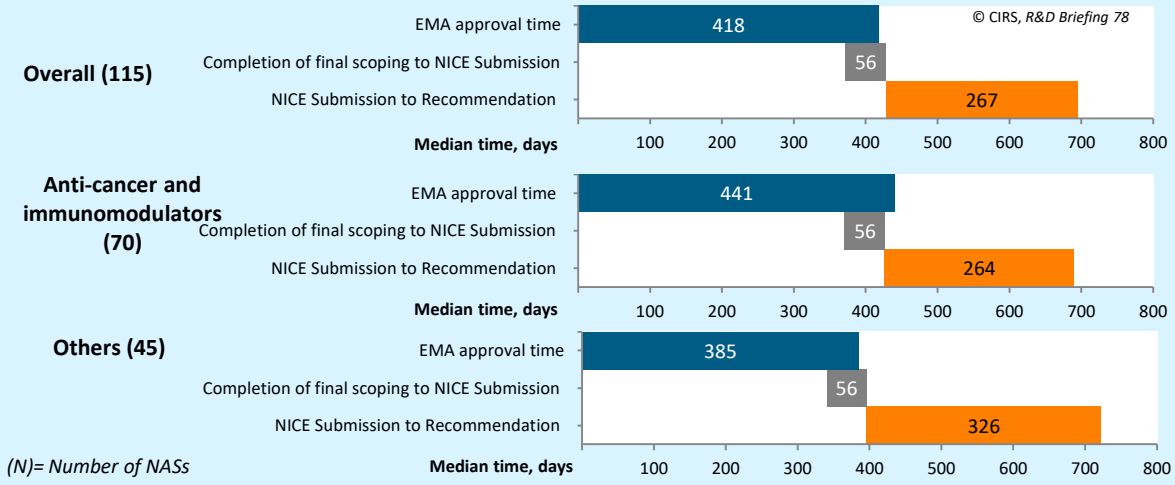


Figure 26: Breakdown of rollout time in England



In England, before NICE appraisal process, scoping occurs 46 median days before EMA approval in 2015-2019.

In England, not all NASs undergo the NICE appraisal process. Scopes are first developed before marketing authorisation is achieved. In 2015-2019, the completion of final scoping occurs 46 median days before EMA approval (Figure 26). After the scoping process, the appraisal topic is referred to NICE for development by the Department of Health. In 2015-2019, the time taken from NICE submission to HTA recommendation was 267 median days. Anti-cancer and immunomodulators take 25 median days earlier for time from EMA approval to completion of final scoping than other NASs. The time from NICE submission to HTA recommendation is also faster for anti-cancer and immunomodulators (264 median days) as compared to other NASs (326 median days, Figure 26).

Figure 27: Type of NICE recommendations (n=115)

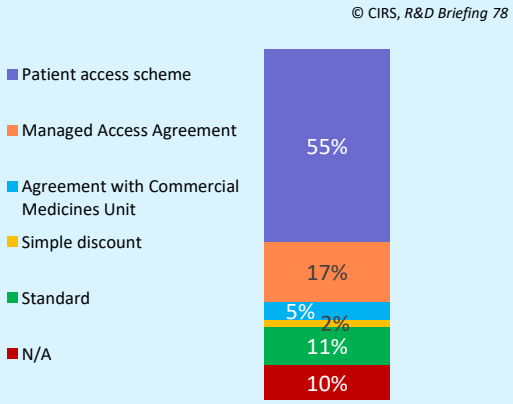
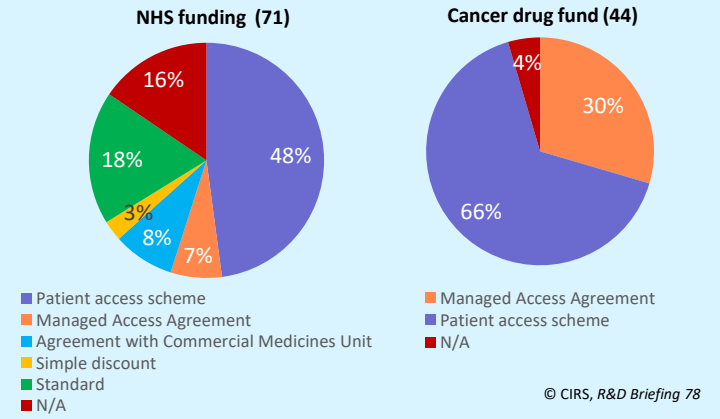


Figure 28: Breakdown of NICE recommendations by funding agreements



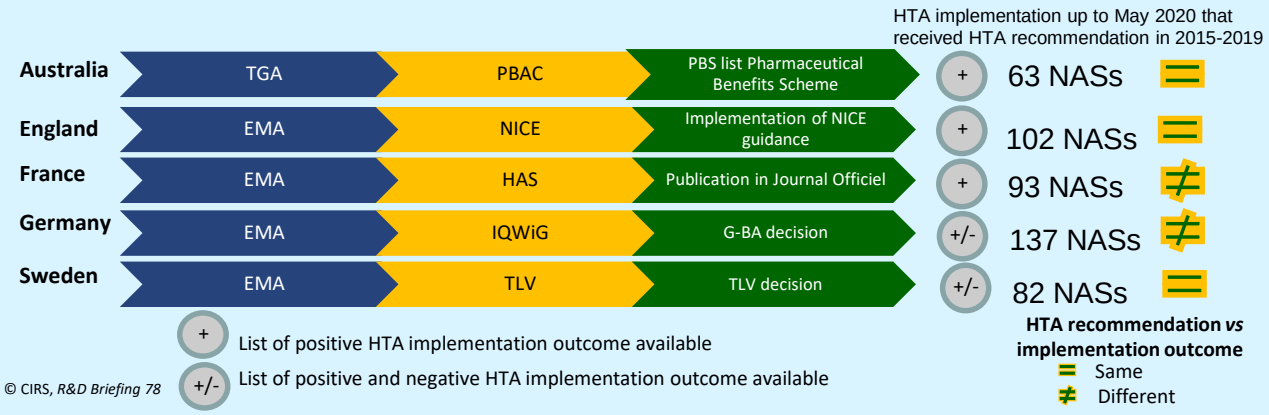
The majority of NICE recommendations (79% of 115 NASs) were provided through funding agreements in 2015-2019.

In England, drugs can be provided through various funding agreements: Simple discounting; Agreement with Commercial Medicines Unit; Patient Access Scheme (PAS) and; Managed Access Agreement (MAA). PAS allow patients to have a technology when NICE's assessment of value, on the current evidence base, is unlikely to support the list price and can be introduced through simple discounting or complex schemes. MAA allows earlier access to drugs while further evidence is collected to address clinical uncertainty. Of the 115 NAS that received a NICE recommendation in 2015-2019, the majority were funded through the PAS (55%), followed by MAA (17%, Figure 27).

The Cancer Drug Fund (CDF) was established by the government in 2011 as a temporary solution to support clinicians and their patients to gain access to cancer drugs not routinely available on the NHS. Drugs receiving a positive NICE recommendation were funded by routine baseline commissioning budgets within 90 days of NICE final guidance. On 29 July 2016, the new CDF was introduced, providing earlier access to promising new treatments through MAA and interim funding. Interim funding ends 90 days after positive final guidance is published, at which point funding will be switched to baseline commissioning budgets. 58% of 75 anti-cancer and immunomodulators that received a HTA recommendation in 2015-2019 were funded through the CDF. Of the 44 CDF drugs, 66% were funded by baseline funding through PAS, 7% by CDF through MAA, and 11% by new CDF through MAA (Figure 28).

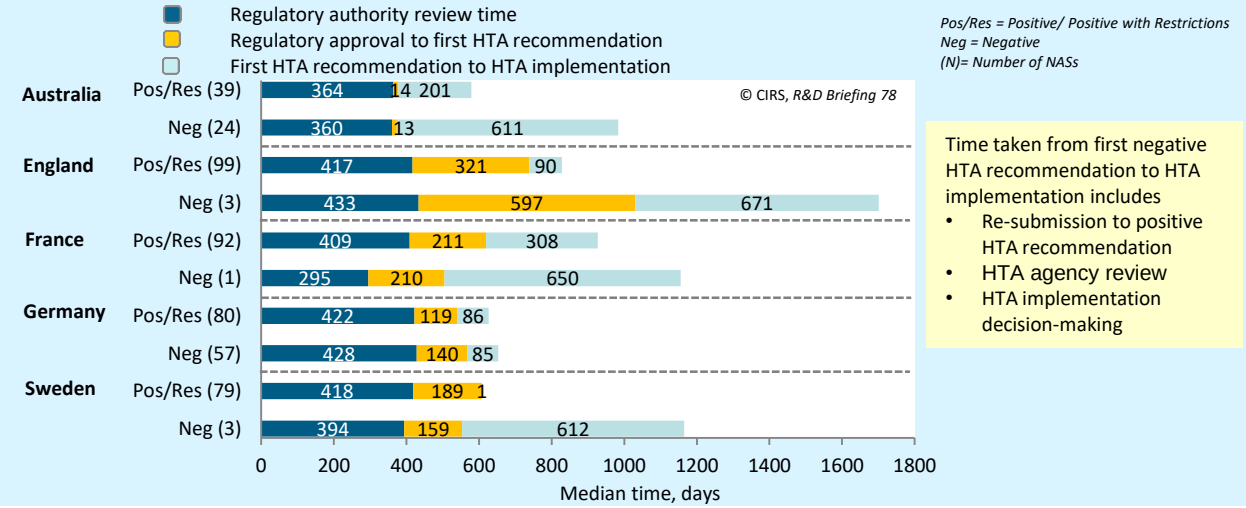
OVERVIEW OF HTA IMPLEMENTATION

Figure 29: Comparison of the regulatory and HTA implementation across targeted jurisdictions



HTA recommendations are used by payers to support reimbursement decisions. In this report, the database was extended beyond HTA information to collect HTA implementation outcome and dates. Figure 29 illustrates the key agencies involved in the regulatory approval all the way through to the implementation of HTA. Data were collected only on HTA implementation in this cohort up to May 2020 to explore the availability of new medicines in these jurisdictions. In Germany, if G-BA decides that the new pharmaceutical does not have any additional benefit over the appropriate comparator, it will be included in the reference price system within six months of market launch. If a pharmaceutical without additional benefit cannot be allocated to a reference price group, a reimbursement price will also be agreed on. The annual treatment costs must not exceed those of the appropriate comparator.

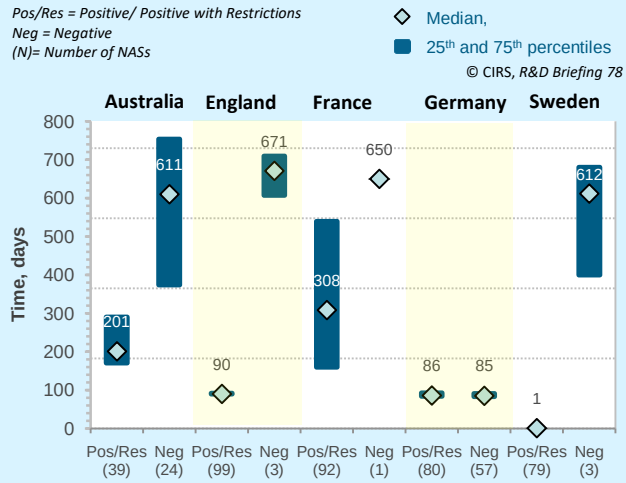
Figure 30: Breakdown of rollout time for implemented drugs with HTA recommendation in 2015-2019



Time taken from first negative HTA recommendation to HTA implementation includes

- Re-submission to positive HTA recommendation
- HTA agency review
- HTA implementation decision-making

Figure 31: Rollout time from first HTA recommendation to implementation



France took the longest time to receive a HTA implementation for new medicines, 308 median days after first HTA recommendation (Figure 30).

HTA implementation dates reflect the availability of new medicines. Germany showed the quickest time from regulatory approval to HTA implementation (median, 218 days). The variation between time from first HTA recommendation to HTA implementation shows the diversity in implementing HTAs (Figure 31). In Sweden, HTA was implemented immediately after TLV recommendation. In England, drugs must be implemented within 3 months of a NICE recommendation by law and 30 days for NASs on the Early Access to Medicines Scheme (EAMS) and fast track appraisal. Drugs in the CDF can be available before the publication of guidance through MAA. In Germany, according to The Act on the Reform of the Market for Medical Products (AMNOG), G-BA needs to make a decision 3 months after an IQWiG recommendation.

METHODOLOGY

The data on individual NASs appraised by HTA agencies in 2015-2019 were collected using public domain data derived from the agencies' official websites.

Only the first recommendation based on the first assessment reports were considered. HTA agencies provide recommendations/ advice on the medicines that can be implemented by the healthcare systems. In Australia, England, Scotland and Sweden, HTA recommendations not to implement are binding. However, in Canada, France, Germany and Poland, a relevant decision-making body such as the Ministry of Health makes the final reimbursement decision. PBAC can defer a recommendation pending the provision of specific additional information that would be relevant and important to its recommendation.

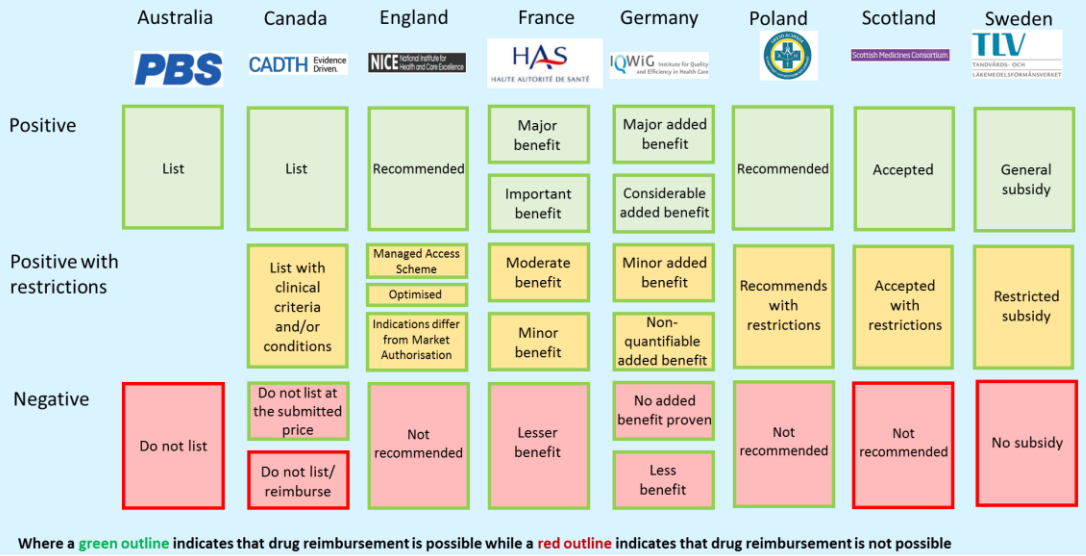
The HTA recommendations in this report have been classified into the following categories: *positive, positive with restrictions* and *negative*. Figure 32 illustrates how the specific recommendations by the eight HTA systems fall into this trichotomous categorisation.

There are a number of cases that reflected the different HTA approaches based on the regulatory approved label; these are illustrated in Figure 33.

Scenario 1: For France and Germany, the HTA agencies' assessment of the added therapeutic benefit rating for a product may be for a sub-indication of the approved regulatory label, with possible different assessment outcomes for each sub-indication. The final HTA outcome for these cases was classified in this study as *positive with restrictions*.

Scenario 2: In the case in which more than one HTA dossier was submitted by companies for the same drug based on different sub-indications of an approved regulatory label and obtained different first HTA recommendations, the final HTA outcome was classified as *multiple*. In this study, this occurrence was observed in Australia, Germany and Scotland.

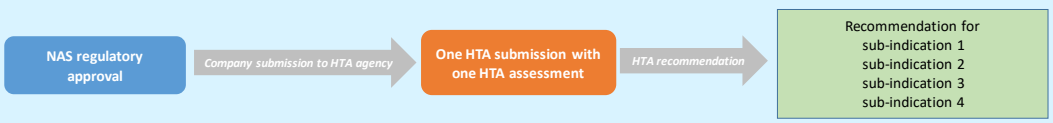
Figure 32: Trichotomous categories of HTA recommendations



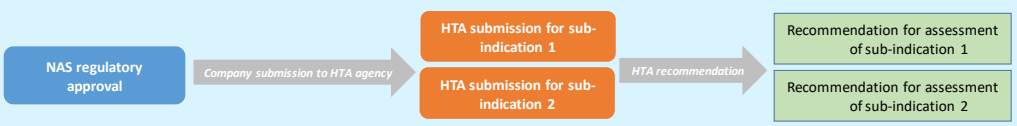
Where a green outline indicates that drug reimbursement is possible while a red outline indicates that drug reimbursement is not possible

Figure 33: Special cases of HTA recommendations

Scenario 1 – HTA recommendations were based on assessments of sub-indication of approved regulatory label



Scenario 2 – HTA recommendations were multiple as companies submitted dossier based on sub-indications of approved regulatory label



DEFINITIONS

Anti-cancer drugs

In this Briefing, anti-cancer drugs refers to anti-cancer and immunomodulators (ATC code L).

Exclusion criteria

Applications that are excluded from the study:

- Vaccines
- Any other application, where new clinical data were submitted
- Generic applications
- Those applications where a completely new dossier was submitted from a new company for the same indications as already approved for another company
- Applications for a new or additional name, or a change of name, for an existing compound (i.e. a 'cloned' application)

First assessment report

The first assessment report is the earliest assessment available. Note that for some drugs; for example, those with the same INN, strength and presentation, are listed more than one time. The reasons may be twofold – consideration of the drug in more than one indication or re-assessment of the drug by the agency.

Health technology assessment (HTA)

For the purpose of this project, HTA refers to the assessment and appraisal of pharmaceuticals prior to reimbursement. The HTA process includes clinical assessment, economic assessment and an appraisal that results in either a coverage recommendation or recommendation.

HTA review time

Time (calendar days) calculated from the date of submission to the date of recommendation by the HTA agency. Note: The HTA recommendation refers to the recommendation at national level.

Managed entry agreements (MEAs)

Arrangements between companies and HTA agencies that allow early access of new drugs while managing uncertainty around their financial impact or performance.

New active substance (NAS)

A chemical, biological, biotechnology or radiopharmaceutical substance that has not been previously available for therapeutic use in humans and is destined to be made available as a 'prescription-only medicine', to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans; the term NAS also includes:

- An isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously available.
- A biological or biotech substance previously available as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process and which will require clinical investigation.
- A radiopharmaceutical substance that is a radionuclide or a ligand not previously available as a medicinal product. Alternatively, the coupling mechanism linking the molecule and the radionuclide has not been previously available.

Parallel review

Pharmaceutical companies submit evidence to the regulatory agency that prove the efficacy, safety, quality of the product. However, during the regulatory review process, companies submit dossiers to HTA bodies so that the two review steps can occur in parallel. Following the regulatory approval, HTA recommendation will be provided to companies for drug reimbursement. This sequence is available in Australia and Canada. In this report, a drug is identified as parallel if HTA recommendation is earlier than regulatory approval.

HTA implementation date

Publication date of HTA implementation.

Regulatory submission gap

Date of submission at the first regulatory agency to the date of regulatory submission to the target agency.

Regulatory review time

Time (calendar days) calculated from the date of submission to the date of approval by the agency; this time includes agency and company time. Note: The EMA approval time includes the EU Commission time.

Rollout time

Date of submission at the regulatory agency to the date of HTA recommendation at the target jurisdiction (calendar days).

Sequential review

Regulatory review is conducted first to determine the benefit-risk profile of a new medicine, followed by the HTA review to assess the value of the medicine for a reimbursement decision. The regulatory-HTA sequence is seen at a national level in many countries, and also at a super-national level in Europe where a centralised regulatory decision made by the European Medicines Agency is followed by jurisdictional HTA recommendations by member states.

HTA ORPHAN/RARE DISEASE-RELATED PATHWAYS

Figure 34: HTA orphan/ rare disease-related pathways

Country	HTA Orphan/ Rare Disease-Related Pathways
Australia	**Rule of rescue:** A principle that favours listing of medicines with the following circumstances applied concurrently: • No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. • The medical condition defined by the requested restriction is severe, progressive and expected to lead to premature death. • The medical condition defined by the requested restriction applies to only a very small number of patients. • The proposed medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition. **Life Saving Drugs Program (LSDP):** LSDP provides fully subsidised access for eligible patients to expensive and life saving drugs for life threatening and rare diseases. The LSDP is separate to the PBS. All LSDP medicines have been considered by PBAC but not recommended for the PBS due in part to the high cost of the medicine. **Highly specialised drugs:** The Highly Specialised Drugs (HSD) Program provides access to specialised Pharmaceutical Benefits Scheme (PBS) medicines for the treatment of chronic conditions which, because of their clinical use and other special features, have restrictions on where they can be prescribed and supplied.
Canada	There is no separate CADTH review process but in March 2016, the standard HTA recommendation Framework was revised to make special consideration drugs for rare diseases. Note: The regulatory agency in Canada (Health Canada) do not currently have an orphan policy.
England	**Highly specialised technologies (HST):** A separate review process for very rare conditions. These evaluations have a higher cost-effectiveness threshold than technology appraisals. Following changes introduced in April 2017, NICE set a maximum additional QALY threshold of £300,000 for highly specialised treatments, under which they will automatically be approved for routine commissioning. This is ten times higher than the standard NICE threshold of £30,000 for non-specialised treatments.
France	There is no separate HAS review process but France offers early access of innovative drugs, including orphan drugs, through the Temporary Licensing System (ATU).
Germany	For orphan drugs, additional therapeutic benefit is considered to be proven at marketing authorisation as long as the annual SHI expenditure for the entire population is below EUR 50 million. IQWiG only assesses information provided by the companies on patient costs and patient numbers. The IQWiG recommendations for orphan drugs are categorized as "positive" within this briefing. Once the EUR 50 million threshold is exceeded, companies are required to submit data on additional therapeutic benefit and orphan drugs are evaluated and prices renegotiated in the same manner as for all other drugs. The assessment of orphan drugs are conducted by G-BA, and the approach for evidence appraisal is similar to the non-orphan assessed by IQWiG. However, the orphan assessment report only determines the extent of additional benefit, and the categories 'no additional benefit' or 'less benefit' are not applicable. Under the GSAV law implemented in July 2019, additional real-world evidence can be requested by G-BA at the initial assessment for drugs with conditional approval and all orphan drugs.
Poland	There is no separate AOTMiT process but there are ongoing plans to introduce a separate procedure for rare and ultra-rare diseases such as the introduction of multi-criteria decision analysis (MCDA) method (Polityka Lekowa Państwa 2018–2022).
Scotland	**Orphan medicine:** A medicine with European Medicines Agency (EMA) designated orphan status (conditions affecting fewer than 2,500 people in a population of 5 million) or a medicine to treat an equivalent size of population irrespective of whether it has orphan status. **Ultra-orphan medicine:** To be considered as an ultra-orphan medicine all criteria listed should be met: • the condition has a prevalence of 1 in 50,000 or less in Scotland, • the medicine has an EMA orphan designation for the condition and this is maintained at time of marketing authorisation, • the condition is chronic and severely disabling, and • the condition requires highly specialised management. Submissions for medicines that are validated as ultra-orphan according to this definition will be assessed by SMC and will then be available to prescribers for a period of up to three years while further clinical effectiveness data are gathered. After this period the company will be asked to provide an updated submission for reassessment and SMC will make a decision on routine use of the medicine in NHS Scotland. For medicines used at end of life and for very rare conditions, companies may ask for the medicine to be considered at a Patient and Clinician Engagement (PACE) meeting. This additional step allows SMC to hear more evidence from patient groups and clinicians on the added value of a medicine which may not always be captured in the company's submission. The output from a PACE meeting is a major factor in SMC decision making. Companies can also submit or improve a Patient Access Scheme (PAS), which can help to improve the value for money of the medicine.
Sweden	There is no separate review process in Sweden but TLV can consider a higher cost-effectiveness threshold based on unmet need, severity of condition, and limited budget impact due to small populations.

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