2024년 보건의료기술평가학회
추계학술대회

보건의료기술평가(HTA)에서 RWE 활용

2024년 10월 25일 금

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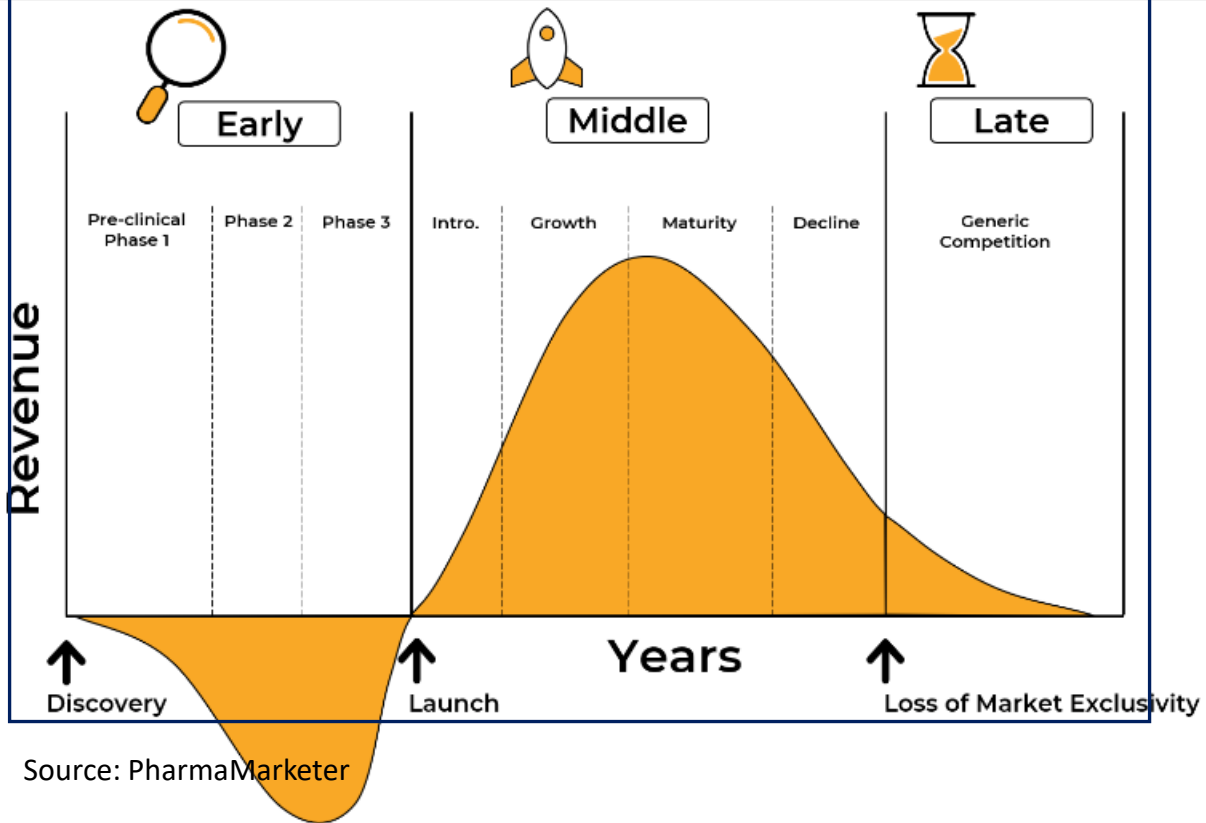
Backgrounds

Lifecycle of medicine

Lifecycle & revenue by years

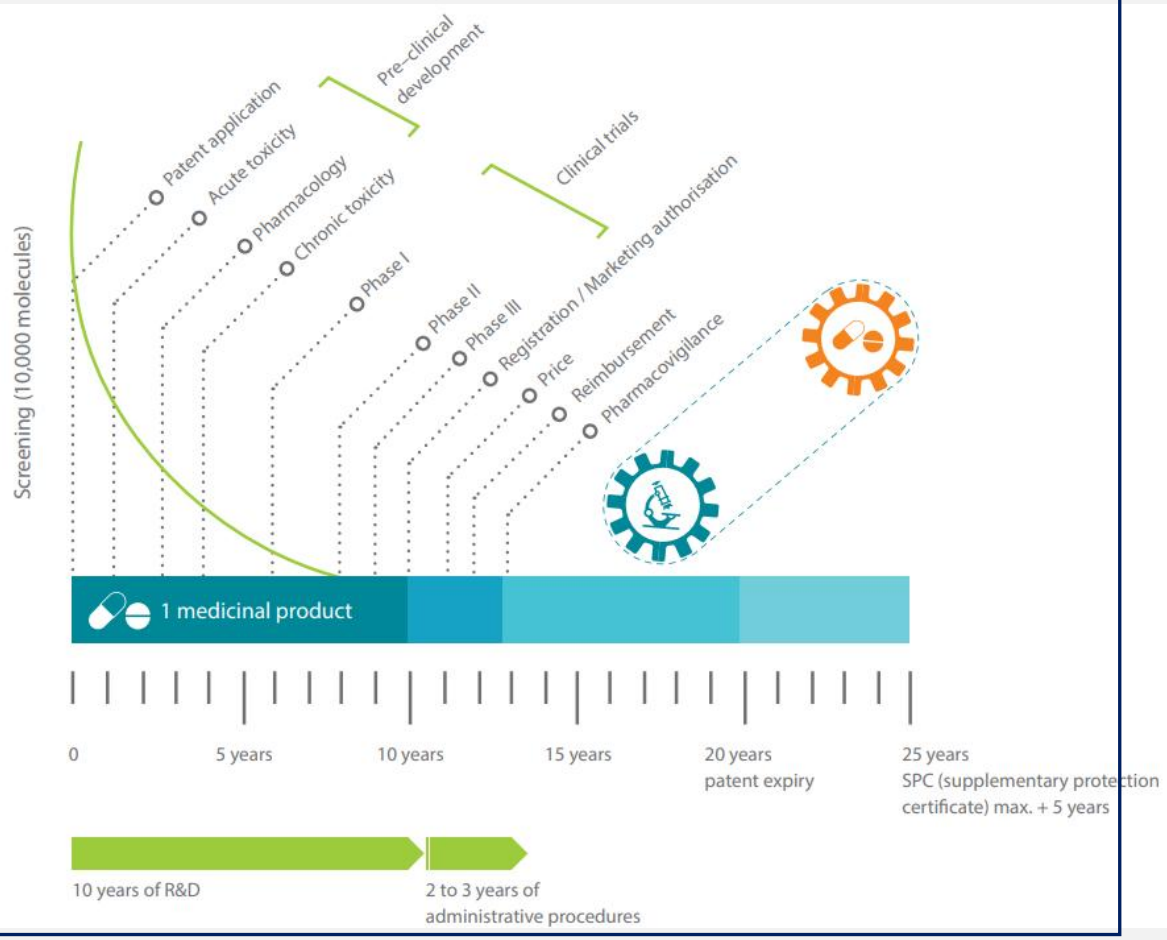
- Revenue by stage



Source: PharmaMarketer

Time to spent on R&D

- **Time to market 8~10 years**

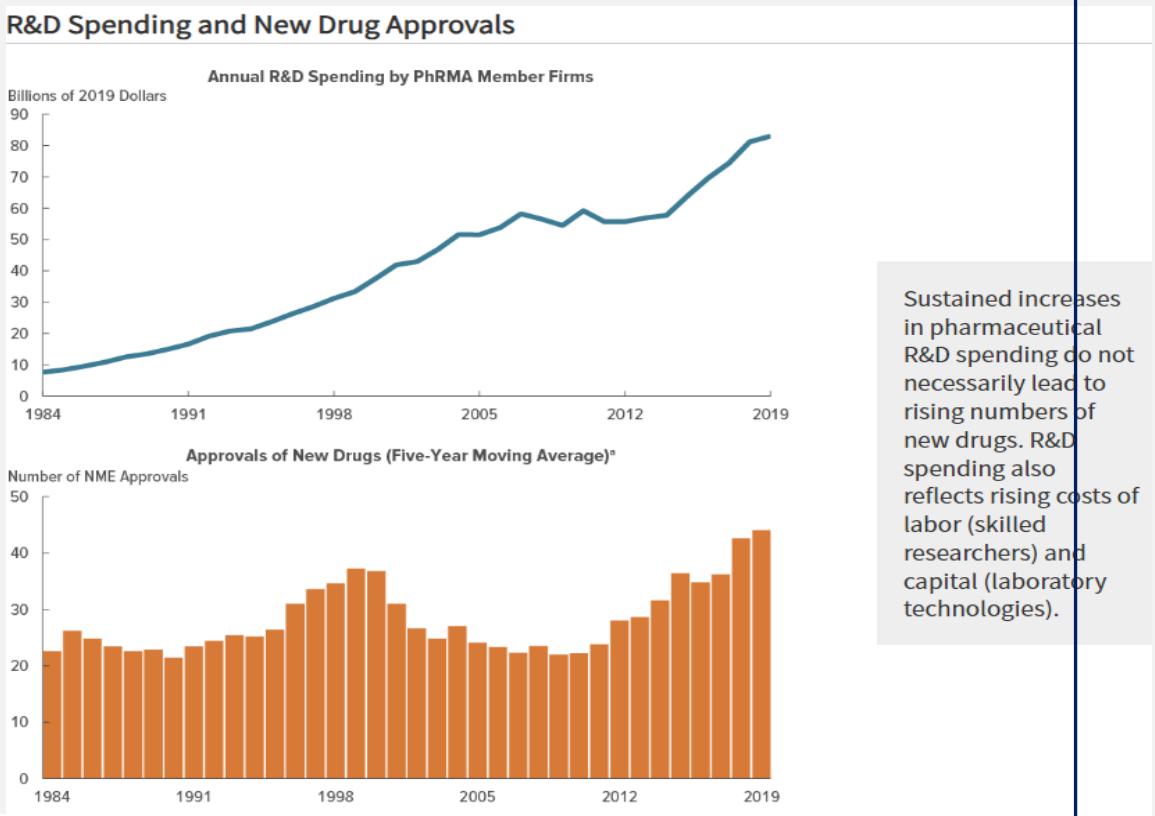


Source: EFPIA, 2024

R&D cost of pharmaceuticals

R&D cost

- In 2019, Pharmaceutical industry spent $ 83 billion dollars

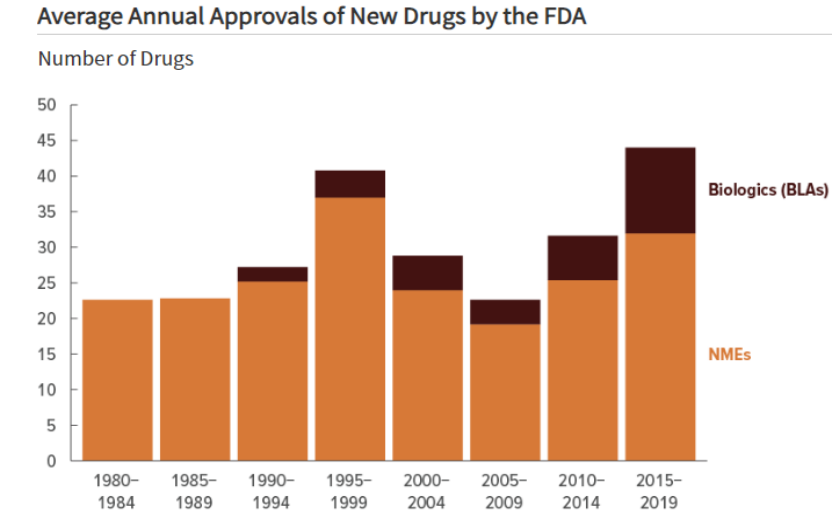


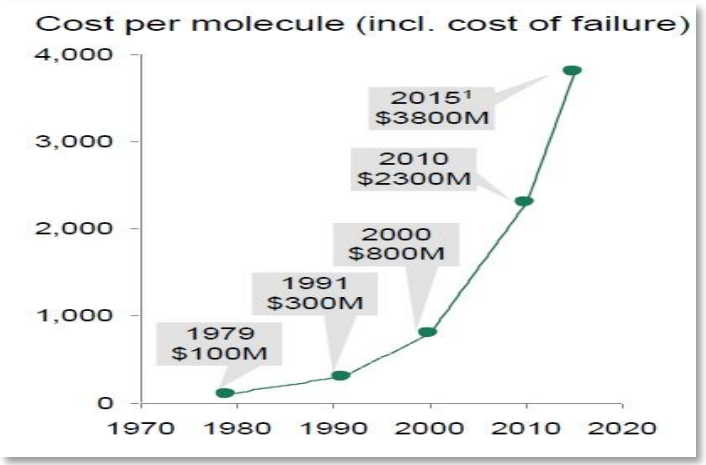
Sustained increases in pharmaceutical R&D spending do not necessarily lead to rising numbers of new drugs. R&D spending also reflects rising costs of labor (skilled researchers) and capital (laboratory technologies).

Data source: Congressional Budget Office, using data from the FDA's Center for Drug Evaluation and Research and PhRMA annual reports (various years). See www.cbo.gov/publication/57025#data.

Source: Congressional Budget Office, 2021.

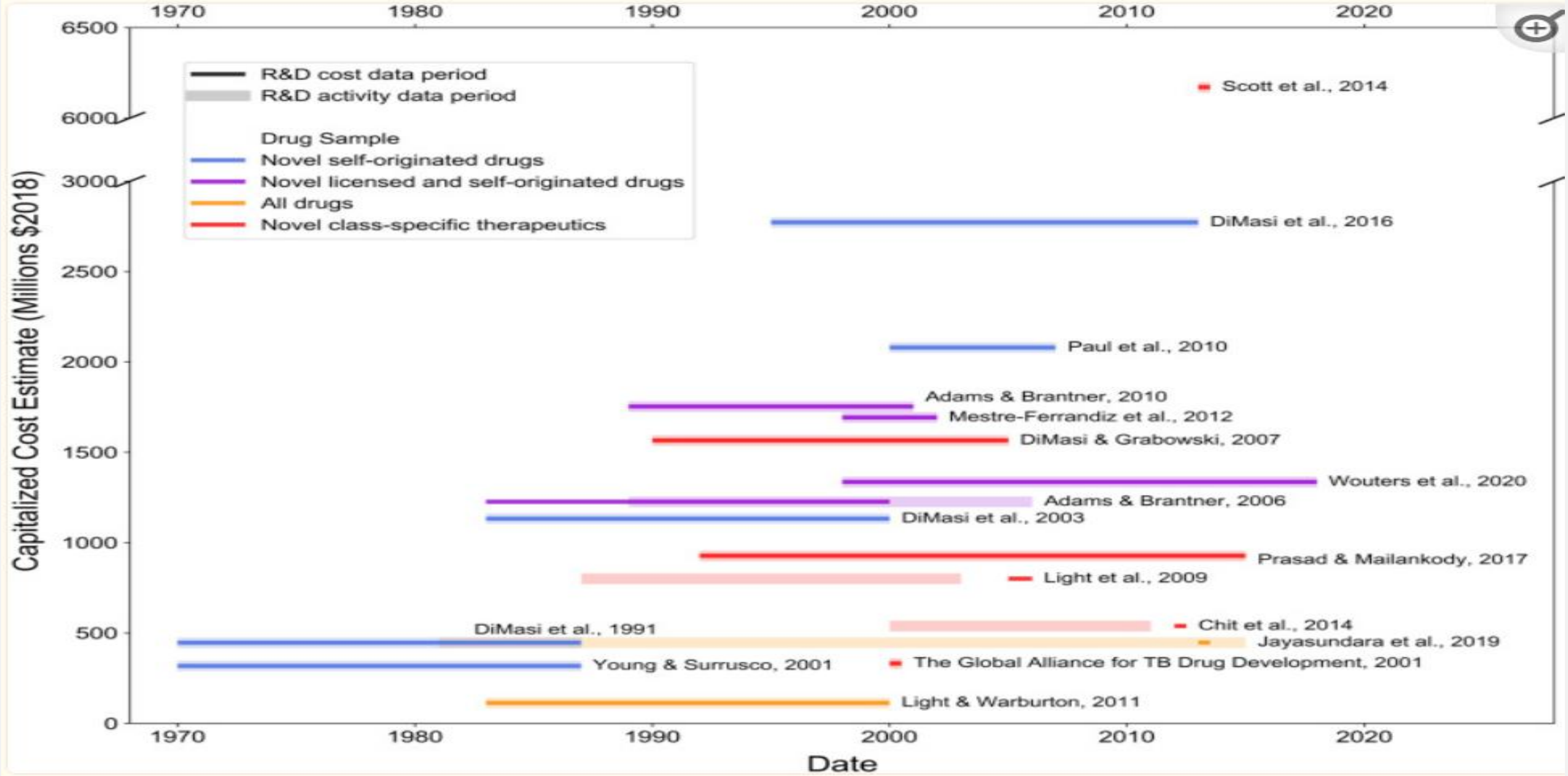
R&D cost per NME





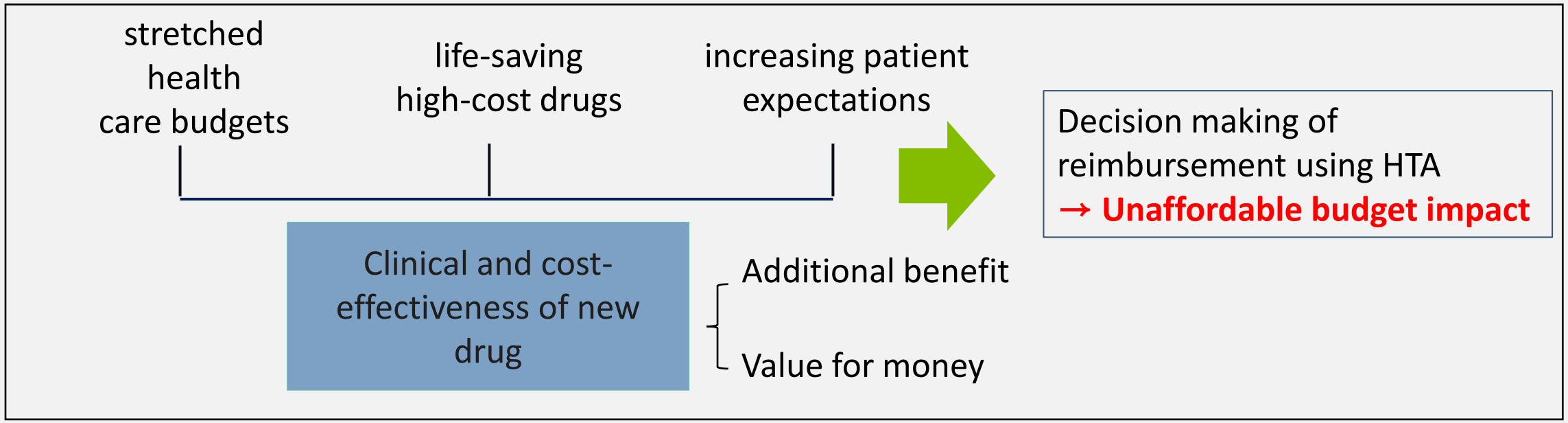
Source: The Boston Consulting Group, 2011

R&D cost of pharmaceuticals



HTA

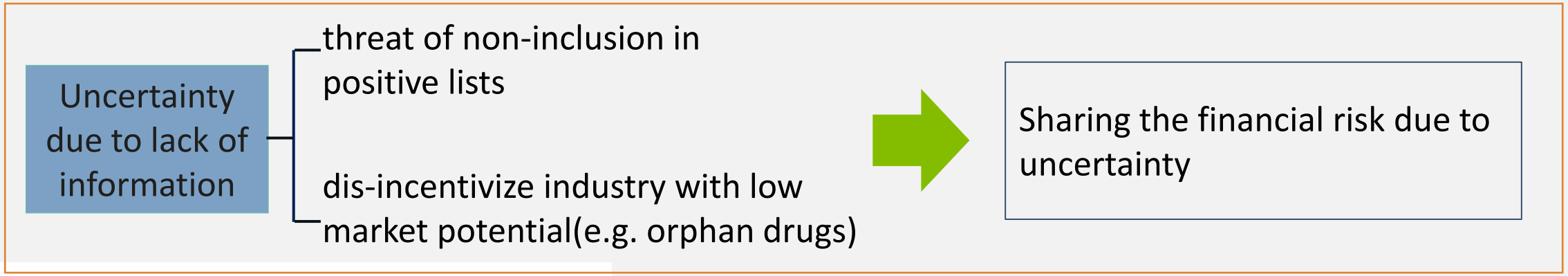
- Conventionally health technology assessment (HTA) agencies decided on treatment effect in the context of Randomized Controlled Trials (RCTs)



Source: Naci H et al., 2024

Lack of evidence in decision-making

- Increasing launch prices at a pace that does not always coincide with improvements in benefits (oncology, orphan drugs)
  - **Lack of evidence**: **only 12(32%)** out of 38 cancer **drugs** of significant improvement in survival in US from 2001-2018
- Many countries have introduced Managed Entry Agreement (MEA), Patient Access Scheme (PAS) or price-volume agreements
  - MEAs are the contract between a manufacturer and a payer, and three independent platforms



Source: LSE report(2013) Managed entry agreements for pharmaceuticals: The European experience

Using RWE

What is RWE & RWD?

- Real-world evidence(RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD
  - Electronic health records (EHRs), Claims and billing activities, Product and disease registries, Patient-generated data

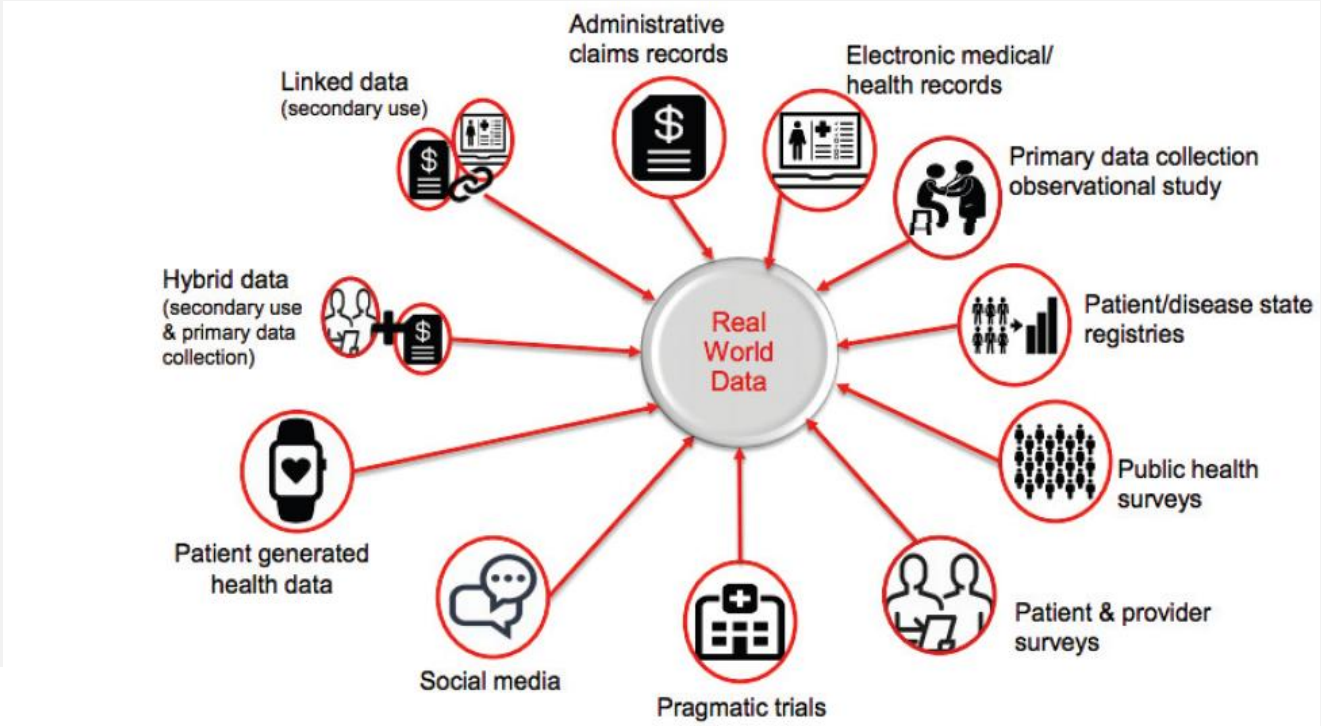


FIGURE 6-1 Possible sources of real-world data.
SOURCE: Yaist presentation, July 17, 2018.

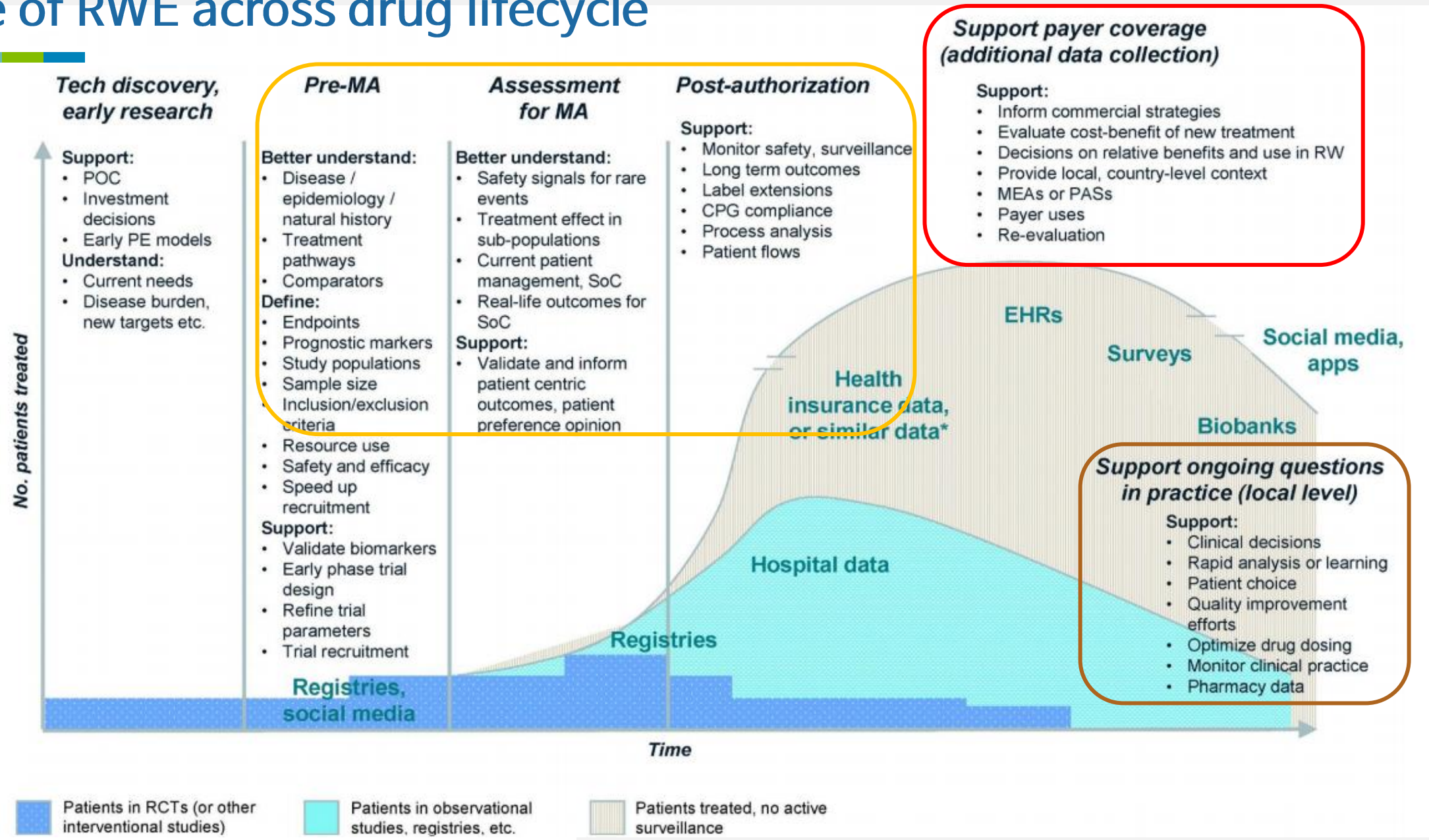
RCT vs RWE

Comparison of evidence generated from randomised controlled trials (RCT) and real-world evidence [5, 7]

	RCT data	Real-world data
Purpose	Efficacy	Effectiveness
Focus	Investigator-centric	Patient-centric
Setting	Experimental	Real-world
Patients	Included as per strict criteria	No strict criteria
Concomitant medications and comorbid illnesses	Only those defined in the protocol allowed	As in real practice
Attending physician	Investigator/designated representative	Many practitioners as chosen by the patient
Comparator	Placebo/standard practice, as per the protocol	As per patient profile/real-world usage of available drugs in the market, at the physician's discretion
Patient monitoring	Continuous	Changeable
Treatment	Fixed pattern	Variable, at physician's discretion
Follow-up	Designed, as per protocol	Not planned; as per usual practice

Source: Rennane S et al., 2021

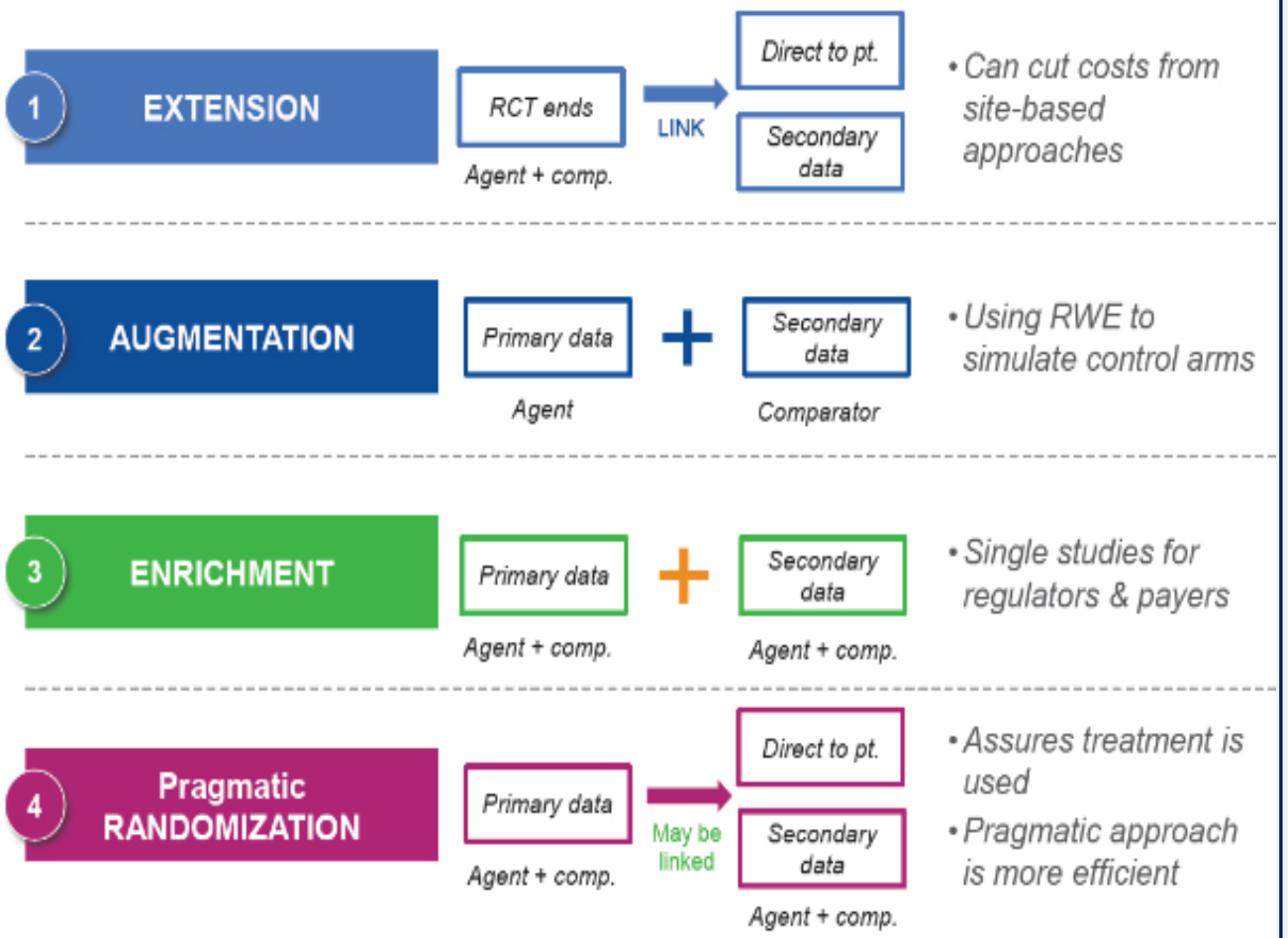
Use of RWE across drug lifecycle



Source: Akehurst R et al., 2023

Use of RWE in approval

Mosiac methodology using RWE



Use of RWE in drug approval

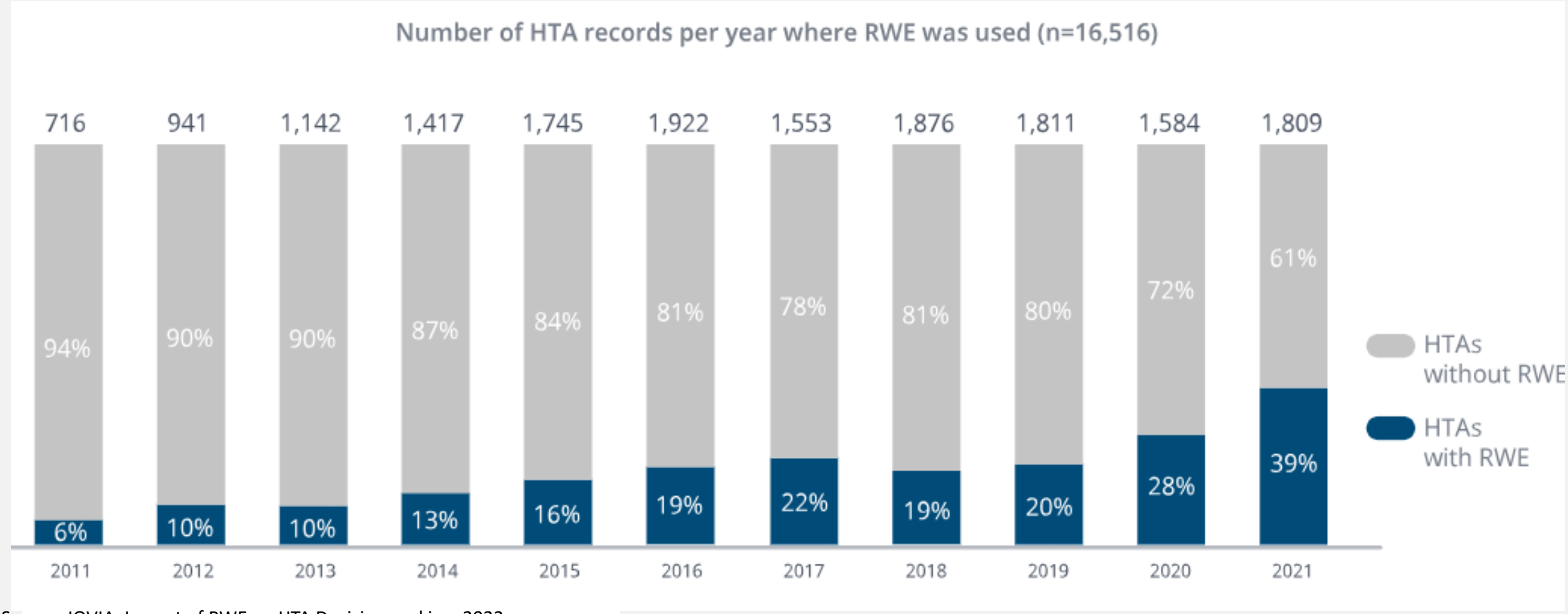
Name of the drug/biologic/device	Source of RWE	Agency involved in regulatory decision making	Month/year	Regulatory action supported
Avelumab	EHR data as historical control for efficacy	USFDA	March 2017	Original marketing application approval
Pembrolizumab	Expanded access study data to support clinical efficacy	USFDA	May 2017	Supplementary indication approval
Lutetium Lu 177 dotatate	Expanded access study data to support clinical efficacy, safety	USFDA	January 2018	Original marketing application approval
Blinatumomab	Retrospective data from clinical sites as historical control for efficacy	USFDA	March 2018	Supplementary indication approval
Palbociclib	EHR data, claims data, post-marketing safety reports to support clinical efficacy, safety in new patient population	USFDA	April 2019	Supplemental indication approval
Tacrolimus	Retrospective observational study of data from the US SRTR	EMAF	July 2021	Supplemental NDA approval

EHRs electronic health records, *EMA* European Medicines Agency, *NDAs* new drug applications, *RWE* real-world evidence, *SRTR* Scientific Registry of Transplant Recipients, *USFDA* US Food and Drug Administration

Source: National Academy Press. Barriers and disincentives to the use of real-world evidence and real-world data

HTAs with RWE

- 16,515 HTA reports across 83 HTA bodies spanning 33 countries, the proportion of records incorporating RWE has risen from just 6% in 2011 to 39% in 2021.



Source: IQVIA. Impact of RWE on HTA Decision-making. 2022.

HTAs with RWE (2)

- In three quarters of the examples, the RWE provided external comparator data for SoC
- In cemiplimab, the pivotal trial lacked a comparator and RWE provided data on BSC

				RWE USE AND IMPACT			
MARKET	PRODUCT	ORPHAN STATUS	UNMET NEED	EXTERNAL COMP. DATA	INTERVENTION EFFECTIVENESS	OTHER	HTA OUTCOME
NICE	lenalidomide	✓	✓	✓			Positive + PAS
	midostaurin	✓	✓	✓			
	chlormethine	✓	✓	✓			Restricted + PAS
	brexucabtagene autoleucel	✓	✓	✓			
	blinatumomab	✓	✓	✓			
TLV	venetoclax	✓	✓	✓			Positive
NICE	venetoclax	✗	✓	✓		✓	
	avelumab	✗	✓	✓	✓		Positive + PAS
TLV	entrectinib	✗	✓	✓			Positive
	cemiplimab	✗	✓	✓			

Types & sources of RWD in reimbursement

Types of RWD	Sources of RWD				
	Disease and Other Registries	Claims Database	Health Surveys	Electronic Medical Records	Wearables, Personal Tracking Devices
1. Disease context (incidence, prevalence, transitional probabilities)	IN, JP, KR, MY, SG, TW, TH	IN, JP, KR, MY, SG, TW, TH	IN, JP, KR, MY, SG, TW, TH	IN, JP, KR, MY, SG, TW	TW
2. Patient population (age, sex, ethnicity, geographical location, income, education, insurance, medical history)	IN, JP, MY, SG, TW, TH	IN, JP, KR, MY, SG, TW, TH	IN, JP, KR, MY, SG, TW, TH	IN, JP, MY, SG, TW, TH	IN, JP, MY, SG, TW
3. Intervention & comparator (dosage, treatment continuation, waning of effect, discontinuation rates and reasons for discontinuation)	IN, JP, KR, MY, SG, TW, TH	IN, JP, KR, MY, SG, TW		IN, JP, KR, MY, SG, TW, TH	IN, JP, MY, SG, TW
Adherence (direct measures of drug levels, prescription refill rates, clinician assessments)	TW, TH	IN, JP, KR, MY, SG, TW	IN, JP, MY, SG, KR	IN, JP, KR, MY, SG, TW, TH	IN, JP, MY, SG, TW
4. Outcomes					
Safety (adverse drug events)	IN, JP, KR, MY, SG, TW, TH	IN, KR, MY, SG, TW		IN, JP, KR, MY, SG, TW, TH	TW
Effectiveness (surrogate or final outcomes for eg, mortality)	IN, JP, KR, MY, SG, TW, TH	IN, JP, KR, MY, SG, TW, TH		IN, JP, KR, MY, SG, TW, TH	IN, JP, MY, SG, TW
Patient reported outcomes (generic or disease specific measures)	IN, JP, KR, MY, SG, TW, TH		IN, JP, KR, MY, SG, TW, TH	TH	IN, JP, MY, SG, TW
Cost (cost or resource use)		IN, JP, KR, MY, SG, TW, TH	KR, TH	IN, JP, KR, MY, SG, TW, TH	

Source: Kc S. et al. 2023. IN, India; JP, Japan; KR, Korea; MY, Malaysia; SG, Singapore; TW, Taiwan; TH, Thailand

RWE Guidance from regulatory & HTA bodies

FDA, USA

2017 - Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

2018 - Use of Electronic Health Record Data in Clinical Investigations

2021, draft - Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products

2021, draft - Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

2021, draft - Data Standards for Drug and Biological Product Submissions Containing Real-World Data

2022 - Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products

2023, draft - Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

2023 - Considerations for the Use of RWD and RWE To Support Regulatory Decision-Making for Drug and Biological Products

2024, draft – RWE: Considerations regarding NIS for Drug and Biological Products

EMA, EU

2021 – Guideline on registry-based studies

2023 – Data Quality Framework for EU medicines regulation

ICH, M14

General principles on plan, design, and analysis of pharmacoepidemiological studies that utilize RWD for safety assessment of medicines

ENCePP, EU

2023 – Guide on Methodological Standards in Pharmacoepidemiology, Rev. 11

Swissmedic, CH

2023 - Swissmedic position paper on the use of real world evidence

HAS, FR

2021 - Real-world studies for the assessment of medicinal products and medical devices

MHRA, UK

2021 – Guidance on the use of RWD in clinical studies to support regulatory decisions

2021 – Guideline on randomized controlled trials using RWD to support regulatory decisions

NICE*, UK

2022 – NICE RWE Framework

Health Canada

2018 - Use of Electronic Health Record Data in Clinical Investigations

Canada's D&HTA* (+ Health Canada)

2023 – Guidance for reporting RWE

PMDA, Japan

2014 – Guidelines for the conduct of pharmacoepidemiological studies in drug safety assessment with medical information databases

2017 – Basic Principles on the use of medical information databases in post-marketing pharmacovigilance

2020 – Points to consider for ensuring the reliability of post-marketing database study for regenerative medical products

2021 – Basic Principles on utilization of registry for applications

NMPA, China

2021 – Guidance for Real-World Data Used to Generate Real-World Evidences (Interim)

2022 – Guidance on the Use of Real-World Evidence to Support Drug Development and Regulatory Decisions

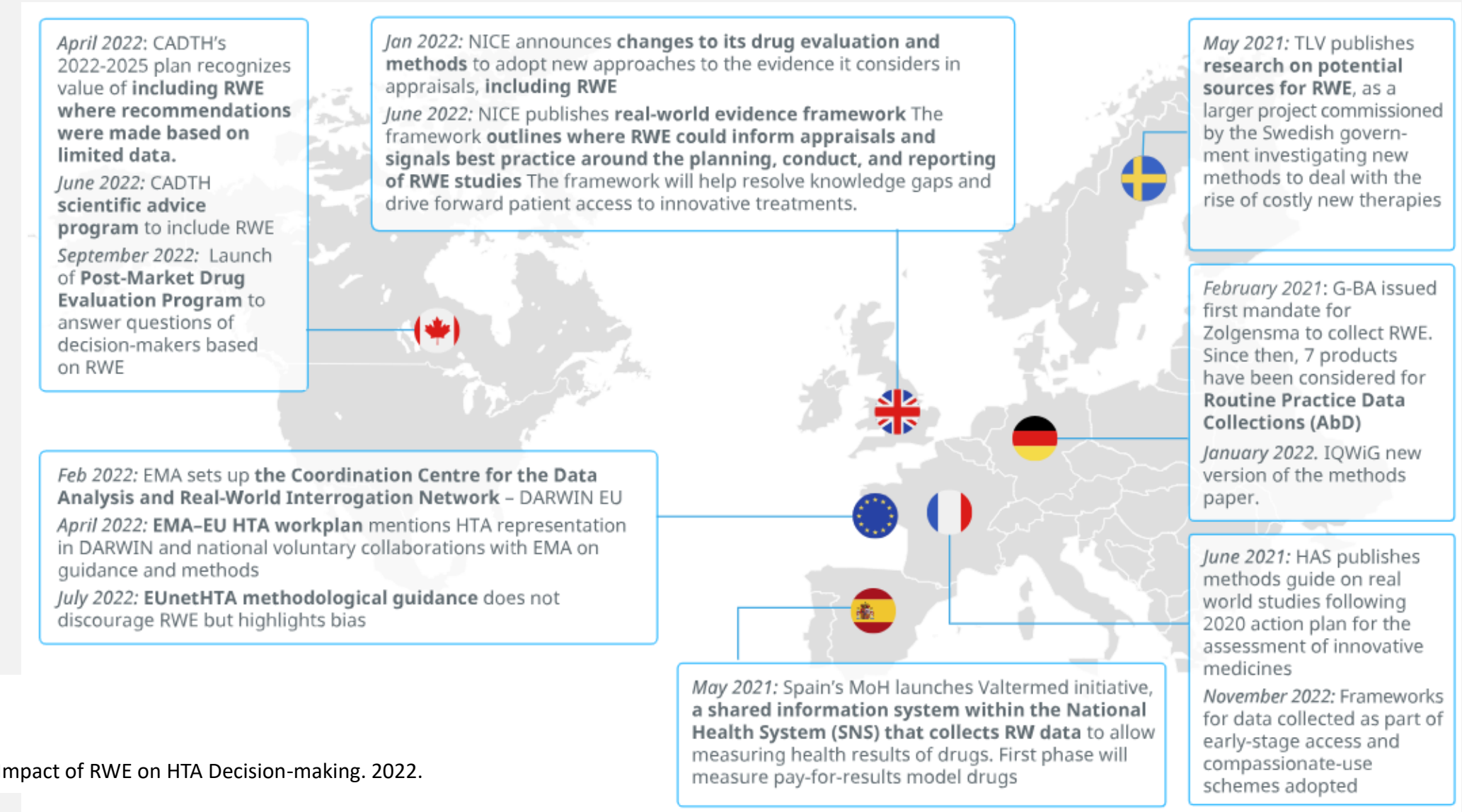
2023 – Guidance on Communication with Regulatory Agency on Real- World Studies to Support Product Registration

2023 – Guidance on the Design and Protocol Development of Real-World Studies for Drugs

Source: Klungel O et al., Joint HMA/EMA workshop. 2024

RWE Guideline from HTA bodies

- EUnetHTA guideance in July 2022

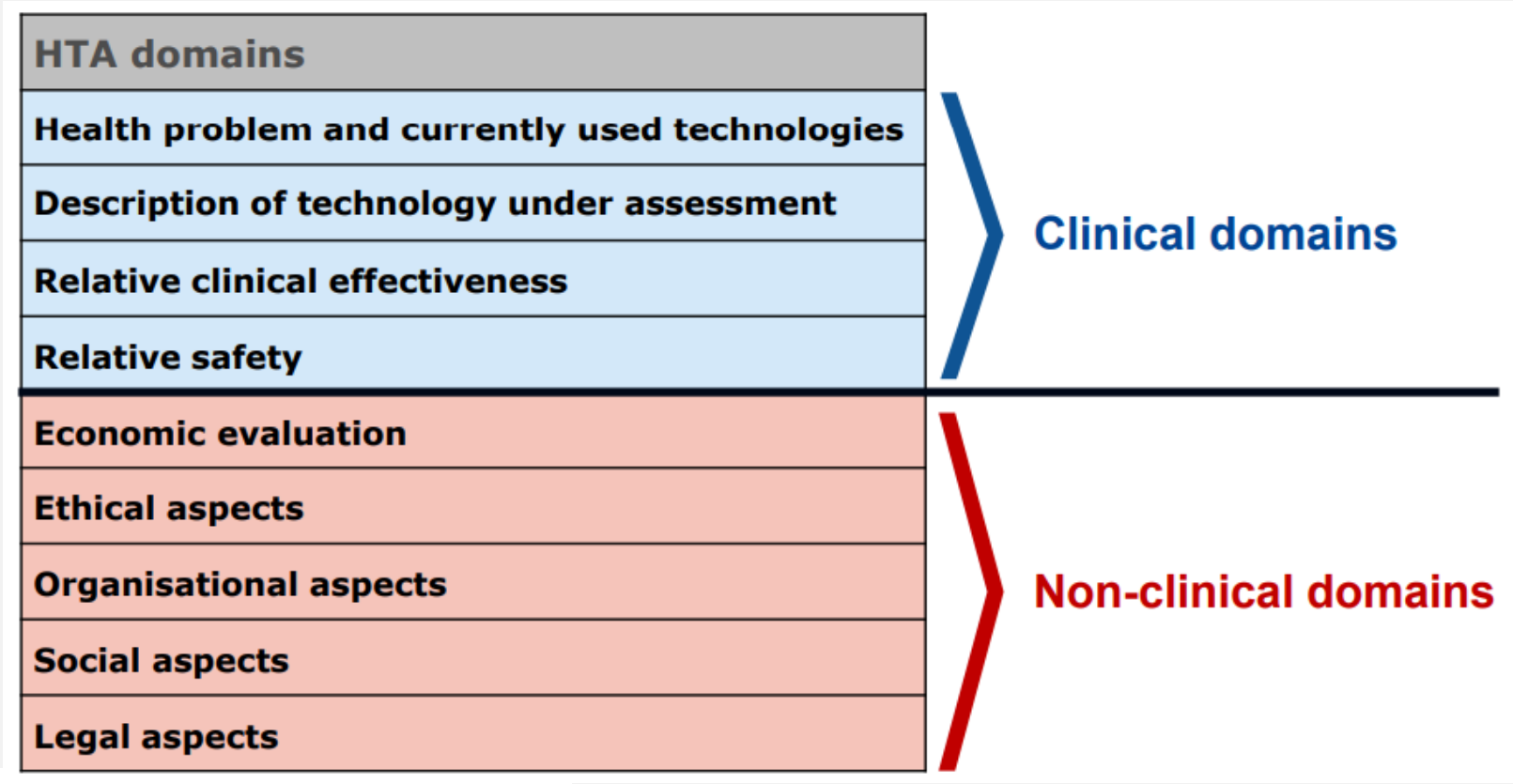


Source: IQVIA. Impact of RWE on HTA Decision-making. 2022.

EU

HTA domains

- HTA is the systematic evaluation of the properties, effects, or impact of a health technology in comparison to another technology



Source: Valverde JA . 2023.

Regulatory process vs HTA

- Joint framework

- All Member States have different HTA systems
- National legislations and procedures
- Different methodologies and assessment criteria

Source: Valverde JA . 2023.

EUROPEAN MEDICINES AGENCY

- Single licensing system
- Single EU legislation
- Well defined and agreed assessment criteria

EU HTA regulation

- Joint framework for clinical assessment
- Common methodology and approach for clinical assessments and scientific consultations

NATIONAL

- Use of joint clinical assessment in national decision-making
- Non-clinical assessments
- Decision making on pricing and reimbursements

EUnetHTA

- EUnetHTA to create an effective & sustainable network across Europe
  - The facilitation of efficient HTA resource use
  - The creation of a sustainable system of HTA knowledge sharing
  - The promotion of good practice in HTA methods and processes
  - >80 partners consisting national, regional, and non-for-profit agencies

2004 The European Commission **establishing a sustainable European network on HTA**

2005 Call for project proposal answered by a group of **35** organisations throughout Europe

2006 EUnetHTA **Project** (2006-2008)

2009 EUnetHTA **Collaboration** (2009)

2010 EUnetHTA **Joint Action 1** (2010-2012): To put into practice an HTA collaboration

2012 EUnetHTA **Joint Action 2** (2012-2015): To strengthen the cross-border HTA collaboration

2016 EUnetHTA **Joint Action 3** (2016-2021)

Source: EUnetHTA

Joint Clinical Assessment (JCA)

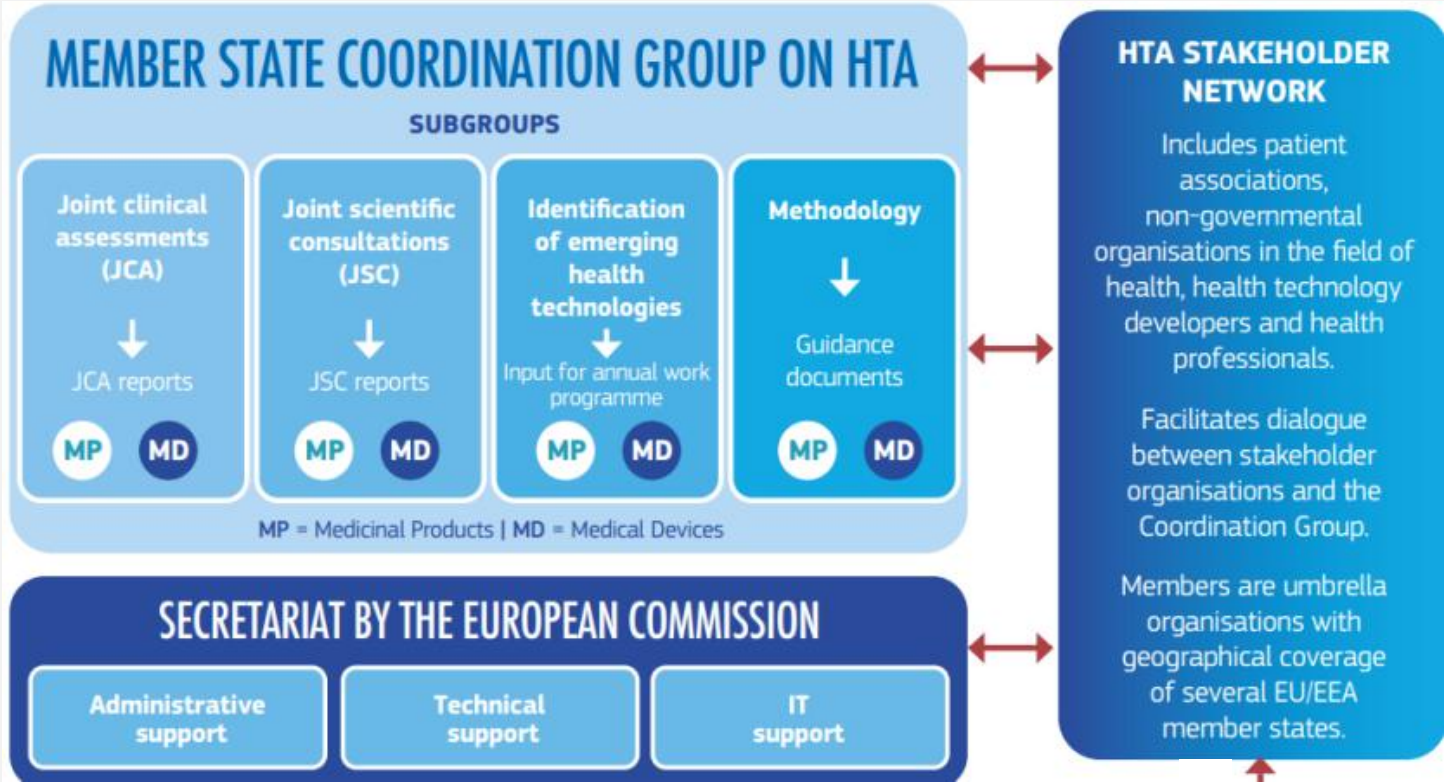
- This initiative sets out implementing rules to ensure that EU-level assessments of new medicines are conducted in good time
  - EUnetHTA Joint Assessments (JA) by EUnetHTA partners in different countries

EU HTA cooperation

Source: Valverde JA . 2023.

Joint HTA activities

- Joint Clinical Assessments (JCA) on:
  - **medicines** first 3 years: cancer medicines and advanced therapy
    from January 2028: + orphan medicinal products
    from 2030: full scope
  - a selection of high-risk medical devices and in-vitro medical devices
- **Joint Scientific Consultations (JSC)**
  - in parallel with the EMA
- **Methodology for joint HTA work**
- Identification of emerging techology



Source: Valverde JA . 2023.

Regulation (EU) 2023/2282

- Adoption 15 December 2021
- Entry into force 11 January 2022
- **Entry into application 12 January 2025**
- Main objectives: establishing a support framework and procedures for cooperation of Member States on health technologies at Union level
- **HTA Regulation - Key principle**
  - Joint work on common scientific, clinical aspects of HTA
  - Driven by Member State HTA bodies
  - Ensure high quality, timeliness and transparency
  - Ensure involvement of stakeholders
  - Ensure use of joint work in national HTA processes

HTA R

- The Parallel EMA/EUnetHTA 21 Joint Scientific Consultations (JSCs) under the EUnetHTA 21 service closure & HTA Regulation in January 2025

Joint Scientific Consultations (JSC)

Home › Joint Scientific Consultations (JSC)

Parallel EMA/HTA body (HTAb) Scientific Advice during Interim Period post EUnetHTA 21

[UPDATE]

The Parallel EMA/EUnetHTA 21 Joint Scientific Consultations (JSCs) under the EUnetHTA 21 service contract will have to be completed by September 2023 and all available slots have already been allocated. To bridge the interim period between the closure of EUnetHTA 21 and the full application of the HTA Regulation in January 2025, EMA and national HTAb will offer Health technology developers (HTDs) the opportunity for parallel scientific advice:

HTDs will be able to apply for **Parallel EMA/HTA body (HTAb) Scientific Advice** from September 2023, when EUnetHTA 21 ceases to operate, until January 2025 when Regulation (EU) 2021/2282 on health technology assessment will become fully applicable.

The G-BA (Gemeinsamer Bundesausschuss/Federal Joint Committee, Germany) will function as the HTA Coordination Contact and facilitates a centralised HTAb recruitment.
In order to apply for a Parallel EMA/HTAb Scientific Advice, HTDs should complete the application form and submit the form and its annexes via Eudralink to the HTA Coordination Contact (interimadvice.hta@g-ba.de) copying EMA. Applicants should request such parallel scientific advice three months before the standard submission deadline. For more information, see Scientific Advice Working Party.

The selection criteria, identical to the ones of the HTA Regulation, can be found again in the Guidance on Parallel EMA/HTA body (HTAb) Scientific Advice.
The result of the selection will also depend on the resources available to each HTA body.

A minimum of two HTA bodies may actively participate on a voluntary basis. If the minimum number of active HTA bodies is not reached, the request will continue as EMA-only scientific advice.

As an outcome of the procedure, developers will receive a scientific advice letter from EMA and individual written recommendations from participating HTA bodies.

Regulation (EU) 2024/1381 of 23 May 2024

- Pursuant to Regulation (EU) 2021/2282 on health technology assessment

Document 32024R1381

Commission Implementing Regulation (EU) 2024/1381 of 23 May 2024 laying down, pursuant to Regulation (EU) 2021/2282 on health technology assessment, procedural rules for the interaction during, exchange of information on, and participation in, the preparation and update of joint clinical assessments of medicinal products for human use at Union level, as well as templates for those joint clinical assessments

C/2024/3320

OJ L, 2024/1381, 24.5.2024, ELI: http://data.europa.eu/eli/reg_impl/2024/1381/oj (BG, ES, CS, DA, DE, ET, EL, EN, FR, GA, HR, IT, LV, LT, HU, MT, NL, PL, PT, RO, SK, SL, FI, SV)

In force

ELI: http://data.europa.eu/eli/reg_impl/2024/1381/oj

Expand all Collapse all

Languages, formats and authentic version

	BG	ES	CS	DA	DE	ET	EL	EN	FR	GA	HR	IT	LV	LT	HU	MT	NL	PL	PT	RO	SK	SL	FI	SV
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PDF - authentic OJ																								
e-signature																								

Source: European Union

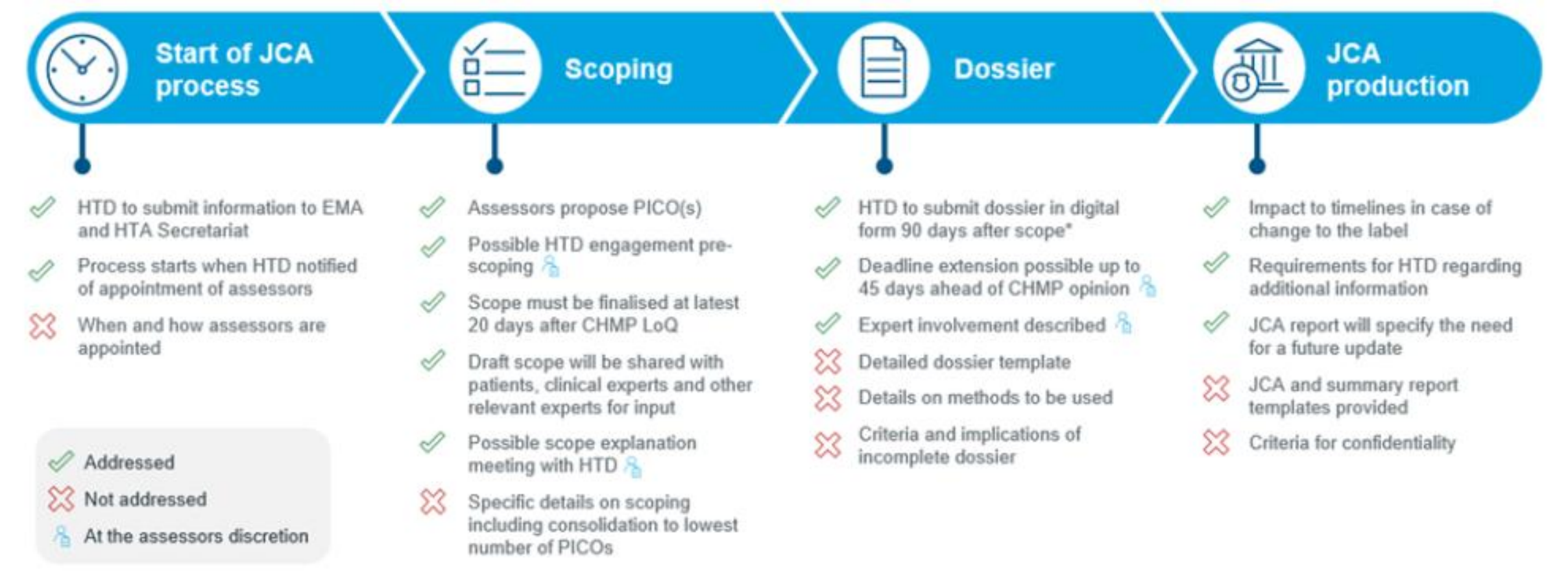
HTA R

- Six IAs are outlined in the HTAR, with the draft of the IA on JCA for medicinal products

• Procedural rules for JCA medicinal products	Q4 2023
• Procedural rules for the prevention of conflict of interest	Q1 2024
• Cooperation by exchange of information with the EMA	Q1 2024
• Procedural rules for JSC medicinal products	Q2 2024
• Procedural rules for JCA medical devices and IVD medical devices	Q3 2024
• Procedural rules for JSC medical devices and IVD medical devices	Q4 2024

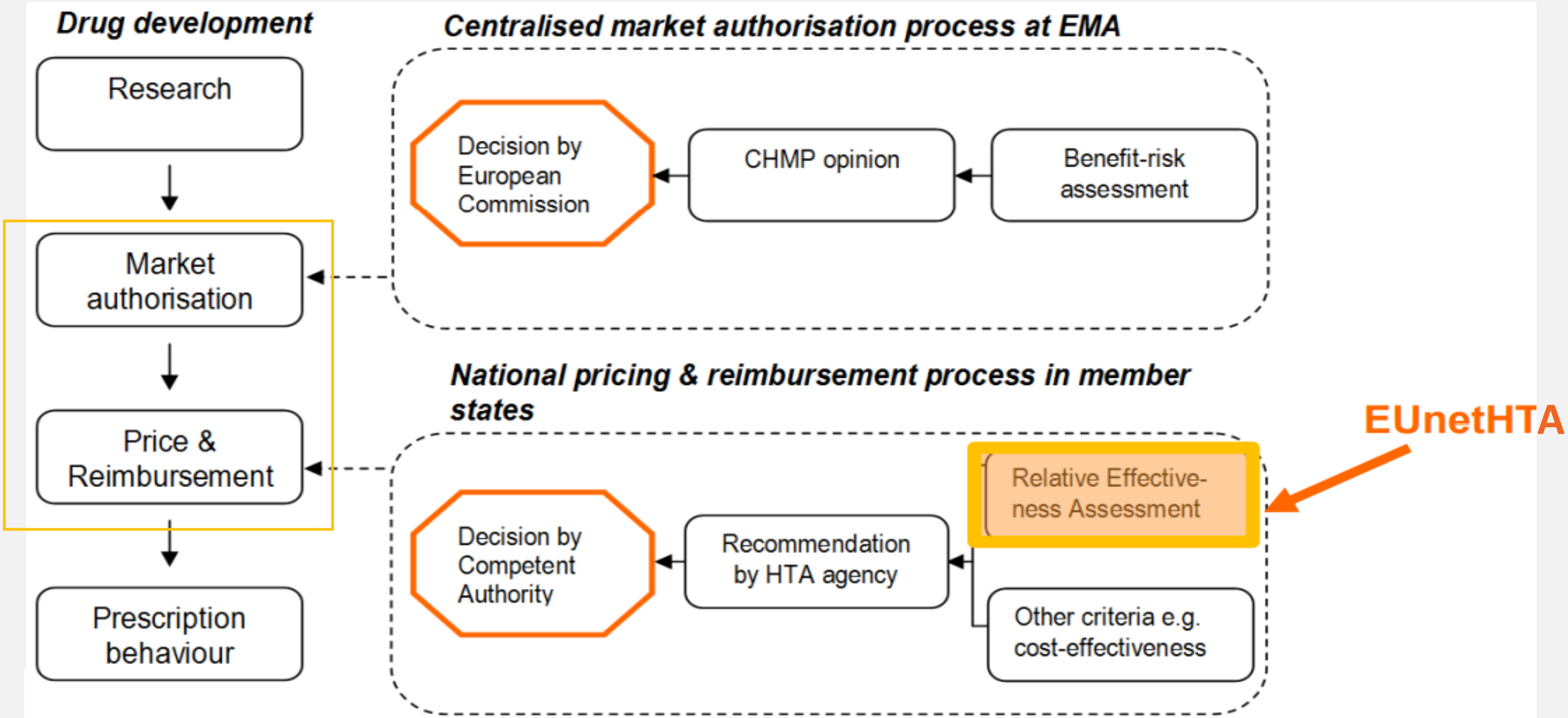
HTA R

- draft of the IA on JCA for medicinal products



Source: HIRA Sympisum in 2024

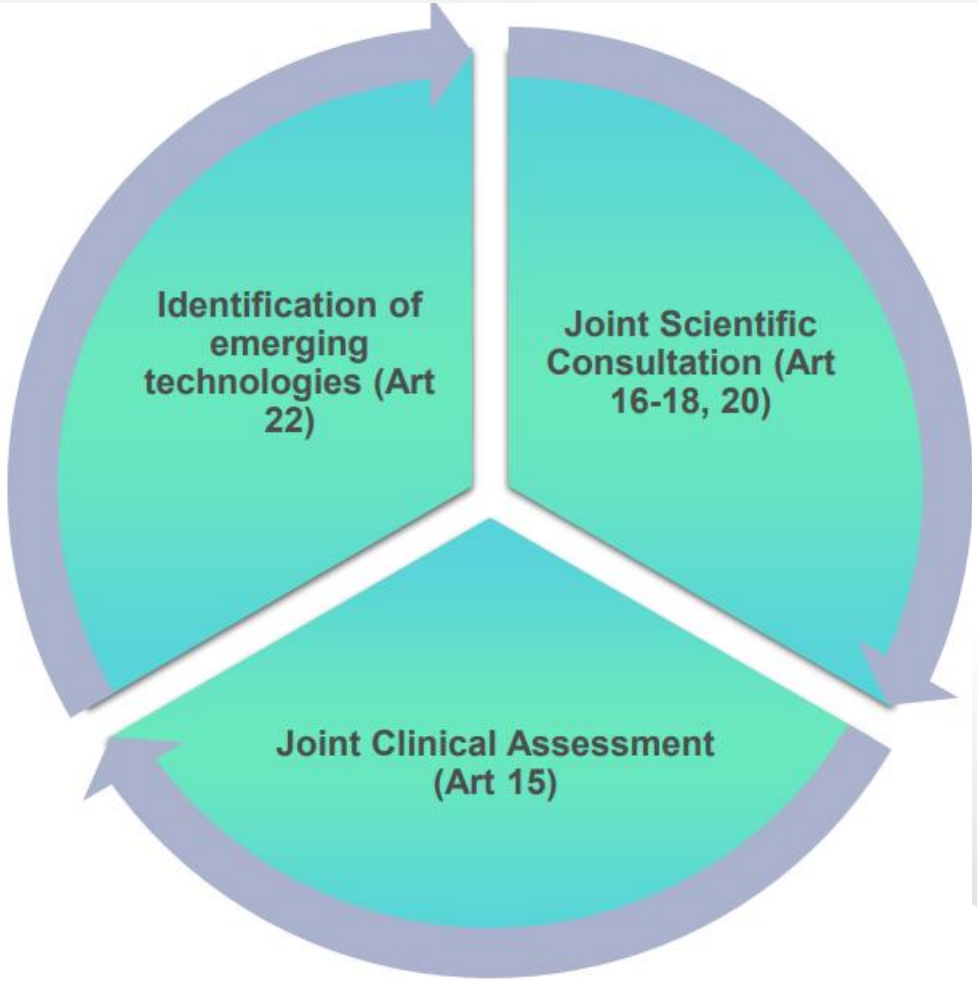
Regualatory & HTA process



Source: Goettsch W . 2023.

Collaboration with EMA

- JCA, JSC

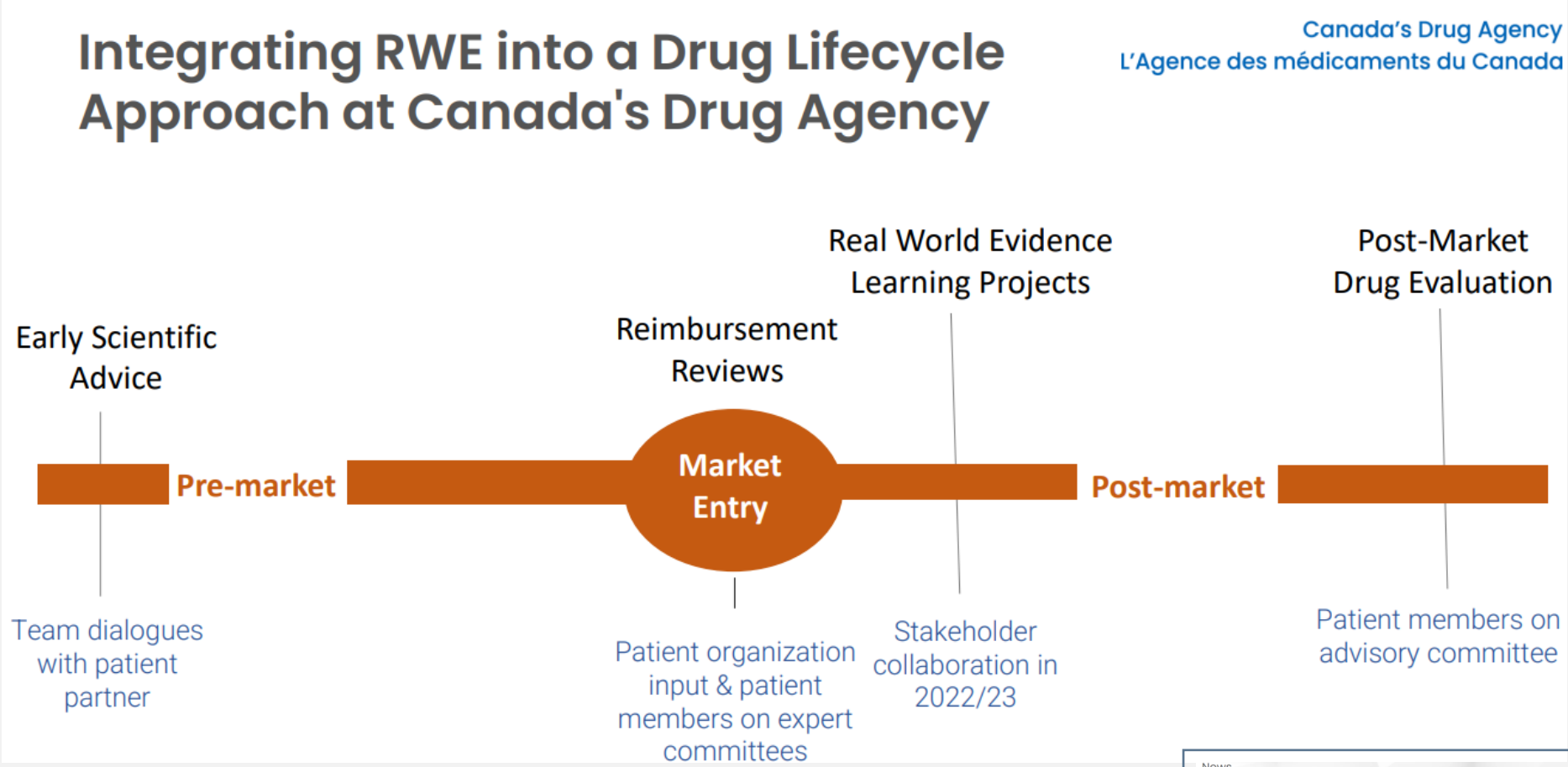


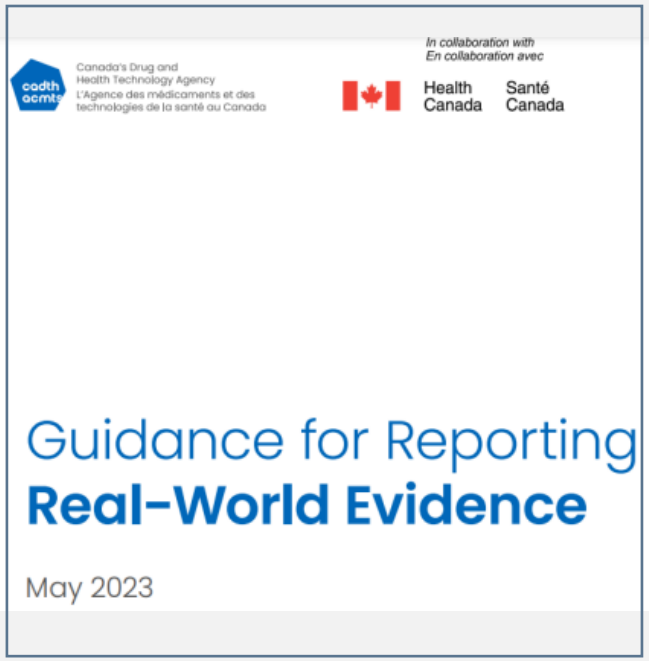
Implication

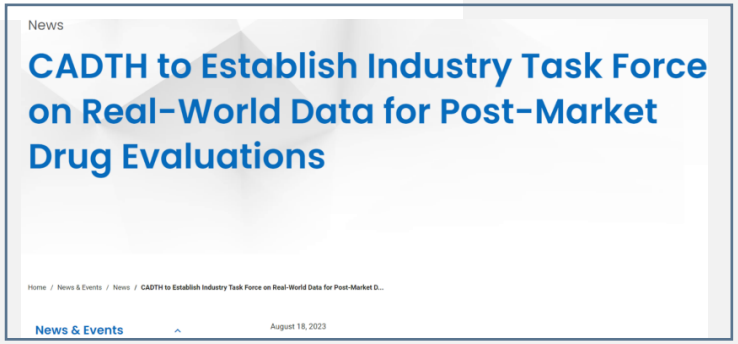
- New HTA methods are needed
  - Internationalization
  - Adaptation to a new era of personalized medicine
  - Extrapolation of results using RWD and big data
  - Allignment with methdological development for regulators and patients

Canada

Canada's Drug Agency (CDA)







Source: HIRA Sympisum in 2024

Challenges

- Methods and results may not be complete and/or accurately reported using best practices for the type of study involved.
- RWE submission may not include a robust study design and a clear justification of why RWE is appropriate.
- Submission may not clearly identify the gaps that RWE is intended to address.
- Lack of standardized reporting and poorly reported RWE can slow the review Process.

Source: HIRA Sympisum in 2024

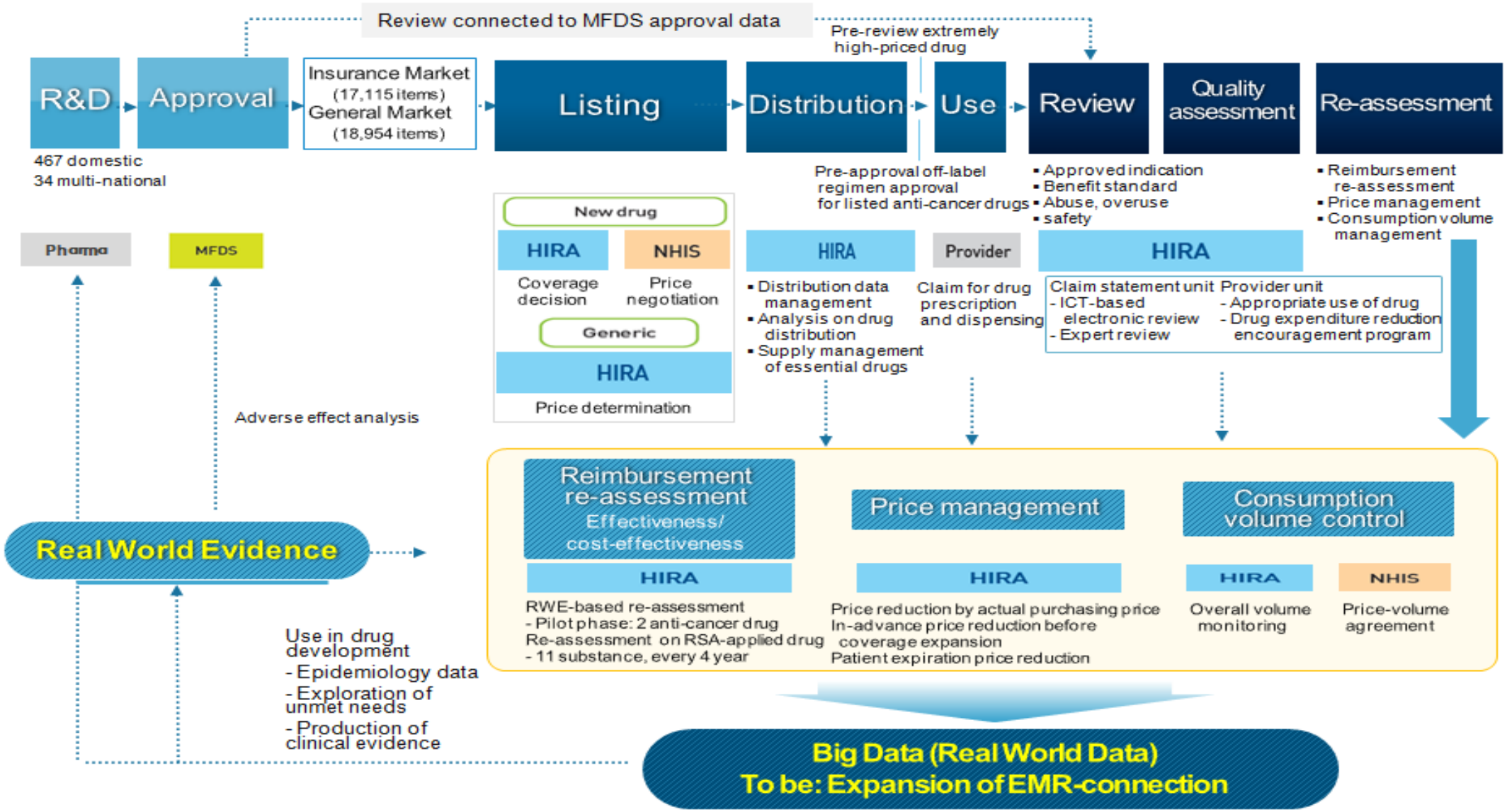
Implication

Pricing & reimbursement in Korea

- Pharmaceutical benefit system
  - Positive list system introduced in Dec. 2006
  - Listing clinically economically effective drugs

- Alternative(Supplementary) system for coverage
  - Risk sharing scheme for pharmaceuticals (from Jan. 2014)
  - Economic evaluation exemption tract (from June. 2015)
    - Rare disease drugs where the economic evaluation is difficult to be conducted
  - Off-label drug use
    - Off-label drug use for oncology: submission of RWD assessment every year
  - Adoption Cases with MEA [Risk Sharing Scheme]
    - One drug for acute lymphoblastic leukemia (ALL) among children
    - Financial-based risk sharing scheme

Healthcare process in Korea



RWE with HTA

- Initial HTA submission and HTA reassessment

Categories		TLV	NICE	IQWiG	HAS	AIFA	ZIN
IRD (Initial reimbursement discussions)	Real World Data(RWD) accepted	Under specific circumstances	Under specific circumstances	Under specific circumstances	Under specific circumstances	Under specific circumstances	Under specific circumstances
	Real World Evidence(RWE) Appraisal	RWD possible in exceptional circumstance	RWD possible in exceptional circumstance	No	No	No	No
PEA (Pharmacoeconomic analyses)	Real World Data(RWD) accepted	Under specific circumstances	Under specific circumstances	No	Under specific circumstances	Under specific circumstances	Under specific circumstances
	Real World Evidence(RWE) Appraisal	On the basis of RWD regarded as reliable	On the basis of RWD regarded as reliable	No	On the basis of RWD regarded as reliable	On the basis of RWD regarded as reliable	On the basis of RWD regarded as reliable
CRS (Conditional reimbursement schemes)	Real World Data(RWD) accepted	NA	NA	NA	Effectiveness and/or Cost-effectiveness	Effectiveness and/or Cost-effectiveness	Effectiveness and/or Cost-effectiveness
	Real World Evidence(RWE) Appraisal				Identification of evidence gap between RCT and RWE	Identification of evidence gap between RCT and RWE	Identification of evidence gap between RCT and RWE

AIFA, Italian Medicines Agency(Italy); Has, High Authority for Health(France); HTA, Health Technology Assessment; IQWiG, Institute for Quality and Efficiency in Healthcare(Germany); NICE, National Institute for Health and Care Excellence(UK); TLV, Dental and Pharmaceutical Benefits Agency(Sweden); ZIN, National Healthcare Institute(Netherlands).

Sources: Makady 등(2017)

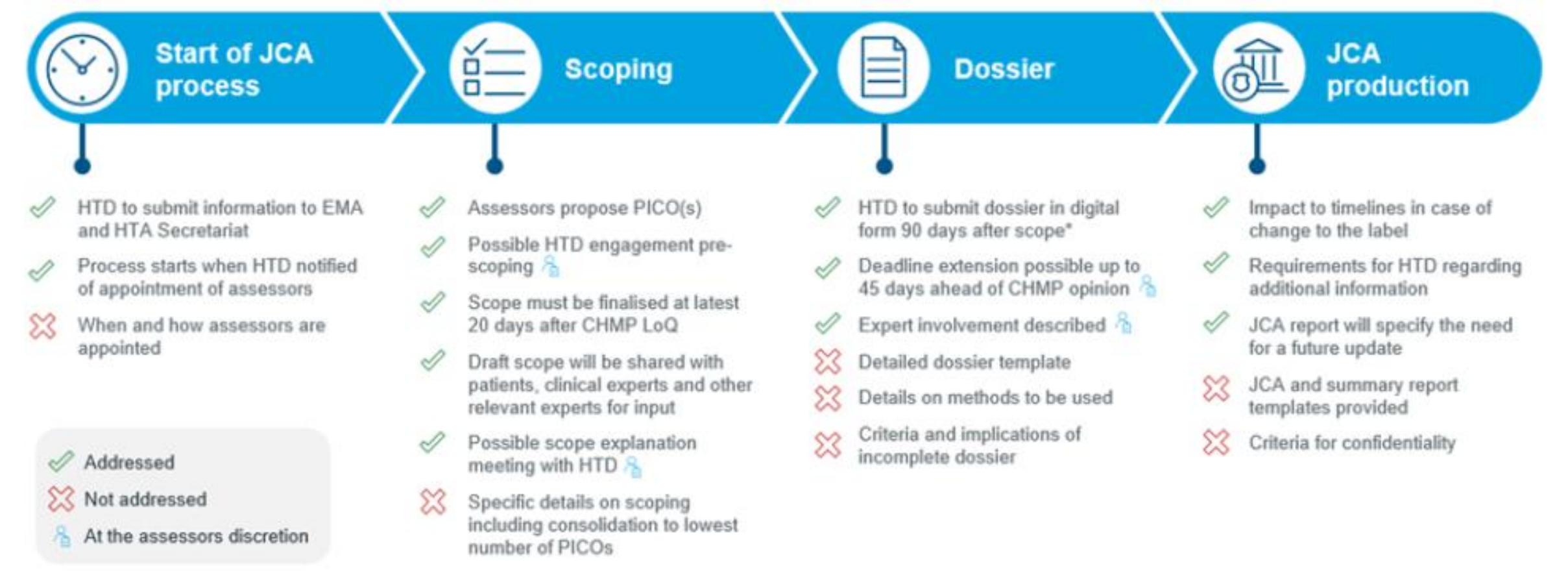
Challenges

	Accelerated Access	Reassessment/Review
Challenges	• Privacy and confidentiality requirement • Hard to explain differences in RCTs and RWE outcomes • Early access inhibiting RCT enrollment • Agreement on the objective of a registry data • Not always clear whose responsibility for colleting RWE	• Ambiguous agency guidance, requirements and methodologies • Hard to gain agreement on the right data both quality and type • Limited standardization b/t agencies • trade-offs b/t price and access
Opportunities	• Growing acceptance of RWE for conditional reimbursement decisions • Observational trials as continuation of RCTs • Pan-European consent form for expanding use of RWD • RWD in disease areas where patients are less risk averse	• RWE better in demonstrating benefits in real world • Developing datasets to address multiple endpoints • Improving quality and credibility from Linkage of accredited academic institutions • PRO & involving patient organizations strengthening data • Sharing of approaches across rare diseases • Early engagement to agree predefined RWE strategies and valuable outcomes

Sources: Gill,J.L. et. al., RWE in Europe Paper | (2016)

HTA R

- draft of the IA on JCA for medicinal products



Source: HIRA Sympisum in 2024

Thank you