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New Pan-EU HTA:

How can biopharma navigate the Joint Clinical Assessment?

ISPOR Europe Symposium

Vienna, Austria

8 November 2022

Agenda

Topic		Speaker
Introduction to the EU joint HTA regulation and JCA process		**Tommy Bramley, PhD** AmerisourceBergen Senior Vice President, Global Consulting UK
Joint Clinical Assessments: What do we need to agree on?		**Michael Drummond, DPhil** Professor Emeritus Centre for Health Economics University of York UK
Industry perspectives on a fit-for-purpose EU system of Joint Clinical Assessment		**Mihai Rotaru** Senior Manager, Market Access European Federation of Pharmaceutical Industries and Associations (EFPIA) Belgium
A future looking at the HTA perspective: Trick or treat?		**Alberto Rubio, MBA** Senior Director, International Service Head Market Access PharmaLex Spain
Closing and Q&A		**Tommy Bramley, PhD**

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New Pan-EU HTA:

Introduction to the EU joint HTA regulation and JCA process

Tommy Bramley, PhD
Senior Vice President, Global Consulting
AmerisourceBergen

London, UK

Further convergence: Pan-European HTA follows centralized market authorization for pharmaceuticals— What is the future path for Pan-European HTA?

January 12, 2022

Formal enactment of EU HTA Regulation by the European Parliament and the Council of the EU

2022–2024

Pilot phase, formation of a Coordination Group (one member per EU country; main tasks: establishment of formal and methodological guidance), formation of a stakeholder network

January 12, 2025

JCA **mandatory for oncology drugs, ATMPs** and implementation of JSC

January 13, 2028

JCA **mandatory for orphan drugs**

January 13, 2030

JCA **mandatory for all drugs** registered centrally by the EMA

Key: ATMP – Advanced Therapy Medicinal Product; EMA – European Medicines Agency; EU – European Union; HTA – Health Technology Assessment; JCA – Joint Clinical Assessment; JSC – Joint Scientific Consultation

Four pillars of Pan-EU HTA, with Joint Clinical Assessments in the centre

Coordination group

Coordination group with members of member states, hosted by the European Commission, regular exchange with a stakeholder network

Four subgroups

(more allowed)

- **Joint Clinical Assessments**
- **Joint Scientific Consultations**
- **Identification of emerging health technologies**
- **Development of methodological and procedural guidance**

Principles of the Joint Clinical Assessment

Health policy

- Improving **access** to medicines
- Promotion of **innovation**
- Promotion of **comparative effectiveness**
- **Preference for RCTs;** however, observational data and RWE data also could be used

Enhancement of transparency in decision making

- **Harmonization** of methodological requirements
- Based on standards of **evidence-based medicine**
- **Active involvement of stakeholders** through "stakeholder network"
- JCAs are **not legally binding;** however, they are to be "given due consideration"

Avoidance of redundancies/ parallel structures

- **One dossier instead of 27** (avoidance of redundancies both for companies and assessors)
- **Provision of HTA on EU level** for countries without national HTA structures
- **Data** already submitted to the JCA **must not be submitted again** on the national level
- **Complementary clinical data might be asked** for on the national level

Preservation of national decision-making sovereignty

- **"Classic" HTA separation: assessment vs appraisal**
- JCA should be **free of value judgment** and summary on the added medical benefit
- **Final appraisal** is to be done **on the national level**
- **Decisions on pricing, pricing regulation, and reimbursement remain on the national level**

Key: EU – European Union; HTA – Health Technology Assessment; JCA – Joint Clinical Assessment; RCT – Randomized Controlled Trial; RWE – Real-World Evidence

What is the process of the Joint Clinical Assessment?

1. Parallel to the regulatory filing, pharmaceutical companies file a **"letter of intent" to formally start the process**
2. JCA subgroup initiates an assessment scope: Request for information on critical parameters from all member states following PICO scheme ("**PICO survey**"), to be answered in approximately 2 weeks
3. **Determination of scope** by the subgroup, PICO consolidation (assessor and co-assessor)
4. **Submission of the dossier 45 days PRIOR** to positive opinion by CHMP, at the latest
5. **Assessment report** of coordination group **30 days AFTER EU Commission Decision**

Key: CHMP – Committee for Medicinal Products for Human Use; EU – European Union; JCA – Joint Clinical Assessment; PICO – Population, Intervention, Comparator, and Outcomes

One PICO scheme per country—27 to be consolidated to one
Does heterogeneity on country level lead to process uncertainty?

Population

Intervention

Comparator

Outcomes

Study design/ methodology

Relevance of subgroups

Determined by label

Different comparators due to different standards of care and availability

Patient relevance, acceptance of surrogates, patient preferences

Acceptance of uncertainty and of indirect comparisons, generation of long-term data

Degree of heterogeneity

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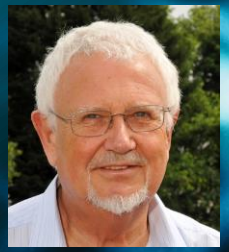
New Pan-EU HTA:

Joint Clinical Assessments: What do we need to agree on?



Michael Drummond, DPhil

Professor Emeritus
Centre for Health Economics
University of York, UK

Some background

The EU Regulation focuses on the clinical component of health technology assessment (HTA) since, in principle, this is more transferable among member states

However, member states use clinical evidence for HTA in different ways and may have different views on the relevance of different categories of evidence

In addition, HTAs compare the new technology with current standard of care, which may differ among member states

Differences of opinion, or perspective, will be discussed in the Member State Coordination Group on HTA (HTACG), as they develop the plan for Joint Clinical Assessments (JCAs)

EUnetHTA is producing a series of practical guidelines on the relevant topics

Things we need to agree on

Use of direct and indirect treatment comparisons

Validation and use of surrogate endpoints

Relevance and use of real-world evidence

Use of direct and indirect comparisons

Some HTA agencies in member states focus mainly on head-to-head comparisons from RCTs; others are willing to consider indirect treatment comparisons through network meta-analysis

The treatment comparisons made in existing RCTs may not be relevant to some member states if their current standard of care is different

In some cases (e.g. treatments for rare diseases), only single-arm clinical studies will be available (with or without historical controls)

How far will JCAs depart from the head-to-head comparisons in RCTs, and will this be presented in a separate analysis?

Key: HTA – Health Technology Assessment; JCA – Joint Clinical Assessment; RCT – Randomized Controlled Trial

Validation and use of surrogate endpoints

Sometimes the clinical data presented consists of biomarkers or intermediate outcomes (e.g. disease-free survival)

HTA agencies differ in the extent to which they accept these outcomes and the level of validation they require to demonstrate surrogacy (for final endpoints, such as overall survival)

Although there is a clear preference in all quarters for patient-centred outcomes, there is a need to agree on the basis for including intermediate outcomes in JCAs

The EUnetHTA practical guideline on outcomes (endpoints) specifies some requirements for JCA reporting[1]

1. EUnetHTA 21. D4.4 Outcomes (Endpoints). Version 0.3. September 2022.

Relevance and use of real-world evidence (RWE)

RWE has a several uses in HTAs, including describing current care and projecting costs and/or effects in the long-term

The most controversial use of RWE is in estimating relative clinical effect, due to the potential biases in observational studies

Agreement is required on which categories of RWE can be considered in JCAs and the analytical approaches that can be used to minimise potential biases

Also, should JCAs say anything about the RWE that might be gathered after the market entry of technologies, or is this best viewed as a matter for member states?

Note: EUnetHTA has 2 Project Plans that bear on some of these issues: D4.5 Applicability of Evidence and D4.6 Validity of Clinical Studies.

Absolutist position	Nuanced position
Head-to-head RCTs are the only form of reliable evidence on relative effectiveness.	While it's true head-to-head **RCTs** are the best source of evidence on relative effectiveness, they **may not compare the most relevant alternatives**, are often **short-term**, and usually rely on surrogate endpoints. It is just important to understand the areas of uncertainty in interpreting evidence from alternate approaches as part of the decision-making process. In addition, **there may be some technologies for which head-to-head RCTs do not exist** (e.g. some medical devices and some rare disease treatments).
All use of surrogate endpoints is dubious.	As mentioned above, **many RCTs rely on surrogate endpoints**. The **main point is that surrogates are properly validated**. There are established approaches for this. One of the most common surrogates, progression-free survival, is not fully validated in certain tumor types, but it is in others. Again, **the decision on relevance of a surrogate should be case-specific.**
Real-world data are so fraught with bias that they are unusable.	**Real-world data have many potential uses in HTA**, such as in projecting long-term outcomes, examining the impact of therapy in real-world settings, or estimating treatment durability**. Issues of potential bias mainly relate to the use of real-world data to estimate relative treatment effect**. **These biases can (and should) be recognized and corrected for.**

Concluding remarks

The development and conduct of JCAs raises many methodological and practical issues

Most of these issues can be resolved through discussion, as long as there is a willingness to accept a nuanced approach

The practical guidelines being developed by EUnetHTA represent a good start

In the longer term, companies will be able to discuss the data requirements for JCAs through joint scientific consultations

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Industry perspectives on a fit-for-purpose EU system of Joint Clinical Assessment

Mihai Rotaru
Sr Manager, Market Access
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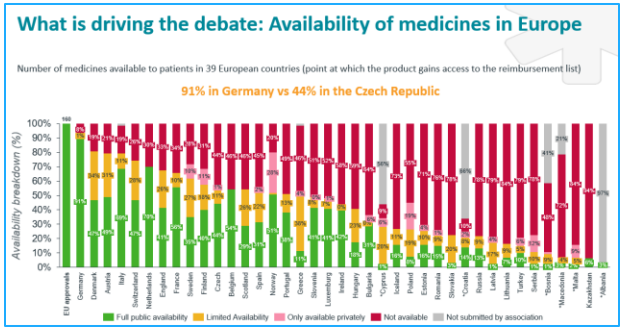
The different root causes of unavailability and delay



- **10 interrelated factors explain unavailability and delays**, it is not possible to untangle their impact with perfect precision

- These are **rooted in the medicines access systems and processes in the EU Member States** and **the corresponding impact on commercial decision making**
- Their resolution requires **significant efforts in the Member States**, some will benefit from EU-level cooperation

Category	Potential root causes
The time prior to market authorisation	1. The speed of the regulatory process 2. Accessibility of medicines prior to marketing authorisation
The price and reimbursement process	3. Initiation of the process 4. The speed of the national timelines and adherence
The value assessment process	5. Misalignment on evidence requirement 6. Misalignment on value and price 7. The value assigned to product differentiation and choice
Health system readiness	8. Insufficient budget to implement decisions 9. Diagnosis, supporting infrastructure and relevance to patients
Delay from national to regional approval	10. Multiple layers of decision-making processes

Source: EFPIA/CRA report. The root cause of unavailability and delay to innovative medicines. June 2020.

Misalignment on clinical evidence requirements

Acceptance of clinical evidence by decision makers as a driver of patient access delays

- **Diverging and frequently unpredictable clinical evidence requirements create confusion, inefficiencies, and market access delays**
  - **Between EMA and HTA agencies**
  - **Between national HTA agencies**

Acceptance of evidence characteristics by EMA

and six national HTA bodies, based on self-assessment by agency representatives

Legend

Accepted | **Often accepted** | **Case-dependent** | **Often not accepted** | **Not accepted**

Evidence characteristics (for the clinical or cost effectiveness assessment)		Autho-rization	Health technology assesment						Level of align-ment among HTA bodies
		EMA	UK-ENG	IT	NL	PL	PT	SE	
Population	• Target population as authorized by EMA	[N/A]							50%
	• Use of biomarkers								100%
	• Extrapolation to other populations								33%
Comparator	• Selected comparator								100%
	• Class effects								33%
	• Indirect comparisons								50%
Clinical end points	• PFS as endpoint								50%
	• Other surrogate endpoints (non PFS)								0%
	• Absence of QoL data								50%
Trial design and data sources	• Real-world evidence								100%
	• Network Meta-Analysis								50%
	• Single armed trials								50%
	• Novel trial designs								50%
	• Cross over in trial								33%
	• Evidence from small population								67%
	• Short time period								50%
Statistical analysis	• Absence of statistical significance								67%
	• Post-hoc subgroup analyses								83%
	• Clinical relevance of effect acc. to EMA								67%
Level of acceptance per agency (HTA bodies and EMA)		79%	68%	42%	47%	79%	37%	58%	

Sources ASC Academics and Ventura, 2020 (see Annex C).

Vintura. Every day counts. 2020.

Key: EMA – European Medicines Agency; HTA – Health Technology Assessment.

The changing face of biomedical innovation

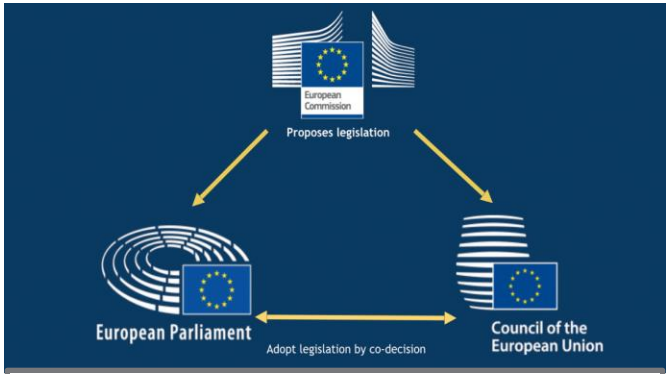
Adding complexity and additional capability requirements to national HTA activity

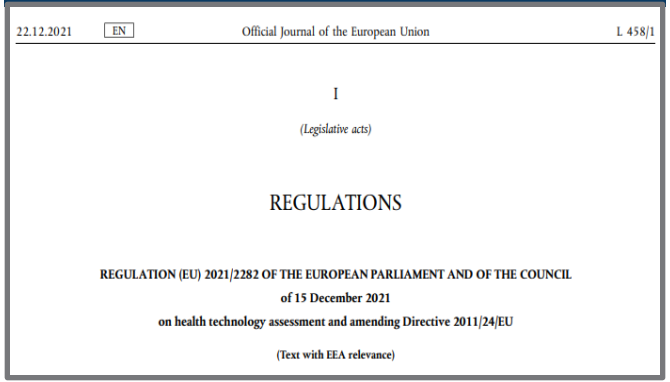
- Rare disease innovation with more **limited information at the time of (initial) marketing authorization**
- **Smaller, focused RCTs, adaptive trial designs, expanded use of single-arm trials, and surrogate and intermediate endpoints**
- Increasing number of **biomarker-specific therapies with co-dependencies with diagnostics** ("precision medicine") and **other technologies** ("integrated solutions")
- **Life cycle approach** to medicine development and marketing authorization
- **Fast evolution of clinical «standards of care»**

→ ***There is an urgent need to revisit HTA standards and processes but also pricing, reimbursement, and funding principles and pathways***

EU HTA Regulation

Major opportunity that we cannot afford to miss





22.12.2021 EN Official Journal of the European Union L 458/1

I

(Legislative acts)

REGULATIONS

REGULATION (EU) 2021/2282 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 15 December 2021
on health technology assessment and amending Directive 2011/24/EU

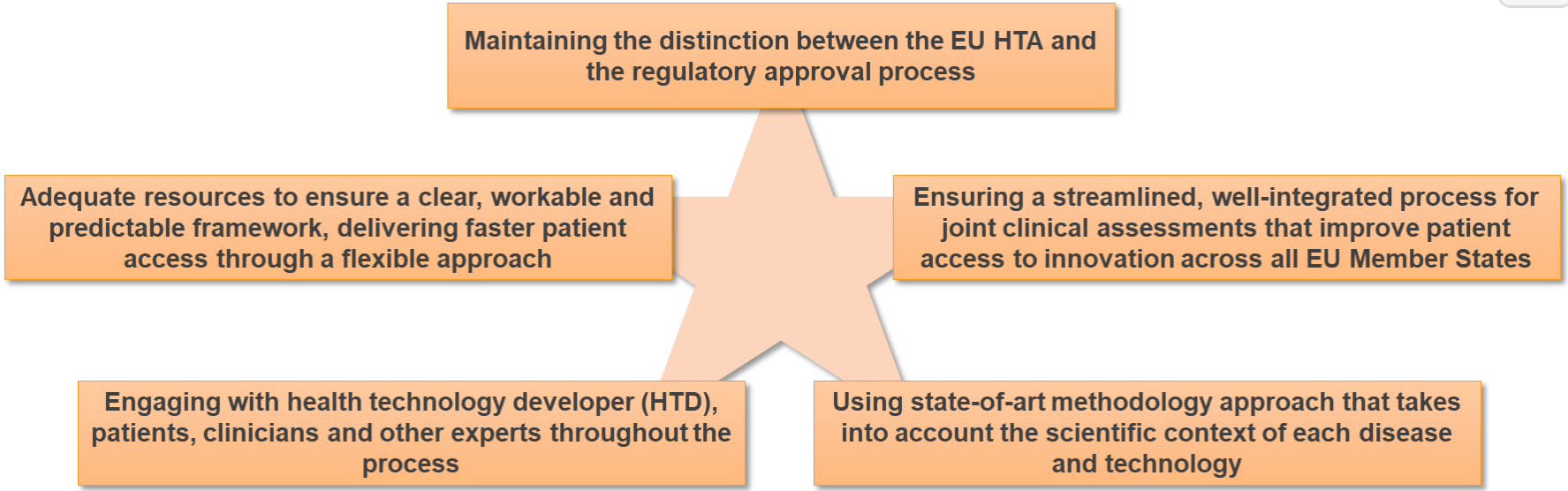
(Text with EEA relevance)

1. Joint Clinical Assessments (medicines, medical devices)
2. Joint scientific consultations (advice to health technology developers on clinical study design; parallel HTA-EMA advice for medicines)
3. Identification of emerging health technologies ("horizon scanning")
4. Voluntary cooperation in other areas (e.g. on other health technologies or non-clinical HTA aspects)

PLUS, a lot of room for Member States and stakeholders to make the implementation successful (or not)

EU HTA Regulation (cont.)

Requirements for value-added



→ ***Based on our initial experience during the implementation phase we believe that a lot more needs to be done—and can be done—in this respect***

National implementation of the EU HTA regulation
What is required next?

- National implementation should have started already, not only from 2025 onward
- Optimal integration of the EU HTA regulation into national decision-making processes requires a strong commitment from national policy makers and is a shared responsibility of all stakeholders, including industry
  - How can EU HTA and JCAs replace national assessment activities?
  - Are there legal/administrative obstacles?
  - Implementation of required national legal/procedural framework before 2025
- Early and systematic engagement in the future production of EU HTA outputs

European Federation of Pharmaceutical Industries and Associations

Thank you!



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New Pan-EU HTA:

A future looking at the HTA perspective: Trick or treat?

Alberto Rubio, MBA
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Madrid, Spain

The new Health Technology Assessment Regulation
For what? and why?

Press release | 22 June 2021 | Brussels

Commission welcomes the move towards more innovative health technologies for patients

"I am very pleased that the European Parliament and the Council have reached a long-awaited political agreement on the Health Technology Assessment Regulation. The Regulation will be a significant step forward ***to enable joint scientific assessments of promising treatments and medical devices at EU level.***

Such high-quality scientific assessments will ***help Member States to take more timely and evidence-based decisions on patient access to their healthcare systems.***
The new Regulation will be crucial for the objectives of EU's Pharmaceutical Strategy and Europe's Beating Cancer Plan, in particular when it comes to facilitating access to innovative medicines and addressing unmet medical needs with important benefits for patients across the EU. Having a strong system for HTA in place is key for a strong European Health Union."

Source: https://ec.europa.eu/commission/presscorner/detail/en/IP_21_3142

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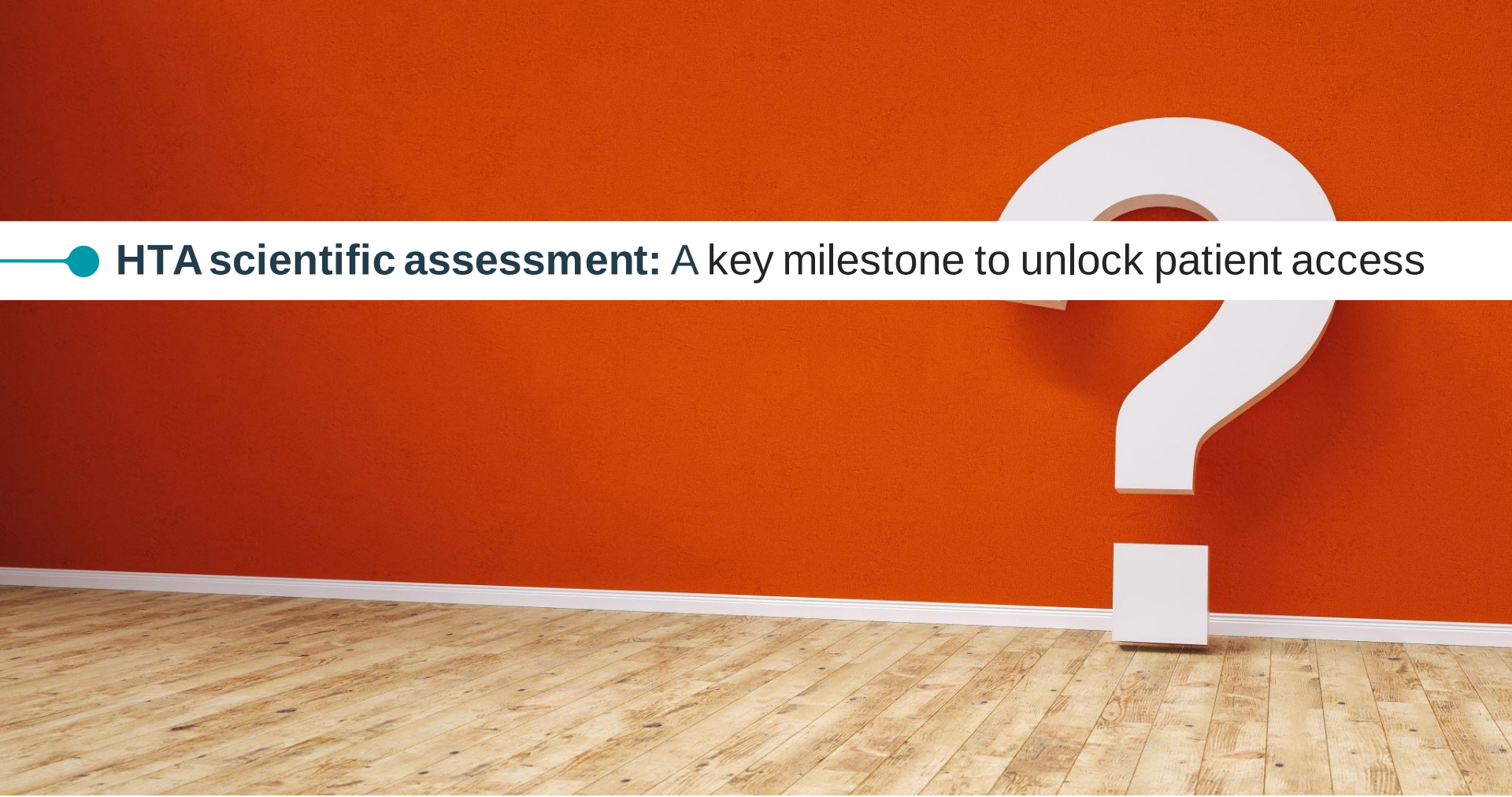
HTA scientific assessment: A key milestone to unlock patient access



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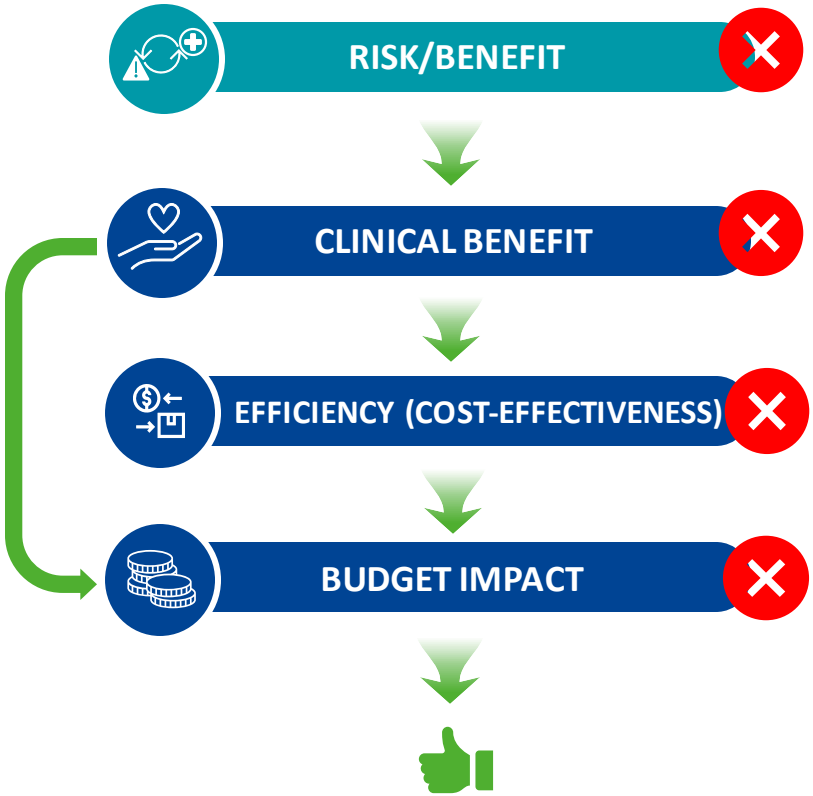
Access to innovative medicines

HTA scientific assessment at the European level instead, or in addition to, national/regional level evaluations

From an established practice in some countries to be irrelevant in others

Different expectations and considerations at a country level



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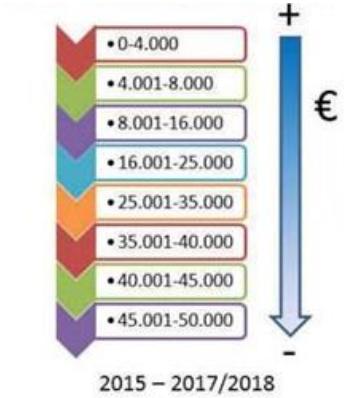
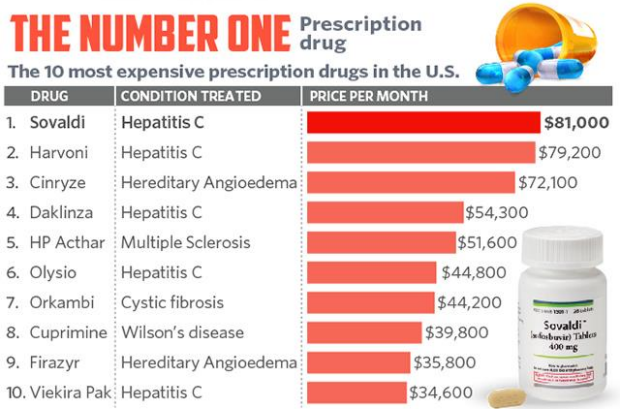
Despite a clear life-saving clinical benefit, access can be challenging



Price-volume agreements for Harvoni and Viekirax



Source: Politico: Good Rx; Spanish Ministry of Health.

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TRICKS …

…or JUST TREATS?

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Should not be about playing tricks from either side . . .with so many known knows

We know what the healthcare challenges and priorities are

Today, **80%** of people >65 have at least one chronic disease

50% have 2 or more chronic conditions

One in six people in the EU have a mild to severe disability

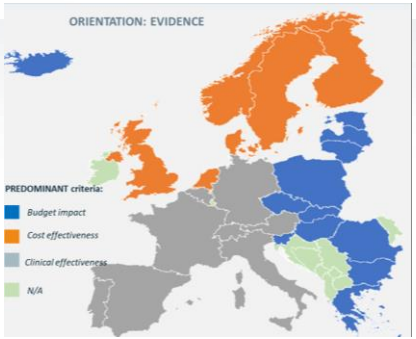
Chronic disease accounts for **77%** of total disease in Europe

10% of the population has to leave jobs due to health problems

We know what innovation is coming

Indeed, multiple innovation areas are appearing on the horizon with the potential to reach the market in the short- to mid-term (1/2)..

We know what drives value evidence assessment



And models to access innovation

Specific strategies

to address a certain driver that can make market access difficult and delay the P&R process

General strategies

to address market access barriers of several indications of the same product or different products with similar characteristics

Other strategies

Beyond the pill, market shaping

Source: Politico: Tackling the tough problem of European health care sustainability; IQVIA/EFPIA Pipeline Innovation Review. 2022.

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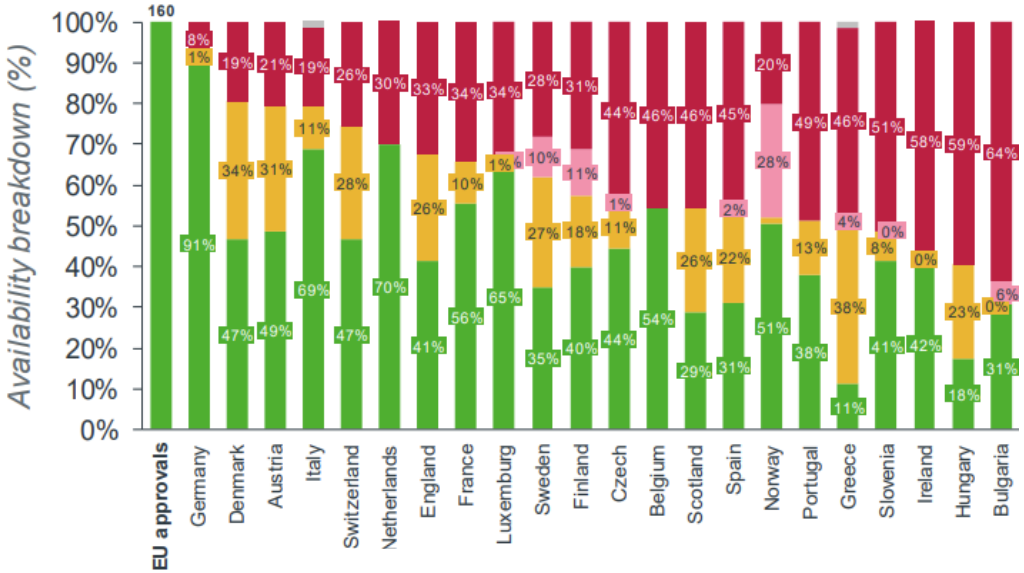
And yet patient access to medicines remains a challenge…

The following data considers drug approvals by the EMA during the 2017-2020 period (a total of 152 medicine approvals)



Reimbursed*

Full public reimbursement

Limited reimbursement*

- *to specific subpopulations*
- *while final decision is pending*
- *to special programs (managed entry agreements,…)*

Not reimbursed

Products rejected during negotiation or still waiting for a decision

Key: EMA – European Medicines Agency; EU – European Union
*Reimbursement decisions are not necessarily aligned with HTA recommendations.
Source: EFPIA Patients W.A.I.T. Indicator 2021 Survey, by IQVIA.

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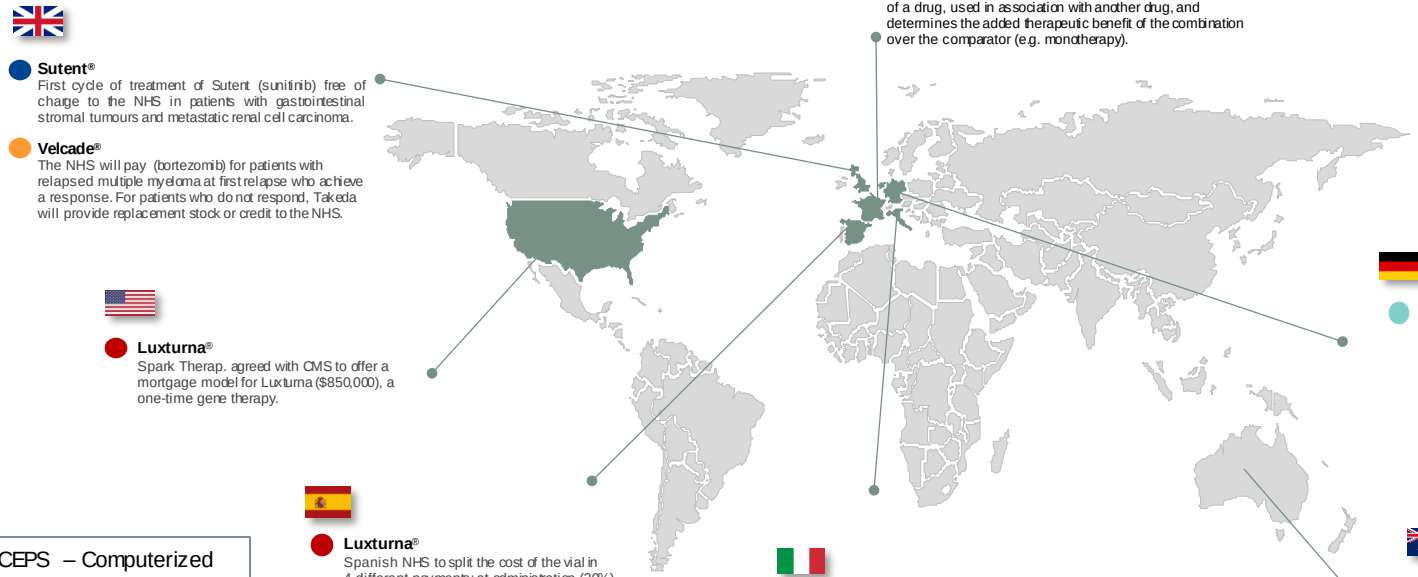
…despite alternative models to overcome HTA "tricks"



- **Financial based agreements**
- **Outcomes based agreements**
- **Mortgage model**
- **Indication based pricing and MYMI**
- **Combination-based pricing**

Sutent®
First cycle of treatment of Sutent (sunitinib) free of charge to the NHS in patients with gastrointestinal stromal tumours and metastatic renal cell carcinoma.

Velcade®
The NHS will pay (bortezomib) for patients with relapsed multiple myeloma at first relapse who achieve a response. For patients who do not respond, Takeda will provide replacement stock or credit to the NHS.

Luxturna®
Spark Therap. agreed with CMS to offer a mortgage model for Luxturna ($850,000), a one-time gene therapy.

CEPS Pricing
The French HTA body assesses the application for coverage of a drug, used in association with another drug, and determines the added therapeutic benefit of the combination over the comparator (e.g. monotherapy).

Immuno-oncology
- Bundle assessments for treatments with multiple indications (>30 in some cases) in **Germany**
- MYMI agreements in **Belgium** and the **Netherlands** to accelerate the access and improve the budget predictability .

Luxturna®
Spanish NHS to split the cost of the vial in 4 different payments: at administration (30%), 1 (20%), 2 (30%) and 3 (20%) years after the infusion.

Zolgensma®
If the patient does not meet the improvement in motor function, the payment would be definitively suspended.

Kymriah®
- Novartis' CAR-T therapy for the treatment of lymphoblastic leukemia and diffuse large B-cell lymphoma.
- Three payments: fat administration, at 6 months and at 12 months depending on clinical outcomes

Pharmaceutical Benefits Scheme
The Australian authorities use a single weighted average price for multi-indication drugs, determined by the value of the product and the existing therapies and weighted by the estimated proportion of drug utilization for each indication.

Key: CEPS – Computerized Equipment Pricing System; MYMI – multi-year-multi-indication; NHS – National Health Service; HTA – health technology assessment

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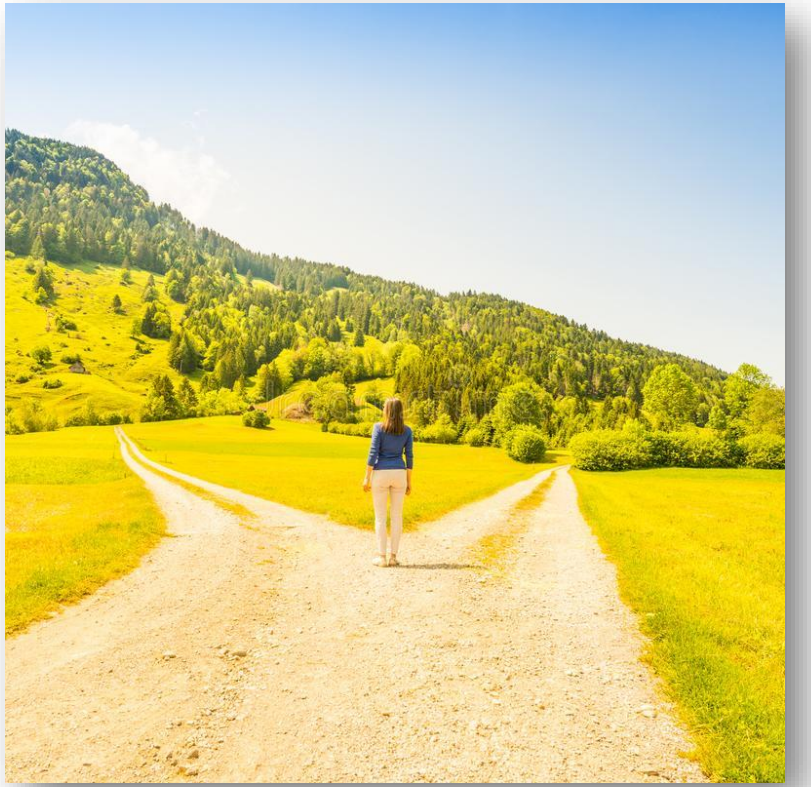
Future looking at the HTA perspective: Trick or treat?



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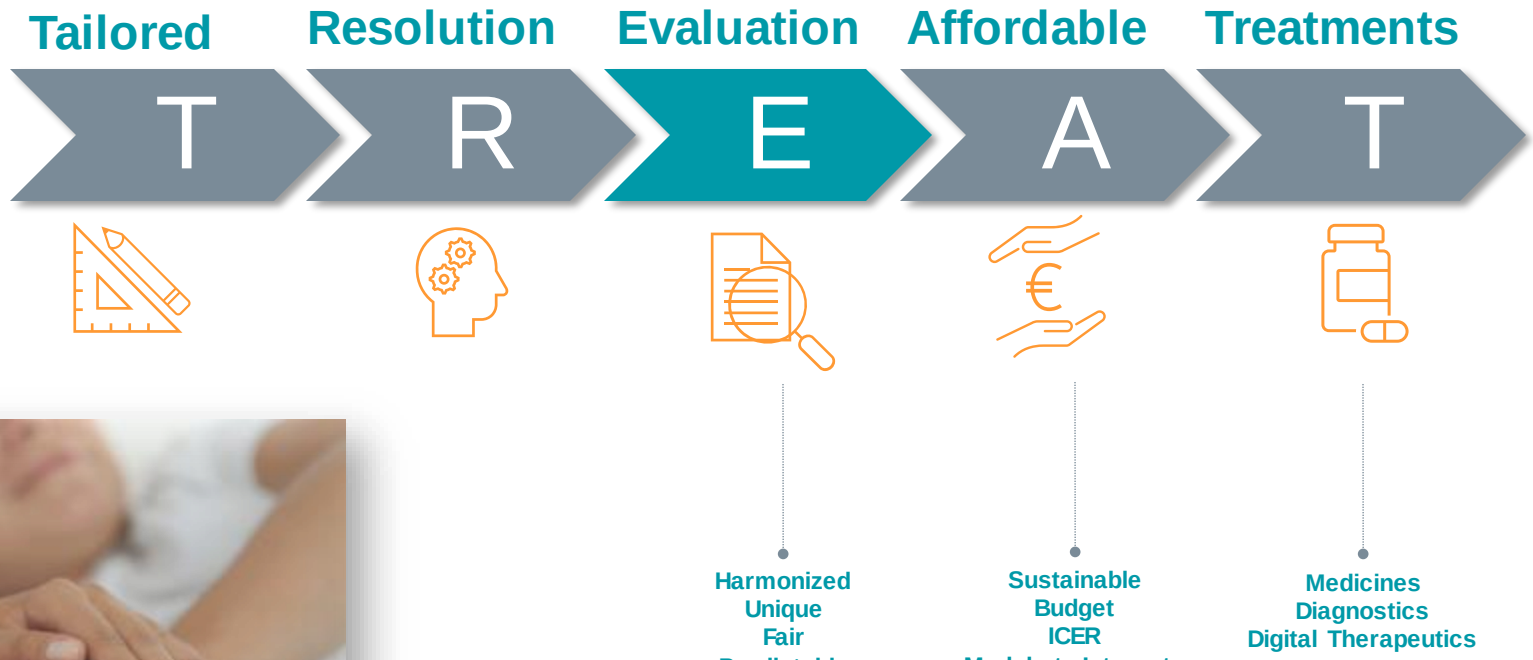
HTA evaluation: Cornerstone for access



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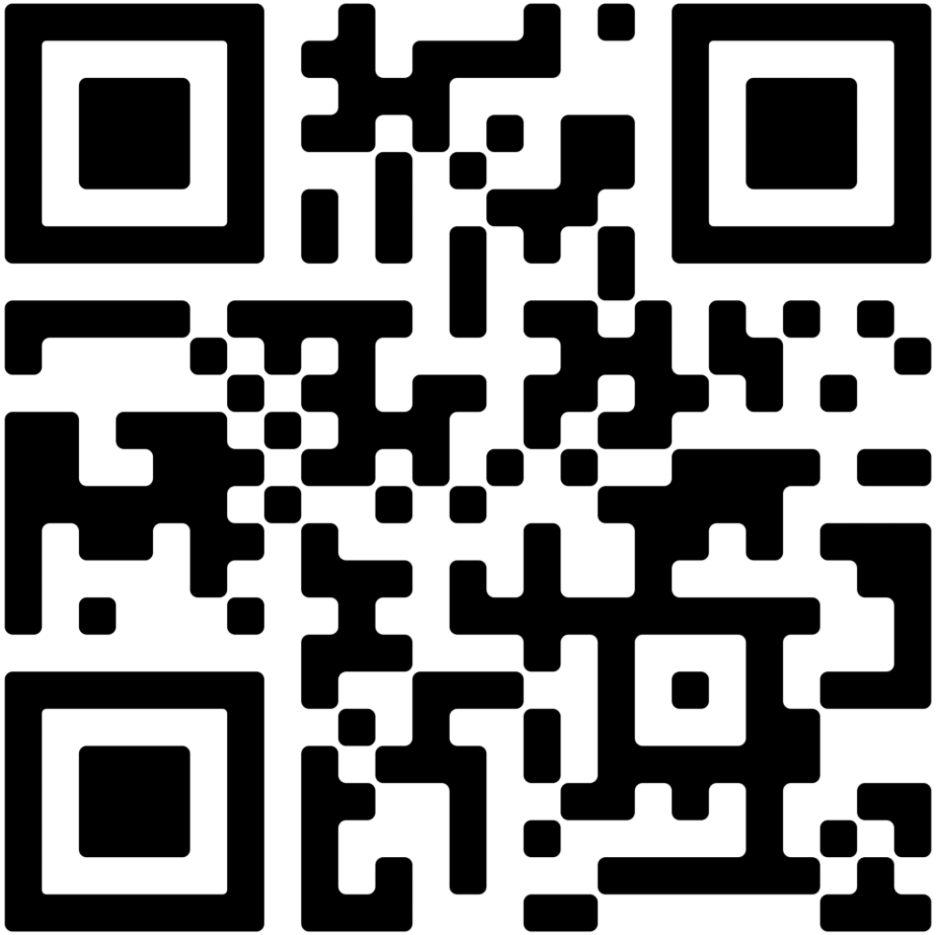
Closing and Q&A



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