NVTAG

Nederlandse Vereniging voor Technology Assessment in de Gezondheidszorg

Early Insights and Experiences with Joint Clinical Assessments (JCA)

Fall symposium October 1st, 2026

Introducing our new board members

Adriënne Rotteveel, PhD
Researcher and project lead health economics and care at RIVM

Frederick W. Thielen, PhD
Assistent professor at ESHPM and researcher at Trimbos Instituut.

Chiara Brouns
Policy & strategic advisor expensive pharmaceuticals at ZN

Agenda

Time	Topics	Speaker
12.15-1.00pm	Registration and lunch	All
1.00 pm – 1.15 pm	Welcome	Maurice Driessen, NVTAG
1.15 pm – 2.00 pm	Learnings from first JCA reports. The EU level perspective	Anne Willemsen *Chair JCA subgroup*
2.00 pm – 2.45 pm	Initial Lessons from the JCA Journey: Implications for Evidence Generation and Business Readiness	Suzette Matthijsse (ONLINE) *JCA-lead Lumanity*
2.45 pm – 3.00 pm	Break	All
3.00 pm – 3.45 pm	The Dutch perspective on conducting and using the first JCAs.	Riam Al Dulaimi *Zorginstituut Nederland – EU-assessor*
3.45 pm – 4.30 pm	The Evolving Landscape of EU HTA: early lessons, challenges, and future direction	Maureen Rutten *Prof. Erasmus School of Health Policy & Management*
4.30 pm – 4.55 pm	Panel discussion	All speakers* **Richard Birnie (Lumanity) will substitute Suzette (online)*
4.55 pm – 5.00 pm	Closure and invitation for drinks	Maurice Driessen

House rules

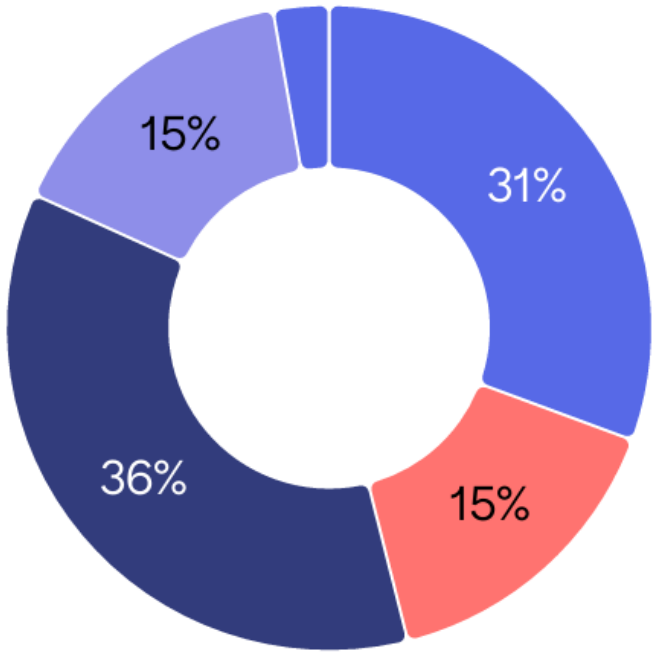
- Keep mobile device on silent mode
- Clarifying question can be asked after presentation
- Please save other questions for the panel discussion
- Slides will be shared on our website after the symposium

Getting to know our audience

- Go to mentimeter.com
- Enter: 1481 1972

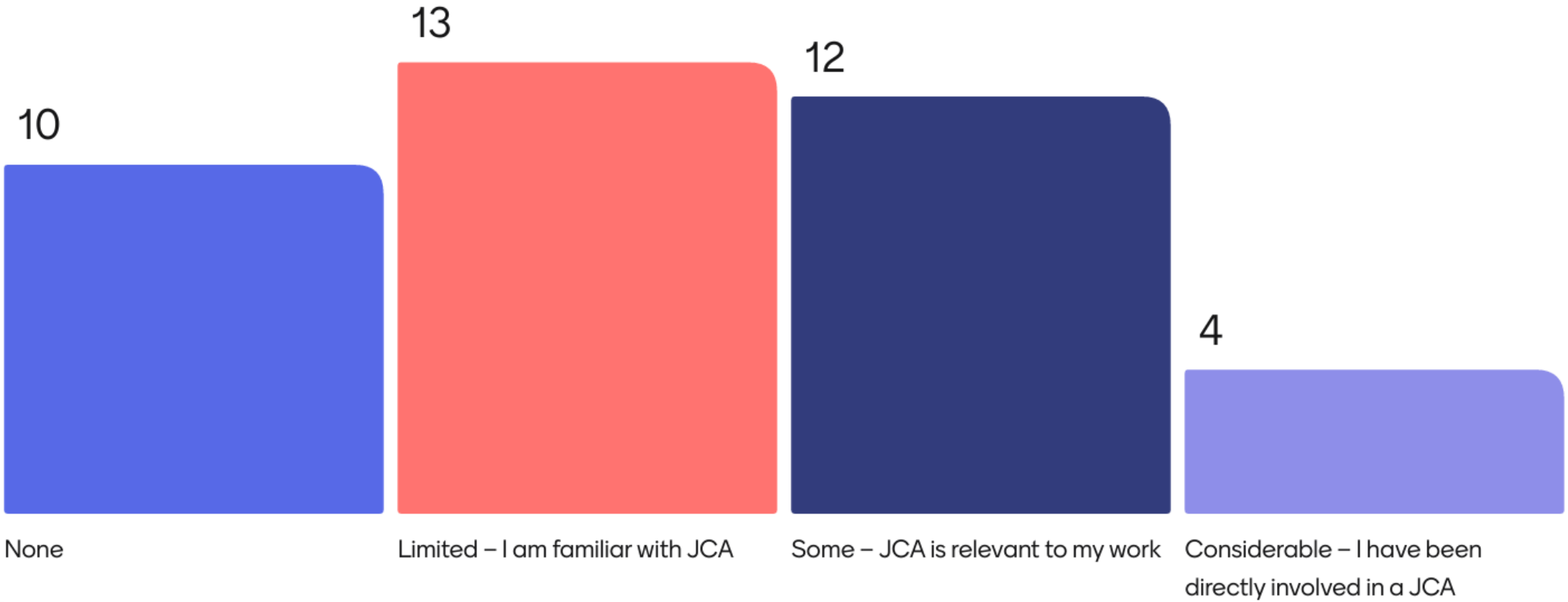
- https://www.menti.com/als1dtvmmwma

Which stakeholder group do you represent today?



31%	Academia/research
15%	Pharmaceutical or medtech company
36%	Consultancy
15%	Government/public sector
0%	Patient organisation
0%	Healthcare provider/professional
0%	Health insurer
3%	Other

How much experience do you have with Joint Clinical Assessment (JCA)?



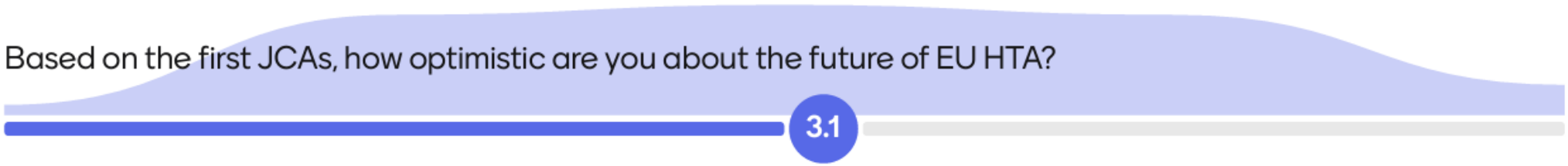
What is the first word that comes to mind when you think of JCA?

Has JCA already changed the way evidence is generated in your organisation or field?

Not at all

To a great extent

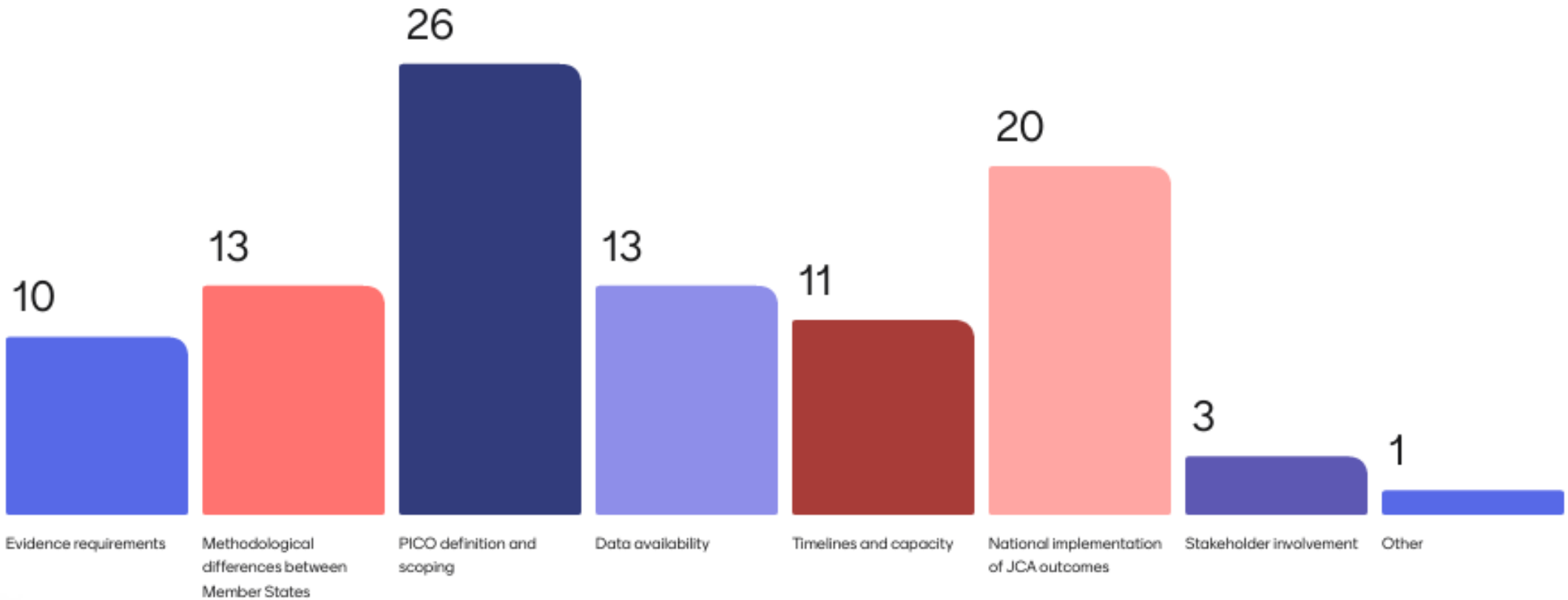
Based on the first JCAs, how optimistic are you about the future of EU HTA?



Very pessimistic

Very optimistic

What do you currently see as the biggest challenge for JCA? (max 3 answers)



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Anne Willemsen

Chair JCA-subgroup

Learnings from the first JCA reports.

The EU-level perspective

HTA CG | MEMBER STATE COORDINATION GROUP ON HEALTH TECHNOLOGY ASSESSMENT

Learnings from the first JCA reports. The EU level perspective

Anne Willemsen, MSc | Chair JCA Subgroup

We've made it!

The first JCAs are a fact and the system is operational.

- **FIRST JCAs PUBLISHED**
  ✓ DONE
- **SYSTEM OPERATIONAL**
  ✓ DONE
- **NEXT: LEARN & TEST**
  → IN PROGRESS

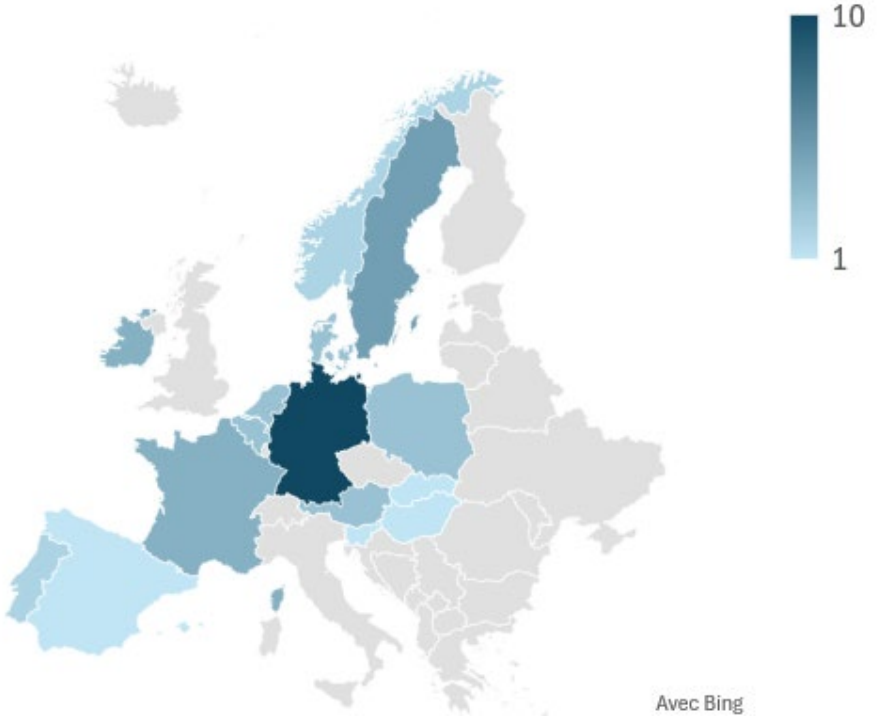
On to the next steps

Generated via AI

Statistics to date*

- 23 initiated JCA* since the start of the HTAR
  - 4 published
  - 4 discontinued
    - 1 withdrawn from EMA and 3 incompliant dossiers
  - 15 ongoing JCA
  - ~25% is ATMP | ~45% is Orphan Designation
  - First accelerated product initiated & one under phased review by EMA

- 15 different MS took assessor and co-assessor roles
  - **18 different HTA bodies!**
- 68 experts selected in total for JCA
  - 44 % clinical expert, 44% patients, 12% carers



** date: 24-09-2026*

EU HTA is no longer a future ambition: It is now delivering public joint clinical assessments!

Regulatory (EU)

EMA

Regulatory approval

- Does technology X work?
- Does the benifit of technology X outweigh the risks?
- Are there any additional needs for technology X post-licencing?

Single licensing system; one EU legislation

Health Technology Assessment

HTAR *assessment*

In JCA: relative assessment of Technology X vs. Technology Y (and others)

- How does it compare to what we already have (fewer harms, in whom etc)

Relative effectiveness and relative safety

Clinical domain only!

- No value judgements
- No conclusions on added value or reimbursement
- Common methodology and approach

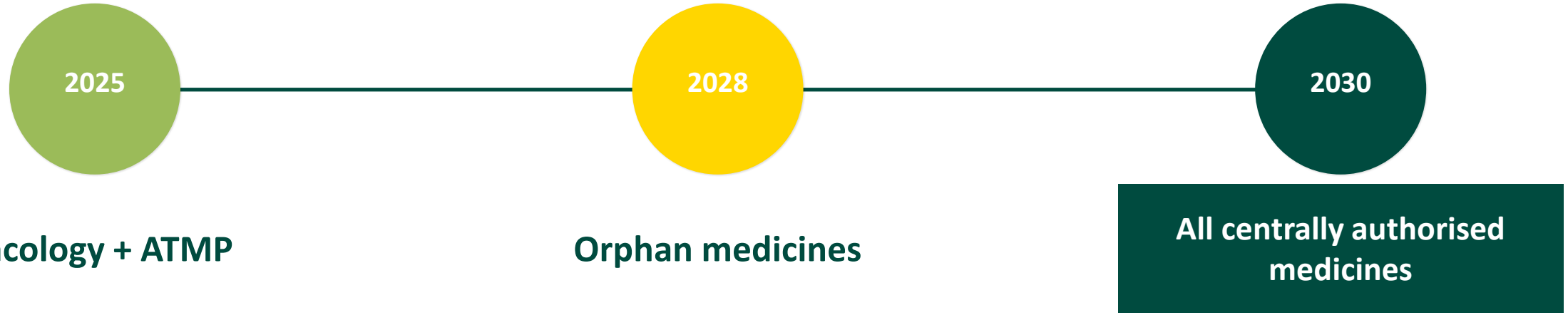
National *appraisal*

Appraisal phase

- e.g. cost effectiveness to be added
- Other considerations?
- Weighing arguments; decision making/reimbursement advice

JCA should be given due consideration in national decision-making

Scaling up



Capacity, predictability and sustainable support become strategic issues.

Process & Timelines

JCA timeline in parallel to EMA

a) Standard

a) Standard procedure for New Chemical Entities
b) Type II variation (Extension of Indication) and accelerated procedure
c) re-initiation of JCA or update of JCA without a new scope
d) Update of JCA with a new scope
e) To be followed by adopted CG

Letter of Intent
- Letter of Intent to both EMA and the HTA Secretariat
- **Please be realistic and provide updates**

HTD shall submit
- SmPC
- clinical overview section
- New therapeutic indication (if applicable)

Final consolidated PICO*
- a) D87
- b) D50

** As per JCA procedural guidance*

HTD submission Dossier

As of the sharing of the scope:
- a) 100 days
- b) 60 days

EC completeness check:
- a) 15 working days
- b) 10 working days

Missing information HTD
- a)15 days
- b)10 days
- 7 days for minor info

Clarifiying/additional info (asked by asr/co-asr)
- 7 to 30 days

HTD to submit new evidence
- No later then 7 days after CHMP

HTD fact check:
- a) 7 days
- b) 5 days

Finalize JCA[e]
- The latest on the day of EC decision granting MA
- c) 180 days
- d) 330 days

JCA	Start JCA at submission to EMA	Scoping phase	Submission dossier	Drafting JCA	Final JCA
EMA[a]	Start MAA	D120 LOQ		CHMP	CD

Guidance for HTDs along the process

Q&A on general methodological and procedural issues for JCA

Guidance filling in the dossier template

Guidance on the validity of clinical studies

Guidance on evidence synthesis

Guidance on outcomes

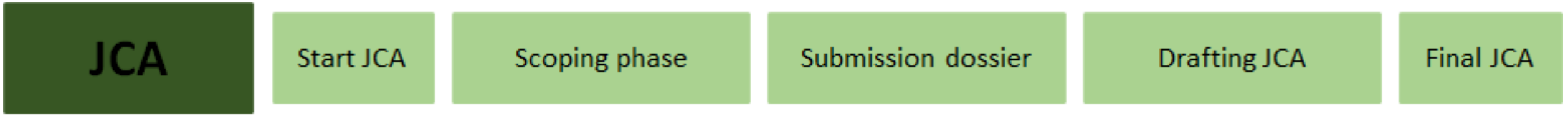
Guidance on reporting requirements (multiplicity, subgroup, sensitivity, post hoc analyses)

Scientific specifications of MP subject to JCA

Guidance on the appointment of (co-) assessor for JCA

Guidance on the scoping process

JCA procedural guidance: process steps

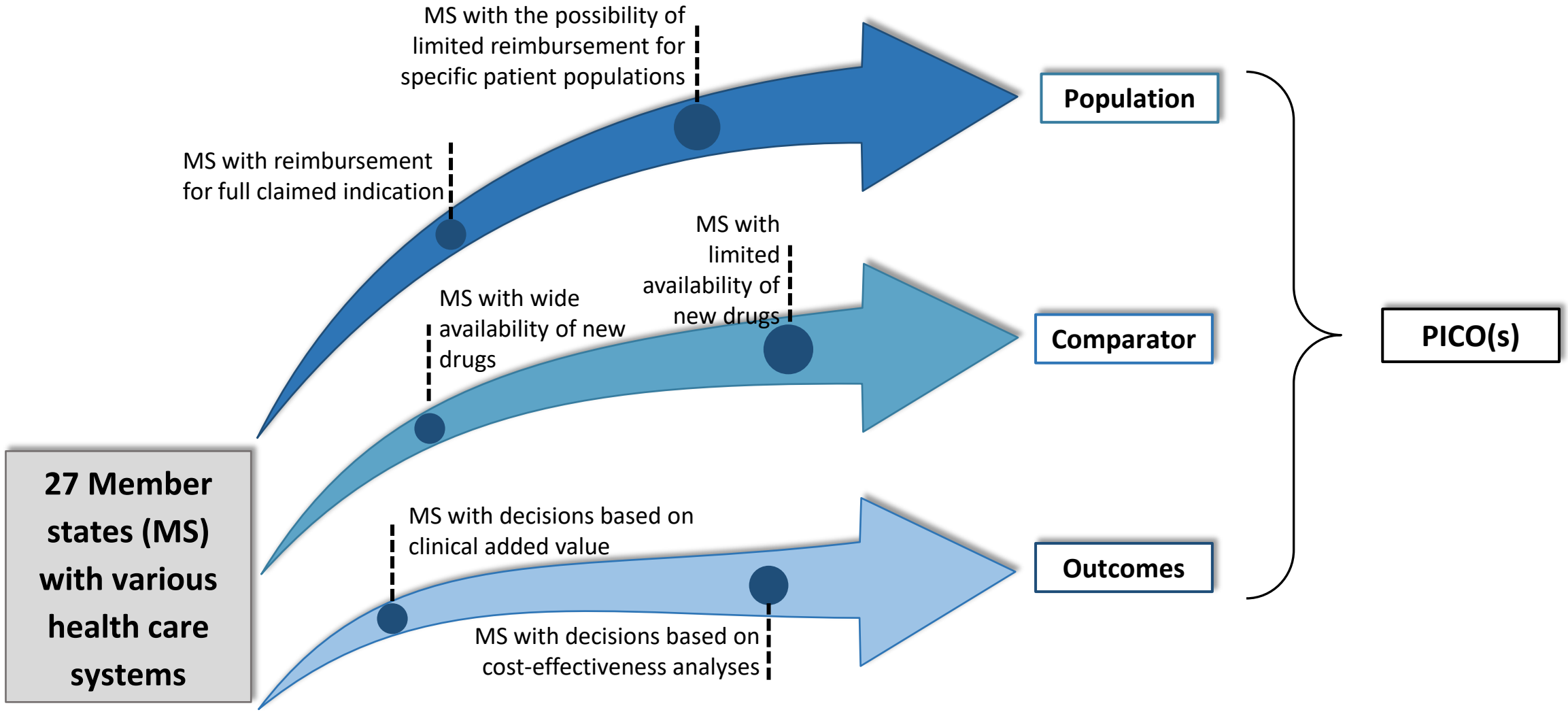


IA JCA: Complete process

Annex to IA JCA
Dossier template

Annex to IA JCA
JCA report template

From policy question to PICO



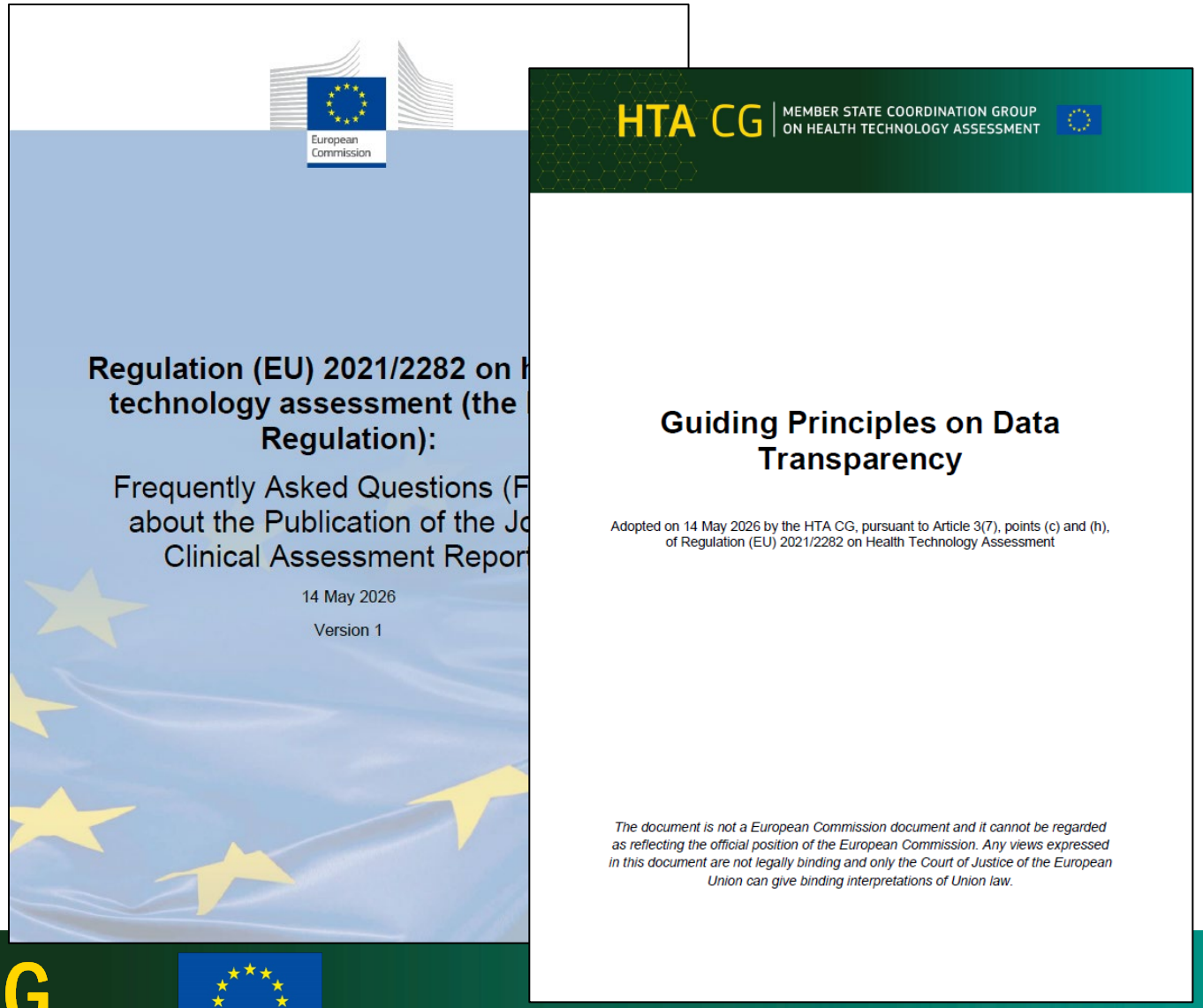
Transparency of process and results

Published on EC website:

- JCA report
- JCA summary report
- HTD dossier
- Factual accuracy check by HTD

➢ Potential redaction of commercially confidential information

➢ Full transparency required for national use



Lessons & key take aways

First four published JCAs: from PICO scope to evidence included

PRODUCT / INDICATION	PICOs IN SCOPE	PICOs WITH DATA SUBMITTED	PICOs INCLUDED	TYPE OF EVIDENCE INCLUDED BY PICO
Ojemda® tovorafenib Paediatric low-grade glioma	8	2	1	PICO 5: Unanchored MAIC
Zepzelca® lurbinectedin + atezolizumab Extensive-stage SCLC, maintenance	1	1	1	PICO 1: Direct RCT: IMforte
Imdyllta® tarlatamab Extensive-stage SCLC after platinum	7	7	7	PICO 1, 4, 6: Direct comparisons PICO 2: Unanchored MAIC PICO 3, 5: Network meta-analysis PICO 7: Bucher ITC, one outcome
Itvisma® onasemnogene abeparvovec IT 5q SMA, ≥2 years	14	7	7	PICO 1: Anchored MAIC[1] + unanchored MAIC[2] PICO 2: Anchored MAIC PICO 3: Direct RCT vs sham / BSC PICO 8 – 11: Same evidence as P1–P2

[1] DMT-naïve patients [2] DMT-experienced patients

First Lessons of the JCA

Multinational collaboration

Member States are successfully pooling scientific expertise across assessor and co-assessor teams.

Indication changes affect scope

Changes in indication can affect the scope and therefore the timelines, also for the health technology developer
~50% of JCA go through an indication change

Timelines are unforgiving

Regulatory and HTA milestones run in parallel. A change in clockstop at regulatory level can affect the JCA plan.

Consistency is built through practice

Common guidance is essential, but experience gained from individual procedures is what informs continuous reflection and helps transform the framework into a reliable operating model

First Lessons of the JCA – adaptations to the process

Refined the assessment scope explanation meeting

E.g. address questions by HTD; explanation of the next procedural steps

Development of Q&A

Via Q&A the methodological guidelines are further clarified, including expectations for the dossiers

Started earlier identification and selection of experts

To allow for early involvement of patients and clinical experts during the development of the assessment scope proposal

Adding explanations to the list of missing items

During the compliance check of the dossier, explanations of the missing items are added to the respective table via footnotes.

First Lessons of the JCA – dossier expectations

Address all PICOs

All PICOs must be addressed and in case of deviations or no evidence availability, an assessable justification must be provided. ***Follow IR 2024/1381, Annex I in detail!***

Transparency is key

Guiding principles on data transparency & FAQ on publication available: results & methods are not considered CCI. Timely CCI check to avoid delayed publication

Conduct SLRs according to scientific principles

Follow section 4.2.1 of Annex I. Report both the search strategy and the results, also in absence of evidence

Short deadlines also after dossier confirmation

After dossier confirmation, additional/clarification question may be asked (usually only 7 days to respond).

Key take aways

Think early about HTA & how to generate relevant evidence!

- MAA process and JCA run in parallel, yet separate procedure

Ensure sufficient competences & resources for developing the dossier

- Start early on your submission dossier and map the PICO landscape

Communication between Regulatory and Market Access departments

Follow the regulations (HTAR and IR) and guidance carefully!

Ensure timely national submission to maximise national usability of the JCA

Thank you!

awillemsen@zinl.nl

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Suzette Matthijsse

JCA-lead Lumanity

Initial Lessons from the JCA Journey: Implications for Evidence Generation and Business Readiness

ONLINE

Initial lessons from the JCA journey

Implications for evidence generation and business readiness

Suzette Matthijsse

Vice President Strategic Advisory Services HEOR, Lumanity

1 October 2026

Lumanity

State of Play

Ojemba® (tovorafenib)

Paediatric low-grade glioma

- 8 PICOs in scope
- 2 PICOs with data submitted
- 208 pages excluding appendices

Imdyllta® (tarlatamab)

Extensive-stage SCLC after platinum

- 7 PICOs in scope
- 7 PICOs with data submitted
- 232 pages excluding appendices

Zepzelca® (lurbinectedin + atezolizumab)

Extensive-stage SCLC, maintenance

- 1 PICO in scope
- 1 PICO with data submitted
- 296 pages excluding appendices

Itvisma® (onasemnogene abeparvovec IT)

5q SMA, ≥2 years

- 14 PICOs in scope
- 7 PICOs with data submitted
- 480 pages excluding appendices

Discontinued JCAs: sasanlimab (withdrawal of MA application by HTD), catequentinib (fails to meet requirements), Tacquell (fails to meet requirements), sintilimab (fails to meet requirements)

Key: JCA, Joint Clinical Assessment; MA, marketing authorization; PICO, population, intervention, comparator(s), outcome(s); SCLC, small cell lung cancer; SMA, spinal muscular atrophy.

JCA readiness can be thought of from three perspectives

Asset-specific readiness

- Have you considered the requirements of the JCA in your evidence generation strategy?
- When do you start preparing?
- How can you anticipate the multiple decision problems?
- What about ex-JCA requirements?

Strategic readiness

- How do you consider the JCA needs within the global needs?
- Have you considered the processes of the EU HTAR in your launch strategy?

Business readiness

- How do you currently work together?
- Where do you anticipate challenges in terms of ways of working under the EU HTAR?
- Do your roles and responsibilities align with the requirements of the EU HTAR?

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Key: EU HTAR, European Union Regulation on Health Technology Assessment; JCA, Joint Clinical Assessment.

The right preparatory activities can make a huge difference to the internal process and outcome of the JCA

1 Early JCA preparation

- Assembling a task-force
- Early PICO simulation to inform evidence generation planning
- *If considering a JSC, this should take place in the early planning phase of clinical development, prior to the Phase III trial*

Timeline:
≥ 24–18 months from submission

2 Pre-assessment scope: evidence generation, pre-scope JCA dossier development

- PICO simulation
- JCA gap analysis
- JCA trial SAPs
- JCA PRO SAPs
- JCA strategy
- JCA ITC feasibility assessments
- SLR protocol
- SLR conduct
- JCA trial analyses
- JCA ITCs (SAPs and conduct)
- PICO and strategy updates
- Pre-scope JCA dossier development

Timeline:
From ~18 months from submission

3 Post-assessment scope: finalize JCA dossier, post-submission activities

- Post-scope JCA dossier development
- SLR updates
- JCA trial analyses (post-scope)
- JCA ITCs (post-scope)
- Ongoing strategy refinements
- Response to completeness check
- Response to additional requests
- Redaction

Timeline:
100 days from submission

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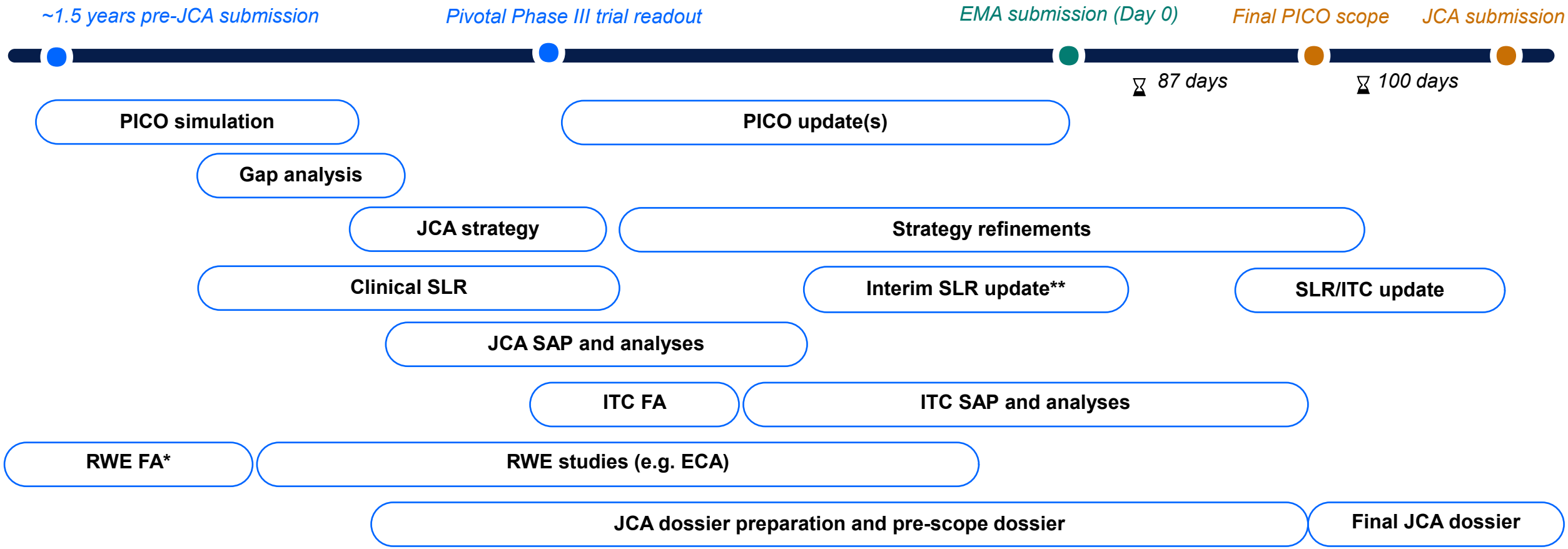
Key: ITC, indirect treatment comparison; JCA, Joint Clinical Assessment; JSC, Joint Scientific Consultation; PICO, population, intervention, comparator(s), outcome(s); PRO, patient-reported outcomes; SAP, statistical analysis plan; SLR, systematic literature review.

Illustrative timelines for key JCA activities

Essential JCA activities should begin at least 18 months pre-submission; however, broader preparedness and strategic planning should start no later than 2 years before.



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Key: ECA, external control arm; EMA, European Medicines Agency; FA, feasibility assessment; GVD, global value dossier; ITC, indirect treatment comparison; JCA, Joint Clinical Assessment; JSC, Joint Scientific Consultation; PICO, population, intervention, comparator(s), outcome(s); RWE, real-world evidence; SAP, statistical analysis plan; SLR, systematic literature review.

Notes: *RWE study requirements may vary, but they can materially affect timelines and should therefore be assessed and planned as early as possible.
** This is optional but helps to minimize updates within the 100-days final scope timeline.

Understand the potential scope

1. Extract all relevant PICOs from the essential sources
2. Construct
3. Consolidate
4. Validate

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Key: PICO, population, intervention, comparator(s), outcome(s).

Map the planned evidence generation to predicted PICOs and confirm the planned analyses meet JCA requirements

Data sources for PICOs to be filled in based on the trial (primary) and in-progress materials (secondary)

HTACG guidelines

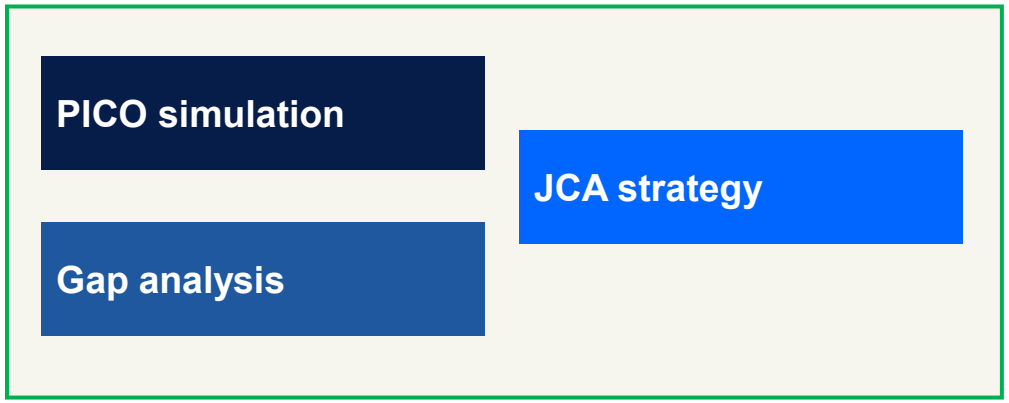
	PICO 1
Population	…
Comparator(s)	…
Outcomes	…

	PICO 2
Population	…
Comparator(s)	…
Outcomes	…

	PICO N
Population	…
Comparator(s)	…
Outcomes	…

Key: HTACG, Coordination Group on Health Technology Assessment; JCA, Joint Clinical Assessment; PICO, population, intervention, comparator(s), outcome(s).

A JCA strategy ensures that the JCA dossier supports EU and global launch requirements, proactively plans for risk reduction, and serves as a key tool for internal stakeholders



Challenges to consider:

- ! Multiple decision problems
- ! Large operational challenge
- ! Public domain
- ! Completeness
- ! Surprises

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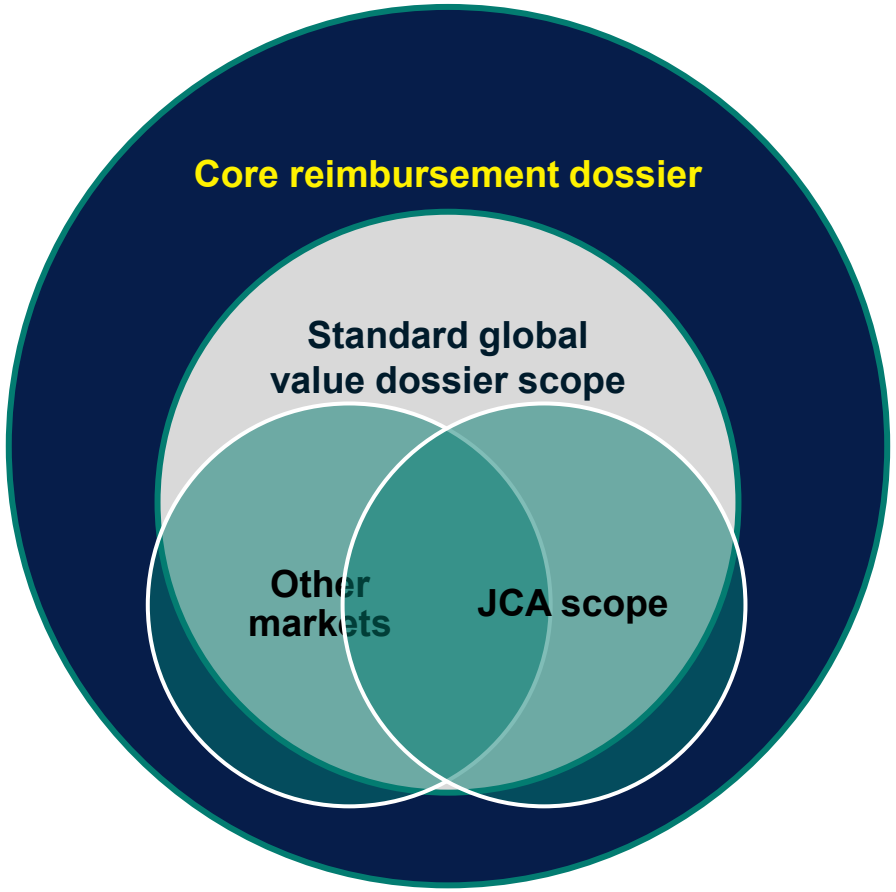
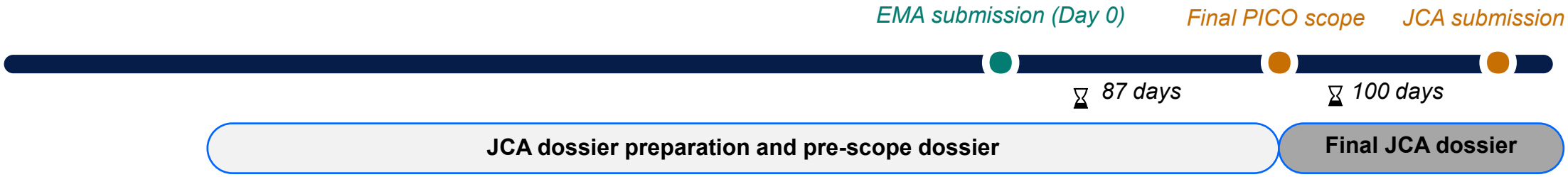
Key: JCA, Joint Clinical Assessment; PICO, population, intervention, comparator(s), outcome(s).

A wider perspective in your strategy



Key: JCA, Joint Clinical Assessment.

An earlier start on the dossier makes the process smoother



A 'pre-scope' dossier is completed based on the predicted PICO questions and the agreed strategy to answering each

- JCA dossier length/complexity drives heavy editorial, formatting and cross-section consistency work
- Early consideration of JCA dossier 'governance' can prevent discussions

The clock is ticking!

- Continue to align plans to JCA guidance

Key: EMA, European Medicines Agency; JCA, Joint Clinical Assessment; PICO, population, intervention, comparator(s), outcome(s).

To ensure success, early cross-functional alignment on key activities and responsibilities will be key

	Illustrative activity (non-exhaustive)	**Regional or global HEVA/MA**	**Local HTA/ affiliates (countries)**	**Med. affairs**	**Regulatory and clinical dev.**
Strategy and engagement	Internal cross-functional alignment				
	PICO prediction and validation				
	JCA strategy development				
	EU HTAR and JCA process management/engagement				
Evidence generation and JCA dossier	Evidence generation, including JCA-specific steps:				
	• SAP review for JCA				
	• Clinical trial analysis for JCA (PLD)				
	• Comparative clinical effectiveness for JCA (ITC)				
	JCA dossier development				

- **R** **Responsible**: Driving decisions forward and managing process
- **A** **Approver**: Final sign-off
- **C** **Contributor**: Provide input, expertise and recommendations
- **I** **Informed**: Stakeholders kept up-to-date on decisions and outcomes

The RACI matrix for JCA should be developed based on your organizational set-up and JCA process, as well as for each specific product undergoing JCA

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Key: HEVA, health economics & value assessment; HTA, health technology assessment; HTAR, Regulation on Health Technology Assessment; ITC, indirect treatment comparison; JCA, Joint Clinical Assessment; MA, market access; PICO, population, intervention, comparator(s), outcome(s); PLD, patient-level data; RACI, responsible, approver, contributor, informed; SAP, statistical analysis plan.

Thank you

Suzette Matthijsse
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NOT A MEMBER YET? BECOME ONE!

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Riam Al Dulaimi

EU-assessor, Zorginstituut Nederland

The Dutch perspective on conducting and using the first JCAs.

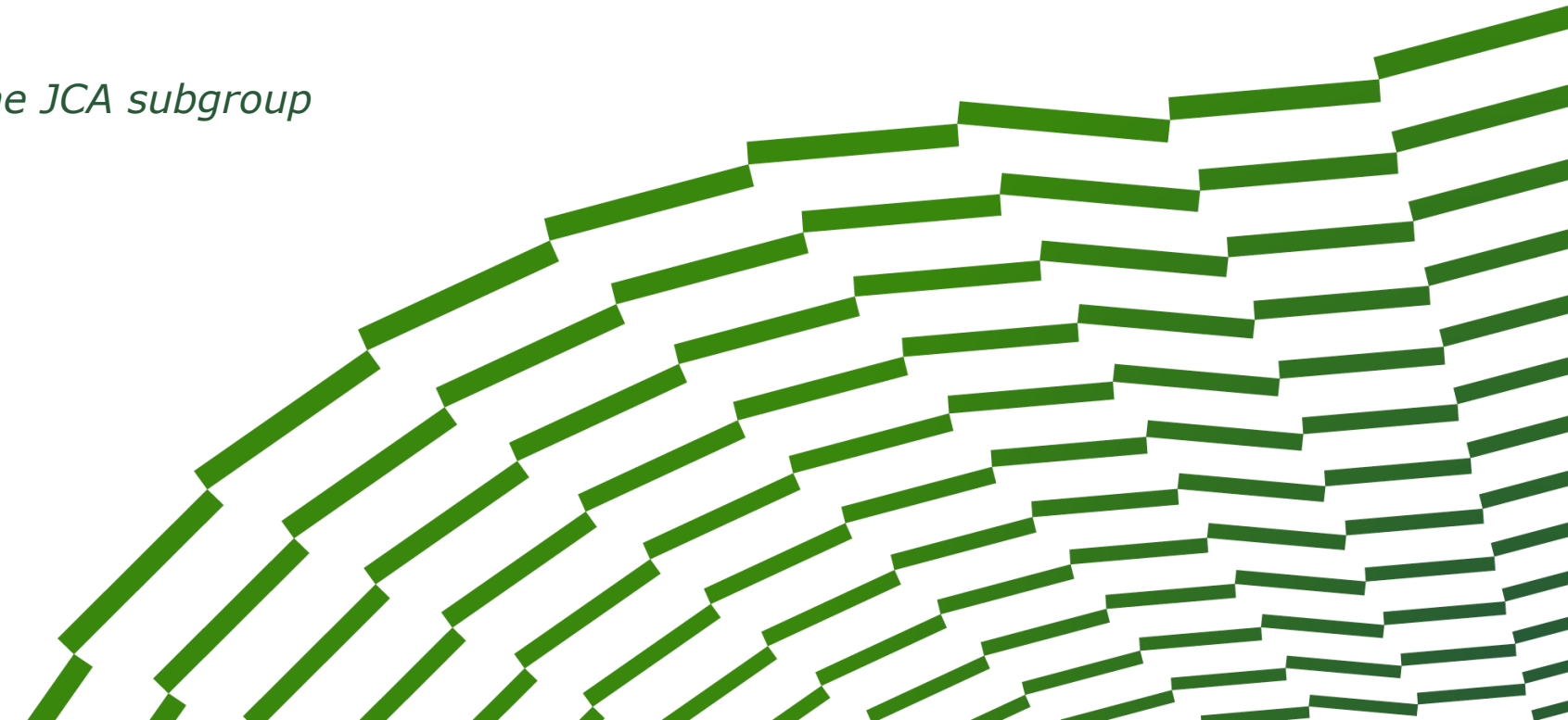
Zorginstituut Nederland

The Dutch perspective on conducting and using the first JCA

Riam al Dulaimi, PharmD

Senior advisor and member of the JCA subgroup

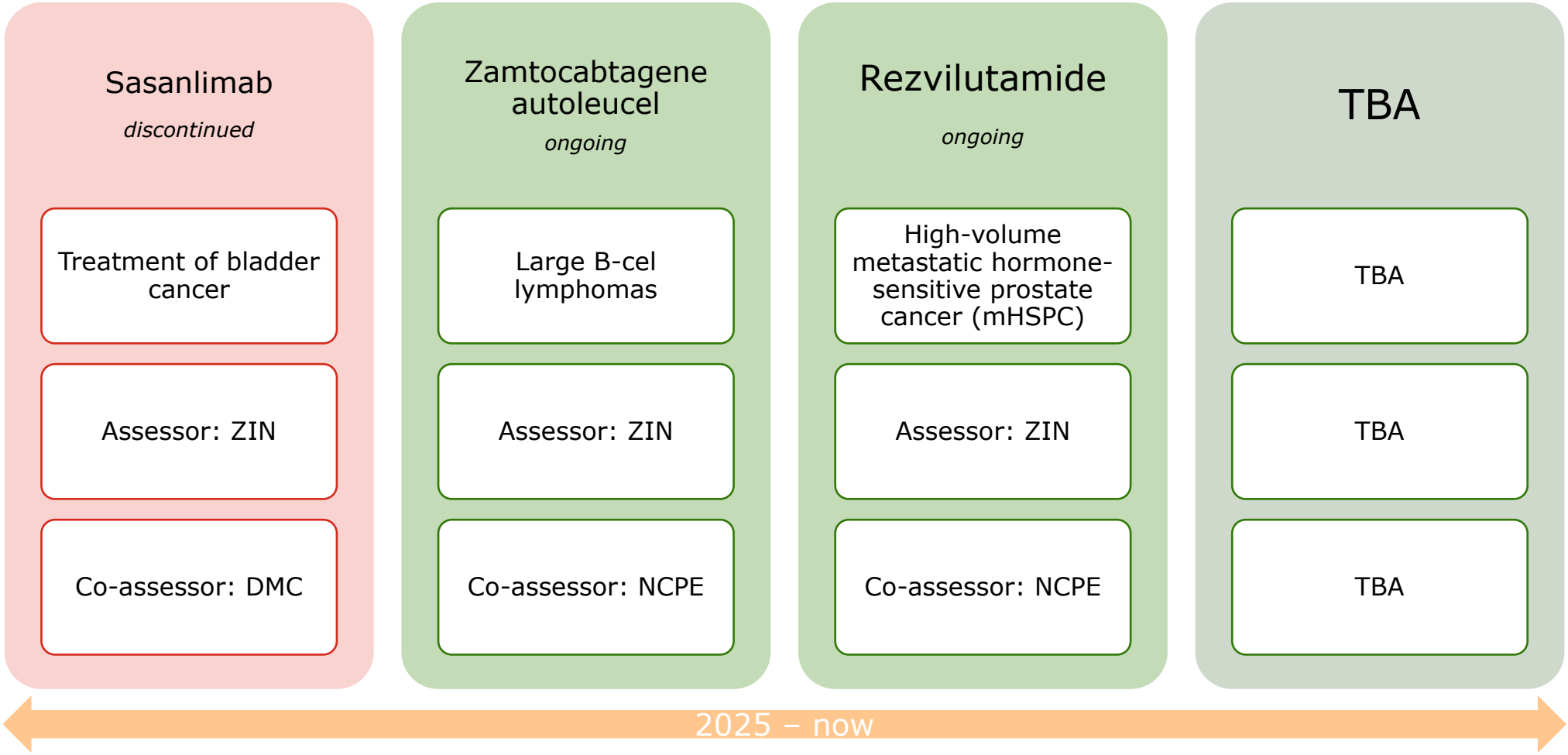
6 October, 2026



| Van goede zorg verzekerd |

Current Status

ZIN’s participation



EU Team

Team expanded from 2 senior level assessors in 2025 to 4 in 2026

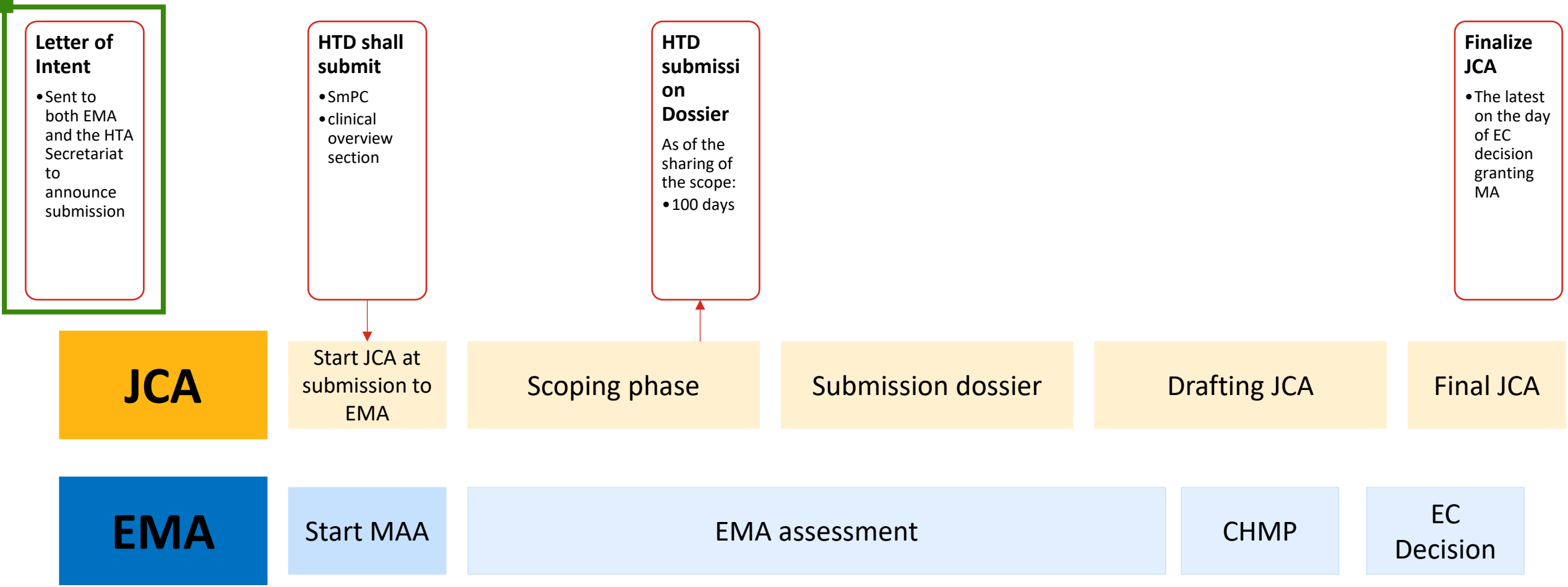
Expected to grow with the upcoming scope expansion

Adapting templates to accompany JCA reports

Training staff to use JCA reports for national assessments

JCA process from start to finish

JCA timeline in parallel to EMA



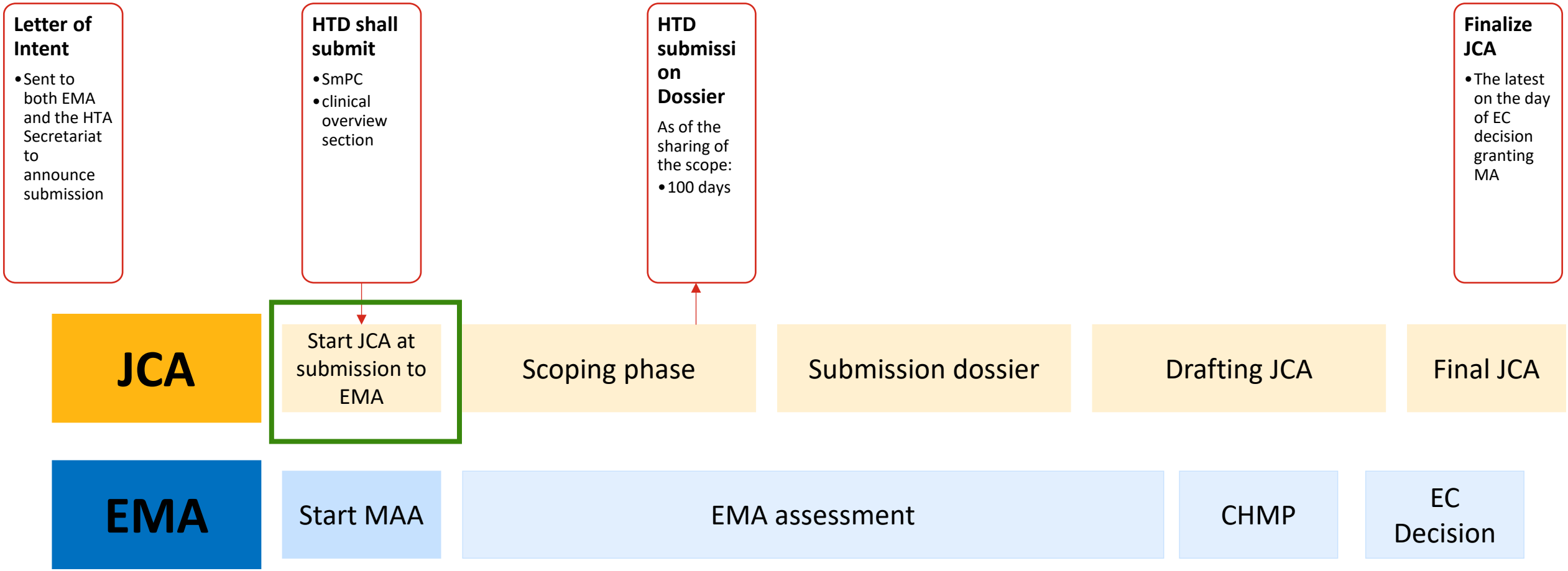
Prior to start JCA

- Periodic meeting with Horizon Scanning (HS) team and (deputy) secretary
  1. Overview of letters of intent
  2. (preliminary) list of medicine HS
  3. Timelines ongoing and upcoming JCAs

- Prioritising medicines potentially to be placed in the ‘lock’ procedure

- Early expert involvement in the case of …
  - complex treatment landscape;
  - limited prior experience in specific therapeutic area;

JCA timeline in parallel to EMA



Start JCA procedure

Announcement start JCA

- Physicians' association and patients' organisations are notified
- Only summarised indication provided (e.g. breast cancer)

Selection clinical and patient experts

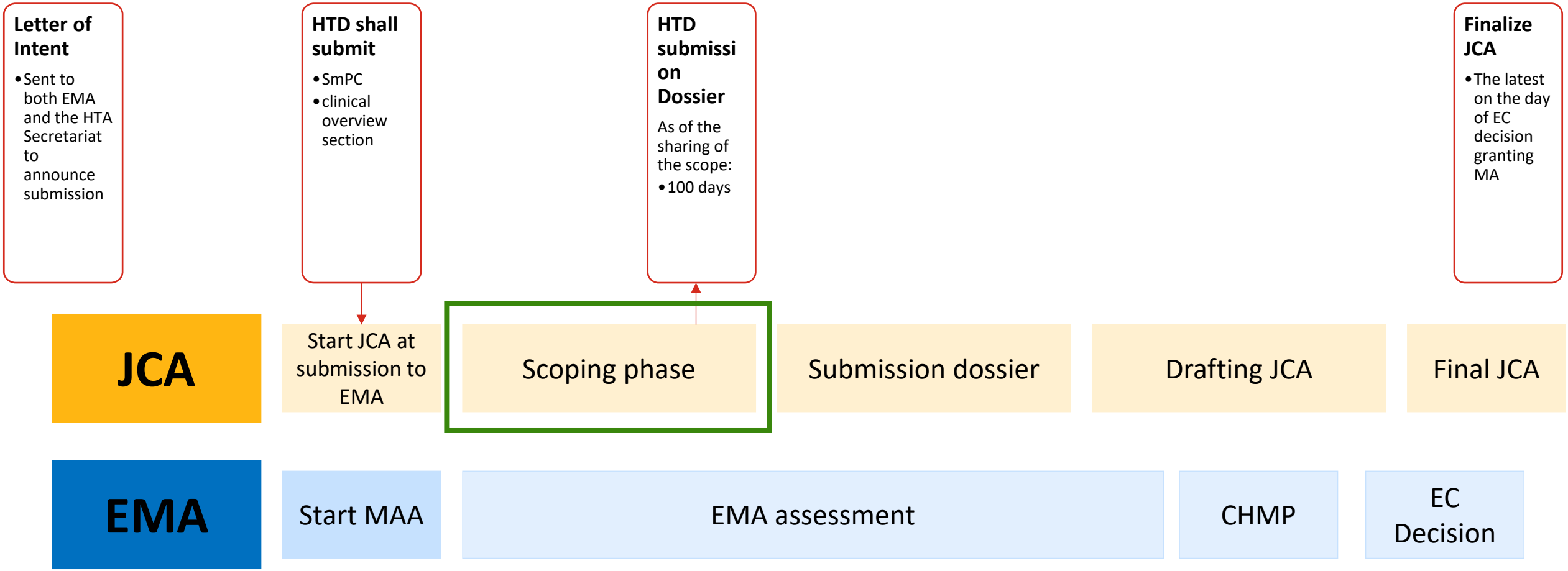
- Physicians' association and patients' organisations delegate expert(s) for input

Signing confidentiality agreement

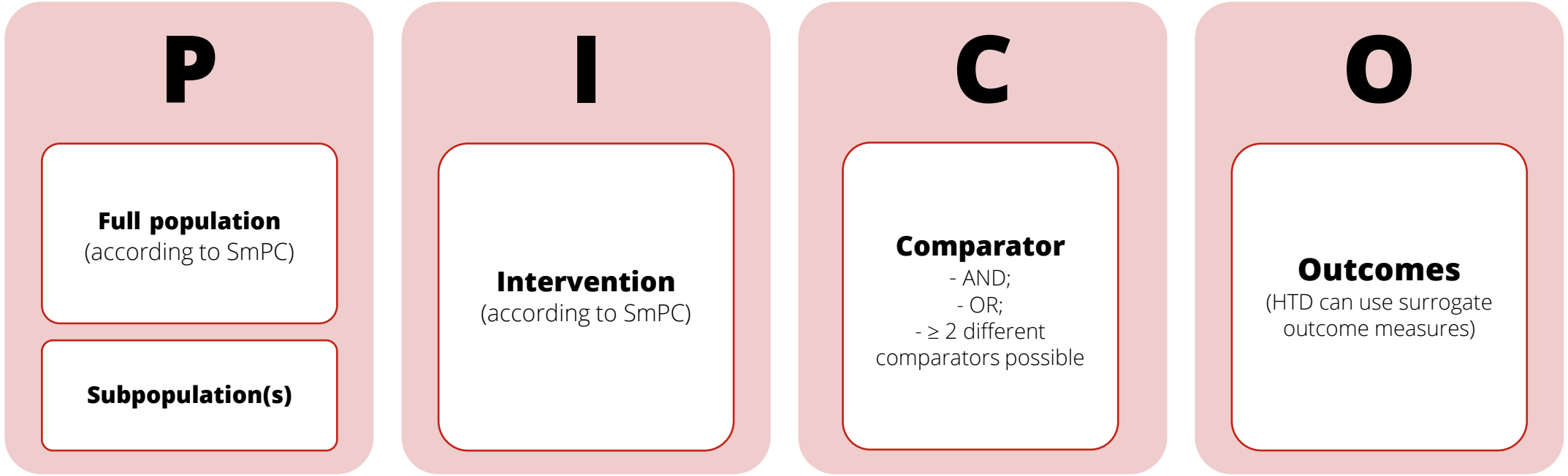
- Prior to sharing of PICO, confidentiality agreement must be signed (on a personal level)

21 days prior to sharing PICO scope

JCA timeline in parallel to EMA



European to Dutch PICO



Dutch PICO based on:

1. *Proposal by asr/co-asr (based on EU guidelines)*
2. *National guidelines*
3. *Prior and ongoing assessments by ZIN*

Dutch PICO scoping

ZIN drafts PICO proposal

- Based on:
  - asr/co-asr proposal ('EU PICO');
  - National guideline;
  - Assessments ZIN

Proposal shared with experts

- In a protected IT environment
- Limited access for experts with signed confidentiality agreement
- Accessible for limited time

ZIN uploads Dutch PICO

- Dutch PICO is uploaded to IT platform

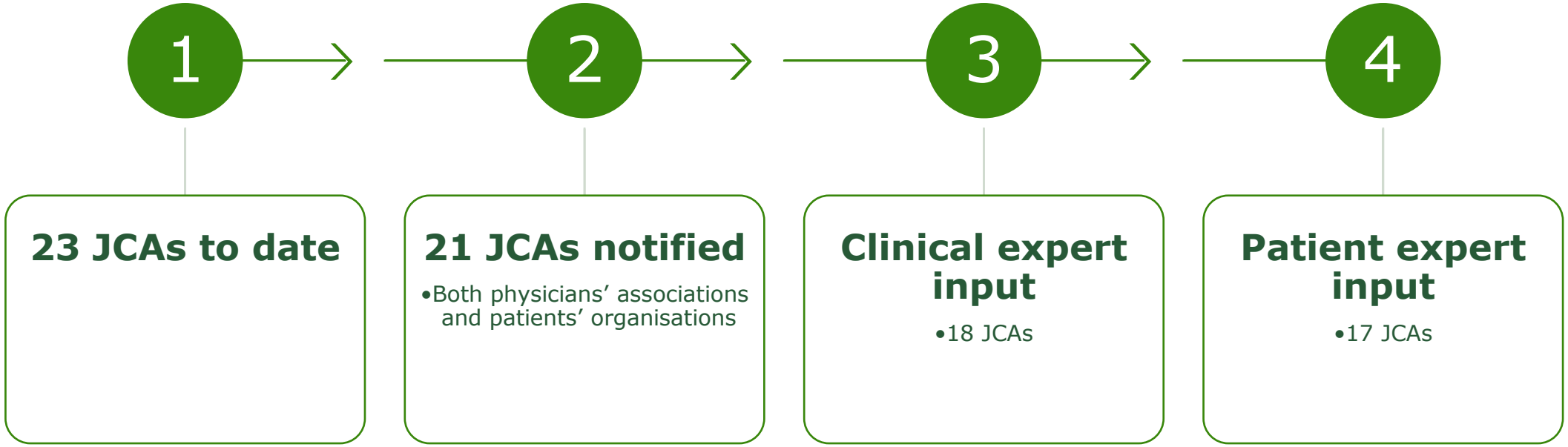
National PICO discussed with assessment team (optional)

- Assessment team might have questions or suggestions for consolidation purposes

21 days

14 days

Reflection PICO scoping



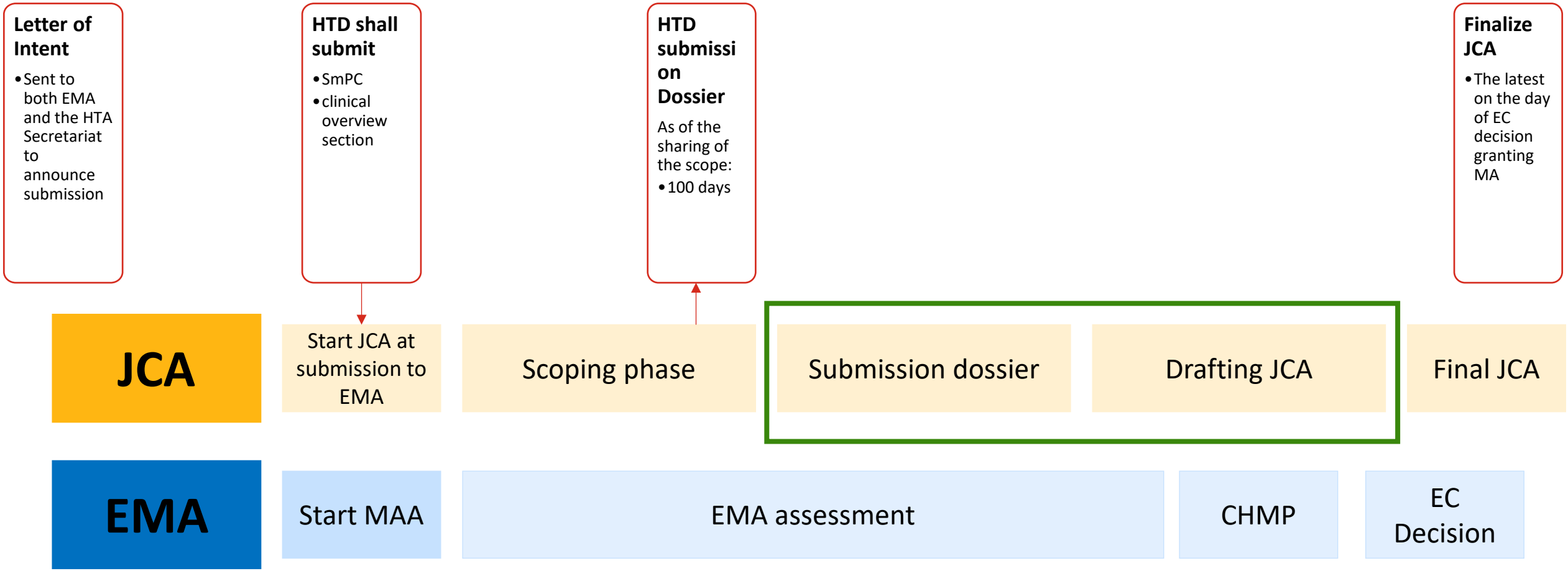
<u>What challenges did we face?</u>

1. Short timeline for input experts
   - Especially problematic for clinical experts
2. Confidentiality
   - No information to be shared without agreement

<u>What did we gain?</u>

1. Scope is based on national practice
   - Especially important for rare diseases
2. JCA report aligned with national needs
   - For national assessment
   - For positioning in treatment landscape

JCA timeline in parallel to EMA



Submission to publication

Assessment scope updates

Due to changes to therapeutic indications

- New scope alignment
- PICOs dropped
- Submission dossier and JCA report updates

Scientific discussions

Ongoing JCAs routinely discussed during JCA subgroup meetings

Review ongoing JCA reports

First, second and third drafts are reviewed by the JCA subgroup

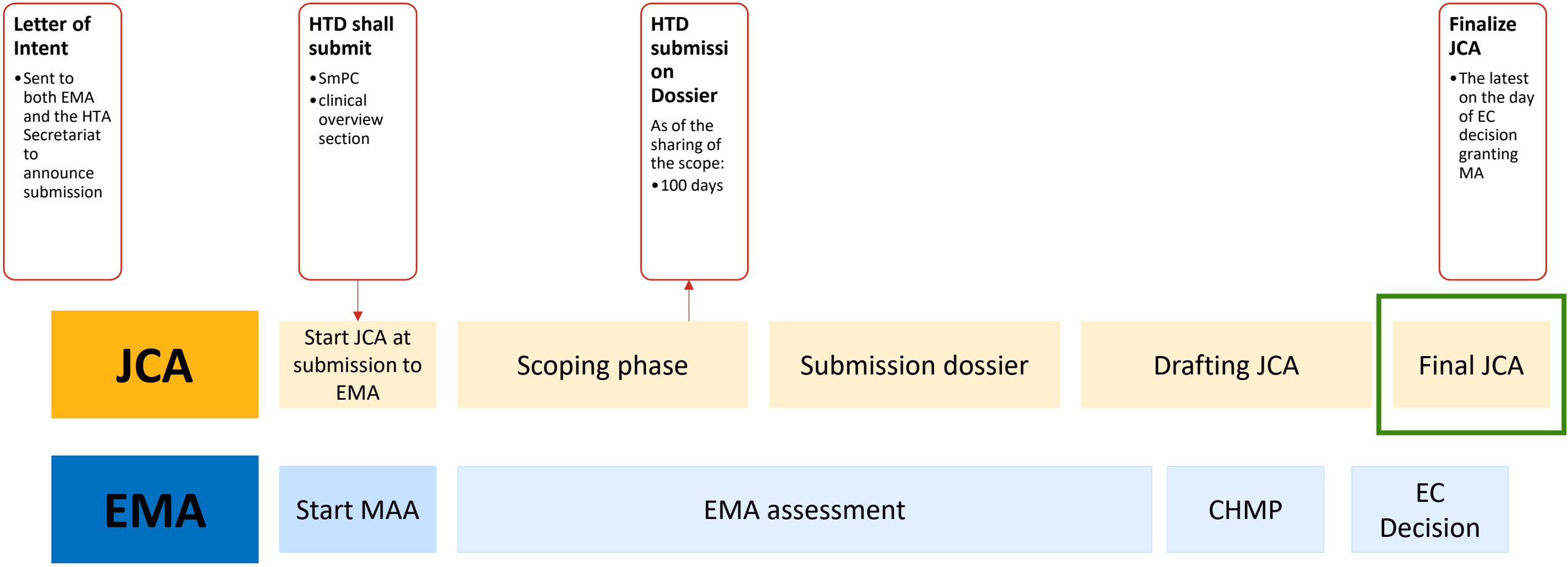
Bridging JCA to national assessment

Internal and external updates

Submission to publication

From JCA to national assessment

JCA timeline in parallel to EMA

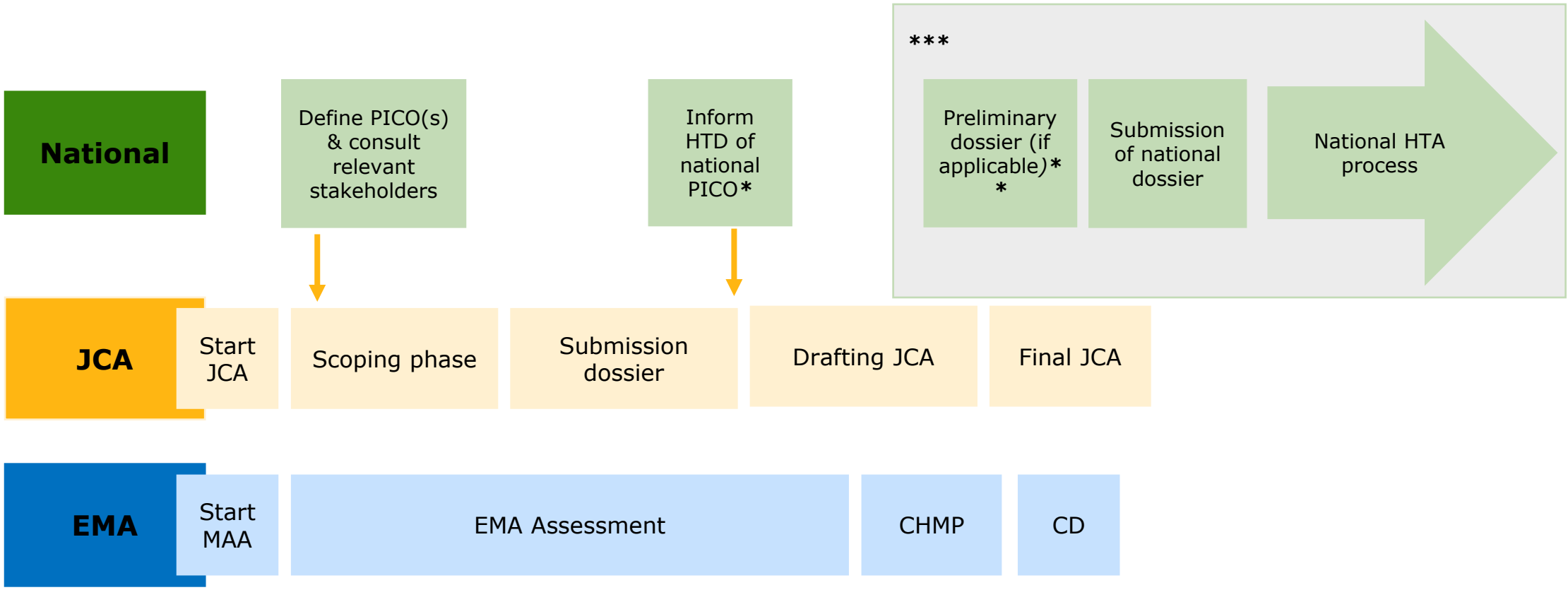


Joint clinical assessment

- JCA report written by two member states
  - Reviewed by JCA subgroup
  - Endorsed by HTA CG
- Contains **no** conclusion or value judgement
- JCA report and submission dossier published shortly after EC decision
  - Input for national appraisal

Dutch assessment

- Must give due consideration to the JCA report
  - National assessment can only start upon publication of JCA report
- National reimbursement dossier still required
  - For claim HTD and pharmaco-economic assessment
  - Submission dossier templates have been updated
    - Requirement: referencing JCA report/submission dossier
- ZIN writes (shortened) assessment report
  - Referencing the JCA-report
  - Add: conclusion therapeutic value (evidence to conclusion) and reimbursement advice



Abbreviations: EMA=European Medicines Agency; CHMP=Committee for Human use of Medicinal Products; CD=Commission Decision on Marketing Authorization; HTD=Health Technology Developer; JCA=Joint Clinical Assessment; MAA=Marketing Authorization Application; PICO=Patient, Intervention, Comparator(s) and Outcome(s);
*: only upon request by the HTD
**: may include a renewed national scoping, this may especially be relevant when the HTD submits much later as the treatment landscape could have changed
***: it should be noted that this figure presents the earliest timepoints possible for these steps, however, the exact timelines will depend on the national submission by the HTDs.

Willemsen A, Rutten-van Mölken M, Al Dulaimi R, Schelleman H, Goettsch W, Timmers L. Preparing for the EU HTA Regulation: Insights from the Dutch Perspective. *J Mark Access Health Policy*. 2025;13(3):35. Published 2025 Jul 24. doi:10.3390/jmahp13030035

First four published JCAs: from PICO scope to evidence included

PRODUCT / INDICATION	PICOs IN SCOPE	PICOs WITH DATA SUBMITTED	PICOs INCLUDED	TYPE OF EVIDENCE INCLUDED BY PICO
Ojemda® (tovorafenib) Paediatric low-grade glioma	8	2	1	PICO 5: Unanchored MAIC
Zepzelca® (lurbinectedin + atezolizumab) Extensive-stage SCLC, maintenance	1	1	1	PICO 1: Direct RCT: IMforte
Imdylltra® (tarlatamab) Extensive-stage SCLC after platinum	7	7	7	PICO 1, 4, 6: Direct comparisons PICO 2: Unanchored MAIC PICO 3, 5: Network meta-analysis PICO 7: Bucher ITC, one outcome
Itvisma® (onasemnogene abeparvovec IT) 5q SMA, ≥2 years	14	7	7	PICO 1: Anchored MAIC[1] + unanchored MAIC[2] PICO 2: Anchored MAIC PICO 3: Direct RCT vs sham / BSC PICO 8 – 11: Same evidence as P1–P2

[1] DMT-naïve patients [2] DMT-experienced patients

HTA CG
Subgroup Joint Clinical Assessment

Publication pivotal study

- Broadly defined patient population
  - Guidelines differentiate between platinum resistant and platinum sensitive patients
- Physician's choice chemotherapy as comparator
  - Consisting of topotecan, lurbinectedin and amrubicin
    - Not all components are used or reimbursed throughout European practice
  - No direct comparison between tarlatamab and individual components of comparative arm

Tarlatamab in Small-Cell Lung Cancer after Platinum-Based Chemotherapy

Giannis Mountzios [1], Longhua Sun [2], Byoung Chul Cho [3], Umut Demirci [4], Sofia Baka [5], Mahmut Gümüş [6], Antonio Lugini [7], Bo Zhu [8], Yan Yu [9], Ippokratis Korantzis [10], Ji-Youn Han [11], Tudor-Eliade Ciuleanu [12], Myung-Ju Ahn [13], Pedro Rocha [14], Julien Mazières [15], Sally C M Lau [16], Martin Schuler [17 18], Fiona Blackhall [19], Tatsuya Yoshida [20], Taofeek K Owonikoko [21], Luis Paz-Ares [22], Tony Jiang [23], Ali Hamidi [23], Diana Gauto [23], Gonzalo Recondo [23], Charles M Rudin [24]; DeLLphi-304 Investigators

Collaborators, Affiliations + expand

PMID: 40454646 DOI: 10.1056/NEJMoa2502099

Abstract

Background: Tarlatamab, a bispecific delta-like ligand 3-directed T-cell engager immunotherapy, received accelerated approval for the treatment of patients with previously treated small-cell lung cancer. Whether tarlatamab is more effective than chemotherapy in the treatment of patients whose small-cell lung cancer has progressed during or after initial platinum-based chemotherapy is not known.

Methods: We conducted a multinational, phase 3, open-label trial to compare tarlatamab with chemotherapy as second-line treatment in patients with small-cell lung cancer whose disease had progressed during or after platinum-based chemotherapy. Patients were randomly assigned to receive tarlatamab or chemotherapy (topotecan, lurbinectedin, or amrubicin). The primary end point was overall survival. Key secondary end points were investigator-assessed progression-free survival and patient-reported outcomes. Results of the prespecified interim analysis (data-cutoff date, January 29, 2025) are reported.

Results: A total of 509 patients were randomly assigned to receive tarlatamab (254 patients) or chemotherapy (255 patients). Treatment with tarlatamab resulted in significantly longer overall survival than chemotherapy (median, 13.6 months [95% confidence interval {CI}, 11.1 to not reached] vs. 8.3 months [95% CI, 7.0 to 10.2]; stratified hazard ratio for death, 0.60; 95% CI, 0.47 to 0.77; P<0.001). Tarlatamab treatment also had a significant benefit with respect to progression-free survival and cancer-related dyspnea and cough as compared with chemotherapy. The incidence of adverse events of grade 3 or higher was lower with tarlatamab than with chemotherapy (54% vs. 80%), as was the incidence of adverse events resulting in treatment discontinuation (5% vs. 12%).

Conclusions: Treatment with tarlatamab led to longer overall survival than chemotherapy among patients with small-cell lung cancer whose disease had progressed during or after platinum-based chemotherapy. (Funded by Amgen; DeLLphi-304 ClinicalTrials.gov number, NCT05740566.).

Dingemans AC, Fruh M, Ardizzoni A et al. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2021; 32(7): 839-853. https://doi.org/10.1016/j.annonc.2021.03.207.
Mountzios G, Sun L, Cho BC, et al. Tarlatamab in Small-Cell Lung Cancer after Platinum-Based Chemotherapy. N Engl J Med. 2025;393(4):349-361. doi:10.1056/NEJMoa2502099

JCA report

- Trail population split to address relevant subpopulation
  - Platinum-resistant and sensitive patients
  - Disease progression within and after 6 months
- Outcomes provided for comparisons with individual components of the comparator arm
  - Unanchored MAIC, NMA, Bucher ITC

Table 11: Assessment scope and overview of submitted data per PICO

Population Intervention PICO no.	Comparator	Results submitted [yes/no]	HTD's reason for omission	Data included in the JCA report [yes/no]
Population A				
Adult patients with extensive-stage small cell lung cancer (ES-SCLC), who require systemic therapy following disease progression on or within 3 months after first-line treatment with platinum-based chemotherapy (Treatment free interval [TFI][a] <3 months, platinum-resistant).				
Intervention: Tarlatamab monotherapy				
PICO 1	Topotecan	yes[b]	–	yes[b]
PICO 2	CAV	yes[b]	–	yes[b]
Population B				
Adult patients with ES-SCLC who require systemic therapy following disease progression at least 3 months after first-line treatment with platinum-based chemotherapy (TFI[a] ≥3 months, platinum-sensitive).				
Intervention: Tarlatamab monotherapy				
PICO 3	Retreatment with platinum-based chemotherapy[c]	yes[b]	–	yes[b]
PICO 4	Topotecan	yes	–	yes
PICO 5	CAV	yes[b]	–	yes[b]
Population C				
Adults with ES-SCLC in whom the disease progresses during or after first-line platinum-based therapy with a recurrence-free interval of ≤6 months or who are not suitable for retreatment with a platinum-based chemotherapy				
Intervention: Tarlatamab monotherapy				
PICO 6	Topotecan OR CAV	yes[b]	–	yes[b]
Population D				
Adults with ES-SCLC in whom the disease has progressed after first-line platinum-based therapy with a >6 month recurrence-free interval and who are suitable for retreatment with a platinum-based chemotherapy				
Intervention: Tarlatamab monotherapy				
PICO 7	Cisplatin in combination with etoposide[c] OR Carboplatin in combination with etoposide[c]	yes[b]	–	yes[b]

Zorginstituut Nederland

Further questions?

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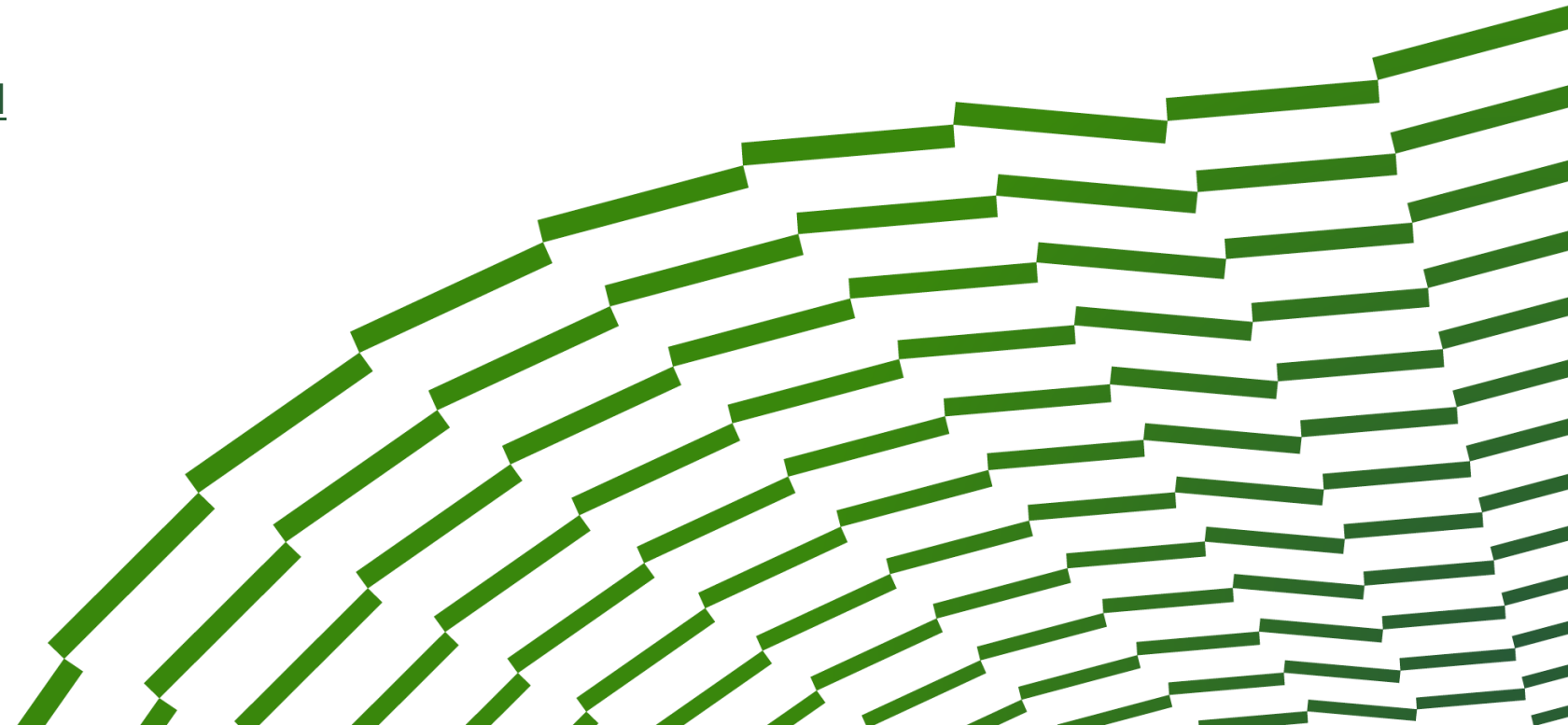
19 September 2025



| Van goede zorg verzekerd |

Agenda

Time	Topics	Speaker
12.15-1.00pm	Registration and lunch	All
1.00 pm – 1.15 pm	Welcome	Maurice Driessen, NVTAG
1.15 pm – 2.00 pm	Learnings from first JCA reports. The EU level perspective	Anne Willemsen *Chair JCA subgroup*
2.00 pm – 2.45 pm	Initial Lessons from the JCA Journey: Implications for Evidence Generation and Business Readiness	Suzette Matthijsse (ONLINE) *JCA-lead Lumanity*
2.45 pm – 3.00 pm	Break	All
3.00 pm – 3.45 pm	The Dutch perspective on conducting and using the first JCAs.	Riam Al Dulaimi *Zorginstituut Nederland – EU-assessor*
3.45 pm – 4.30 pm	The Evolving Landscape of EU HTA: early lessons, challenges, and future direction	Maureen Rutten *Prof. Erasmus School of Health Policy & Management*
4.30 pm – 4.55 pm	Panel discussion	All speakers* **Richard Birnie (Lumanity) will substitute Suzette (online)*
4.55 pm – 5.00 pm	Closure and invitation for drinks	Maurice Driessen

NVTAG

Nederlandse Vereniging voor Technology Assessment in de Gezondheidszorg

Maureen Rutten

Professor at Erasmus School of Health Policy & Management

The Evolving Landscape of EU HTA: early lessons, challenges, and future direction

Erasmus School of
Health Policy
& Management

The evolving landscape of EU HTA

Early lessons, challenges, future direction

Dr. Maureen Rutten-van Mölken, PhD
Professor of Economic Evaluation of Innovations for Health
m.rutten@eshpm.eur.nl

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Erasmus University Rotterdam

Initial 4 Joint Clinical Assessments, all orphan drugs

Tovorafenib
Ojemda®

HTD: Ipsen

Indication: montotherapy in children ≥6 months with paediatric low grade glioma harboring a BRAF fusion or rearrangement, or BRAF V600 mutiation, after progression on ≥ 1 prior systemic therapies

N PICO's in scope /subm /incl: 8/2/1

Duration: 378 days

Assessors: Ireland/Germany

Methods: unanchored MAIC

Lurbinectedin
Zebzelca®

HTD: Pharma Mar

Indication: maintenance treatment of adult patients with ES-SCLC whose disease has not progressed after 1st line indication therapy with atezolizumab, carboplatin, and etoposide

N PICO's in scope /subm /incl: 1/1/1

Duration: 384 days

Assessors: Germany/Portugal

Methods: direct RCT

Tarlatamab
Imdylltra®

HTD: Amgen

Indication: adult patients with ES-SCLC who require systemic therapy following disease progression on or after 1st line treatment with platinum-based chemotherapy

N PICO's in scope /subm /incl: 7/7/7

Duration: 356 days

Assessors: Germany/Hungary

Methods: direct comparison (PICO 1,4,6), unanchored MAIC (2), NMA (3,5), Bucher ITC (7)

Onasemnogene abeparvovec
Itvisma®

HTD: Novartis

Indication: patients ≥2 years with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene

N PICO's in scope /subm /incl: 14/7/7

Duration: 473 days

Assessors: Ireland/France

Methods: anchored +unanchored MAIC (1), anchored MAIC (2), direct RCT vs sham/BSC (3), same evidence as P1,2 (8-11)

Some general observations (1)

- **Scientific quality of the JCA report is generally regarded as high**
- **HTD's made great efforts to address PICO's requested**
- **PICO scoping determines evidence complexity**
  - A single product can require very different analyses across Member States (MS)
- **Evidence certainty is PICO-specific**
  - Substantial emphasis not only on reporting uncertainties but on explaining their potential impact on interpretation
- **A good pivotal RCT is necessary but just the starting point**
  - Trial blinding and follow-up matter
- **Indirect treatment comparisons become strategically important**
  - ITC, NMA, MAICs, accepted but heavily challenged
  - data quality of source studies behind the indirect comparisons scrutinized

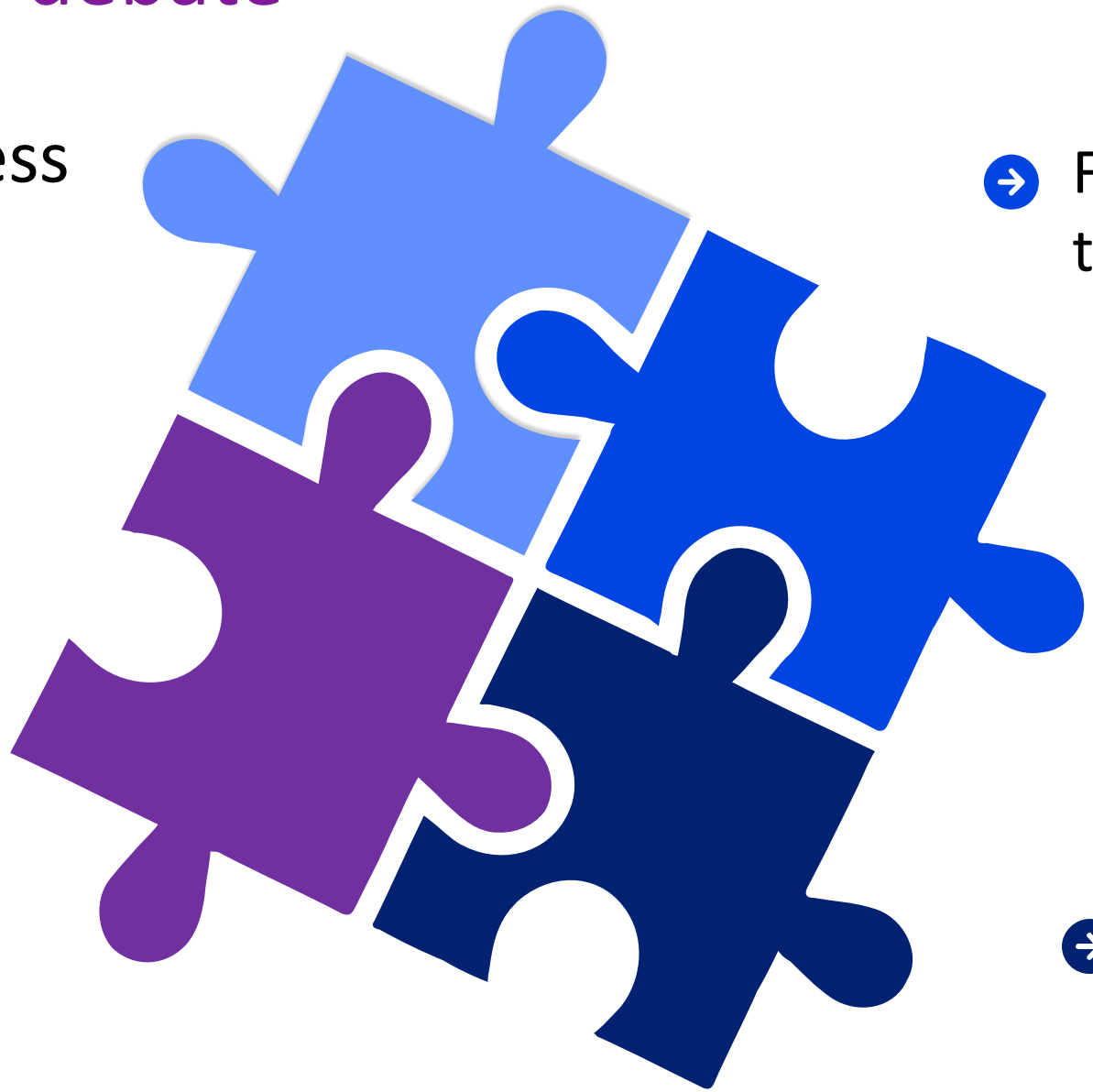
Some general observations (2)

- **Patient-reported outcomes are critical**
  - Survival benefits need to be interpreted alongside symptoms, functioning, HRQoL and treatment burden
- **The last pre-specified data cut, with the longest observation, is the most relevant to HTA.**
- **Safety evaluation is under close examination**

- **There is a clear tension between assessor's expectations, methodological rigor, transparency requirements, data availability, and the practical constraints.**

Four areas of debate

- Inclusiveness vs Evidence
- From Evidence to Value



- Procedural challenges
- Methodological standards

1.
Inclusiveness
versus
Evidence

Trade-off between no. of PICO's and strength of evidence (1)

- Creating subpopulations, by splitting the pivotal trial, for which the randomization was not stratified increases risk of:
  - **Type 1 error: falsely assuming an additional benefit**
    - Imbalance baseline characteristics between arms: Risk of bias/confounding is larger in smaller, unstratified subgroups → can produce apparent benefit that isn't real.
    - The more subgroups sliced out, the higher the chance that one shows "significant" result by chance alone
  - **Type 2 error: falsely not offering a potentially beneficial medicine.**
    - Reduced sample size: lower power to detect a real effect

Trade-off between no. of PICO's and strength of evidence (2)

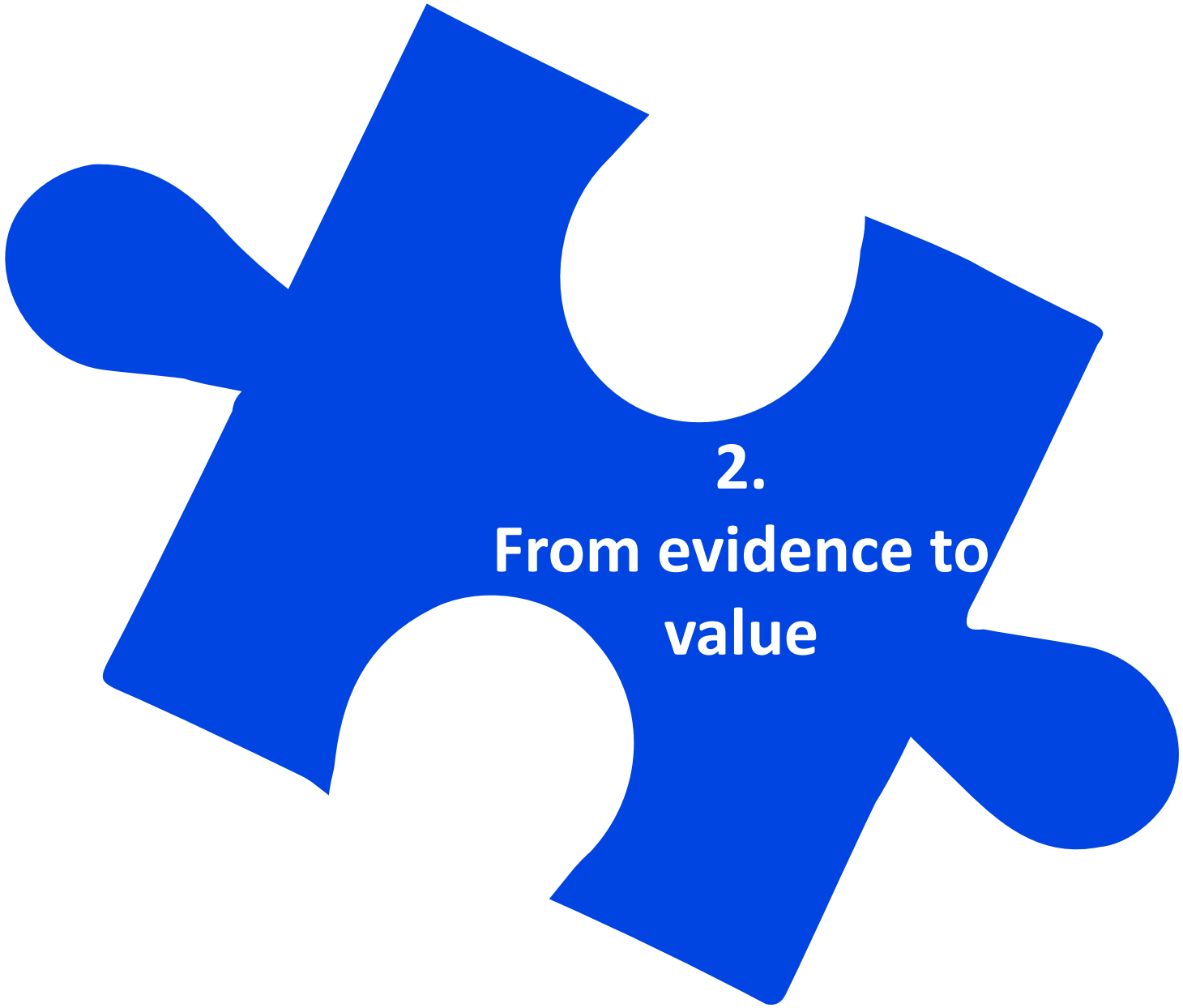
- **Does the desire to have evidence for multiple subpopulations outweigh breaking the randomization of the pivotal trial?**

- **Should the main comparator be the best possible SoC?**

Justification for subpopulations is thin

- Tarlatamab: Treatment-free Interval (TFI) <3 vs ≥3 months and ≤6 months vs > 6 months after first-line platinum chemotherapy; 3 months is also used in European guidelines but 6 months?
- Tovorafenib: Is the difference between a BRAF V600E mutation and a BRAF fusion or rearrangement, or BRAF V600 (non-E) mutation so relevant for prognosis?
- SMA: 6 (originally 7) populations seems too much for such a rare disease: e.g. max 3 vs max 4 copies of SMN2gene, being able to walk independently

- **If a high standard of evidence is requested from HTD, shouldn't a high standard of justification be requested from JCA CG?**


2.
From evidence to
value

Value-centered appraisal falls within the remit of the MS

- JCA report elegantly avoids any conclusion but how to translate the evidence into an opinion about added therapeutic value?
  - MS with and without a categorical benefit system
  - E.g. German clinical benefit rating, France SMR rating vs CEA-countries

- Smaller countries with less mature HTA systems are asking for help

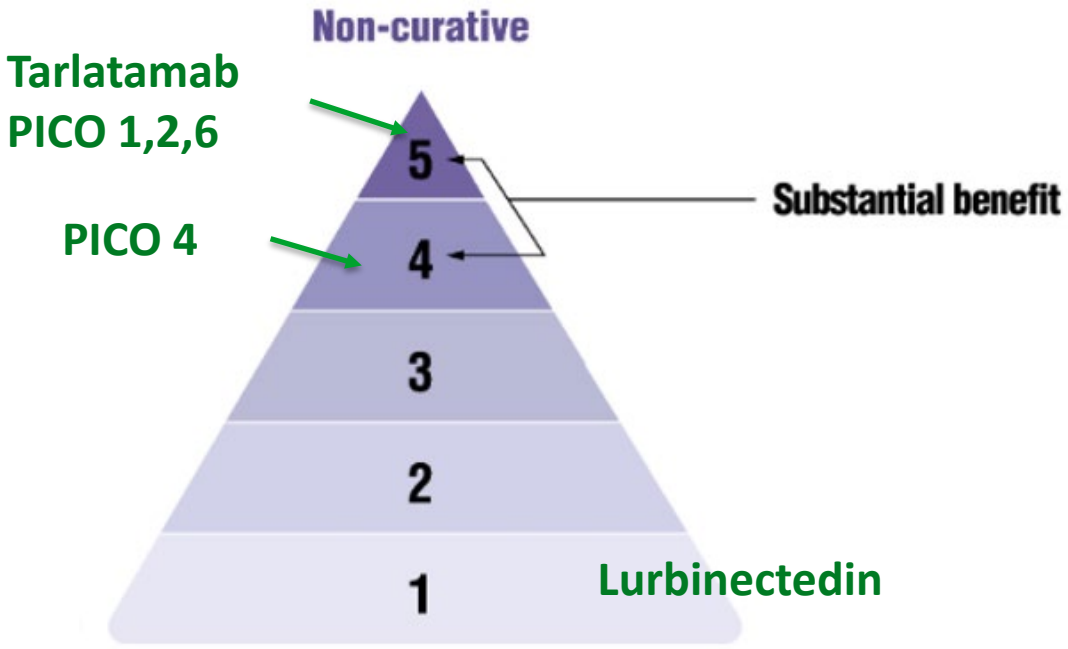
- Couldn't a least a consensus on the acceptability of the level of uncertainty be reached? Evidence does not change at MS's border!

- **Is it really not possible to come to an overall conclusion on the overall clinical value of the evidence?**

ESMO Magnitude of Clinical Benefit Scale

IF median OS with SoC is < 12 months

Grade 4^	HR*≤0.65 + gain ≥ 3 months
	Increase in 2-yr survival ≥ 10% (if ≥ 20% of ptnt in experimental arm has reached 2-yr OS)
Grade 3	HR*≤ 0.65 + gain ≥2 - <3 months
Grade 2	HR*≤ 0.65 + gain ≥1.5 - <2 months
	HR*>0.65-0.7 + gain ≥1.5 months
Grade 1	HR*> 0.7 or gain <1.5 months



* lower-limit 95% CI of the HR

^ adjusted to grade 5 in case of QoL benefit and or less G3-4 toxicities

ESMO magnitude of clinical benefit scale (ESMO-MCBS) tool

3.
Methodological
standards

Some “critiques” from the assessors

- **Tovorafenib:**
  - Limited dataset from single-arm trial only
  - Serious critique on statistical analyses, HTD-errors, not providing data

- **Lurbinectedin:**
  - No formal hypothesis testing on later data cut (Feb 12, 2025), but the OS benefit of the earlier data cut was not confirmed (July 24, 2024)

- **Tarlatamab:**
  - Unequal % of missing info on 1st subsequent therapy after progression
  - PFS, ORR: unblinded investigator assessment
  - unequal % of missing scans to assess ORR and DoR
  - Challenge: multi-comparator arm “Investigator's-choice chemotherapy”

Some “critiques” from the assessors

- **Onasemnogene abeparvovec** (epidural injection)
  - No head-to-head comparison of this new way of administering the medicine to Zolgensma IV, Spinraza, Evrysdi
  - The original claimed population included patients ≥6 months was changed into ≥2 yrs some PICO’s became irrelevant
  - Evidence provided per PICO does not 100% match population in PICO
  - Failing to reject the null hypothesis of no difference is not evidence of equivalence

Some “critiques” on PRO

- **Tarlatamab:**
  - Long-enough observation period for PRO’s?
  - PRO completion declined very rapidly
  - Unequal length of observation period for PRO’s
  - Imbalanced questionnaire return rates

- **Onasemnogene abeparvovec**
  - Relevance of minimal clinically important difference (MCID)?

“Critiques” Indirect Treatment Comparisons and Network meta-analysis (NMA)

- **Transitivity assumption** (all patients could have been randomized to any of the interventions) likely to be violated, because it requires:

  - **Similarity**: similar distribution of effect modifiers across treatment comparisons
  - **Homogeneity**: treatment effect homogeneous across all studies
  - **Consistency**: direct and indirect treatment effects should be in agreement (limited possibility to test this)
  - Interventions are missing at random (impossible when they do not overlap chronologically)

“Critiques” on MAIC

- **Tovorafenib; Tarlatamab:** Unanchored MAIC → highly uncertain results
  - Reweighting the individual patient data from the pivotal trial substantially reduced the effective sample size (ESS), leading to statistical imprecision for the resulting effect estimates.
  - This may indicate poor covariate overlap between studies, potentially leading to issues with bias and coverage
  - Adjustment for a limited number of measured and reported prognostic factors/effect modifiers. → Potential for residual confounding.
  - Insufficient validation of key assumptions on positivity and overlap assumptions of MAIC were not assessed.

What can realistically be expected?

- Acknowledge that we cannot apply the methodological standards developed for common diseases without **accounting for rarity**.
- Appropriate use of single-arm studies, target trial emulation, external controls, real-world evidence, Bayesian approaches, surrogate endpoints
- **Conditional approval** linked to post-marketing evidence generation to validate claims on (long-term) benefits should be considered when RCT's cannot reasonably be conducted

4.
Procedural
challenges

Operational challenges

- Growing assessment volumes
- Mobilization of expertise across MS
- Review capacity
- Stakeholder involvement and interactions

	Carer	Clinical expert
Onasemnogene abeparvovec	2	1
Lurbinectedin	1	1
Tarlatamab	2	2
Tovorafenib	1	1

- Integrating non-binding JCA outputs into national assessment processes
- Adapting submission templates and reporting formats.

Achieving the aims of the EU HTA-regulation*?

? To improve the availability for EU patients of innovative technologies in the area of health

✓ To promote convergence in HTA tools, procedures and methodologies

? To ensure efficient use of resources and strengthen the quality of HTA across the EU

? To improve business predictability

Regulation (EU) 2021/2282

* (+Norway, Iceland, Lichtenstein)

What may the future bring?

Increase early dialogue capacity

One European PICO (best SoC)?

Appropriate methods when RCT's cannot reasonably be expected

What level of uncertainty is acceptable

Help MS with conclusion on value

Agenda

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1.00 pm – 1.15 pm	Welcome	Maurice Driessen, NVTAG
1.15 pm – 2.00 pm	Learnings from first JCA reports. The EU level perspective	Anne Willemsen *Chair JCA subgroup*
2.00 pm – 2.45 pm	Initial Lessons from the JCA Journey: Implications for Evidence Generation and Business Readiness	Suzette Matthijsse (ONLINE) *JCA-lead Lumanity*
2.45 pm – 3.00 pm	Break	All
3.00 pm – 3.45 pm	The Dutch perspective on conducting and using the first JCAs.	Riam Al Dulaimi *Zorginstituut Nederland – EU-assessor*
3.45 pm – 4.30 pm	The Evolving Landscape of EU HTA: early lessons, challenges, and future direction	Maureen Rutten *Prof. Erasmus School of Health Policy & Management*
4.30 pm – 4.55 pm	Panel discussion	All speakers* **Richard Birnie (Lumanity) will substitute Suzette (online)*
4.55 pm – 5.00 pm	Closure and invitation for drinks	Maurice Driessen

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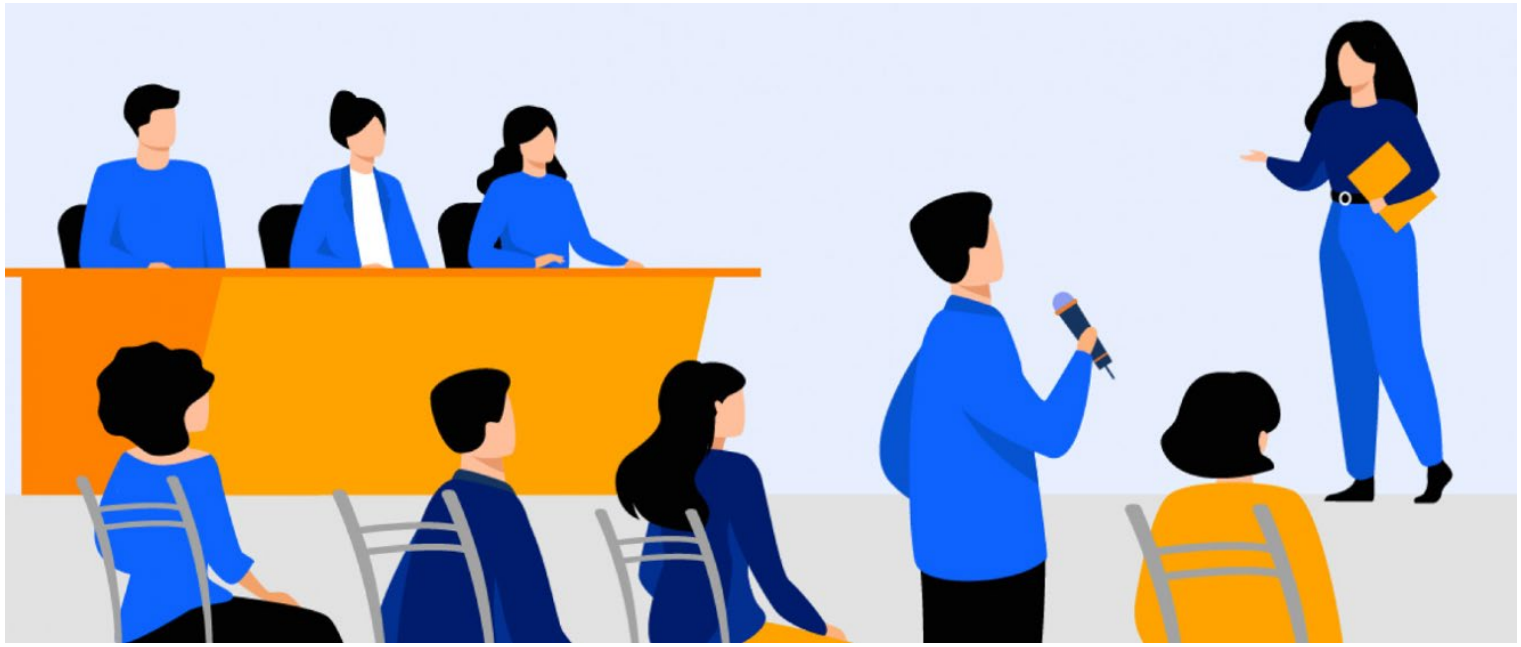
Panel Discussion



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Panel discussion, question #1

Is JCA reducing duplication or adding an additional layer of assessment?

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Panel discussion, question #2

Five years from now we will look back and conclude that JCA has not reduced the evidence burden, it has increased? *(agree/disagree)*

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Panel discussion, question #3

The current JCA-process is unrealistic for rare diseases and orphan medicines *(agree/disagree)*

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Panel discussion, question #4

How will the JCA report facilitate individual country decision making? any examples we have today/experiences

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Panel discussion, question #5

In 30 years JCA will become as accepted as centralized marketing authorisation (EMA) is today *(agree/disagree)*

Upcoming NVTAG events

November 4th, 2026:

Networking event (jong-NVTAG)

April 8th, 2027 (Utrecht)

Spring symposium & NVTAG-prize

Topic: TBD

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