Proper Prior Planning for the Prespecified Post-Hoc (Analysis of) PICOS

How Statisticians can address the opportunities and challenges of EU HTA

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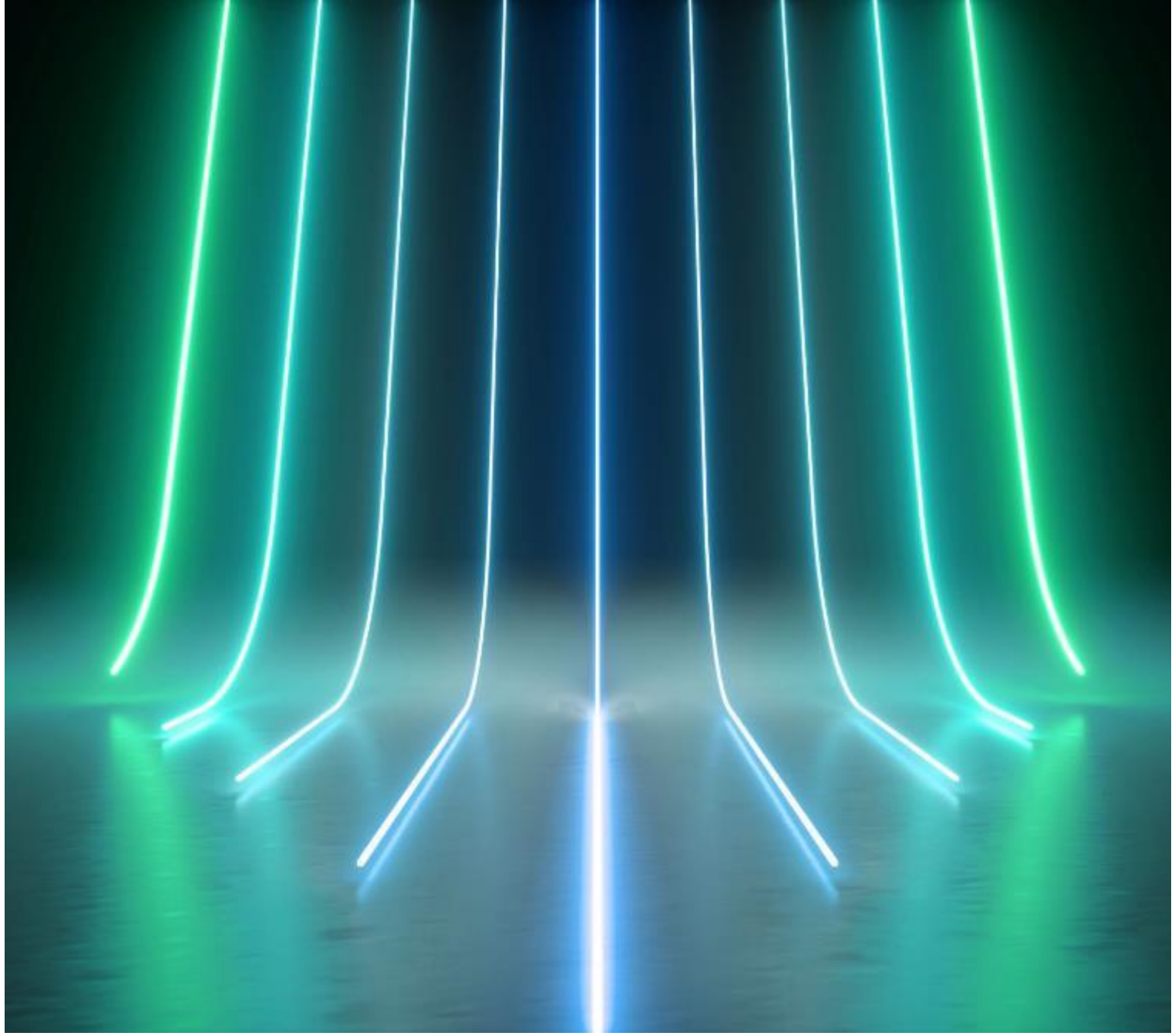
Disclaimer

The views expressed herein are of the presenters only and do not necessarily represent those of the employer of the pharmaceutical industry in general

Agenda

- What is HTA, and how does it use clinical data?
- What is EU HTA Joint Clinical Assessment?
- What does “Proper Prior Planning” really mean?
- Recommended Best Practices



What is HTA, and how is clinical data used in HTA?

Regulators versus Health Technology Assessments (HTAs)

Using the same data in very different ways, to answer different questions

Is it good?

Regulatory

Common Source of Outcome (Absolute)

Is the product safe and effective?

Requirements are (relatively) transparent and seek to be minimal

Recognizes that clinical trials have limitations by design

How good is it?

HTA

Outcome is contextual (Relative)

How much more effective or safer is this product than alternatives?

Is this an appropriate therapy in our unique setting?

Requirements are opaque and intensive

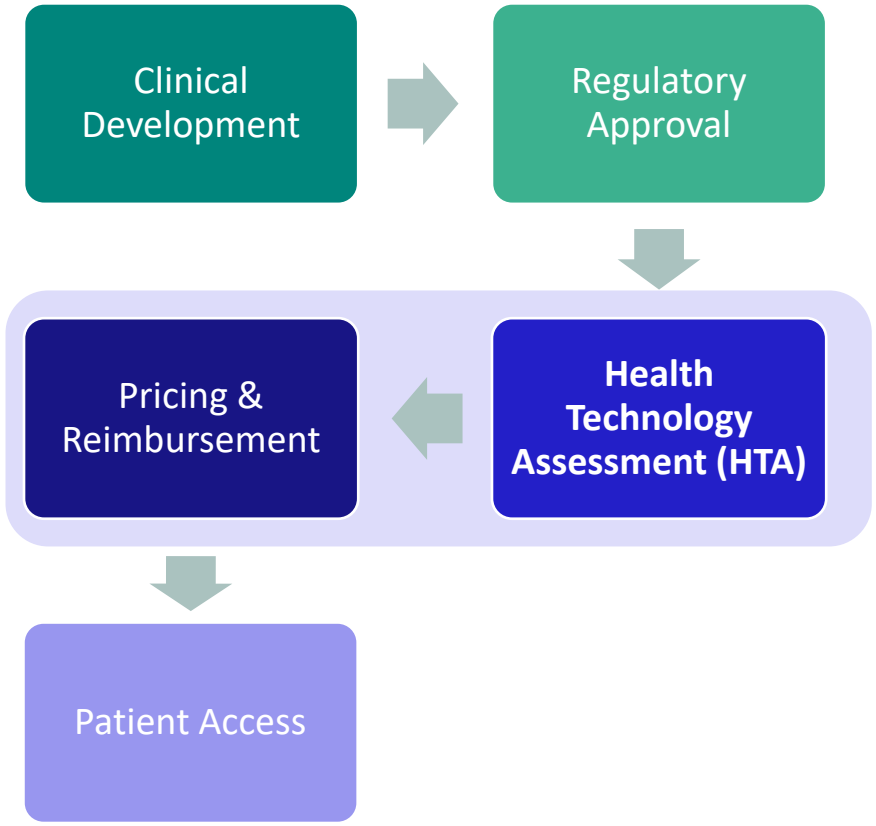
What do we see as increased benefit?

Is the added benefit meaningful?

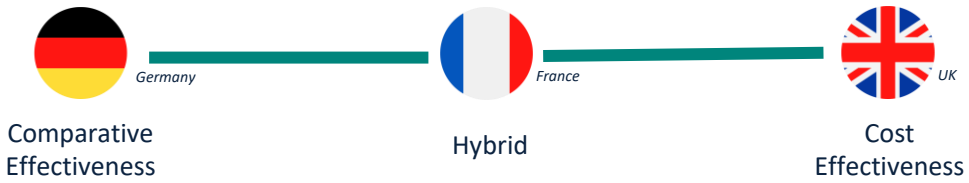
What is value vs costs?

Seek ad-hoc/ re-analyze clinical data

HTAs are an integral part of the pathway leading to Patient Access



- HTA informs decision making about reimbursement and pricing
  - Balancing budgets and resources in the individual healthcare systems
- Multi-stakeholder process (internal and external)
- Different HTA systems exist (e.g. clinical effectiveness, cost-effectiveness)



- >60 countries claim to have HTA*

**WHO Health Technology Assessment Survey 2020/21*

How are access, pricing, and reimbursement decisions made? ("HTA")

Different systems have different:

- data requirements (comparative effectiveness archetype to cost-effectiveness archetype)
- timings
- nature of HTA recommendations (binding non-binding)
- relationships between regulatory processes, HTA body recommendations, pricing and reimbursement decisions

Table 2: HTA Process (By Country)

Country	HTA Recommendations	Breakthrough Treatments and Rare Diseases	Pricing and Reimbursement	HTA and Drug Price Negotiations	HTA and Regulatory Reviews
© Lymphoma Coalition	Are HTA recommendations binding or non-binding?	Is there a regulatory approval process for new medicines?	Is the HTA body responsible for pricing and reimbursement?	Are processes conducted in parallel or are they separate?	Is there a concurrent process in place?
Argentina	Unknown	Yes	Not responsible	Unknown	Unknown
Australia	Non-binding	Yes	Not responsible	Unknown	Yes
Belgium	Unknown	Yes	Not responsible	Unknown	Unknown
Brazil	Binding	Yes	Not responsible	Unknown	Yes
Canada	Non-binding	Yes	Not responsible	Separate	Yes
China	Non-binding	Yes	Not responsible	Unknown	Unknown
Colombia	Non-binding	Yes	Not responsible	Unknown	Unknown
Denmark	Non-binding	Yes	Not responsible	Separate	Unknown
France	Binding	Yes	Not responsible	Separate	Yes
Germany	Binding	Yes	Not responsible	Unknown	Yes
Ireland	Non-binding	Yes	Not responsible	Unknown	Unknown
Israel	Binding	Unknown	Responsible	Unknown	Unknown

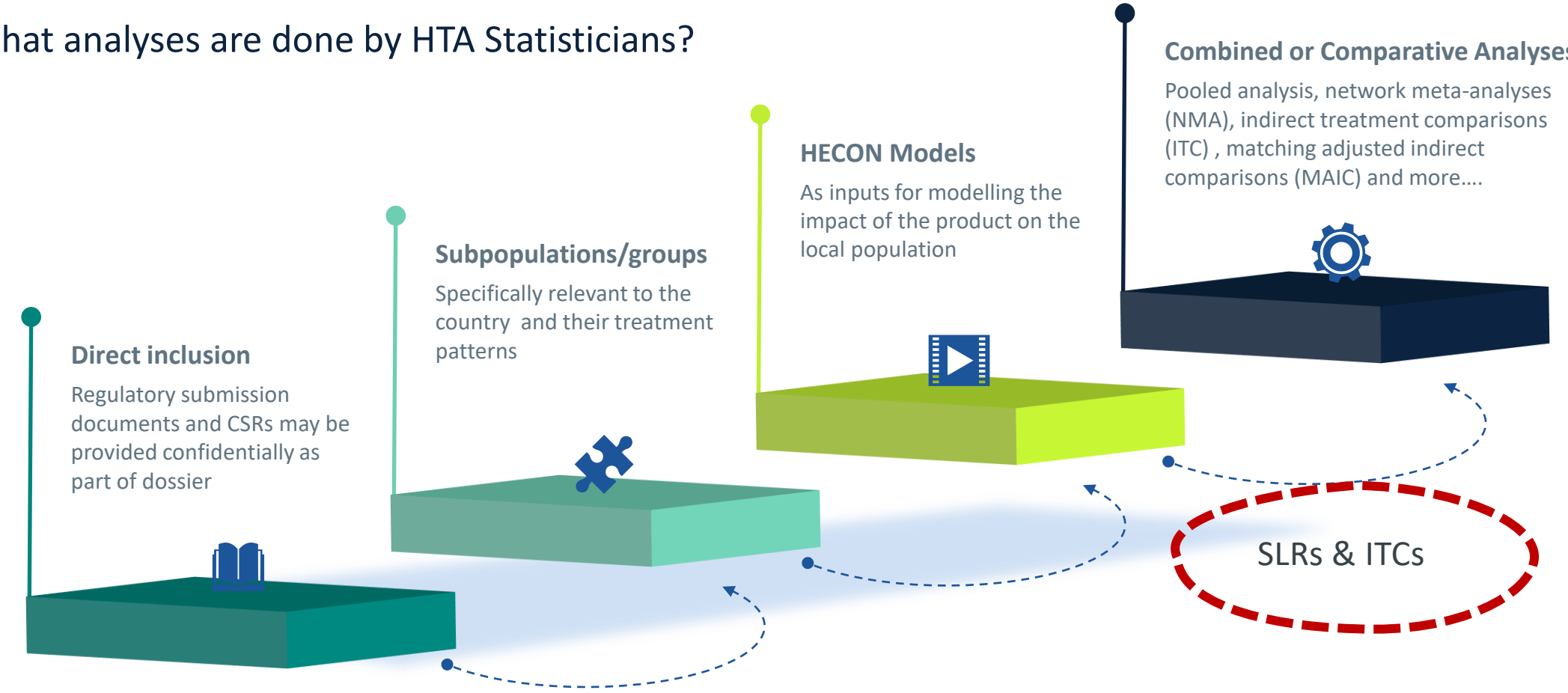
Source: https://lymphomacoalition.org/wp-content/uploads/HTA-Report-Final-A4-2.pdf

HTA Data and Analysis

SLR = Systematic Literature Review
IPD = Individual Patient Data

How does RCT data get used in HTA Dossiers?

…and what analyses are done by HTA Statisticians?



Using the RCT data from all relevant RCTs, but looking at new populations, comparators, new endpoints, and specific methods

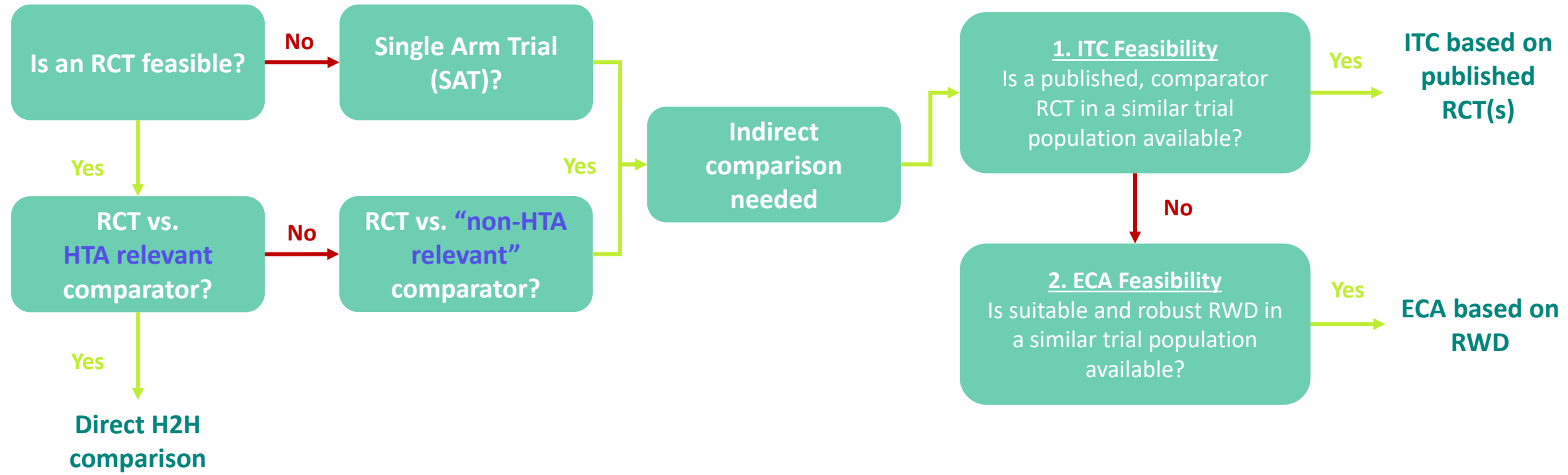
….and integrating non-RCT data when and where appropriate!

RCT = Randomized Clinical Trial, SLR = Systematic Literature Review, ITC = Indirect Treatment Comparison, CSR = Clinical Study Report, HECON = Health Economics

Why Use Indirect Treatment Comparisons?

- HTA seeks to understand **comparative clinical effectiveness** in a specific Population, against specific Comparators, for specific Outcomes
- RCTs are the "gold standard" for direct comparisons – but don't always include all comparators relevant at time of HTA evaluation.
- If indirect evidence is not available from another trial, then an ECA based on RWD can potentially be used to address the evidence gap

Comparative Evidence Options for HTA submissions

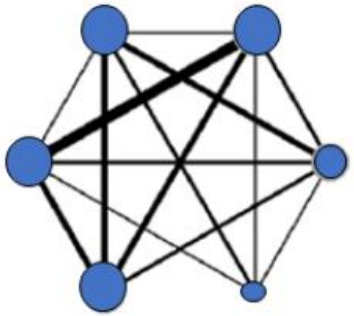


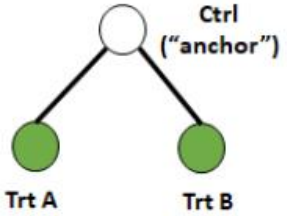
Abbreviations: RCT: Randomized Controlled Trial, ITC: Indirect treatment comparison, ECA: External comparator arm; RWD: Real-World Data; SAT: Single-Arm Trial; H2H: Head-2-Head
Source: Adapted from IQVIA Report to MSD on ITC Usage in European Health Technology Assessments, March 2024

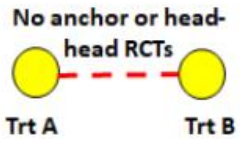
ITCs are all about the choices…and what's available

Types of available data
(aggregate, patient level, or both?)

Evidence structure
(anchored? disconnected?)







Number of therapies to be compared
(e.g., two? many?)

Population heterogeneity
(many differences between study populations?)

Source: https://www.linkedin.com/pulse/choosing-between-methods-indirect-treatment-brian-hutton/

How do HTA Bodies View ITCs?

Acceptability of methods varies across HTA agencies

Method	EUHTA	NICE	IQWIG	PBAC	CADTH	HAS	ICER
Bucher ITC	Yes	Yes	Yes	Yes	Yes	No	Unknown[3]
MAIC/STC	Yes	Yes	Potentially	Yes	Yes	Yes	Unknown[3]
Bucher NMA	Yes	Potentially[1]	No/Potentially[2]	No	Yes	No	Unknown[3]
Frequentist NMA (Lumley)	Yes	Potentially[1]	No/Potentially[2]	No	Yes	Yes	Unknown[3]
Bayesian NMA	Yes	Yes	No/Potentially[2]	No	Yes	Yes	Yes

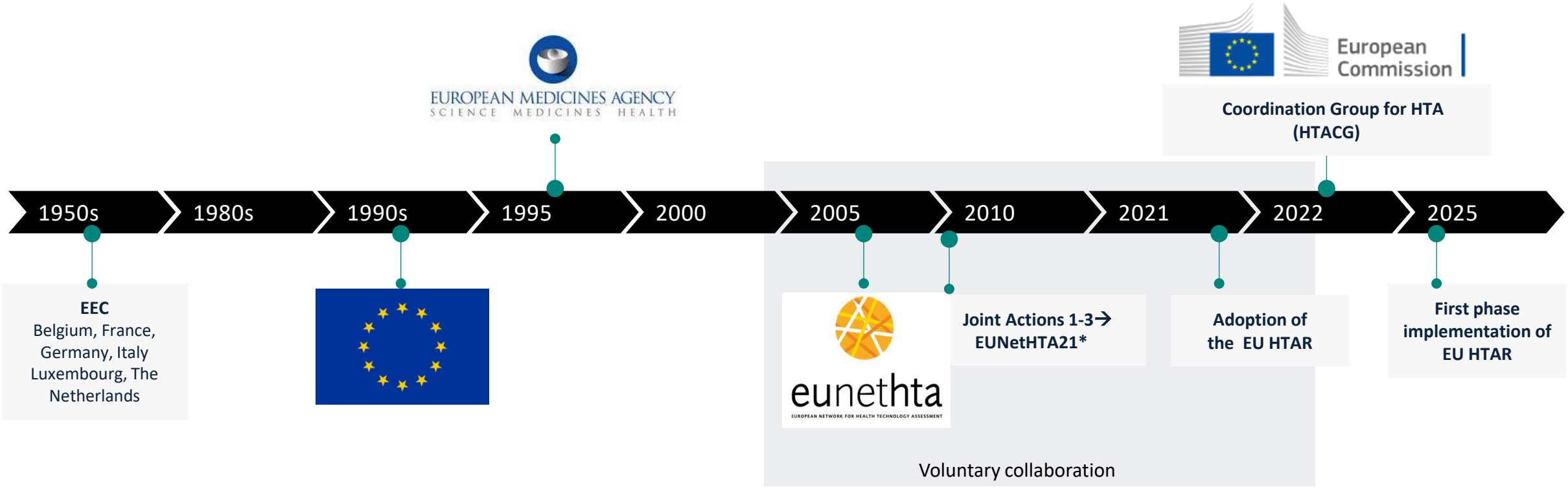
1: NICE has clear preference for Bayesian NMAs, but could consider frequentist approaches if assumptions are satisfied
2: IQWIG does not endorse NMAs but could accept it depending on the research question
3: No statement has been made about those methods

NICE: National Institute for Health and Care Excellence (HTA agency in United Kingdom); IQWiG: German Institute for Quality and Efficiency in Health Care; PBAC is Pharmaceutical Benefits Advisory Committee (HTA advisory in Australia); CADTH: Canada's Drug and Health Technology Agency; HAS is Haute Autorité de Santé (HTA advisory in France); ICER: Institute for Clinical and Economic Review (independent health technology value assessment in the United States)
MAIC: matching-adjusted indirect comparison; STC is simulated treatment comparison; IPD is individual patient-level data; AgD is aggregate data; NMA: Network meta-analysis

Sources:
Internal Review Merck & Co, Inc., Rahway, NJ, USA. November 2023
Member State Coordination Group on Health Technology Assessment, Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons

So What is “EU HTA” and how does it change things?

History of collaboration leading to the EU HTA regulation



*Deliverable finalized and group formally closed in Sept 2023. Eunethta was a joint action/voluntary collaboration involving only 14 MS and UK + No, which has now been replaced by the formal CG which includes all 27 MS.

The EU HTA Regulation

Passed into law in Q4 2021; takes effect starting in 2025

Accessible here

The **mandatory** requirement of **centralised clinical assessment** for patient access of new health technologies to MS of the EU

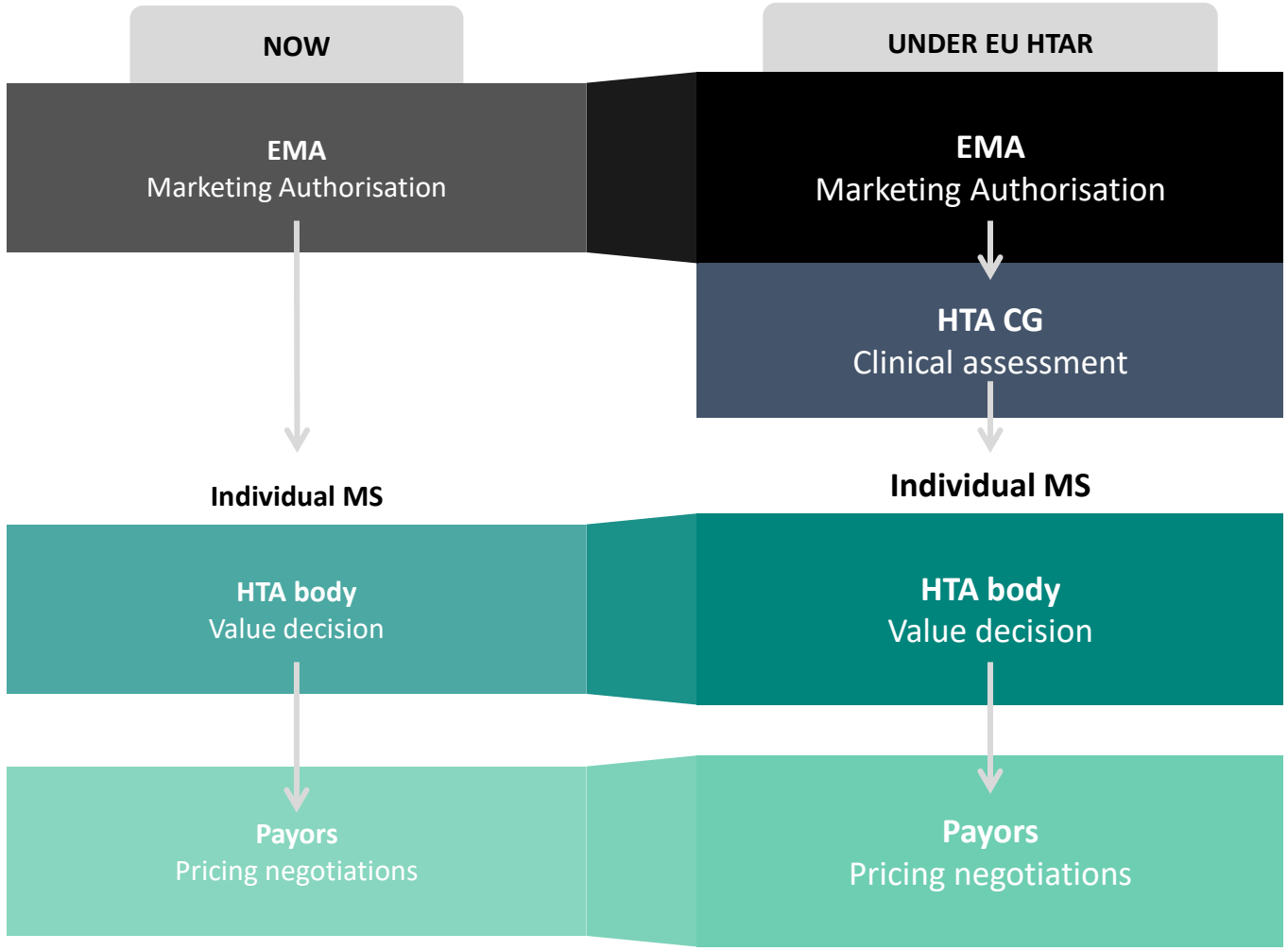
Ambition of EU: Faster and more equitable access across Europe, through higher quality and more efficient HTA across the union

EU, European Union; HTA, Health Technology Assessment; HTAR, Health Technology Assessment Regulation; JCA, Joint Clinical Assessment; MS, Member State.

What does a centralised clinical assessment look like?

Objectives of EU HTAR:

- Reduce duplication of efforts for national HTA authorities and industry
- Facilitate business predictability
- Ensure the long-term sustainability of EU HTA cooperation
- Improve Patient Access equity



CG, Coordination Group; EMA, European Medicines Agency; EU, European Union; HTA, Health Technology Assessment; HTAR, Health Technology Assessment Regulation; MS, Member State.

Summary of Key Elements from the EU HTAR

Single ‘core’ submission of clinical information, data, analyses and other evidence required for the joint clinical assessment (JCA); inclusive of all 27 EU MS needs for data

Joint Clinical Assessment (JCA) report as input into national HTA processes (requirement to “give due consideration”) – **Value decision and health economics** remains at national level

Joint Scientific Consultation (JSC) is an opportunity for the manufacturer to request early HTA scientific advice (with or without parallel EMA advice)

EMA, European Medicines Agency; EU, European Union; HTA, Health Technology Assessment; JCA, Joint Clinical Assessment.

JCA and PICOs

The Assessment Scope for JCA→ PICOs

The assessment scope should include all relevant parameters in terms of the PICO scheme:

- **P**atient population
- **I**ntervention
- **C**omparator(s)
- **O**utcomes

PICO selection is policy-driven, not evidence-driven.

MS should determine their PICO need(s) and a consolidation of requirements should happen

- Timepoint: ~90 days after regulatory submission

CONSEQUENCES

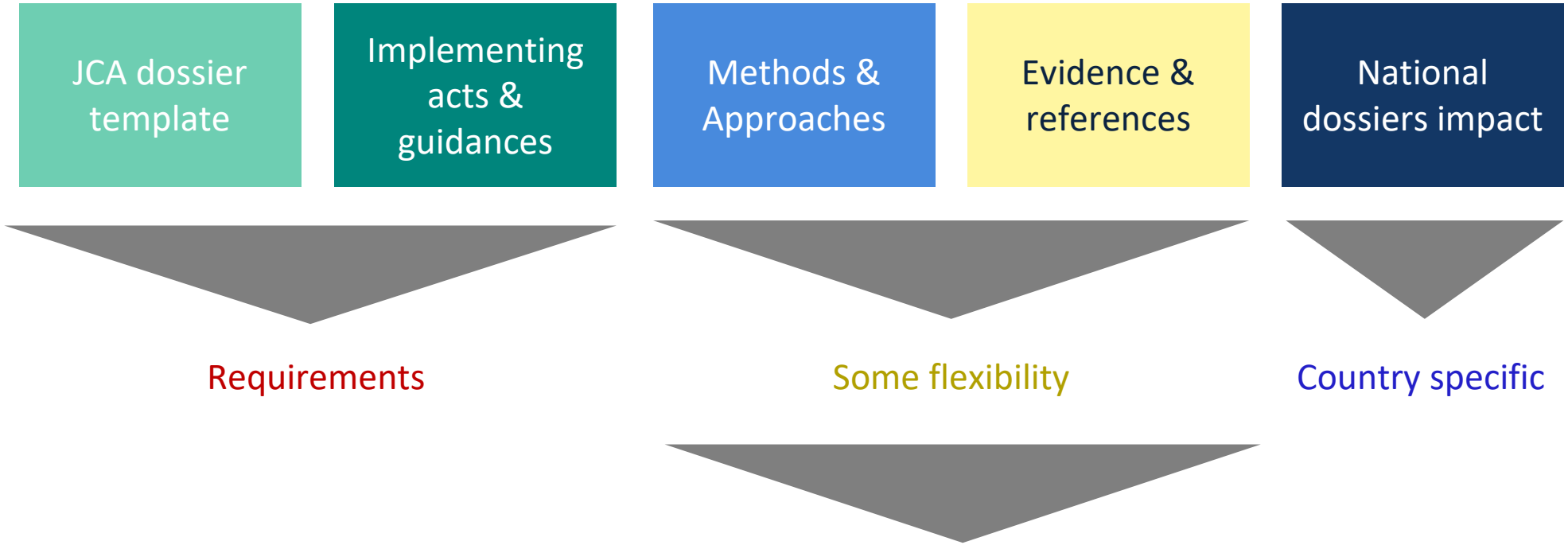
- **More comparisons than in PhIII trials may be requested - substantial volume of indirect treatment comparisons will be necessary**
- Data will become publicly available shortly after regulatory approval
- There can be more PICOs at the national level “delta dossiers”!

CHALLENGES

- **Drug Developers are not involved in PICO determination process (sits at EU level)**
- PICOs **must be estimated internally** for JCA dossier planning
- **High number** of PICOs may be requested for JCA

EU, European Union; JCA, Joint Clinical Assessment; MS, Member State; PICO, Population, Intervention, Comparator(s), Outcomes.

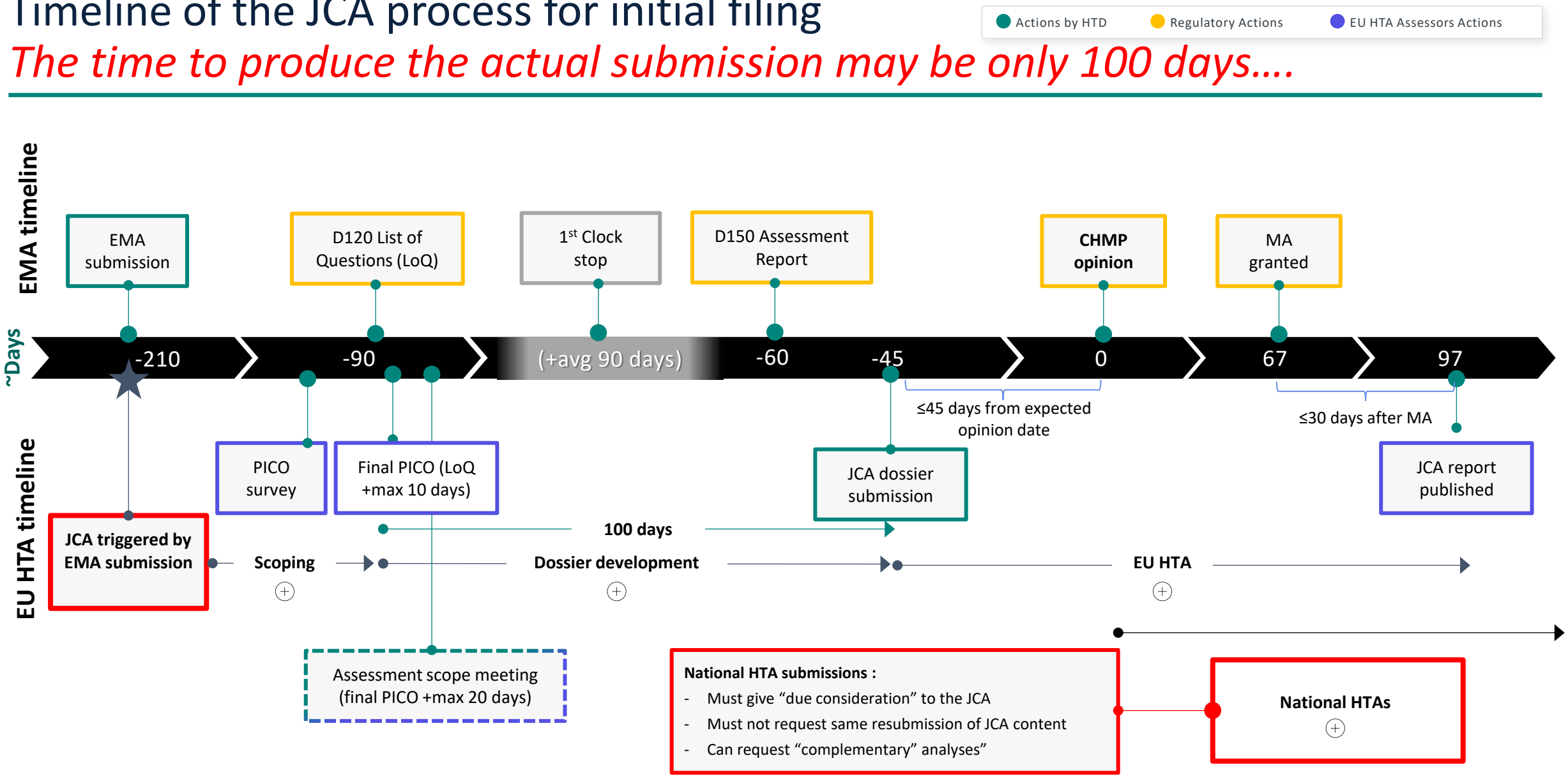
JCA dossier generation: general & project specific considerations



Key requirements: All Statistical Analysis Plans (SAPs) need to be included in the JCA Submission!

Timeline of the JCA process for initial filing

The time to produce the actual submission may be only 100 days….



CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; EU, European Union; HTA, Health Technology Assessment; HTD, Health Technology Developer, JCA, Joint Clinical Assessment; MA, marketing authorization; PICO, Population, Intervention, Comparator(s), Outcomes. LoQ = List of Questions

There will be **A LOT of** Indirect Treatment Comparisons!

Direct evidence on comparators of HTA interest may not be available! Understand your PICOs!

The assessment scope for EU HTA will be based on all the PICOs :

- **P**atient population
- **I**ntervention
- **C**omparator(s)
- **O**utcomes

PICO selection is policy-driven, not evidence-driven.

Member States should determine their PICO need(s) and a consolidation of requirements should happen, approximately ~90-140 days after regulatory submission

EFPIA-Evidera Simulation of EU HTA JCA Process for 3 Oncology Products*:

Category	Product X	Product Y	Product Z
Populations	2	10	10
Comparators	15	8	23
Outcome Categories	5	7	5
Consolidated PICOs	7-16	6-22	23-57

*"Meta-analysis and ITCs will be critical to meet the evidence development requirements of likely multiple PICOs outlined in a JCA scope"**

* Source: https://www.efpia.eu/media/qrjah2ij/efpia-evidera-research-on-eunethta21-methods.pdf

But ALSO -- PICOs will mean different things to different people!

This is an illustrative over-generalization!

1

Preparer

Drug Developer

Population:

As broad as possible

Comparator:

Placebo/Standard of Care

Outcomes:

Required to demonstrate risk-benefit (agreed with regulator)

2

APprover

Regulator

Population:

ITT – as long as no imbalances in safety/efficacy

Comparator:

Placebo/Standard of Care

Outcomes:

As agreed in trial design

3

Payor /HTA

Population:

Driven by the regulatory approval in the context of local treatment landscape

Comparator:

Current standard of care per population

Outcomes:

Very extensive look across many dimensiosn!

4

Provider

Population:

Broken up by the testing/categorization available to them and the type of patients they treat.

Comparator:

Current reimbursed treatments they've used before

Outcomes:

Will vary across providers!

5

Patient

Population:

ME. The population is ME.

Comparator:

Everything possible.

Outcomes:

Will have own unique preferences about tradeoffs across outcomes!

So what will proper prior planning look like?

And why are you calling it “Pre-specified post-hoc analysis of PICOs”?

How do we address the needs of all these stakeholders…..and be “SMART” about it?

https://cdn2.hubspot.net/hubfs/4993491/SMART-digital-resource-2.jpg

Requirement to have (HTA) SAPs

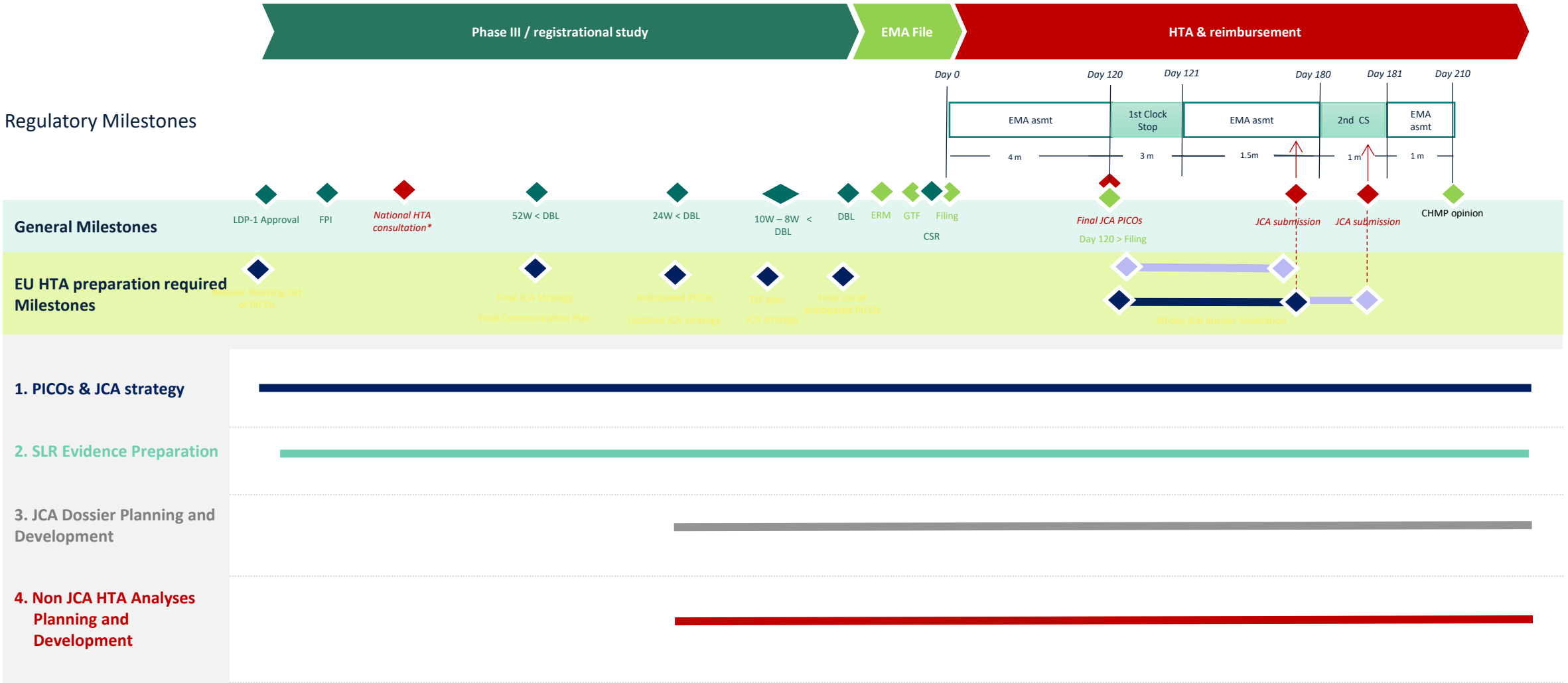
“Post-hoc” analysis in this case means post-hoc to alpha allocation in the trial (and not in the trial SAP)

“Pre-specified” is referring to specifying the analysis per PICO BEFORE database lock – but not necessarily at the time of protocol development!

For ITC’s, one big concern: SLR data must be current within 90 days of submission!

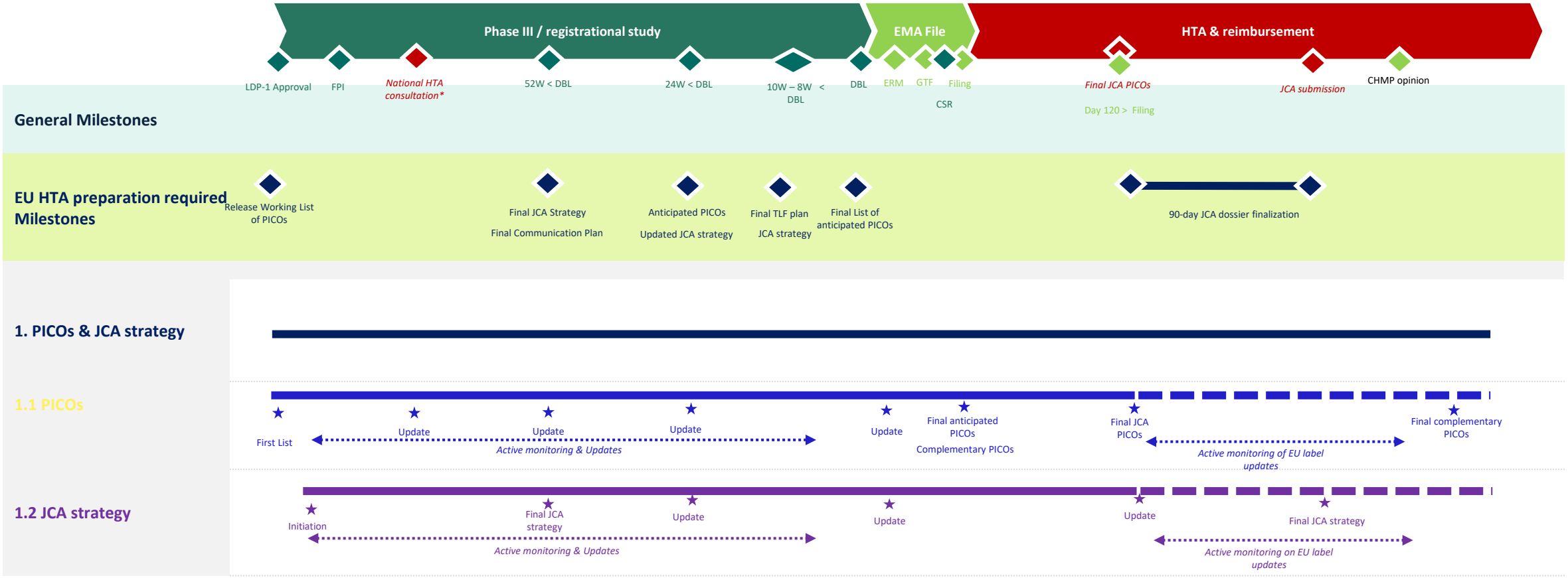
Why “Pre-specified post-hoc analysis”?

What is “Proper Prior Planning” going to look like?
One View! of General and EU HTA Milestones

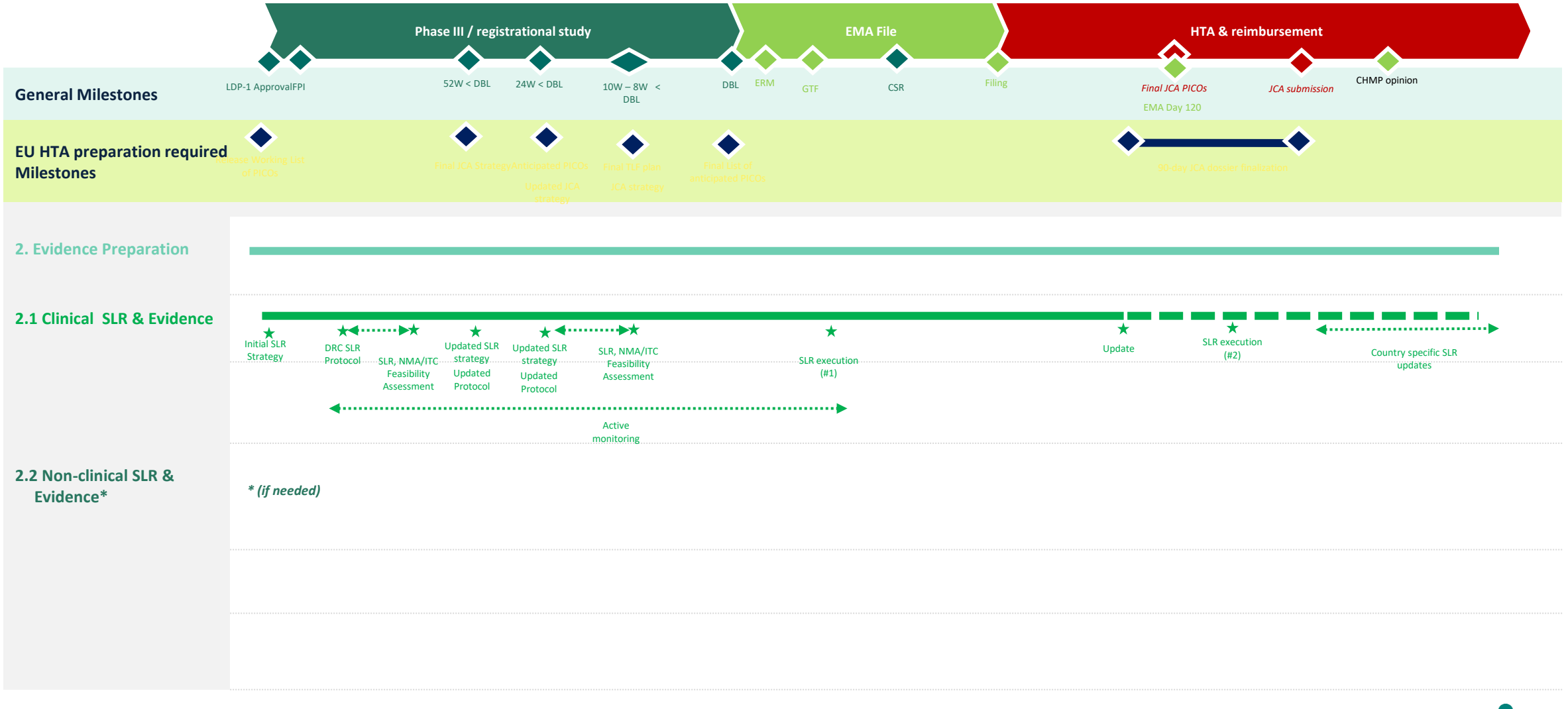


Anticipation: Planning for the Universe of PICOS and Analyses

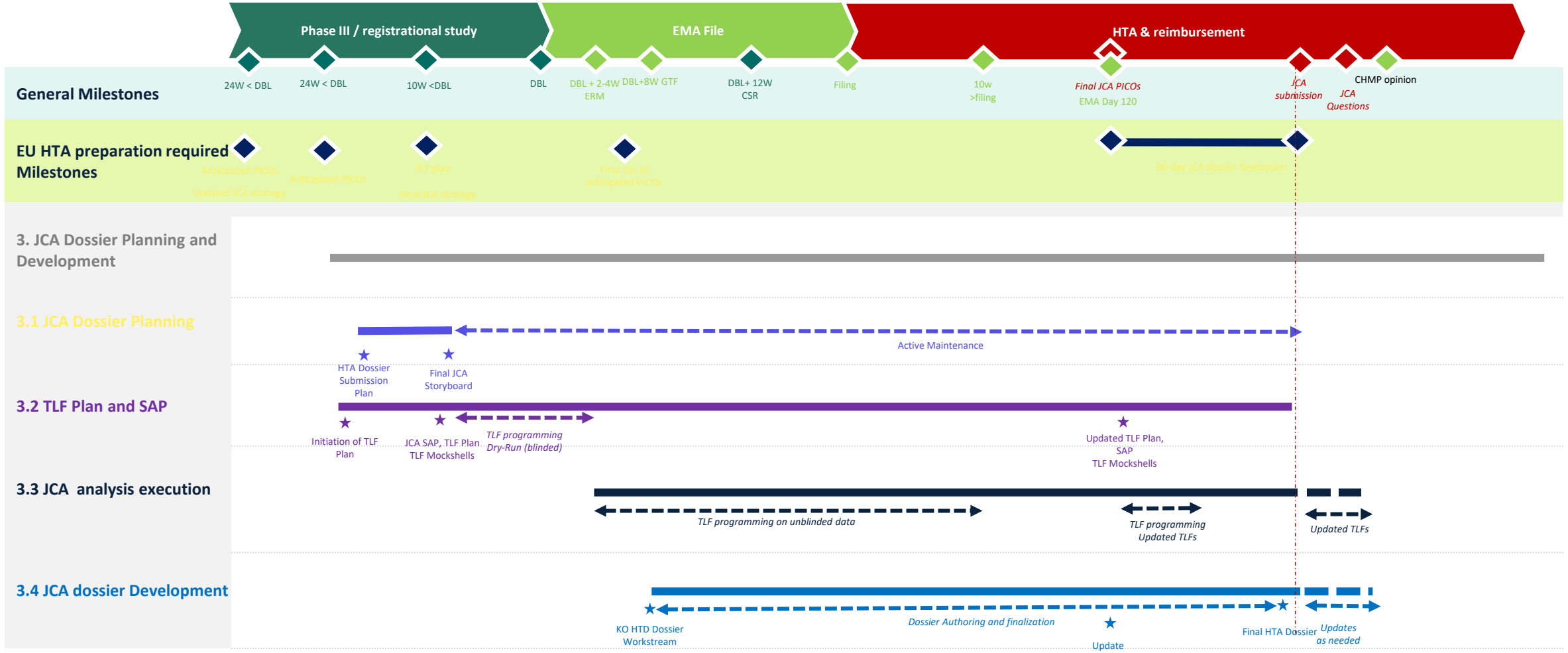
PICOs and JCA strategy



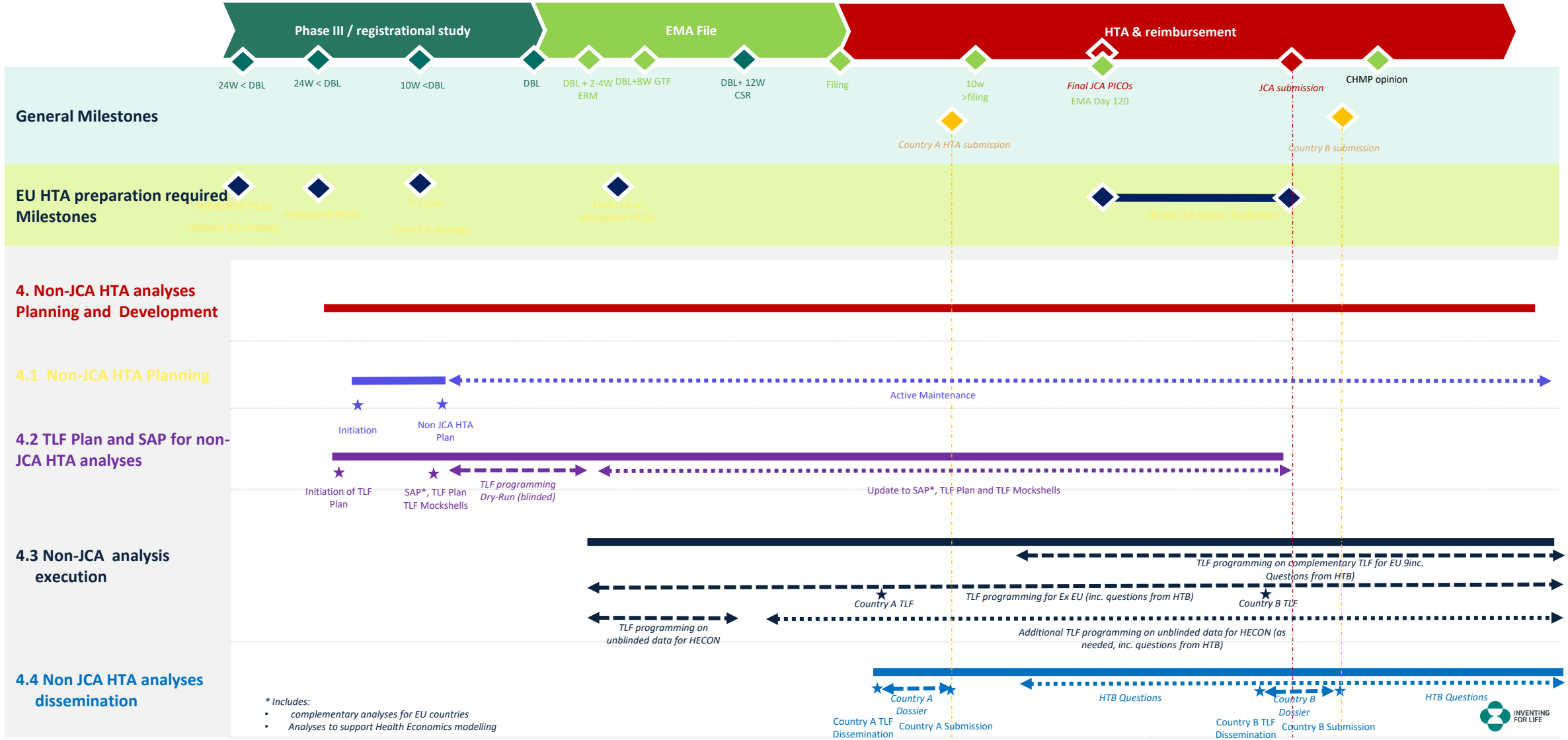
Planning for bringing in SLR data for indirect treatment comparisons
Evidence Preparation



Delivery – Finalizing the SAP, Executing the Analysis
JCA Dossier Planning and Development



It's not over until it's over – National Submissions! ("Delta Dossiers")
Non-JCA* HTA analyses planning and Development



Are there some recommended best practices?

Key Process Steps for Conducting an ITC: It's all about good planning for the SLR – and having an SAP

This slide outlines key process steps that should be performed for robust ITC evidence-generation to meet external requirements for impactful HTA.

Identification of effect modifiers and prognostic variables

[Pre SLR] Preliminary ITC SAP written

Ensure relevant information is being collected in the SLR

ITC Analytical Feasibility Assessment (incl. evaluation of similarity assumption)

ITC Method Selection*

[Post SLR] ITC SAP finalized reflecting ITC analytical feasibility assessment

ITC

PICO Definition | Data collection (SLR) | Data analysis (Indirect treatment comparison) | Communication

PICO → ITC Planning → Data Collection → ITC Feasibility assessment → ITC Analysis Planning → ITC Analysis Execution → ITC Results Interpretation → ITC Results Dissemination

SLR/ITC/NMA Protocol Pre-SLR ITC SAP | *SLR conduct* | **SLR Report** | **Final ITC SAP** | *ITC conduct* | **ITC Report**

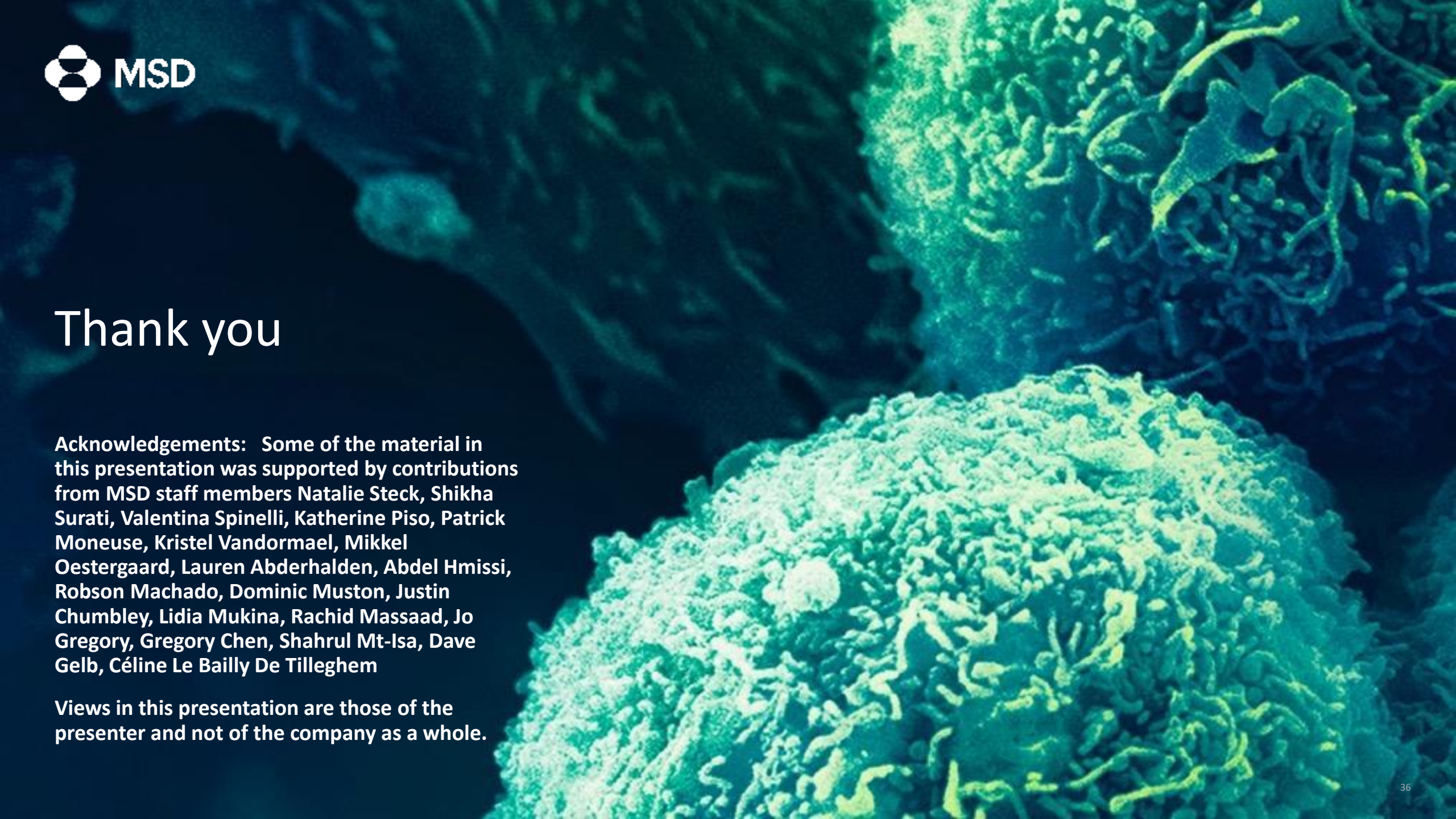
Don't forget that all protocols, SAPs, and possibly, programming code, are part of the EU HTA JCA Submission!

Image Credit: https://www.ranzey.com/generators/bart/index.html

Key Takeaways

- Proper prior planning for HTA is essential
- The use of indirect treatment comparisons is critical for value assessment
- Different HTA bodies have different requirements and preferences – plan for flexibility!
- Clear and transparent disclosure is key to building trust
- Define the differences between regulatory and HTA nomenclature of “pre-specified” and “post-hoc”

ANTICIPATE YOUR PICOS!



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