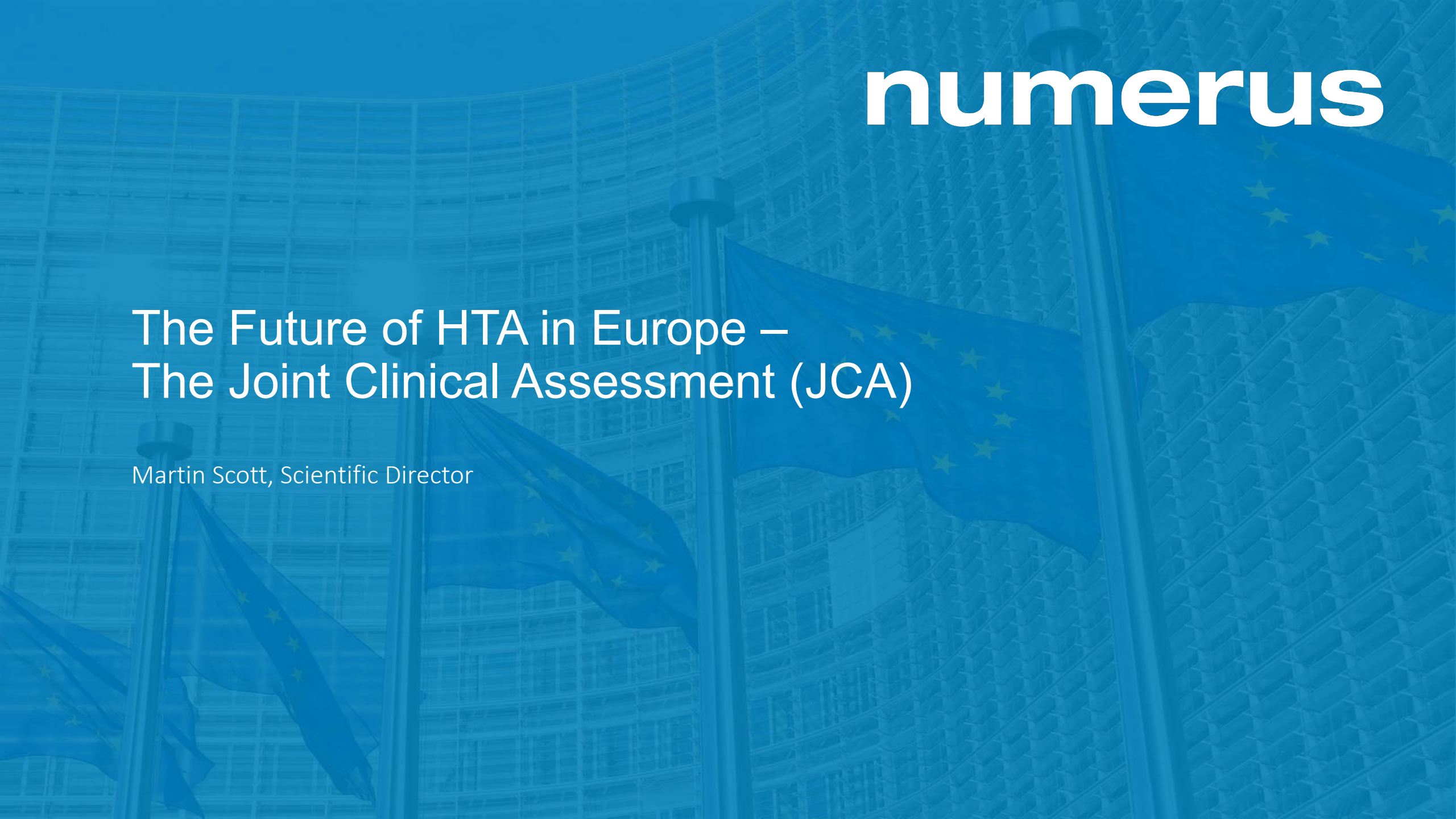

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The Future of HTA in Europe – The Joint Clinical Assessment (JCA)

Martin Scott, Scientific Director

EU HTA Regulation

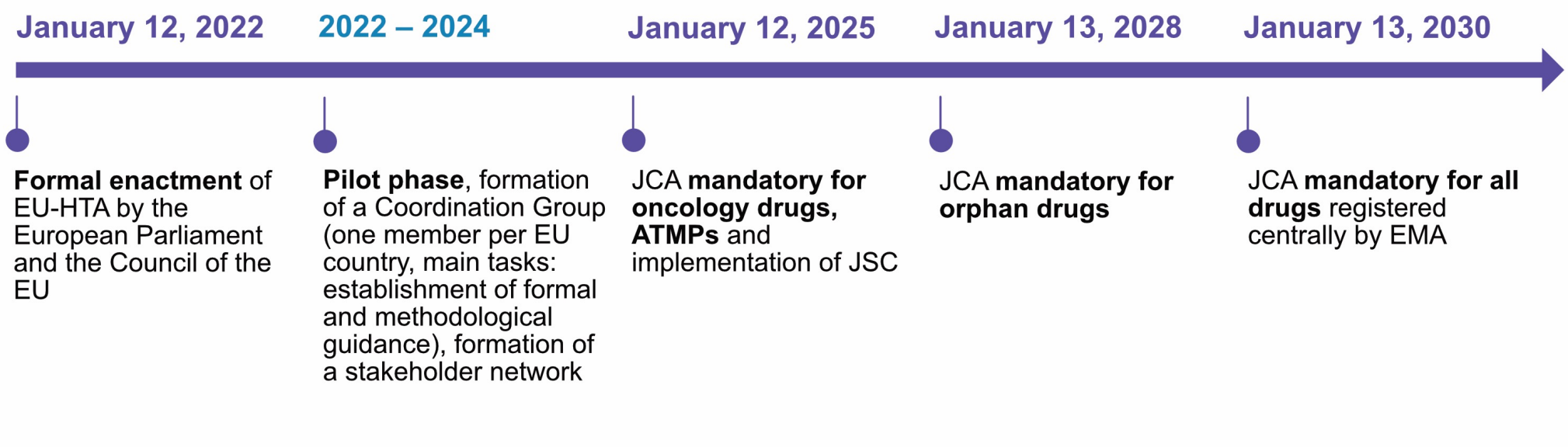
- Regulation foresees that all information, data, analyses of evidence be contained in a joint clinical assessment (JCA) to be submitted only once at Union level by the health technology developer.
- The JCA should
  - include a description of the relative effects observed for the health outcomes analysed, including numerical results and confidence intervals, and an analysis of scientific uncertainty
  - include the strengths and limitations of the evidence (for example, internal and external validity).
  - be a factual scientific analysis and should not contain any value judgement

➢ Fixing of criteria for pricing and reimbursement decisions remain solely a matter of national competence.

EU HTA Regulation

- In the context of this Regulation, the term "give due consideration", when applied to a joint clinical assessment report, means that the report should be considered for any HTA at Member State level.
- The JCA should be part of the documentation that supports the national HTA process. However, the content of the joint clinical assessment report is scientific in nature and should not be binding on those authorities or bodies or on Member States.
- Member States should be able to perform complementary clinical analyses…including those related to patient groups, comparators or health outcomes other than those included in the JCA report, or using a different methodology.

European Regulation - Timing



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EUnetHTA 21 – Guidelines

- D4.2 - Scoping Process
- D4.3 - Direct and Indirect Comparisons
  - D4.3.1 - Practical Guideline Direct and Indirect Comparisons
  - D4.3.2 - Methodological Guideline on Direct and indirect comparisons
- D4.4 - Endpoints
- D4.5 - Applicability of Evidence – multiplicity, subgroup, sensitivity & post-hoc analyses
- D4.6 - Validity of Clinical Studies
- D5.1 - JCA Submission Dossier Template

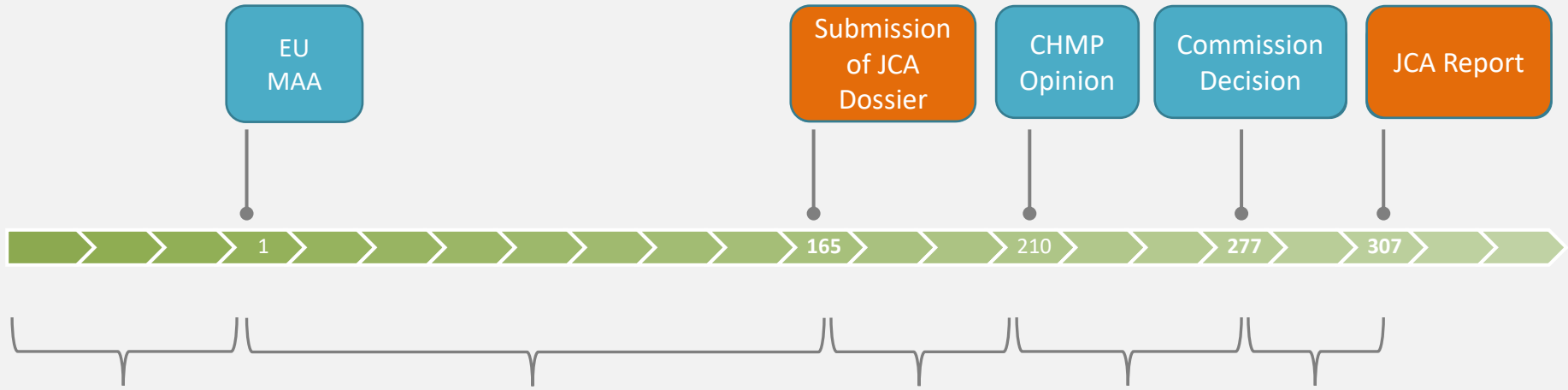
https://www.eunethta.eu/jointhtawork/

EUnetHTA 21 - Guidelines

- Guidelines intended to support the member state assessors in their decisions and assessment evaluations
  - Not intended to be prescriptive or “recipe” for the HTD
  - Generally very vague (i.e. ”one should/can consider….”)
  - Summary of best practice

https://www.eunethta.eu/jointhtawork/

Standard MAA and JCA Timelines



Presentation - Centralised procedure at the European Medicines Agency (europa.eu)

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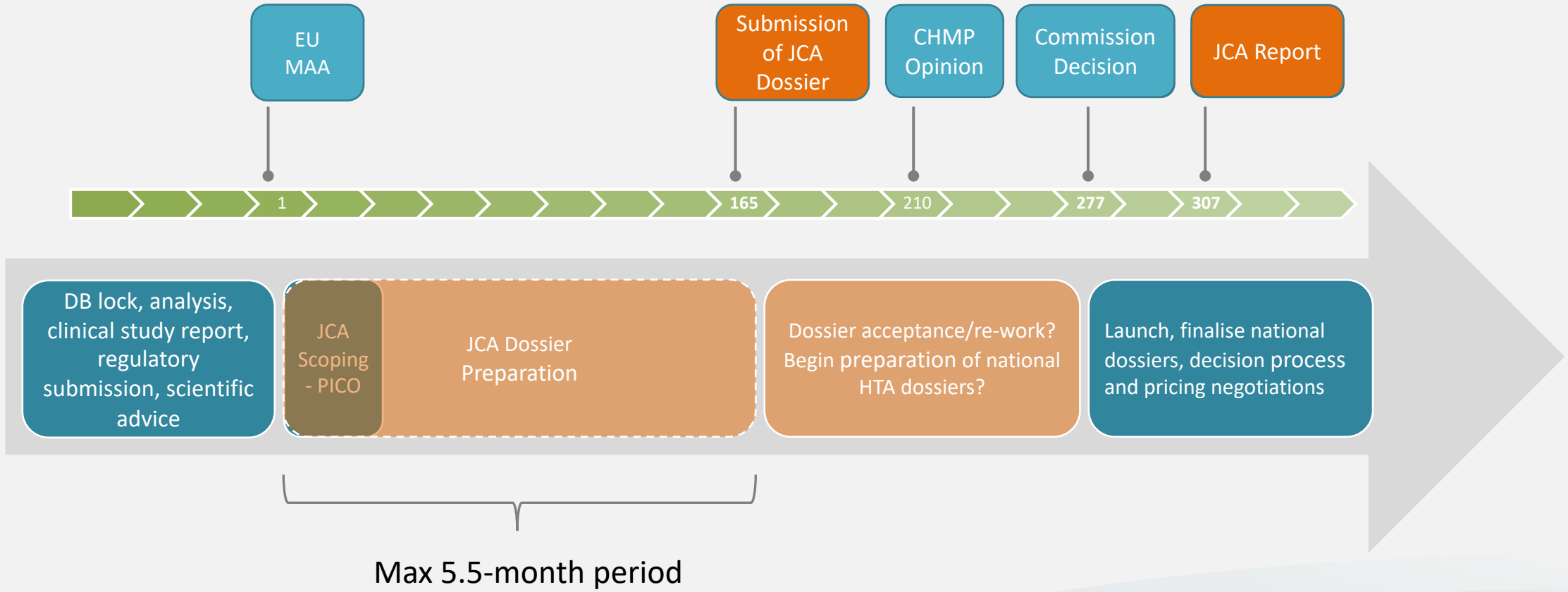
Standard MAA and JCA Timelines



[Presentation - Centralised procedure at the European Medicines Agency (europa.eu)]

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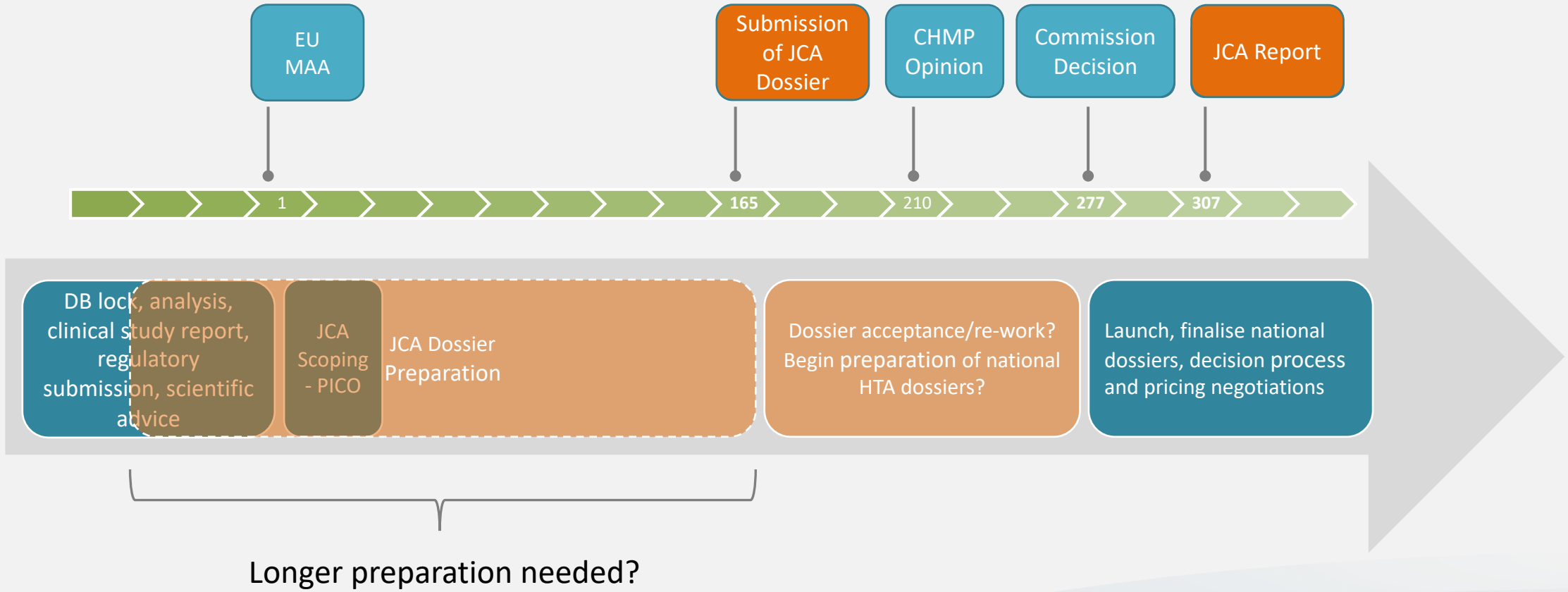
Standard MAA and JCA Timelines



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Evidence Generation (PICOs)

Populations | Comparators

Outcomes

Intervention should be known. Posology?

To be determined during the Scoping Phase!

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Potential Evidence Shortfalls

- Population
  - Does not adhere to local, national practice, or label
    - Possibility of building a sub-population? Randomised? Sample size problems? – Power?
- Comparator
  - Additional treatment arms
  - External control arm for single arm trials
- Outcomes
  - Acceptance of biomarker/surrogates e.g. (PFS, tumour response rates, etc..)?
  - Immature data / follow-up too short e.g. < 6 months – low power
  - AEs not collected in a true ITT principle
  - Wrong estimand used – incompatible trial design

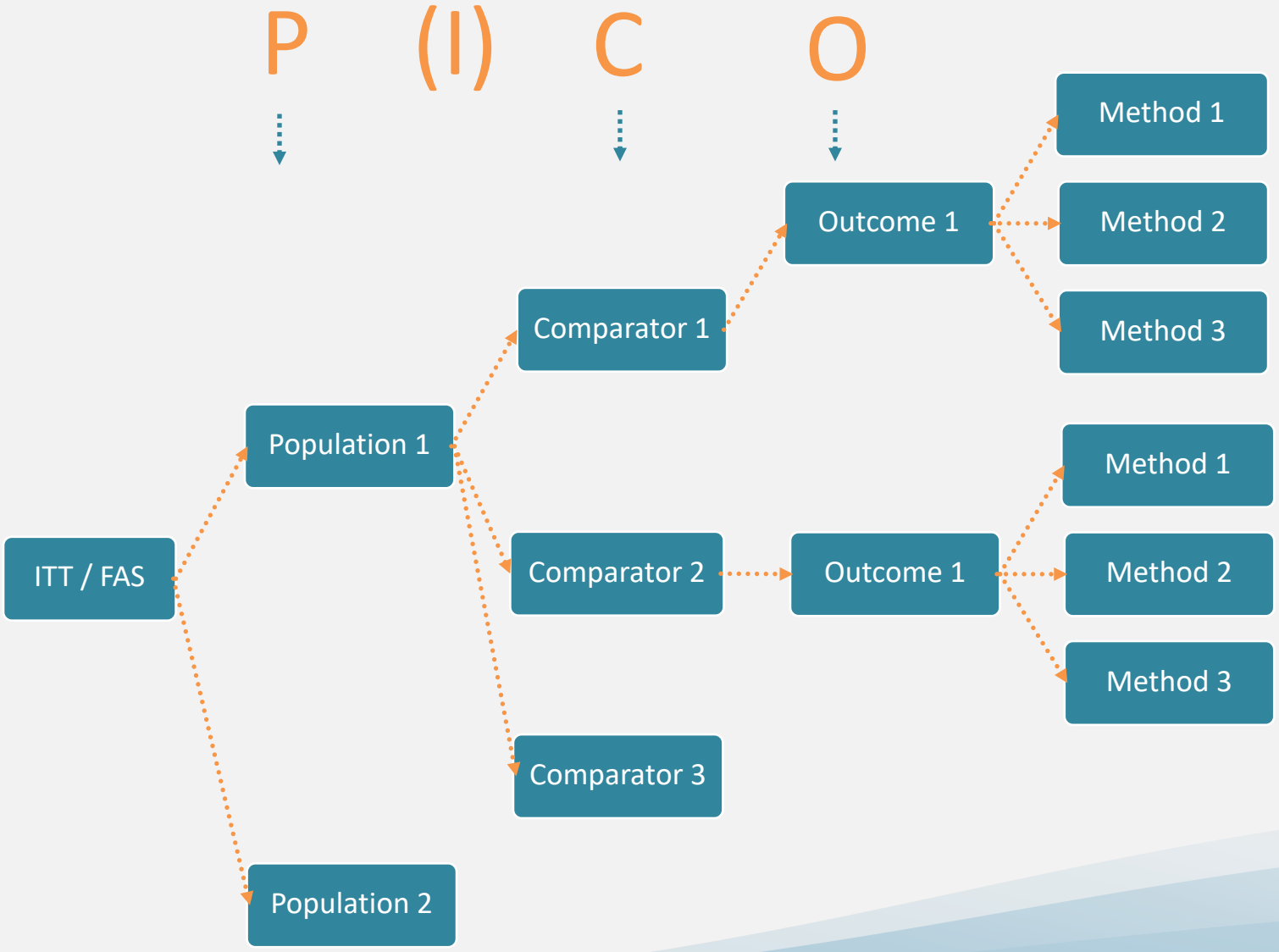
Analyses Unknowns

- Multiple estimands for each endpoint?
  - Eg Treatment policy vs Hypothetical vs On Treatment.
  - General handling of intercurrent events and missing data
- Subgroup analyses for all endpoints?
  - Post hoc or only a priori?
  - All safety outcomes?
  - Adjustments for multiplicity?
- Comprehensive “AMNOG style” safety analysis?
  - Including estimates of RR, OR and RD, confidence intervals and p-values for all preferred terms, SOCs and aggregated classes (e.g. SAEs, CTC >=3, AES l/t discontinuation, etc..)
  - Time to event analyses (including all KM graphs)
- Indirect treatment comparisons
  - General acceptance of ITCs or not
  - Acceptance of some methods over others (Bucher, NMA, STC, MAIC,…)

Analysis Unknowns

- Multiplicity and transparency
  - Adjust or not
- Inclusion of RWD
  - Incorporated into randomised design; or as
  - External ‘control’
  - Quantifying bias assessment (QBA), tipping point analyses

Exponential Expansion of Analyses



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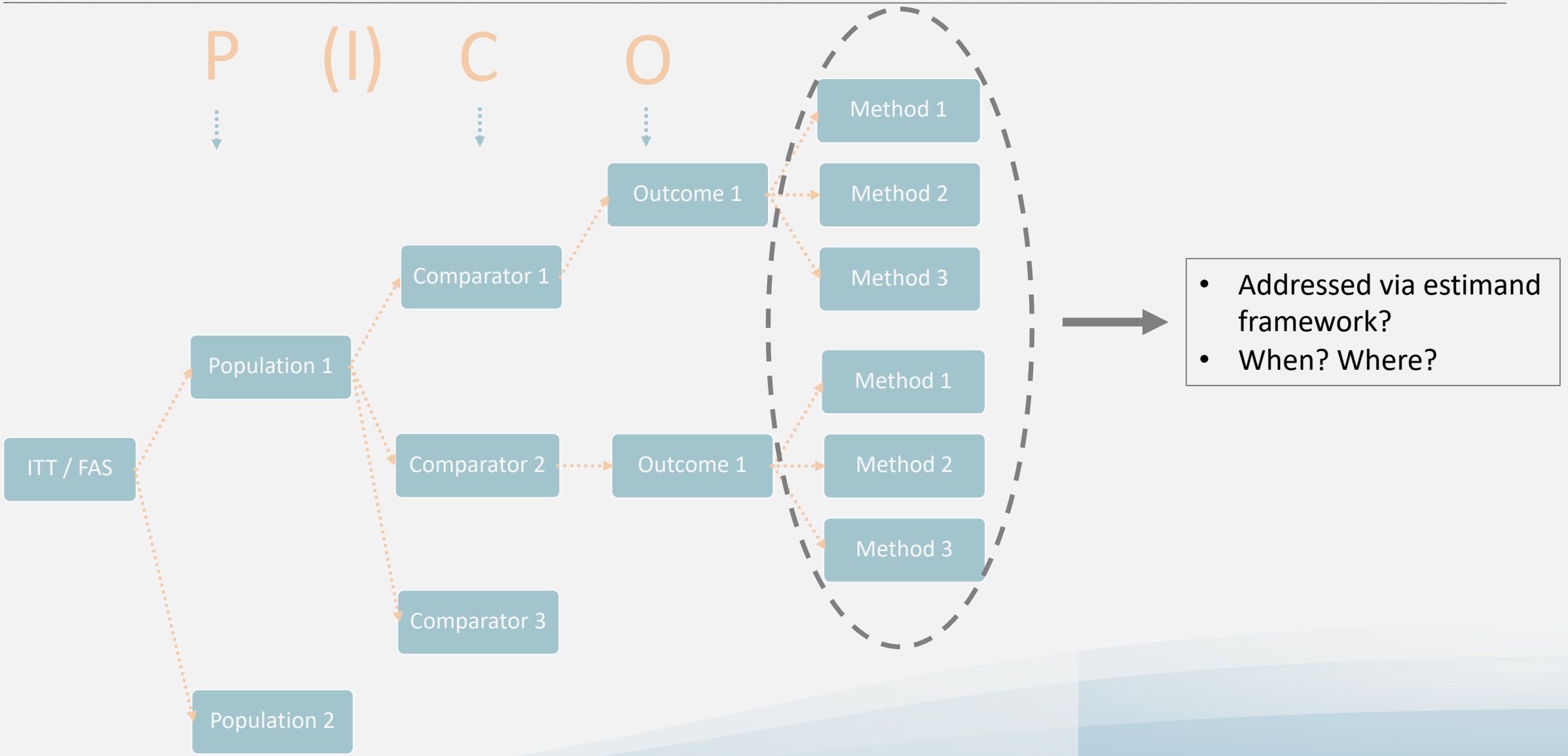
Exponential Expansion of Analyses



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Unknowns become Known During Scoping?

- Last minute re-analysis for multiple stakeholders

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Summary

- EU JCA starts in January 2025 for oncology drugs and ATMPs
- Current EUnetHTA 21 guidelines on methods are ‘final’, but very vague and represent a least common denominator of scientific consensus – we will see a tightening up?
- The current scoping process of member states will likely result in many PICOs and the need to conduct 100s of analyses

Summary

- The JCA timelines are inextricably linked to those of the marketing authorisation -> evidence submitted much earlier than currently

Points for Sponsors to Consider

- Early planning of potential PICOs and their respective analyses will be necessary (e.g. begin phase III?).
- Reach out to local HTA early on (formalised in the form of early scientific advice?)
- Risk management by generating more evidence during phase III (e.g. > 1 comparators, QoL response endpoints)