8th EFSPI Regulatory Statistics Workshop

Basel, 13th September 2023

Update on Joint HTA work under the EU HTA Regulation

Dr David McConnell

Statistician and Senior Heath Technology Assessor, NCPE

Methodology Subgroup of the HTA Coordination Group

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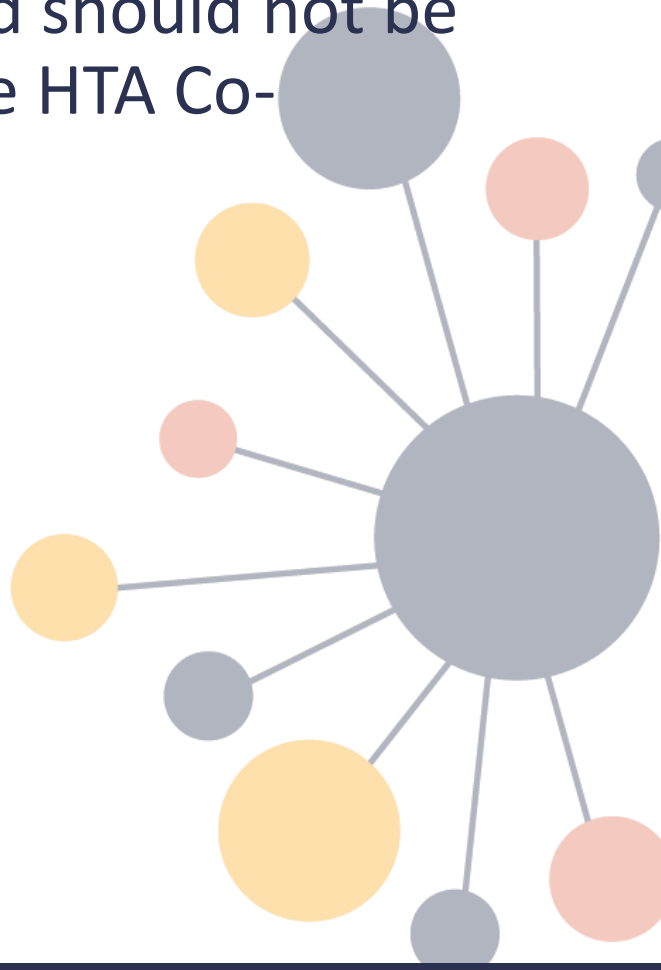
Disclaimer

The views expressed in this presentation are my own and should not be interpreted as representing the position of the NCPE, the HTA Co-ordination Group, or the EUnetHTA21 consortium



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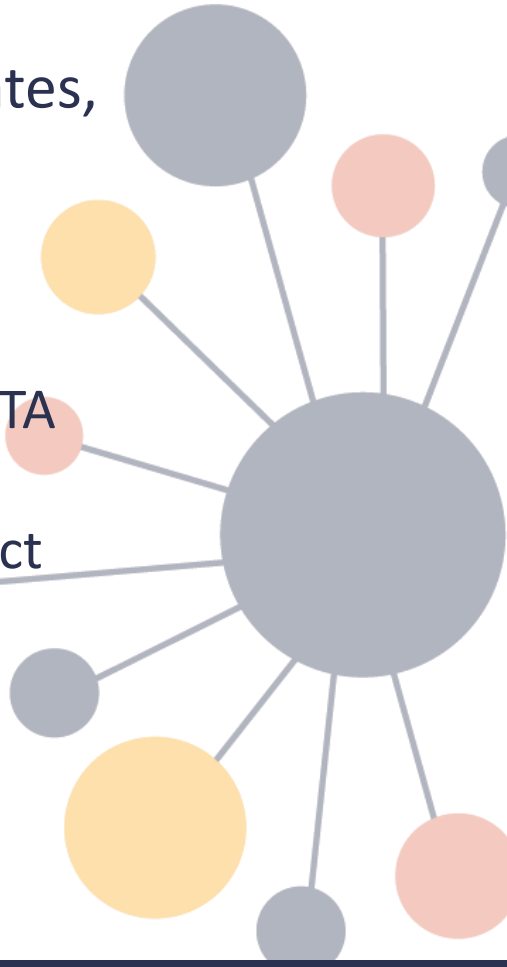
EU Health Technology Assessment Regulation

- The Regulation on HTA (Regulation EU 2021/2282) entered into force in January 2022 and applies as of January 2025
- Establishes a framework for co-operation on HTA across member states, including:

- **Joint Clinical Assessments (JCAs)**
  - European-level relative effectiveness assessment
  - All new medicines, mandatory
  - Gradual introduction from 2025 with oncology and ATMPs

- **Joint Scientific Consultation (JSCs)**
  - Early scientific advice from HTA bodies, in parallel with EMA
  - All medicinal products, subject to prioritisation
  - Voluntary participation from HTDs



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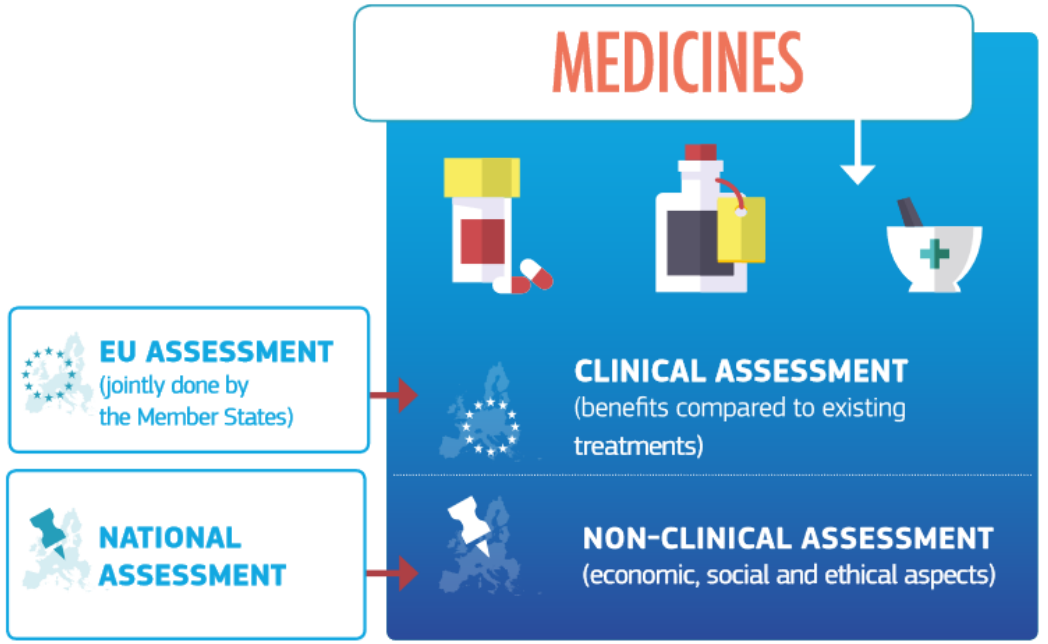
Joint Clinical Assessments

- **Relative (i.e. comparative) clinical effectiveness** of the product being assessed versus relevant comparators
  - Does not include other aspects of HTA such as cost-effectiveness modelling
- Scientific analysis of relative effects, including degree of certainty and strengths and limitations of the evidence
- JCA cannot make 'value judgements,' e.g. conclusions on added benefit – this remains with member states



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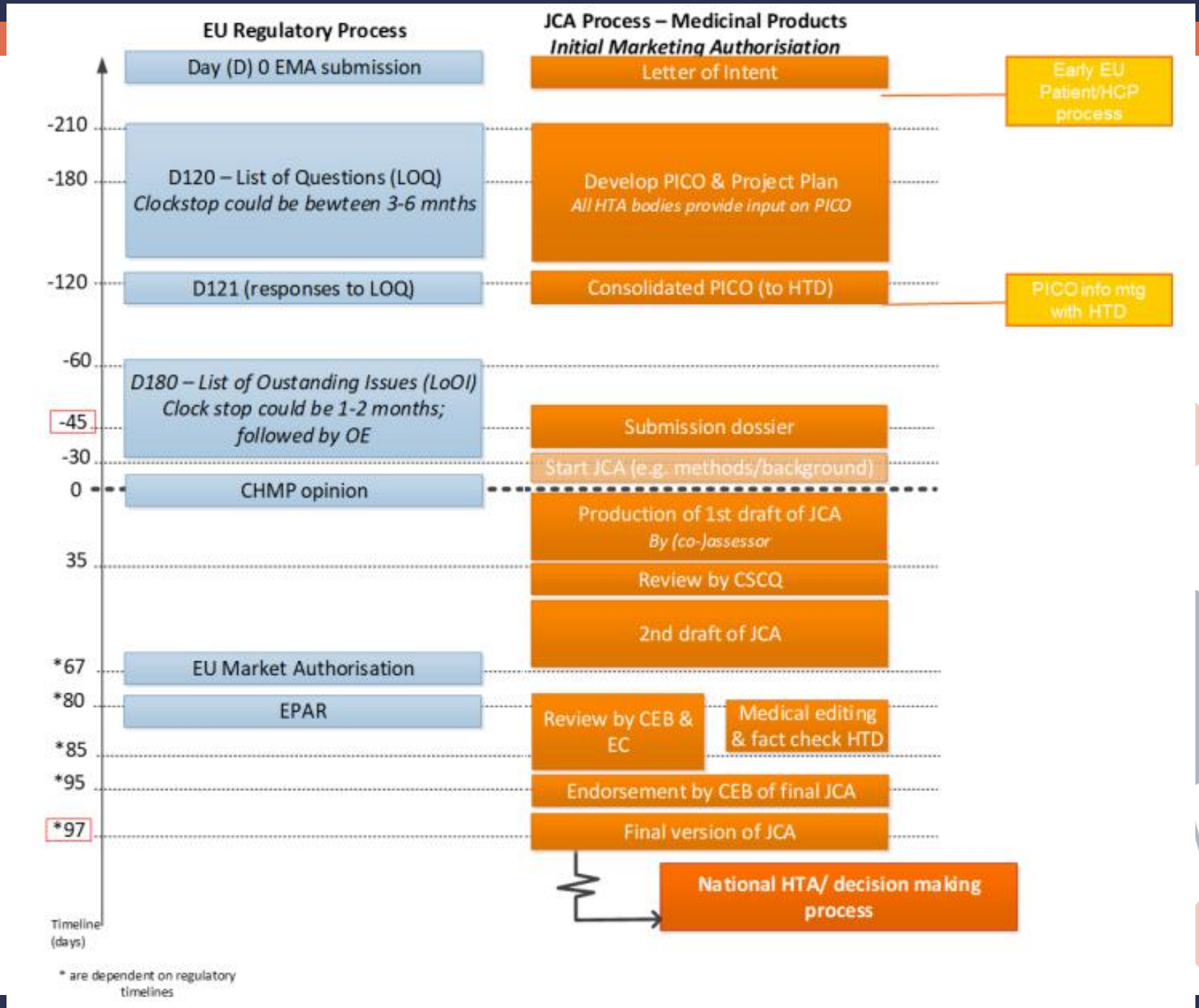
- JCA in parallel with regulatory assessment
- Distinct processes with distinct remits



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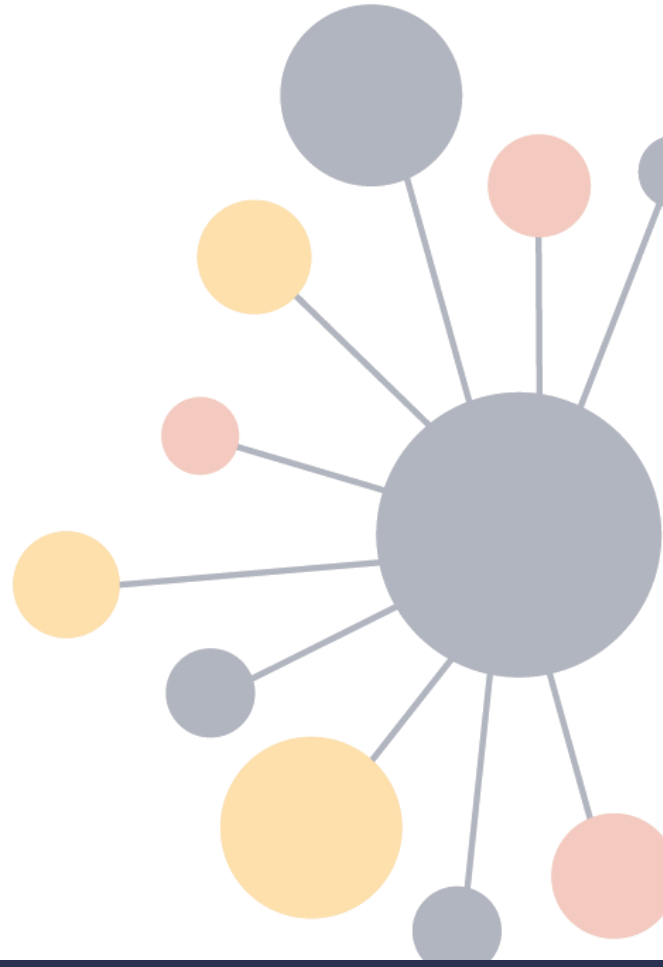
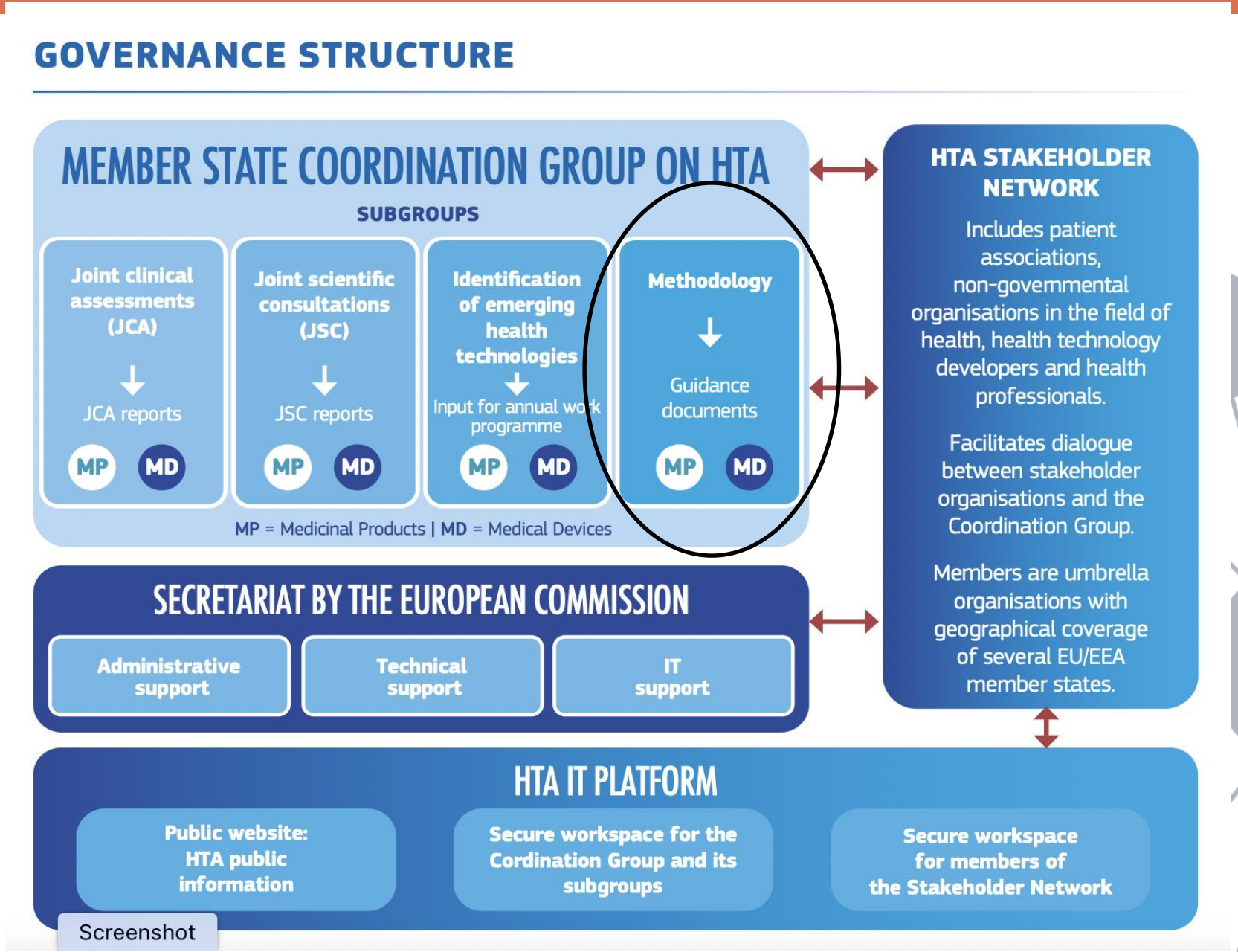
How does HTA differ from regulatory assessment?

- Clinical effectiveness component of HTA often involves greater focus on:
  - Relative effectiveness versus all relevant comparators
    - Evidence synthesis and/or indirect comparisons often required
  - Applicability/generalisability of evidence to clinical practice
    - External validity of trials
    - Different effect measures
    - Effectiveness beyond trial follow-up period
  - Estimation over inference
  - Range of different clinical outcomes
    - Effects of direct relevance to patients – survival, quality of life
    - Outcomes relevant to healthcare systems



2023-24:
Adoption of implementing acts, methodological and procedural guidance

2025:
Application



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Guideline development: EUnetHTA21

- Service Contract for the Provision of Joint Health Technology Assessment (HTA) Work Supporting the Continuation of EU Cooperation on HTA:
  - Guideline development for JCA and JSC
  - Production of JSC
- Deliverables form the basis for methodological and procedural guidance to be adopted by the HTA Coordination Group, and to inform the implementing acts

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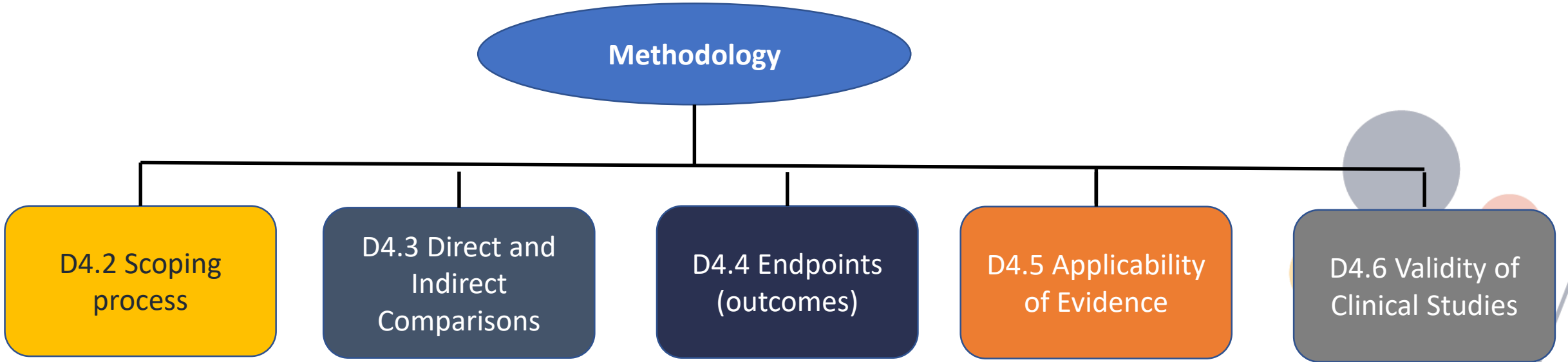
Key EUnetHTA21 Deliverables



Also relevant for this audience…

D5.1 JCA Submission Dossier Guidance

D5.2 JCA Assessment Report Template

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D4.2 – Scoping Process

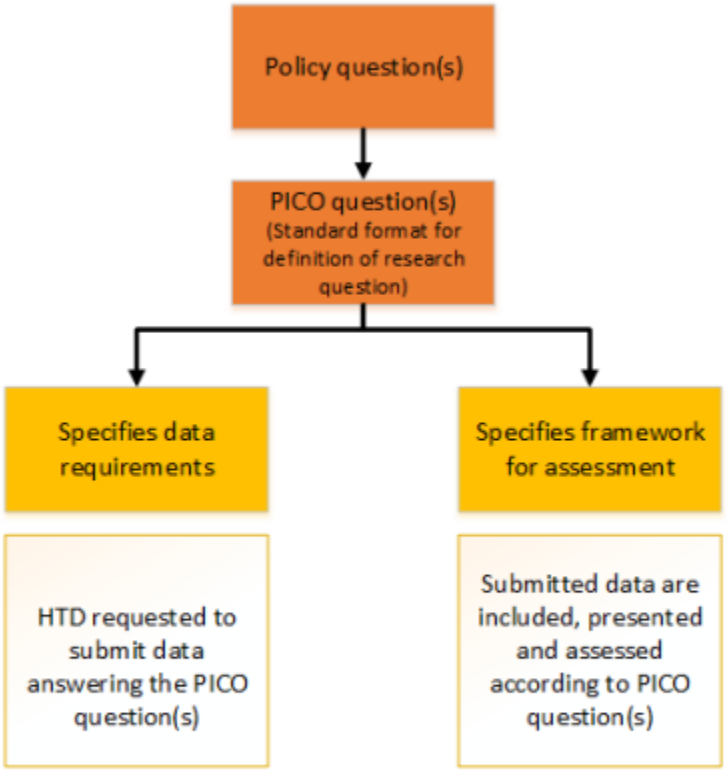
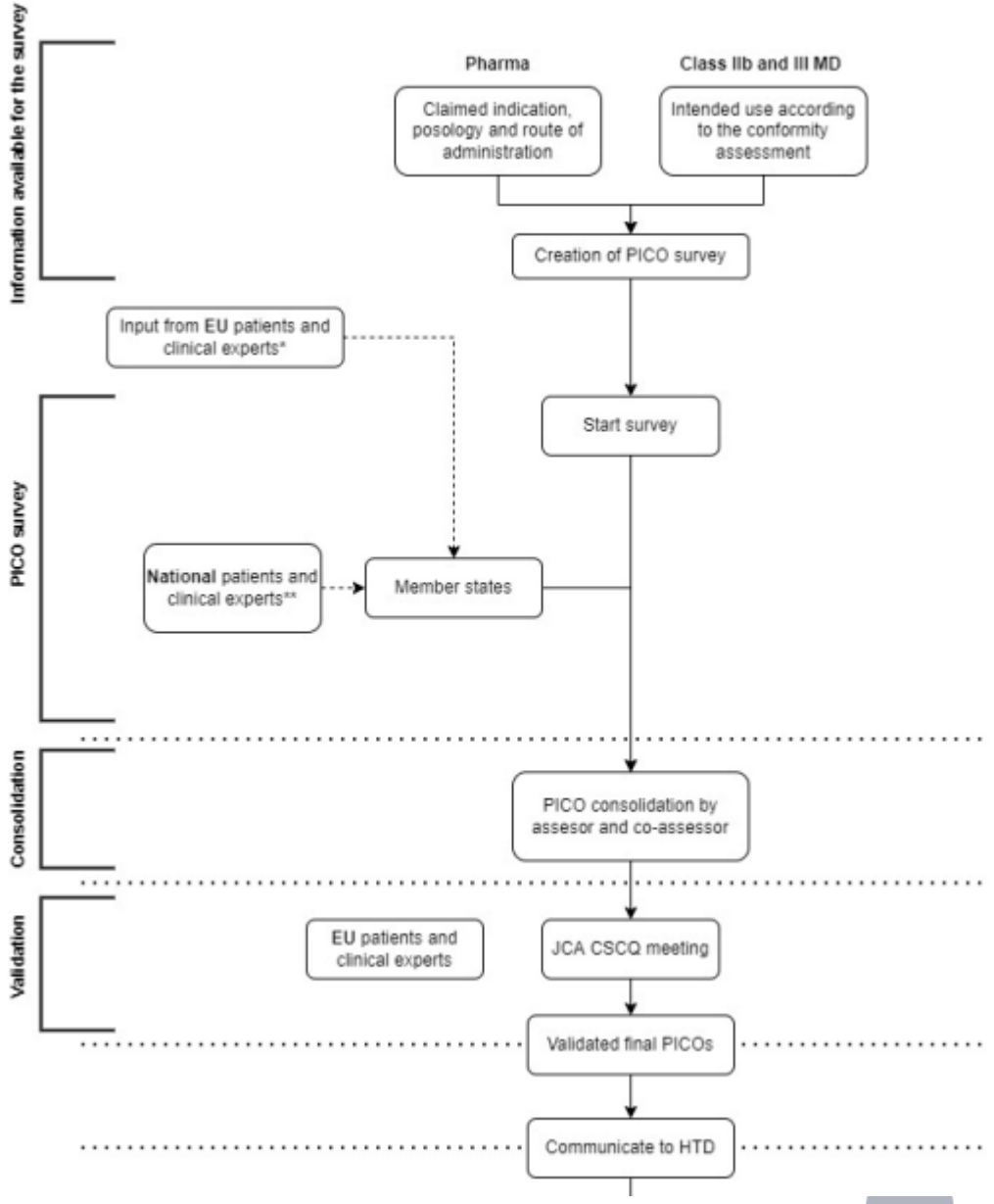


Figure 1-1: Role of the PICO in the assessment
HTD=health technology developer; PICO=Population, Intervention, Comparators, Outcomes.



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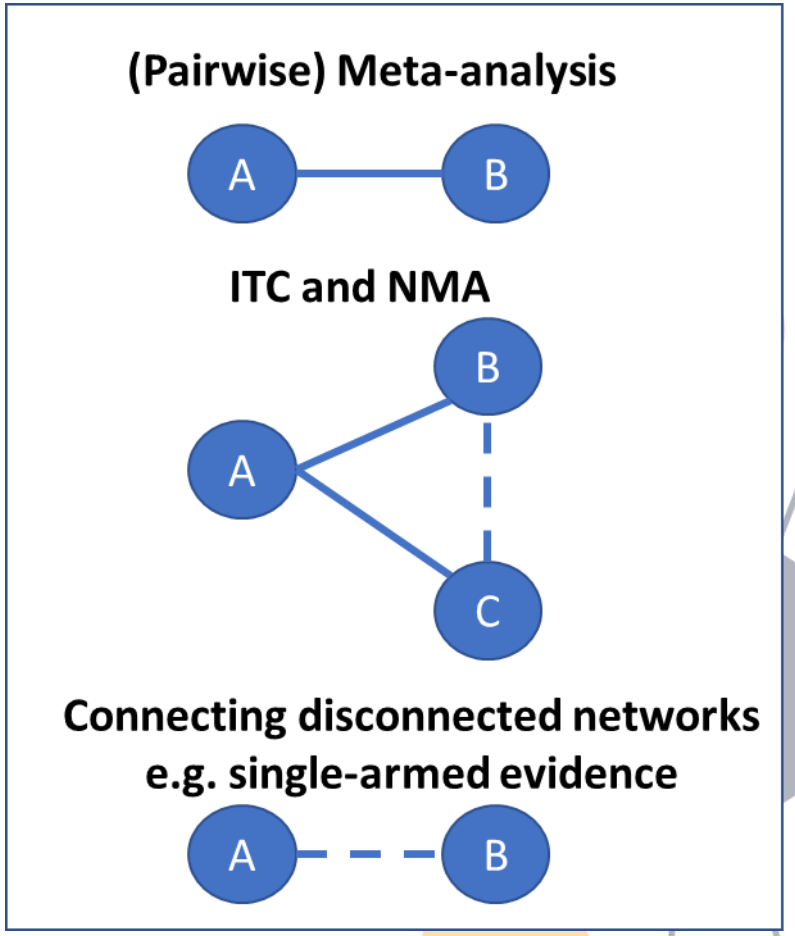
D4.3 - Direct and Indirect Comparisons

Scope: Assessment of quantitative evidence synthesis in JCAs

Outputs: two guidelines aimed at JCA assessors but also of interest to HTDs

- Methodological guideline (update of 2015 document):
  - Assumptions, strengths, weaknesses and applicability of evidence synthesis methods
- Practical Guideline:
  - How to assess the evidence synthesis component of a JCA submission, and report the results.



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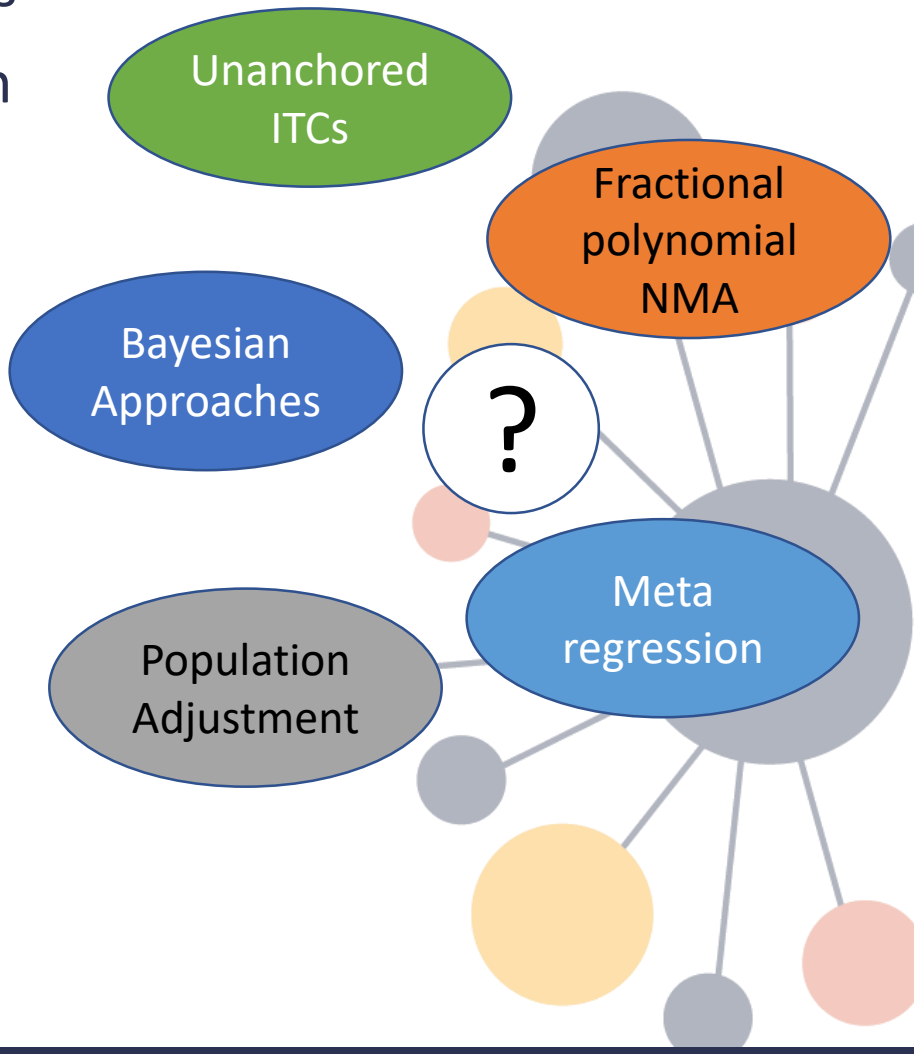
D4.3 – Acceptability of evidence synthesis in JCAs

- Acceptability of methods differs between HTA bodies
- Pragmatic approach: most (reasonable) methods can be of value for JCA in principle, provided underlying **assumptions** hold and target **effect estimate** is relevant
- Onus on **HTD to provide evidence of validity** of analyses that they submit
  - Lack of suitable alternatives does not imply validity!
- JCA will assess the validity and uncertainty of the results
  - acceptability is a decision for individual MS



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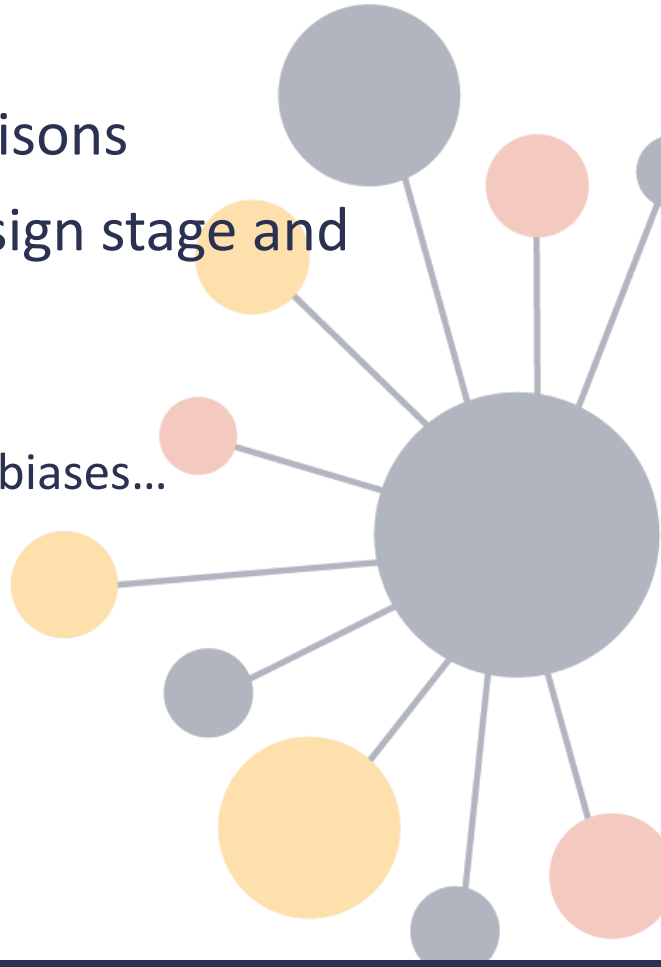
Single-armed trials in the EUnetHTA21 guidelines

- Single-armed trials require **external controls** or un-anchored **indirect treatment comparisons** to estimate relative treatment effects
  - Non-randomised studies, with additional challenges
  - Considerable limitations compared with RCT-based comparisons
- Consider potential need for indirect comparisons at study design stage and plan accordingly – potential role for JSC here
- What can help?
  - Consideration of target estimand, study-level differences, time-related biases…
  - Systematic approach towards confounder identification
  - Pre-specification
  - Availability of IPD (as opposed to aggregate data only)
  - Sensitivity analysis



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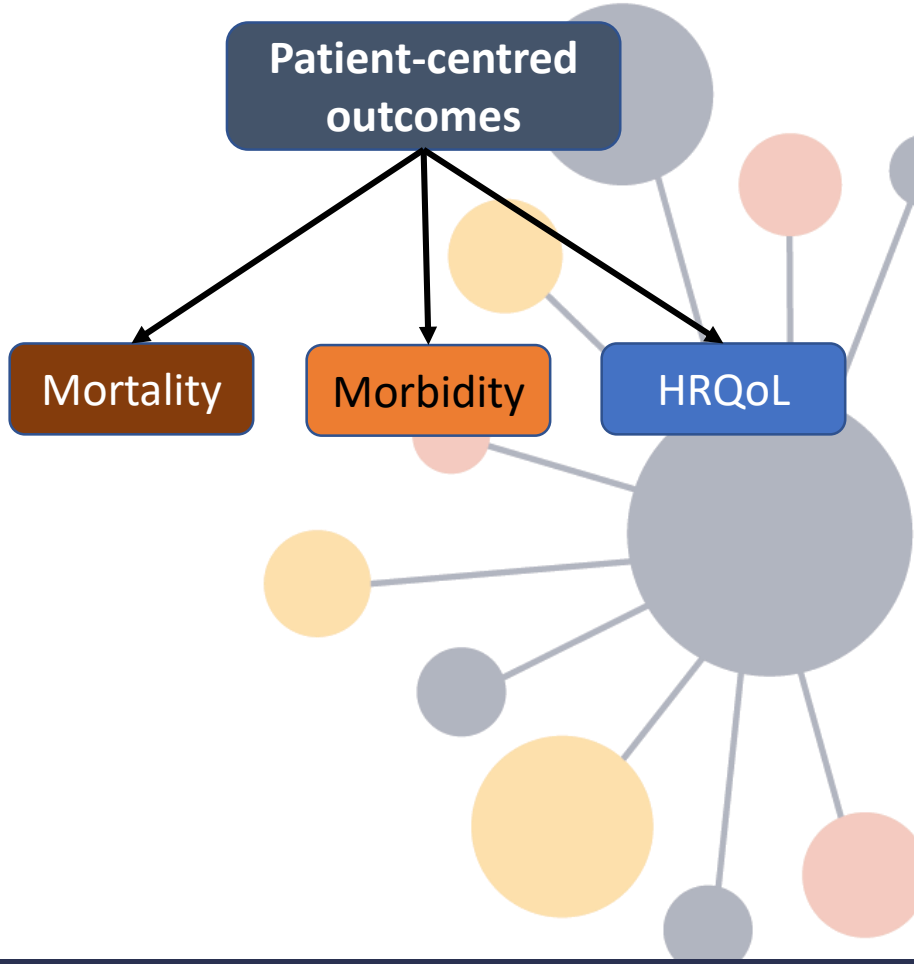
D4.4 Endpoints

- **Guidance for**
  - MS on selecting outcomes during **scoping** process
  - JCA assessors on the **measurement and analysis** of outcomes
- **Selection of outcomes is a matter for MS**
  - Should reflect evidence requirements for national HTA processes
  - Long-term, **patient-centred outcomes,** generally preferable for HTA purposes and should be used where possible
  - Identification of relevant outcomes should involve **patients and clinicians**



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Can surrogate outcomes be used in JCA?

Surrogate and/or intermediate outcomes:

- May be requested by MS if deemed relevant
- May be presented by the HTD if insufficient data for a requested outcome exists
  - HTD should provide evidence to support the use of the surrogate in this situation
  - Assessment of the strength of this relationship to form part of JCA

Advice to HTDs: many outcomes are predictable - start preparing now!

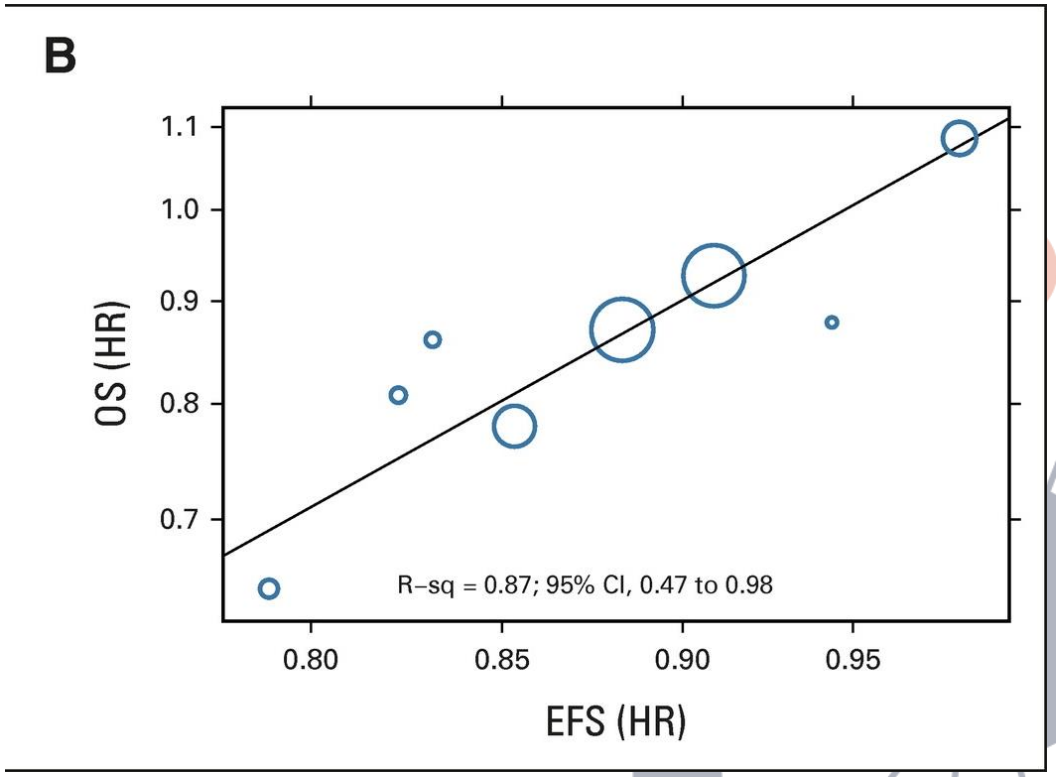

Figure: Trial-level association between treatment effects on EFS and OS in newly-diagnosed AML
Norsworthy et al, Journal of Clinical Oncology 2022

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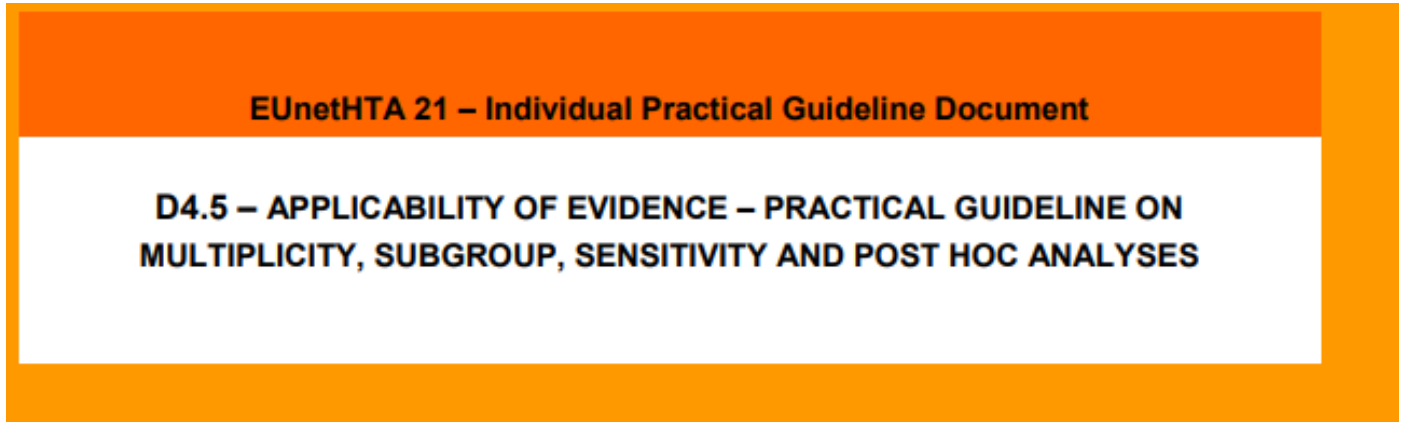
D4.5 – Applicability of Evidence



- **Key challenge:** Scientific question of the JCA PICO(s)
  - may differ from that of the pivotal trial(s)
  - may involve multiple studies and evidence synthesis
- 'JCA-wide' multiplicity control not achievable… or even well-defined
- JCA assessors to identify and report potential sources of multiplicity
- **Long-term:** improved pre-specification and multiplicity control of HTA-relevant endpoints achievable?

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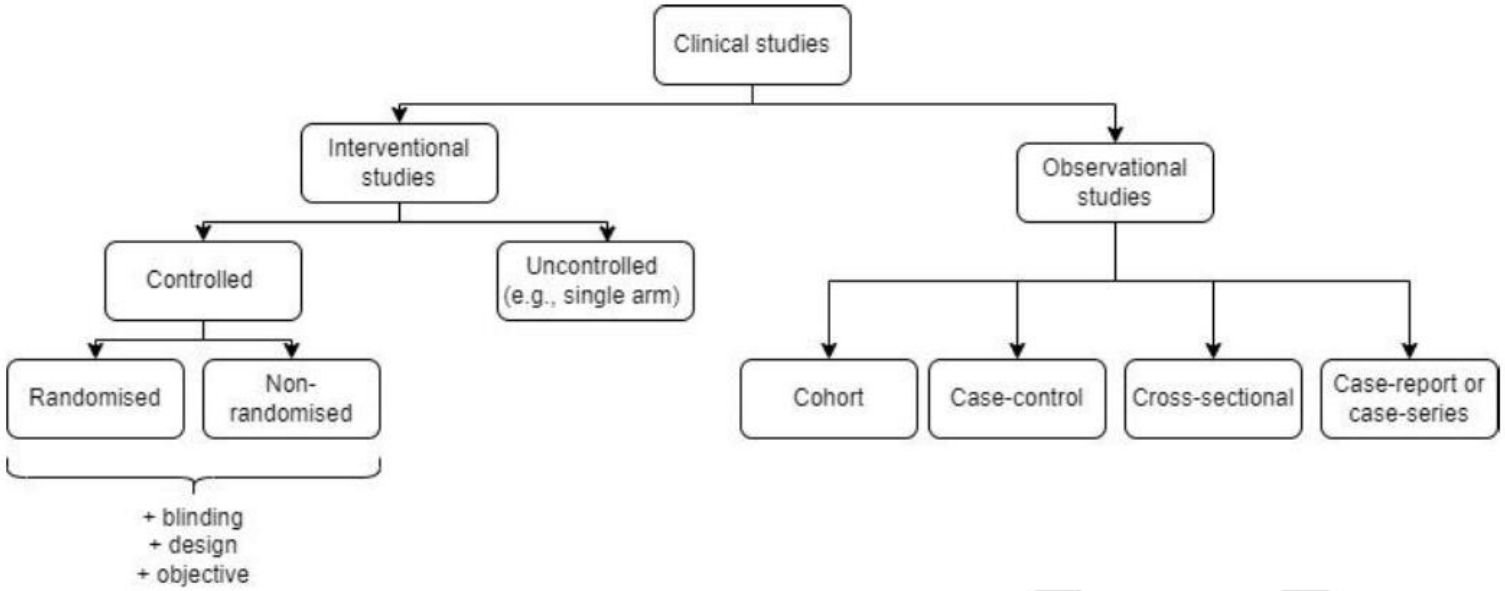
D4.6 - Validity of Clinical Studies

- Guidance for assessors on study designs and their **internal and external validity**
- Guidance on issues of validity arising from **platform trials, basket trials and RWE**



- Standardised tools recommended for internal validity, e.g., Cochrane RoB, ROBINS-I,…
- External validity - relevance to PICO question(s)
- Performed by **JCA assessors** – onus on HTDs to make the required information available

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General remarks

- Scope of JCA is comparative clinical effectiveness, specified via PICO
- Methodological guidelines propose a scientifically rigorous but pragmatic approach to evidence for JCAs
- HTA aims to answer different questions than regulatory assessment
  - Not a given that same evidence can answer both
- Long-term: greater involvement of HTA bodies in shaping evidence generation through
  - Joint Scientific Consultation
  - More general dialogue - like this workshop!

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Thank you for listening

Further Reading

- EUnetHTA21 Guidelines available (until end of 2023) at:

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

- Information on HTACG and ongoing work on the HTA Regulation
  - https://health.ec.europa.eu/health-technology-assessment/regulation-health-technology-assessment/member-state-coordination-group-hta-htacg_en
  - https://health.ec.europa.eu/health-technology-assessment_en

Contact

- DMcConnell@stjames.ie