Institute for Quality and Efficiency
in Health Care (IQWiG)

Experiences from the first JCAs with some clarifications on data presentation, indirect comparisons and risk of bias assessment

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Regulatory approval vs. Health Technology Assessment

Regulatory

EMA

- **Efficacy:** Does technology X work?
- **Safety:** Any risks of technology X (current and post-licencing)?
- **Benefit-Risk Balance:** Does the benifit of technology X outweigh the risks?

- **single licensing system** (centralised procedure)
- EU Legislation (Directive 2001/83/EC)

Health Technology Assessment (HTA)

EU-HTA

- **relative effectiveness and safety**: assessment of technology X vs. Y (and others)
- How does it **compare to what we already have**? (benefits, harms, ...)

- **No value judgements**
- **No conclusions on added value or reimbursement**
- EU-HTA regulation 2021/2282
- Common methodology and approach

National HTA

- **appraisal** of the overall clinical added value
- **decision-making process** (reimbursement, pricing)
- Other considerations (e.g. cost effectiveness to be added)

- JCA shall be given due consideration in national decision-making
- Responsibility for the methodology and approach remains with the member states

Domains of HTA assessments
Implementing the EU HTA assessment regulation

Clinical domains

- Identification of a health problem and current health technology
- Examination of the technical characteristics of the health technology under assessment
- **Relative clinical effectiveness**
- **Relative safety**

Non-clinical domains

- Cost and economic evaluation
- Ethical aspects
- Organizational aspects
- Social aspects and
- Legal aspects

Relative clinical effectiveness / safety
Implementing the EU HTA assessment regulation

- HTA focuses specifically on the **added value** of a health technology in comparison with other **new or existing health technologies**
- Relative clinical effectiveness
  - Mortality
  - Morbidity
  - Health-related quality of life
- Relative safety
  - Adverse events

Article 9: Joint clinical assessment reports and the dossier of the health technology developer

1. A joint clinical assessment shall result in a joint clinical assessment report that shall be accompanied by a summary report. Those reports shall not contain any value judgement or conclusions on the overall clinical added value of the assessed health technology and shall be limited to a description of the scientific analysis:

   (a) of the relative effects of the health technology as assessed on the health outcomes against the chosen parameters which are based on the assessment scope as set out pursuant to Article 8(6);

   (b) of the degree of certainty of the relative effects, taking into account the strengths and limitations of the available evidence.

Article 9: Joint clinical assessment reports and the dossier of the health technology developer

2. The dossier shall meet the following requirements:

   a) the submitted evidence is complete with regard to the available studies and data that could inform the assessment;

   b) the data has been analysed using appropriate methods to answer all research questions of the assessment;

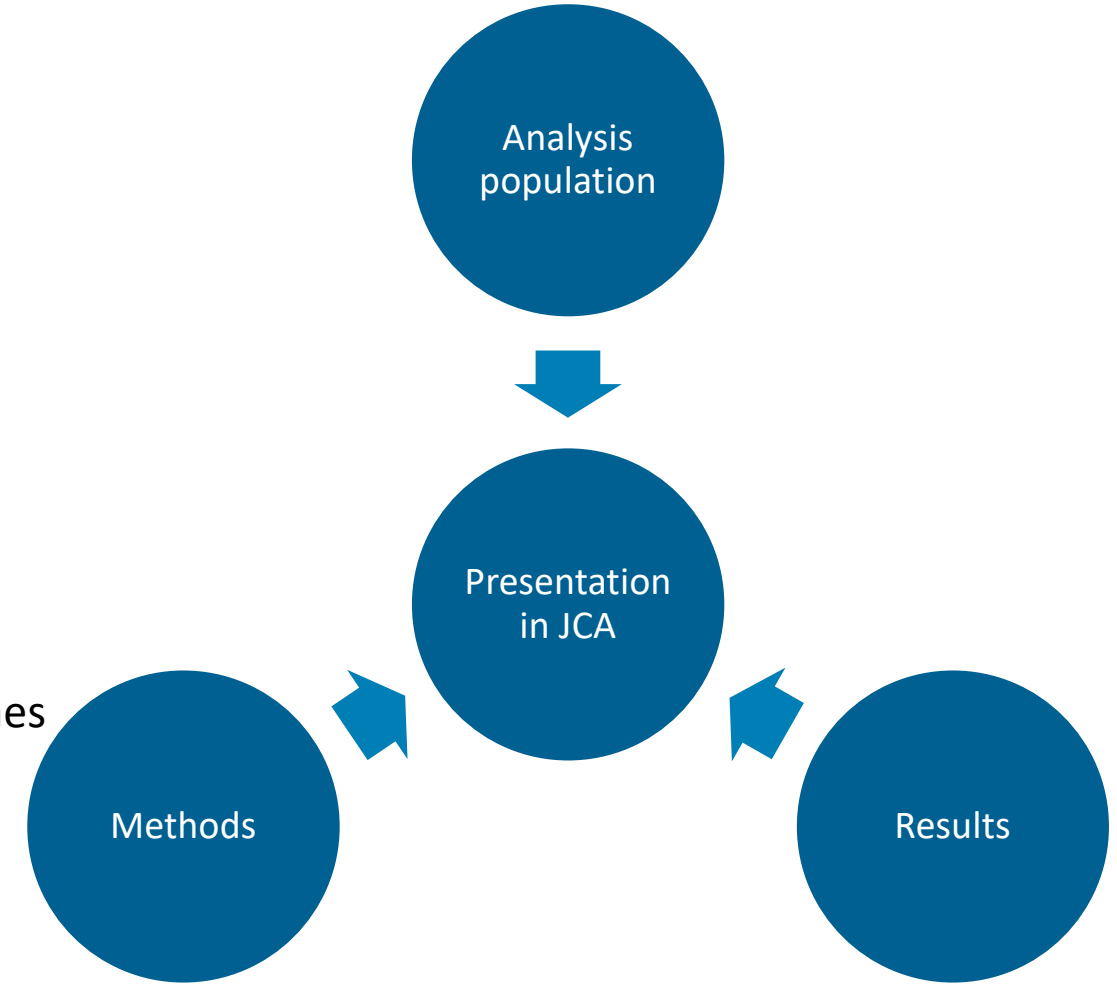
   c) the presentation of the data is well structured and transparent, thereby allowing for an appropriate assessment within the limited timeframes available;

   d) it includes the underlying documentation in respect of the submitted information, thereby allowing the assessor and co-assessor to verify the accuracy of that information.

Statistical issues

Results will only be presented if we have full understanding of

- Analysis population
  - E.g. patient flow and Table 1
- Statistical methodology
  - Comprehensible description
  - Source code for complex analyses
- Standard information for the results
  - 2x2 tables for binary outcomes
  - Baseline, change from baseline for continuous outcomes
  - Figures (Kaplan-Meier curves, trend curves)
  - Effect estimates shall correspond to the standard information



Example for problematic presentation
Mixed model repeated measures (MMRM)

- Which effect is intended to be estimated?
  - Change from baseline at a specific time point
  - Change from baseline, averaged over the full study period
  - Slopes of the change form baseline

- Specification required:
  - Baseline, change from baseline for continuous outcomes
  - Which effect estimates and p-values are presented?
    - Specification of the underlying model (e.g. for subgroup analyses)
    - SAS statements: estimate, lsmeans, contrast
  - Source code of the implementation

Statistical issues

Results will only be presented if we have full understanding of

- Analysis population
  - Patient
- Statistical r
  - Compr
  - Source
- Standard in
  - 2x2 tab
  - Baseline, change from baseline for continuous outcomes
  - Figures (Kaplan-Meier curves, trend curves)
  - Effect estimates shall correspond to the standard information

Results from analyses that are not presented in a complete, transparent and comprehensible form cannot be included in the report.

What is the correct estimand?

- The estimand framework *ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials* was initiated to address the different perspectives of the stakeholders within the health care system, such as patients, physicians, regulatory boards as well as HTA bodies.

1. Treatment Policy estimand (Intention-to-Treat [ITT] principle) ✓
2. Composite estimand ✓
3. While-on-Treatment (✓)
   - May require complex analyses with additional assumptions
4. Hypothetical estimand ✗
   - Critical, because a population, in which the intercurrent event does not occur, is often of limited clinical interest
5. Principal stratum ✗
   - Analysis of the population relies on assumptions that cannot be proven

- Implementation of the estimand will be considered in the Risk of Bias (RoB) assessment.

Clarification on the Risk of Bias assessment

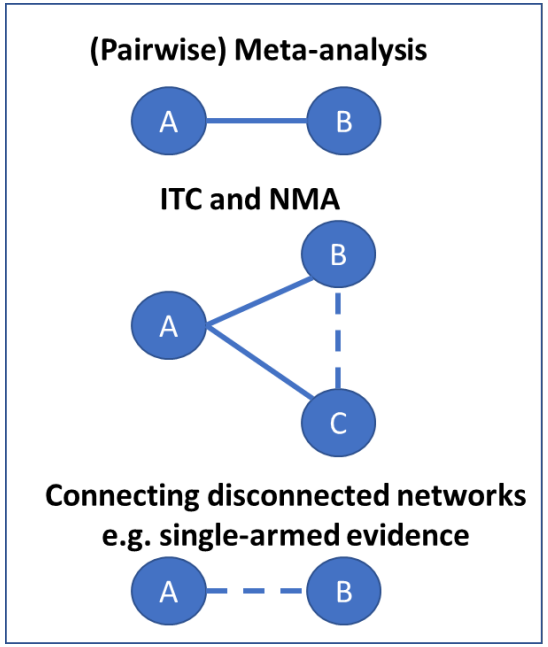
- Assessing the Risk of Bias (RoB) is an essential part of the JCA (‘degree of uncertainty’).
- Guidance on the validity of clinical studies for joint clinical assessments
- “the degree of certainty of the relative effects, taking into account the strengths and limitations of the available evidence”.
  - **Internal validity**
  - External validity
  - Statistical precision

- The risk of bias for outcomes such as OS and PFS will be evaluated from the perspective of the treatment policy estimand.

Study Outcome	Random sequence generation (confounding bias)	Allocation concealment (confounding bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Overall risk of bias
DeLLphi-304	Low	Low	Low				Low	
Overall survival				Low[b]	Low	Low	Low	Low
PFS				High[c]	Low	Low	Low	High
ORR				High[c]	High[d]	Low	Low	High
DoR				High[c]	High[e]	Low	Low	High
BPI-SF (Item 3)				High[f]	High[g]	Low	Low	High
Dyspnoea (composite score				High[f]	High[g]	Low	Low	High
Health-related quality of life, disease specific (EORTC QLQ-C30, EORTC QLQ-LC13)				High[f]	High[g]	Low	Low	High
Health status (EQ-5D-5L, incl. VAS)				High[f]	High[g]	Low	Low	High
Any AE				High[h]	High[i]	Low	Low	High
Serious AEs				Low[j]	High[i]	Low	Low	High
Severe AEs (CTCAE grade ≥ 3)				Low[j]	High[i]	Low	Low	High
Death related to AEs				Low[j]	High[i]	Low	Low	High
Treatment discontinuation due to AEs				High[k]	High[i]	Low	Low	High
Treatment interruption due to AEs				High[k]	High[i]	Low	Low	High

General methodological approaches covered

- Direct comparisons from RCTs – individual studies or pairwise meta-analysis – **highest certainty of evidence**
- Indirect Treatment Comparisons (ITC) from RCTs
  - Bucher‘s method for anchored indirect comparisons
  - Network meta-analyses (NMA)
  - Population-adjusted methods for indirect comparison
- Unanchored ITCs, e.g. comparisons of single armed trials with external controls (non-randomised studies)
  - The assumptions are so strict that, according to the EU guidelines for evidence synthesis, they are generally not met in practice

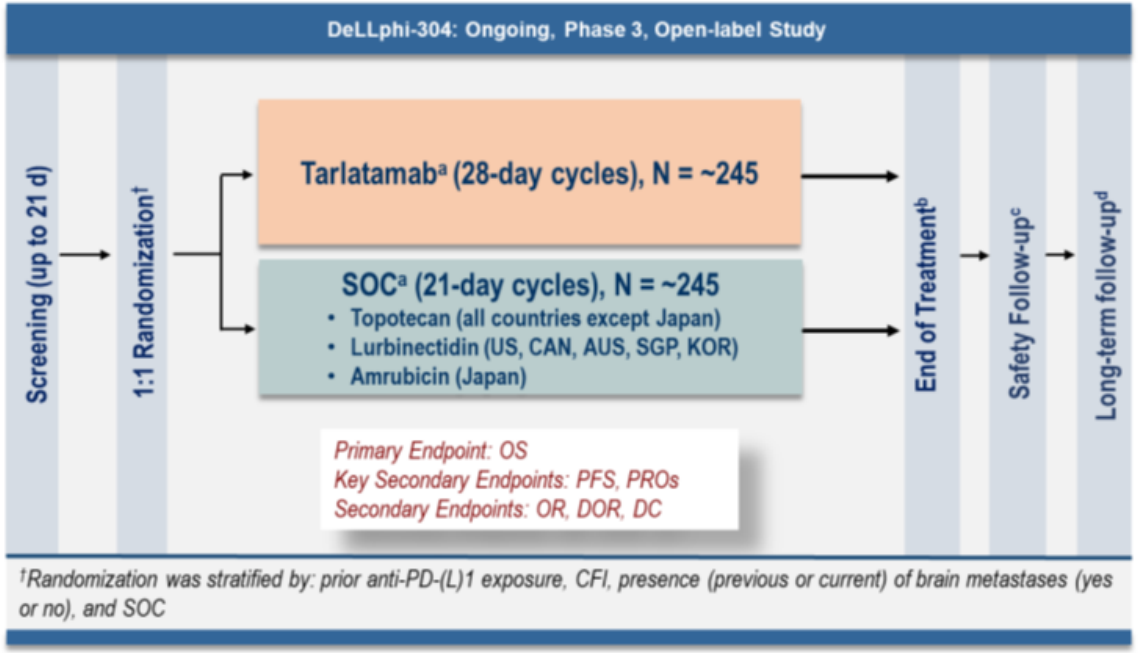


➔ Acceptability of uncertainty and value of relative effects on outcomes → decided at member state level

JCA 202417 – evidence basis for the JCA

Main Study – DeLLphi-304

- RCT, Phase III, global, open-label
- Adult patients with histologically or cytologically confirmed ES-SCLC who progressed or recurred after first-line treatment with platinum-based chemotherapy



Relevant subpopulations of DeLLphi-304 informed the PICOs as follows:

DIRECT COMPARISON

DeLLphi-304 → PICO 1, PICO 4, PICO 6

NMA

DeLLphi-304, Baize 2020, von Pawel 1999 → PICO 3, PICO 5

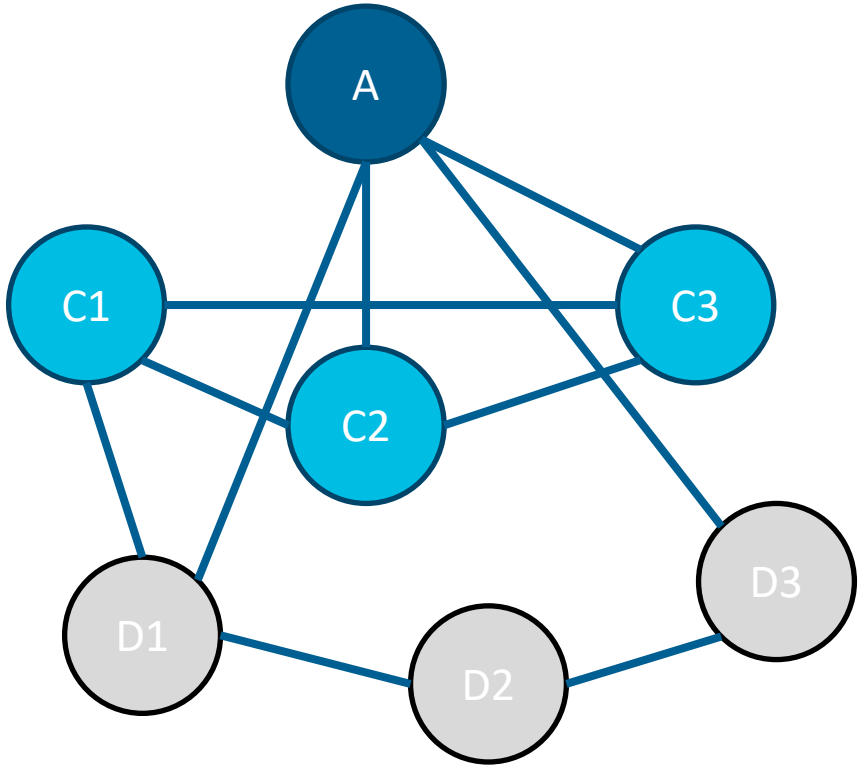
UNANCHORED MAIC

DeLLphi-304 GFPC 0501 → PICO 2

ANCHORED ITC (Bucher)

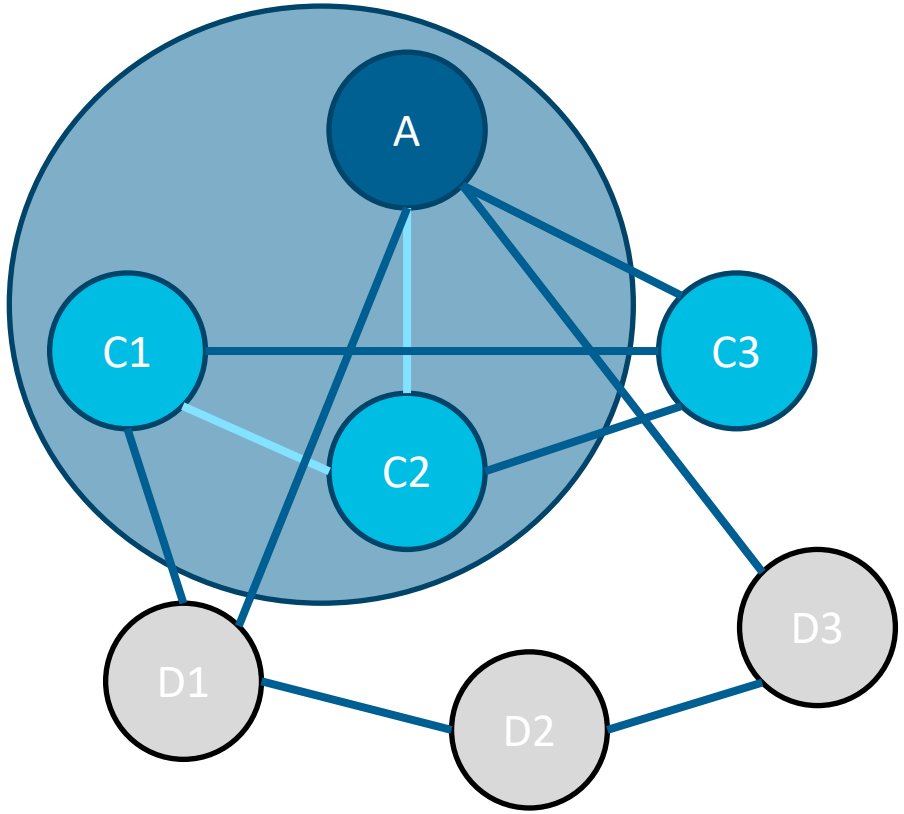
DeLLphi-304 Baize 2020 → PICO 7

Indirect comparisons: network meta-analyses



A: intervention
C1, C2, C3: comparators in the scope of JCA (at least in 1 PICO)
D1, D2, D3: not part of any PICO of the JCA

Indirect comparisons: network meta-analyses (NMAs)



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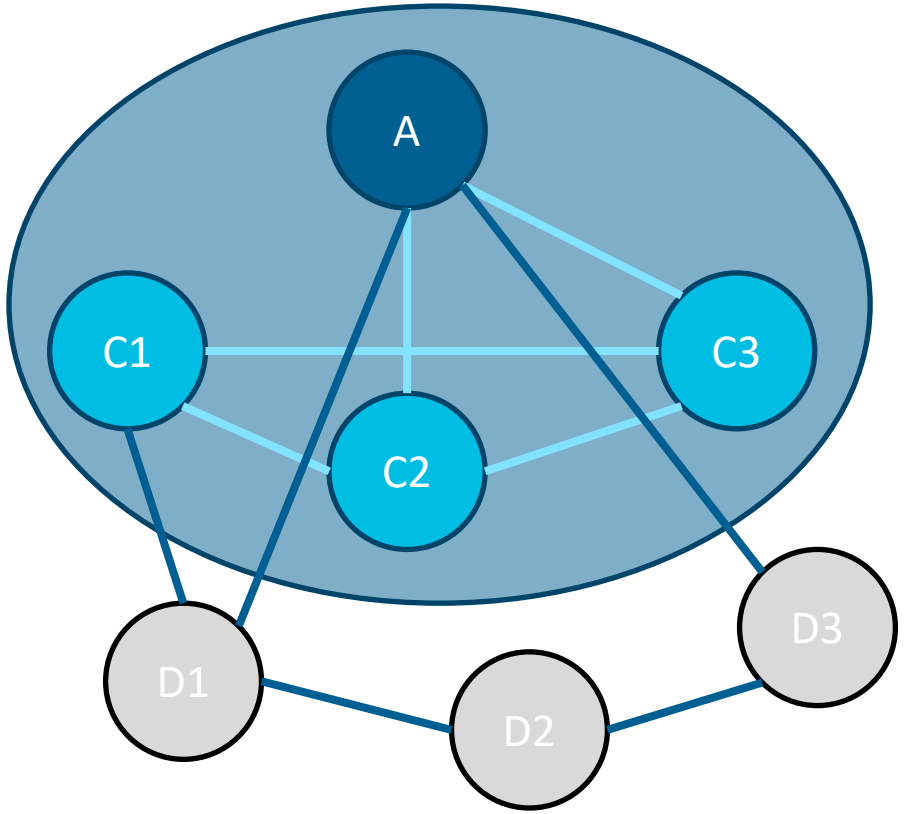
PICO: A vs. C1

1. Bucher via common comparator C2 ✓

Indirect comparisons: network meta-analyses (NMAs)



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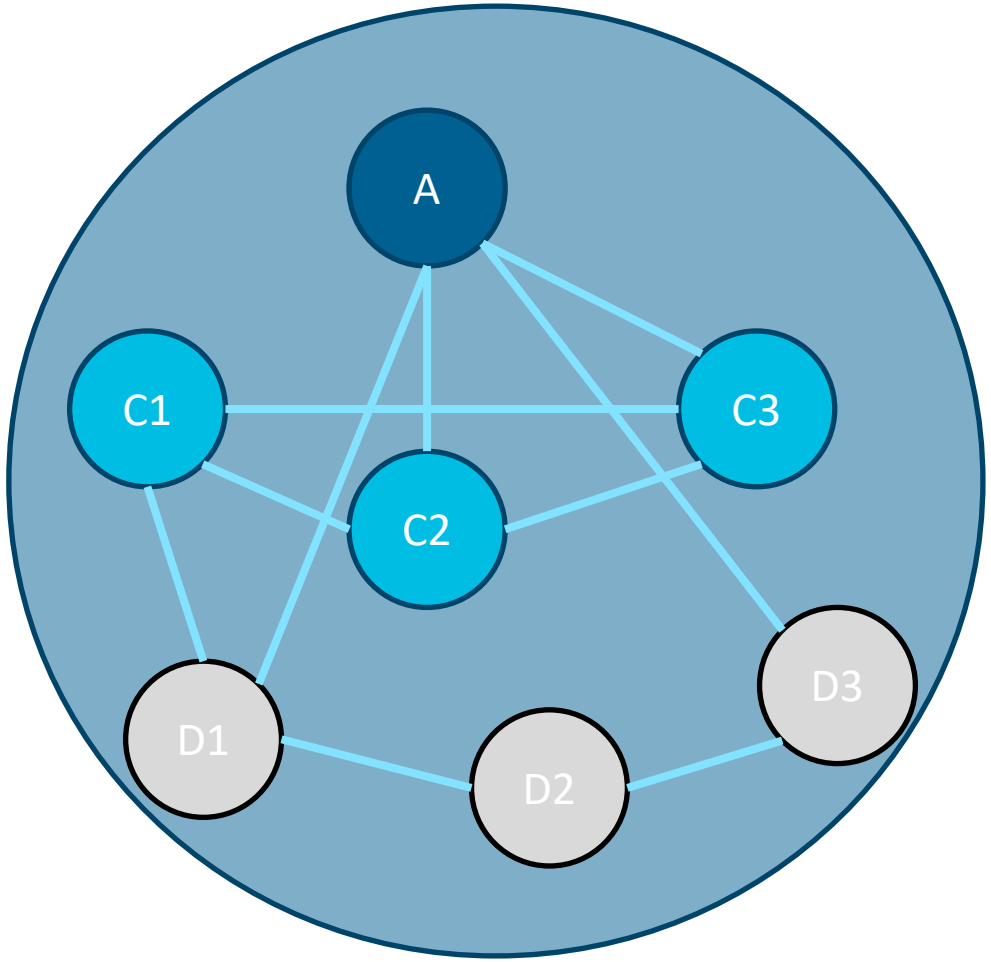
PICO: A vs. C1

1. Bucher via common comparator C2 ✓
2. Population-level NMA with C2 and C3 ✓

Indirect comparisons: network meta-analyses (NMAs)



A: intervention
C1, C2, C3: comparators in the scope of JCA (at least in 1 PICO)
D1, D2, D3: not part of any PICO of the JCA

PICO: A vs. C1

1. Bucher via common comparator C2 ✓
2. Population-level NMA with C2 and C3 ✓
3. Full model NMA with comparators outside of the JCA

Indirect comparisons: network meta-analyses (NMAs)

- **Guidelines are available**
  - Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons
  - Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons
- **Important**
  - **Appropriate discussion of the underlying assumptions is required.**
  - Present the complete data used for the indirect comparisons (transparency!)
  - Appropriate description of the methodology with corresponding references
  - Submit the source code

Additional requests – a nice idea with limitations

- During the JCA, the assessors/co-assessors can request additional information
  - e.g. clarification regarding the statistical analysis
- This would be a good way to clear up inconsistencies that only become apparent upon closer inspection of the dossier and the appendices
  - Clinical study reports, study protocols, SAPs
  - Appendices with data and results specific for the JCA
  - Source code
- However, due to the **time constraints**,
  1. additional requests should be **avoided**
  2. additional requests should be **answered timely** ➔ otherwise, answers cannot be considered in the report

Guidelines, instructions and templates

- Guidelines, e.g.
  - Methodological and Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons
  - Guidance on reporting requirements for multiplicity issues and subgroup, sensitivity and post hoc analyses
- Filling-in instructions, e.g.
  - Guidance on filling in the joint clinical assessment (JCA) dossier template – Medicinal products
- Templates
  - Available for the dossier and for the **tables**
- Questions and Answers on general methodological and procedural issues for joint clinical assessments

- Available at https://health.ec.europa.eu/health-technology-assessment/key-documents_en

Take home messages in order to submit an assessable dossier

1. **Read timely**
   - Guidelines
   - Fill-in-instructions
   - Templates for the tables (data, results)

2. **Start early** with the documentation of the statistical analyses

3. **Plan carefully** the use of resources for
   1. Filling in tables
   2. Description of statistical analysis
   3. Lyrics

Thank you for your attention!

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Questions and comments:

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