PICO Schemes:

How to approach the Equity / Excellence Dilemma

Université de Strasbourg
June 19th, 2026

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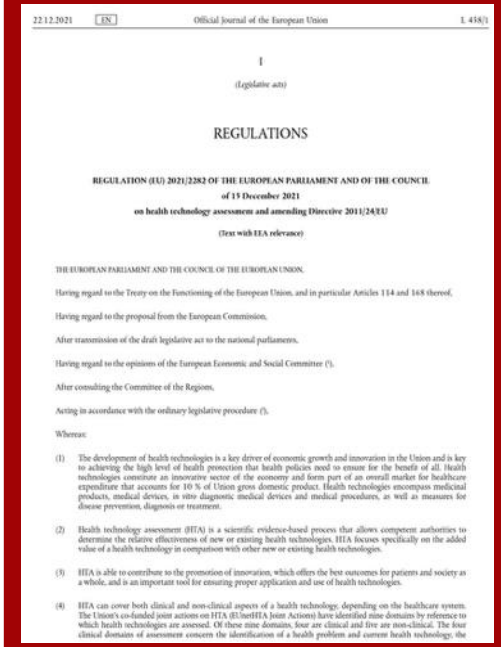
AGENDA

1. Origin of the Equity/ Excellence Dilemma
2. Relevance for Methodological Guidance Documents
3. Strategic Consideration/ Proposal

The Origin of the Equity/ Excellence Dilemma: *Article 8.6 & Recital 25 mandate 'Inclusiveness' …*



22.12.2021 EN Official Journal of the European Union L 458/1

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(Legislative acts)

REGULATIONS

REGULATION (EU) 2021/2282 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 15 December 2021
on health technology assessment and amending Directive 2011/24/EU
(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Articles 114 and 168 thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinions of the European Economic and Social Committee (1),

After consulting the Committee of the Regions,

Acting in accordance with the ordinary legislative procedure (2),

Whereas:

(1) The development of health technologies is a key driver of economic growth and innovation in the Union and is key to achieving the high level of health protection that health policies need to ensure for the benefit of all. Health technologies constitute an innovative sector of the economy and form part of an overall market for healthcare expenditure that accounts for 10 % of Union gross domestic product. Health technologies encompass medicinal products, medical devices, in vitro diagnostic medical devices and medical procedures, as well as measures for disease prevention, diagnosis or treatment.

(2) Health technology assessment (HTA) is a scientific evidence-based process that allows competent authorities to determine the relative effectiveness of new or existing health technologies. HTA focuses specifically on the added value of a health technology in comparison with other new or existing health technologies.

(3) HTA is able to contribute to the promotion of innovation, which offers the best outcomes for patients and society as a whole, and is an important tool for ensuring proper application and use of health technologies.

(4) HTA can cover both clinical and non-clinical aspects of a health technology, depending on the healthcare system. The Union's co-funded joint actions on HTA (EUnetHTA Joint Actions) have identified nine domains by reference to which health technologies are assessed. Of these nine domains, four are clinical and five are non-clinical. The four clinical domains of assessment concern the identification of a health problem and current health technology, the

Recital 25: The assessment scope for joint clinical assessments should be inclusive and should reflect all Member States' needs in terms of data and analyses to be submitted by the health technology developer.

Article 8.6. The assessment scope shall be inclusive and reflect Member States' needs in terms of parameters and of the information, data, analysis and other evidence to be submitted by the health technology developer. The assessment scope shall include in particular all relevant parameters for the assessment in terms of:

(a) the patient population;
(b) the intervention or interventions;
(c) the comparator or comparators;
(d) the health outcomes.

https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32021R2282

… but … how to integrate e.g., Recital 9?

Recital 9: …to propose legislation on a European system for HTA as soon as possible and to harmonise transparent HTA criteria in order to assess the added therapeutic value and relative effectiveness of health technologies compared with the best available alternative, that takes into account the level of innovation and benefit for patients.

What if requested comparators are not the best available alternative?

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… how to integrate e.g., Recital 5?

Recital 5: HTA can improve scientific evidence used to inform clinical decision-making and patient access to health technologies, including where a health technology becomes obsolete. ….

What if e.g., an aged comparator should be obsolete to the benefit of patients?

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… how leverage Recital 3?

Recital 3: HTA is able to contribute to the promotion of innovation, which offers the best outcomes for patients and society as a whole, and is an important tool for ensuring proper application and use of health technologies.

What if a Member State requests a PICO scheme that clearly offers inferior outcomes to patients compared to current Standard of Care?

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… but … how leverage Recital 2?

Recital 2: Health technology assessment (HTA) is a scientific evidence-based process that allows competent authorities to determine the relative effectiveness of new or existing health technologies. HTA focuses specifically on the added value of a health technology in comparison with other new or existing health technologies.

What is the role of EU HTA if 'other new' technologies are clearly superior to 'existing health technologies' (e.g. SMA)?

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… but … how leverage Recital 8?

Recital 8: …the Council acknowledged the key role that HTA has as a health policy tool to support evidence-based, sustainable and equitable choices in healthcare and health technologies for the benefit of patients. …

What if ***evidence*** indicates that ***equitable choices*** suggested by member states are less effective and/ or harbour additional harm (e.g. Chemo vs CIT)?

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The Bottom Line:

Recital 1: The development of health technologies is a key driver of economic growth and innovation in the Union and is key to achieving the high level of health protection ….

- Innovation is achieved by 'Excellence'
- 'Equity' is of major importance BUT it is primarily a health policy issue. The role of EU HTA in equity is unclear

https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32021R2282

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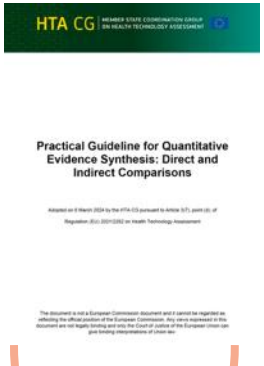
VARIOUS METHODOLOGICAL GUIDANCES HAVE BEEN DEVELOPED

Methods ***Guideline*** ITC



Practical ***Guideline*** ITC

Outcomes/ Endpoints

Specifications of Medicinal Products in Scope

Multiplicity Guidance

Validity of Clinical Trials

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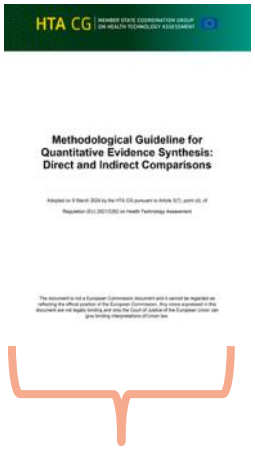

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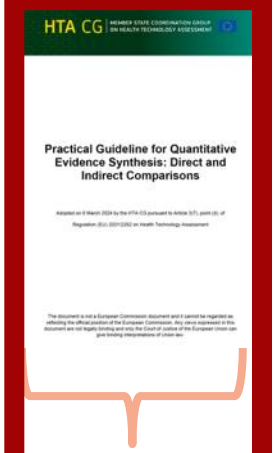

Practical ***Guideline*** ITC

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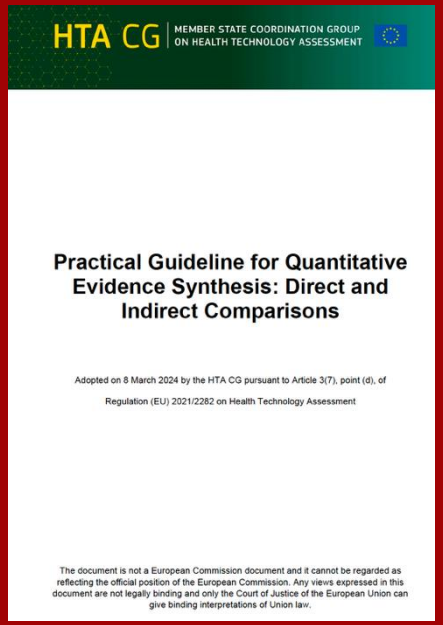
TAKING AN EXAMPLE: EVIDENCE SYNTHESIS


HTA CG | MEMBER STATE COORDINATION GROUP ON HEALTH TECHNOLOGY ASSESSMENT

Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons

Adopted on 8 March 2024 by the HTA CG pursuant to Article 3(7), point (d), of Regulation (EU) 2021/2282 on Health Technology Assessment

The document is not a European Commission document and it cannot be regarded as reflecting the official position of the European Commission. Any views expressed in this document are not legally binding and only the Court of Justice of the European Union can give binding interpretations of Union law.

3.2. Assessment of exchangeability

The fundamental assumption of exchangeability, which is required for (network) meta-analysis, is operationalised by assessing the properties of similarity, homogeneity, and, in the case of indirect comparisons, consistency.

- *Similarity: Studies comparable with regards to effect modifiers (assessed by PICO)*
- *Homogeneity: Statistical testing for homogeneity across typical 5 respective studies*
- *Consistency: Same treatment effect estimated through direct & indirect pathways*

Is such guidance really applicable to all requested PICO schemes?

QUESTIONS TO BE ASKED

1. Do equal methodological requirements apply across all various PICO schemes?

2. How to approach differences in relative effectiveness across the various comparators requested in the different PICO schemes?

   An aside: (Life-) Cycles of Innovation & Evidence Standards differ across Medicinal Products & Medical Devices. Do the same methodological standards apply?

3. How to manage risk of multiplicity across PICO schemes

4. How to avoid inflation of type 2 error across 'aged' comparators

The Bottom Line:

Recital 48: The Coordination Group should develop methodological guidance on the joint work provided for in this Regulation, following international standards of evidence-based medicine. The assessment process should rely on relevant, up-to-date and high quality clinical evidence.

Article 3.7: The Coordination Group shall:
(d) adopt methodological guidance on joint work following international standards of evidence-based medicine;…

Focus of EbM is 'Excellence' (Best Available Treatment) rather than 'Equity' ….

https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32021R2282

Let's always keep the origin of EbM in Mind

*Evidence Based Medicine – What it is and What it isn't**

Some fear that evidence based medicine will be hijacked by purchasers and managers to cut the costs of health care. This would not only be a misuse of evidence based medicine but suggests a fundamental misunderstanding of its financial consequences. Doctors practising evidence based medicine will identify and apply the most efficacious interventions to maximise the quality and quantity of life for individual patients; this may raise rather than lower the cost of their care.

Evidence based medicine is not restricted to randomised trials and meta-analyses. It involves tracking down the best external evidence with which to answer our clinical questions.

*Sackett DL et al. BMJ 1996; 312: 71-72

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CURRENT STATE OF PLAY

Table 2: 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 1 (full claimed indication)				
Patients 6 months of age and older with paediatric LGG harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have received one or more prior systemic therapies				
Intervention: Tovorafenib				
PICO 1	Individualised treatment, comprising multiple treatment options[a]: ▪ Vinblastine[b] ▪ Combination of carboplatin and vincristine[b,c] ▪ TPCV combination therapy[b] ▪ Combination of dabrafenib and trametinib[d] ▪ Everolimus[e] ▪ Bevacizumab in combination with chemotherapy[b]	no	No comparator data available	no
PICO 2	Individualised treatment, comprising multiple treatment options[a]: ▪ Vinblastine[f] ▪ Combination of carboplatin and vincristine[f,c] ▪ TPCV combination therapy[f] ▪ Combination of dabrafenib and trametinib[d]	no	No comparator data available	no
PICO 3	Combination of carboplatin and vincristine[c]	no	No comparator data available	no
PICO 4	Vinblastine	no	No comparator data available	no
Population 2 (BRAF V600E mutation in patients > 1 year)				
Patients > 1 year of age with paediatric LGG harbouring a BRAF V600E mutation, who have received one or more prior systemic therapies				
Intervention: Tovorafenib				
PICO 5	Combination of dabrafenib and trametinib	yes	–	yes

Population Intervention PICO no.	Comparator	Results submitted [yes/no]	HTD's reason for omission	Data included in the JCA report [yes/no]
PICO 6	Individualised treatment, comprising multiple treatment options[a]: ▪ Vinblastine ▪ Combination of carboplatin and vincristine[c]	no	No comparator data available	no
Population 3 (BRAF fusion, rearrangement, or V600 [non-E] mutation)				
Patients 6 months of age and older with paediatric LGG harbouring a BRAF fusion or rearrangement, or BRAF V600 (non-E) mutation, who have received one or more prior systemic therapies				
Intervention: Tovorafenib				
PICO 7	Trametinib	yes	–	no[g]
PICO 8	Individualised treatment, comprising multiple treatment options[a]: ▪ Vinblastine ▪ Combination of carboplatin and vincristine[c]	no	No comparator data available	no

a: The choice of treatment depends on a patient's individual characteristics.
b: Chemotherapy-based treatment regimens are a treatment option for patients covered by the full claimed indication with the following characteristics: a BRAF alteration other than a BRAF V600E mutation or with a BRAF V600E mutation and insufficient response to dabrafenib in combination with trametinib; aged 6-11 months and from 18 years; no SEGA associated with TSC.
c: A treatment regimen starting with a combination of carboplatin & vincristine may be finished with alternating courses of cisplatin & vincristine with cyclophosphamide & vincristine, due to the risk of carboplatin hypersensitivity.
d: Dabrafenib in combination with trametinib should be used for paediatric patients aged 12 months and older with a BRAF V600E mutation, except for patients who did not respond sufficiently to a first-line therapy with dabrafenib in combination with trametinib.
e: Everolimus is a treatment option for patients with SEGA associated with TSC.
f: Chemotherapy-based treatment regimens are a treatment option for patients covered by the full claimed indication with the following characteristics: a BRAF alteration other than a BRAF V600E mutation or with a BRAF V600E mutation and insufficient response to dabrafenib in combination with trametinib; aged 6-11 months and from 18 years.
g: Results submitted by the HTD to inform PICO 7 are not included in the assessment, due to insufficient information available for the assessment of the study on the comparator.

BRAF: v-Raf murine sarcoma viral oncogene homologue B; LGG: low-grade glioma; SEGA: subependymal giant cell astrocytoma; TPCV: Thioguanine, procarbazine, lomustine, and vincristine; TSC: tuberous sclerosis complex

STRATEGIC CONSIDERATION/ PROPOSAL

Equity and Excellence are both of major relevance

The HTD should:

focus the clinical development program on relative effectiveness data versus the best available comparator

The CG should:

1) determine relative effectiveness across suggested PICO schemes and identify best available comparator
2) adjust methodological requirements for 'secondary' PICOs

European Access Academy

BACK UP

Tovorafenib: A Glance on One Slide

Indication:

- Monotherapy for the treatment of patients 6 months of age and older with paediatric low-grade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies

Guidelines:

- EJC 2024*:
  - Only first line recommendations
  - Mentioning Tovorafenib US approval and EU OD and Firefly 2 planning in 1st line
  - Mentioning targeted treatments for BRAF
- SIOPE 2022**:
  - Only first line recommendations
  - Mentioning targeted treatments for BRAF

Clinical Data:

Firefly 1+:

- P: BRAF altered rr pLGG; fusion: n=101 (74%), rearrangement or fusion: n=14 (10%), V600E mutation: n=22 (16%)
- I: Type II RAF Inhibitor
- C: n/a
- O: efficacy results based on arm 1 (IRC):
  - RANO-HGG: ORR 67%; DOR 16.6m; TTR 3.0m;
  - RAPNO: ORR 51%; DOR 13.8m; TTR 5.3m;
- S: Phase 2; arm 1 (n = 77); arm 2 extension after arm 1 closure (n = 60); data cut-off @ 15 months

EPAR Conclusions:

- Unmet medical need as no authorised treatments in indication
- Positive Benefit Risk Ratio
- Orphan Designation
- Conditional Marketing Authorization: Firefly II RCT data in 1st line expected to provide required additional information

Scoping & HTD Dossier:

- Scoping: 3 Populations/ 8 PICOs; 2 addressed by HTD @ 2yr cut-off
- PICO 5: BRAF V600E; pts > 1yr; comparator dabrafenib & trametinib; PAIC: ORR (Odds Ratio 8.23 [1.11; 61.27]; p = 0.040; RANO-LGG; IRC); sensitivity analyses not significant
- PICO 7: BRAF fusion, rearrangement or V600 (non-E) mutation; comparator trametinib; ORR (Odds Ratio 16.01 [6.03; 42.49]; p<0.001; RANO HGG; IRC)
- Claiming ORR statistical superiority and commenting on high unmet need

JCA-report; focus PICO 5; in addition, significantly more severe AEs (CTCAE >=3)

PICO 5 unanchored MAIC vs Bouffet§; dichotomous outcomes

- 6m PFS (RANO LGG; IRC): RR 1.09 [0.92; 1.30]
- 12m PFS (RANO LGG; IRC): RR 0.92 [0.61; 1.38]
- CR+PR (RANO HGG; INV): OR 0.56 [0.08; 3.84]; p = 0.551
- CR+PR (RANO HGG; IRC): OR 7.26 [0.98; 53.68]; p = 0.052

Cave: Population in Bouffet includes pts with HGG rather than LGG and without prior systemic treatment

PICO 5 unanchored MAIC vs Bouffet§; time to event

- 13.67m vs 36.9m; HR 4.8 [2.14; 11.14]; p = 0.011; RMST difference: -6.64 [-13.16;-0.12]; p = 0.046

PICO 7 not considered due to insufficient evidence

* https://www.ejcped.com/action/showPdf?pii=S2772-610X%2824%2900028-X; ** https://siope.eu/media/documents/escp-low-grade-gliomas-lgg.pdf; + https://doi.org/10.1038/s41591-023-02668-y; § https://www.nejm.org/doi/full/10.1056/NEJMoa2303815; AE: Adverse Event, BRAF: V-Raf Murine Sarcoma Viral Oncogene Homolog B encoding rapidly accelerated fibrosarcoma protein, CR: complete response, CTCAE: Common Terminology Criteria for Adverse Events, DOR: Duration of Response, EPAR: European Product Assessment Report, EJC: European Journal of Cancer, HGG: High Grade Glioma, HR: Hazard Ratio, HTD: Health Technology Developer, INV: investigator assessed, IRC: independent review committee, (p)LGG: (paediatric) Low Grade Glioma, m: months, MAIC: Matching-adjusted indirect comparison, OD: Orphan Designation, ORR: Objective Response Rate, PAIC: Predictive-adjusted indirect comparison, PFS: progression-free survival, PICO: Population/ Intervention/ Comparator/ Outcomes, PR: partial response, pts: patients, RAF: rapidly accelerated fibrosarcoma kinases, RANO: Response Assessment in Neuro-Oncology, RAPNO: Response Assessment in Neuro-Oncology, RCT: Randomised Controlled Trial, rr: relapsed or refractory, RMST: Restricted Mean Survival Time, RR: Relative Risk, SIOPE: European Society for Paediatric Oncology, TTR: Time to Response, yr: year

Tovorafenib: Topline Comments

- Medical Condition with a high unmet medical need
- Limited evidence base in BRAF-altered relapsed/refractory (R/R) pLGG
- No specifically licensed comparator treatments available, therefore patients are currently treated with individualised treatment
- Firefly 1, best available evidence for Tovorafenib is based on a single-arm trial
- Firefly 2, an RCT versus current standard of care chemotherapy in first line LGG patients is currently ongoing
- Due to the limited evidence-base determination of relative effectiveness harbours a particularly high risk of bias in both directions:
    - *Type 1 error: falsely assuming an additional benefit*
    - *Type 2 error: falsely not offering a potentially beneficial medicine to those severely affected children and adolescents*
- Only one parent carer and one clinical expert were included – without any records on how or even if input was considered, i.e. limited expert involvement, which is one of the most critical factors for a successful implementation of the regulation