HPR142

Mind The Gap: Exploring Variation in Guidelines for Indirect Treatment Comparison (ITC) Across Europe

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Objective

- To explore the similarities and differences between ITC guidelines at an EU and country level to bridge potential gaps for national decision-making.

Introduction

- During health technology assessment (HTA), comparative effectiveness evidence for new therapies is required for clinical and/or economic assessments.
- Indirect treatment comparisons (ITCs) and network meta-analyses (NMAs) can estimate relative effectiveness where head-to-head trials are lacking.
- With the introduction of EU Joint Clinical Assessment (JCA) and the multiple PICOs (Population, Intervention, Comparison, and Outcomes) likely required through this process, head-to-head data may not always be available for all comparisons, and therefore use of ITCs can be expected to become more prominent than for national HTA.
- Acceptance of ITCs conducted for EU JCA will also be vital for local value assessment, and therefore ITCs will be subject to both JCA and local guidelines.

Methods

- Key EUNetHTA member agencies were systematically prioritised according to a pre-specified protocol based on their influence, and the quantity and recency of their ITC guidelines.
- ITC methodological elements of interest were identified based on previous reviews of ITC guidance, as listed in Table 1.
- Detail on each element was extracted and compared across EUNetHTA member and JCA guidelines.[1,2]

Results

- Belgium (KCE),[3] France (HAS),[4] Germany (IQWiG),[5] the Netherlands (ZIN),[6] Norway (NOMA),[7] Portugal (Infarmed)[8] and the UK (NICE)[9,10] were identified as the most relevant EUNetHTA countries for inclusion, with a summary of their positioning on key ITC methods provided in Table 1.
- The level of detail varied widely across guidelines. JCA[1,2] and NICE[9,10] guidelines were the most extensive, with latest updates from KCE (2025)[3] now directly referencing JCA.
- Generally, statistical methods guidance did not differ across countries. The greatest contrast was seen in acceptable data sources; unanchored comparisons and real-world evidence (RWE) were only recommended in specific circumstances by JCA[1,2] and NOMA,[7] yet more readily recommended when sufficiently justified by others. NICE provided detailed methods for the use of RWE in ITC,[11] which were not as extensively provided by other countries.

Conclusions

- There is variation in the level of detail provided within national and JCA guidelines for conducting ITCs. Where no detail is provided on key components, this may lead to ambiguity as to whether methods will be universally accepted at EU and national level accepted.
- The greatest contrast between guidelines was the acceptance of data sources (e.g. unanchored comparisons and RWE), whilst statistical methods guidance generally did not differ across countries.

Reflections

- With the role of multiple PICOs in EU JCA, acceptance of ITCs will be important for national decision-making.
- Lack of clarity or insufficient guidance in certain areas, together with inter-country variation, can hinder the development of comprehensive and robust evidence-generation plans to inform the required ITCs across all relevant countries. This poses a risk to consistency in patient access across Europe.
- Robust methods (e.g. systematic identification of effect modifiers, thorough assessments of heterogeneity and incorporation of patient-level data) should be followed as far as possible to maintain statistical rigour, while balancing the need for flexibility where such rigour may not be feasible given data limitations for clinically promising innovations or variation in clinical practice.
- As such, for future revisions to JCA guidelines, greater clarity and specificity in their methodological recommendations or use of alternative evidence source in ITCs, such as RWE, would be beneficial to ensure the robustness of ITCs generated by manufacturers and maximise the likelihood of patient access.
- As national HTA guidelines are updated, increasing reference to JCA guidelines and parity of recommended ITC methods are anticipated.

Table 1: Summary of EUNetHTA ITC guidance

Strong recommendation | Recommendation with caution | Recommendation with strong caution | Not recommended

Market or Country	EU	UK	France	Germany	Portugal	Norway	Belgium	The Netherlands
HTA Agency	JCA	NICE[a]	HAS	IQWiG/G-BA	Infarmed	NOMA	KCE	ZIN
Year	2024	2012–2025	2009	2025	2022	2024	2025	2024
Volume of ITC Guidance (Pages)	56	5 + 8 TSDs[b]	51	17	17	6	4	<1
Influence[c]	NA	Catalyst	Traditionalist	Catalyst	Observer	NA	Traditionalist	Catalyst
Role of ITC/NMA	Where no RCT for comparison of interest, or multiple treatments to compare simultaneously	Where no RCT comparing all treatments of interest	Where direct evidence not available	Where direct evidence not available	Where direct evidence not available	NR	Refers to JCA	Where no RCT for comparison of interest
PICOs Scoping *Recommended methods*	Based on PICO: all available and relevant comparators	Based on scope: all comparators in established practice	NR	All comparators in established practice	All comparators in established practice	Based on PICO: current SoC or most used treatment	Refers to JCA	SoC and the most cost-effective treatment available in Dutch practice
Study Design *Use of single-arm trials*	Where no RCTs	Where no RCTs or to support RCTs	NR	Not recommended	Where no RCTs	Where no RCTs	Where no RCTs	NR
Study Design *Use of RWE*	Where no RCTs	Where no RCTs or to support RCTs	NR	Where no RCTs	Where no RCTs	Where no RCTs	Where no RCTs	NR
TEMs and PFs *Recommended methods for identification*	Literature, clinical validation, subgroup results	Literature, clinical validation	Subgroup results	Subgroup results	Literature, clinical validation	Literature, clinical validation	Refers to JCA	NR
Heterogeneity Assessment *Recommended methods*	Qualitative assessment, statistical tests	Qualitative assessment, statistical tests	Qualitative assessment, subgroup results	Qualitative assessment, statistical tests	Qualitative assessment, statistical tests	No recommended methods, but homogeneity required	Refers to JCA	No recommended methods, but homogeneity required
ITC vs. NMA *When is it appropriate to use NMA vs. ITC*	NMA for multiple comparators or where both direct and indirect evidence, otherwise ITC	NR	NMA for multiple comparators, otherwise ITC	NMA where both direct and indirect evidence, otherwise either	NMA for multiple comparators or where both direct and indirect evidence, otherwise ITC	NMA for multiple comparators, otherwise ITC	NMA for multiple comparators, otherwise ITC	NR
NMA Methodology *Recommended methods including Frequentist vs. Bayesian methods, and FE vs. RE*	Freq. or Bay., Bay. for sparse networks, non-informative priors preferred, RE preferred	Freq. or Bay., non-informative priors preferred (except in sparse networks), FE or RE dependent on heterogeneity	Freq. or Bay., informative priors not recommended, FE or RE dependent on heterogeneity	Freq. or Bay., scenario analyses recommended for different priors, RE preferred	Freq. or Bay., Bay. for few events, non-informative priors preferred, FE or RE dependent on heterogeneity	Freq. or Bay., FE and RE	Refers to JCA	Freq. or Bay.
Population-Adjustment *Recommended methods*	MAIC, STC, ML-NMR, meta-regression	MAIC, STC, meta-regression	Meta-regression	PSM	MAIC, STC, meta-regression	MAIC, STC, ML-NMR (non-TTE)	PSM, refers to JCA	MAIC, STC
Baseline Risk *Recommended methods*	NR	Meta-regression	NR	NR	Meta-regression	NR	NR	NR
Unanchored Comparisons *Recommended methods*	Full IPD generally required	Full IPD generally required	NR	Full IPD generally required	Full IPD generally required	Full IPD generally required	Full IPD generally required	NR
Survival Analysis *Recommended methods for PH assessment and accounting for violations*	PH assumption must be met, alternative methods suggested	PH assumption must be met, alternative methods suggested	NR	PH assumption must be met, does not suggest alternative methods	NR	PH assumption must be met, alternative methods suggested	Refers to JCA	NR

[a]Although the UK contains other HTA agencies such as the SMC and AWMSG, these refer to NICE for guidance on HTA methods and processes. Thus, only NICE guidance was reviewed for the UK. [b]TSDs are also available from NICE containing further guidance.[12] [c]Classifications of HTA agencies according to a TLR by Kumar *et al.* (2025),[13] based on an analysis of their proactivity, and influence and insights provided by expert interviewees.

Abbreviations: **AWMSG:** All Wales Medicines Strategy Group; **EUNetHTA:** European Network for Health Technology Assessment; **FE:** fixed effects; **G-BA:** *Gemeinsamer Bundesausschuss*; **HAS:** *Haute Autorité de Santé*; **HTA:** health technology assessment; **Infarmed:** *Autoridade Nacional do Medicamento e Produtos da Saúde*; **IPD:** individual participant data; **IQWiG:** *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*; **ITC:** indirect treatment comparison; **JCA:** Joint Clinical Assessment; **KCE:** *Kenniscentrum voor de Gezondheidszorg*; **MAIC:** matching-adjusted indirect comparison; **ML-NMR:** multi-level network meta-regression; **NA:** not applicable; **NICE:** National Institute of Health and Care Excellence; **NMA:** network meta-analysis; **NOMA:** Norwegian Medical Products Agency; **NR:** not reported; **PF:** prognostic factor; **PH:** proportional hazards; **PICO:** Population, Intervention, Comparator, Outcome; **PSM:** propensity score matching; **RCT:** randomised controlled trial; **RE:** random effects; **RWE:** real-world evidence; **SMC:** Scottish Medicines Consortium; **SoC:** standard of care; **STC:** simulated treatment comparison; **TEM:** treatment effect modifier; **TLR:** targeted literature review; **TSD:** technical support document; **TTE:** time to event; **ZIN:** *Zorginstituut Nederland*.

References: [1]HTA CG. Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons. 2024; [2]HTA CG. Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons. 2024; [3]KCE. Belgian Guidelines for Economic Evaluations and Budget Impact Analyses: Third Edition. 2025; [4]HAS. Summary Report: Indirect Comparisons Methods and Validity. 2009; [5]IQWiG. Allgemeine Methoden: Entwurf für Version 8.0. 2025; [6]ZIN. Guideline for Economic Evaluations in Healthcare. 2024; [7]NOMA. Submission Guidelines For Single Technology Assessment of Medicinal Products. 2024; [8]Infarmed. Methodology for Pharmacotherapeutic Assessment of Health Technologies. 2023; [9]NICE. NICE Health Technology Evaluations: The Manual. 2025; [10]NICE. CHTE2020 Sources and Synthesis of Evidence; Update to Evidence Synthesis Methods. 2020; [11]NICE. DSU TSD 17. 2015; [12]NICE. NICE DSU TSDs. Available at: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list [Accessed: 22 Sept 2025]; [13]Kumar G, Radu P, Cubi-Molla P, *et al.* Navigating change: a comparative analysis of health technology assessment reforms across agencies - processes, drivers, and interdependencies. Int J Technol Assess Health Care 2025;41:e21. **Acknowledgements:** The authors thank Danielle Kerr for graphic design assistance. This study was funded by Johnson & Johnson Innovative Medicine.