Shifts in the French HTA Transparency Committee's Use of Indirect Comparisons: Insights From a Systematic Review of the French Transparency Committee Opinions

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CONTEXT

Randomized controlled trials remain the 'gold standard' for health technology assessments (HTAs). However, **single-arm trials are often used when comparative trials are not feasible or unethical to conduct**, which can be challenging for traditional HTA. Moreover, in case of multiple treatments in an indication, **all direct comparisons are not feasible especially when clinical developments are concomitant**. In such cases, indirect comparison methodologies provide robust statistical approaches that can be leveraged to generate comparative evidence on relative treatment effects.

OBJECTIVE

This study aims to assess how the French Transparency Committee (TC) has evaluated indirect comparison (IC) methodologies over the past four years. By conducting a comparative analysis of TC opinions issued before and after the release of its updated evaluation doctrine (February 2023)[1], the study highlights shifts in the appraisal and acceptance of ICs.

METHODOLOGY

This study presents a systematic review of TC opinions including IC over an 18-month period before and 29-month period after the publication of the doctrine (May 2021-July 2025). Data were manually extracted to identify the type of IC methodologies, its level of acceptance, and its potential impact on ASMR (added value) ratings. Quantitative and qualitative analyses assessed changes over time.

Specific focus was placed on rare diseases and pediatric indications, where randomized controlled trials are often unfeasible.

RESULTS

Characteristics of Transparency Committee Opinions Analyzed

Among 836 TC opinions analyzed, 162 (19,4%) included an IC, with a slight decrease following February 2023. These 162 opinions resulted in 207 indirect comparisons: 79 (in 64 opinions) issued before the publication of the doctrine, and 128 (in 98 opinions) issued after.

Thus, 25% of the 255 pre-doctrine opinions included an IC, compared to 17% of the 581 post-doctrine opinions.

> In 29% of cases, the indirect comparison was based on single-arm clinical trials, evaluating treatments mainly indicated in oncology (70%), followed by hematology (8%).

> The types of requests associated with these opinions were varied: 77 concerned initial registration, 55 were for indication extensions, and 30 for reassessments.

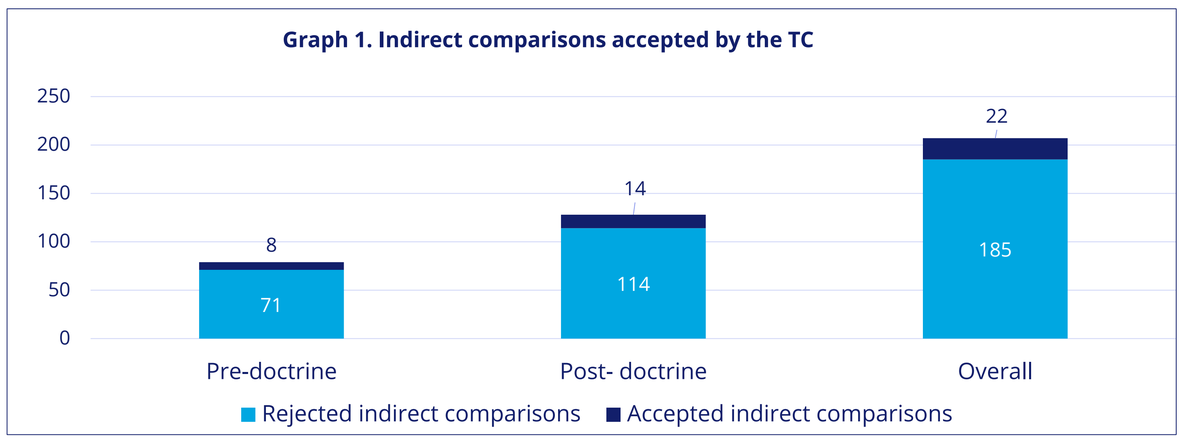
> The therapeutic areas covered by these opinions were diverse, with oncology being by far the most represented (65 opinions, 40%), followed by neurology (13 opinions, 8%), dermatology (11 opinions, 7%), and cardiology (10 opinions, 6%).

> The most commonly used IC method was NMA (43%) followed by MAIC (32%).

Transparency Committee Review

> Despite the evolution of the TC doctrine on ICs, rejection rates remain high regardless of the evaluation period, with only 22 ICs accepted (11%) over the entire analysis period (cf. Graph 1). However, disparities are observed across years, with higher acceptance rates in 2022 (16%) and 2023 (15%), but very few accepted in 2024 (6%).

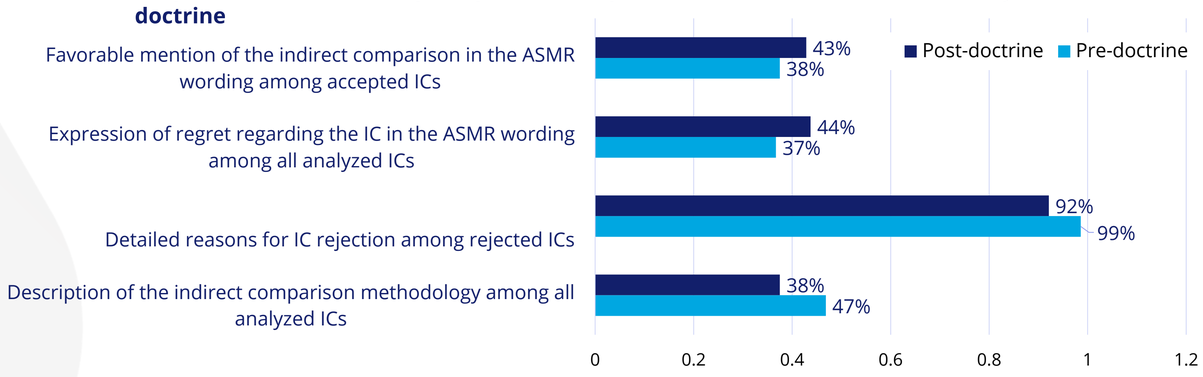
Graph 1. Indirect comparisons accepted by the TC



> Mentions of ICs in ASMR wording increased (38% before *vs*. 43% after doctrine), suggesting improved transparency, although fewer methodological details were reported (cf. Graph 2).

> Notably, the reassessment of Libtayo[2] on cutaneous squamous cell carcinoma represents the only case where an IC directly led to an improved ASMR rating in a subpopulation of the marketing authorization which were facing a therapeutic impasse.

Graph 2. Evolution of HAS perception in TC opinions before and after the February 2023 doctrine

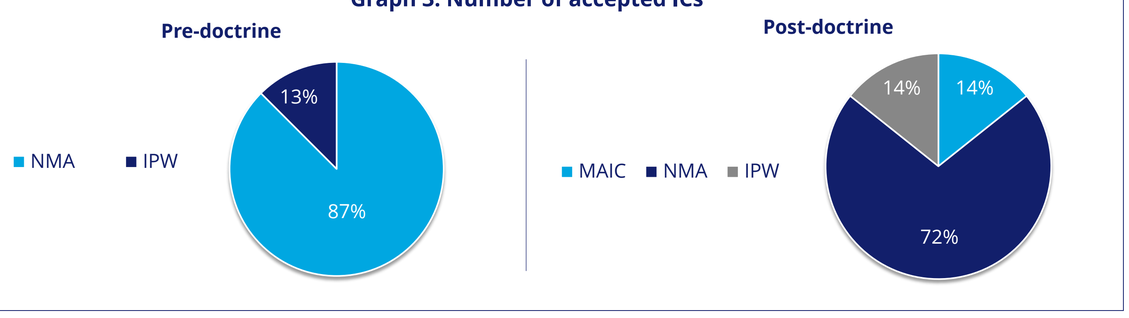


> The inverse probability weighting (IPW) was accepted by the TC in 33% of cases (25% *vs*. 40% in pre and post doctrine period), the NMA in 19% of cases (23% *vs*. 17%), and the MAICs only in 3% of cases (0% *vs*. 4%).

> Among the accepted ICs, NMAs remained the most frequently observed method, although their use is declining. In contrast, MAICs and IPW methods have gained traction since 2023. MAICs, absent prior to 2023, now represent 14% of accepted ICs despite ongoing methodological concerns (cf. Graph 3).

> Only 2 MAICs (single-arm study *vs*. historical cohort) were accepted by TC in a context of rare disease: for Zokinvy[3] (SPHG*) in pediatrics and adults and for Zolgensma[4] (Spinal muscular atrophy) in pediatrics. These MAICs were matched on various factors (age, *etc*.) from individual patient data.

Graph 3. Number of accepted ICs



> A slight improvement in transparency regarding the rejection of ICs was observed: the reasons for rejection were detailed in 92% of cases in pre-doctrine *vs*. 99% after its publication. The main reasons for refusal by the TC were:

- For NMAs, the issues were the failure to meet the assumptions of consistency and transitivity.
- For MAICs, the issues were the unanchored nature of the comparison and the lack of individual patient data across all studies.
- For both methods, common limitations were mentioned, including heterogeneity in patients or study characteristics, small sample sizes, residual confounding bias, and uncertainties related to the consideration of all effect modifiers and prognostic factors.

Specific Focus on Rare Diseases and Pediatric Indications

❖ Pediatric indications, a positive shift toward accepting ICs

> In total, 28 ICs were evaluated by the TC: 10 before the doctrine and 18 after.

> Since the publication of the new doctrine, the acceptance rate of ICs by the TC in pediatric indications has more than doubled (22% [n=4] post-doctrine *vs*. 10% [n=1] pre-doctrine) and favorable mentions in ASMR wordings have also increased (10% of cases pre-doctrine [n=1] *vs*. 17% post-doctrine [n=3]).

❖ Rare diseases indications, an improvement in transparency

> In total, 82 ICs were evaluated by the TC: 25 before the doctrine and 57 after.

> Despite an increase in accepted single-arm trials (100% post-doctrine vs. 50% pre-doctrine), no specific adaptation of the evaluation methodology has been made: overall acceptance remains low and slightly lower than the general case (6% vs. 11%), with no real change over time (8% vs. 5% between the pre and post-doctrine periods).

> An improvement in transparency can be observed: although favorable mentions in ASMR wordings remain rare (5%; n=3), they have increased between the pre- and post-doctrine periods (0% vs. 5% in pre and post-doctrine). Notably, all ICs accepted after the doctrine received a favorable mention in the ASMR wording, unlike in the general case (43%).

CONCLUSION

Despite the growing recognition of ICs, the TC remains cautious, requiring rigorous justification and methodology. **The doctrine** is more aligned with a desire for **methodological clarification and anticipation** than with a radical transformation of practices. **This rigor contrasts with other, more permissive European agencies, particularly within the framework of the Joint Clinical Assessment , where the harmonization of methodological requirements is becoming a central issue for manufacturers[5].**

The results, however, suggest the emergence of differentiated acceptability depending on therapeutic areas or specific clinical situations: pediatric indications are subject to more flexible consideration and conversely, for rare diseases—despite similar methodological constraints— the transparency improved but acceptability remains low, and rejections are still frequent.

This analysis has certain limitations: it is based on published TC opinions, which do not necessarily detail all the methodologies used by manufacturers. Moreover, the specific reasons for rejection are not always documented, which may introduce interpretation bias.

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Notes: ASMR: Improvement in the actual clinical benefit; MAIC: Matching-Adjusted Indirect Comparisons; NMA: Network meta-analysis; *SPHG: Hutchinson-Gilford syndrome or progeroid laminopathies

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