Methodological challenges in the economic evaluation of cell and gene therapies in oncology: Examples of UK and France

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Background

- Cell and gene therapies (C&GT) offer therapeutic solutions for patients with previously untreatable conditions.
- However, these innovative therapies pose significant challenges in terms of health technology assessment (HTA), notably due to the difficulty of conducting traditional randomized controlled clinical trials, as C&GT trials are inherently associated with small patient populations

Objective

- The objective of this study was to **highlight the specific methodological challenges encountered in the economic and clinical evaluation of C&GT**.

Methods

- A targeted literature review was conducted to identify all HTA appraisals of C&GT in oncology in France and UK over the past 5 years (2019–2023).
- The checklist from Drummond *et al.* was used to report and categorize limitations and methodological comments from HTA bodies.
- The statistical implication of each comment was then analyzed to identify the specificity of C&GT when using the standard evidence assessment framework.
- Only limitations mentioned in at least two dossiers were reported in **Figure 2**.
- The NICE geographical scope does not include the entire United Kingdom (UK). For example, Scotland is covered by the Scottish Medicines Consortium (SMC).

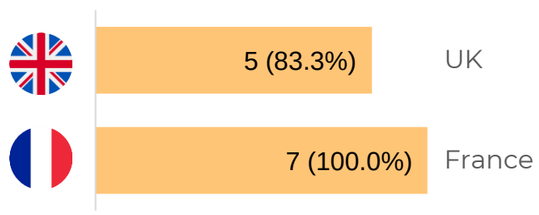
Results

- Seven and six HTA reports from HAS and NICE were reviewed respectively (n=13). The most common indication for both HTA bodies were diffuse large-B cell lymphoma (**Table**).
- All therapies were recommended for reimbursement by the HAS vs five by NICE (**Figure 1**).
- Overall, the main limitations flagged were related to data immaturity (n=10), use of a single-arm trial (n=9), extrapolation to long-term outcomes (n=8), small sample size (n=7), and the presence of a selection bias (n=6) (**Figure 2**).
- When an indirect comparison was conducted, the omission of prognostic factors (n=5) and the heterogeneity of the studies included (n=3) were also highlighted.
- The relevance of the primary endpoint was also mentioned in three appraisals.
- From a methodological standpoint, the main concerns were related to the generalizability and reproducibility of the clinical evidence submitted

Table. Number of dossiers reviewed by indication

Indication	France	UK
Diffuse large B-cell lymphoma	3 (42.9%)	2 (33.3%)
B-cell acute lymphoblastic leukemia	1 (14.3%)	2 (33.3%)
Mantle cell lymphoma	1 (14.3%)	1 (16.7%)
Multiple myeloma	2 (28.6%)	0 (0.0%)
Follicular lymphoma	0 (0.0%)	1 (16.7%)
TOTAL	7 (100.0%)	6 (100.0%)

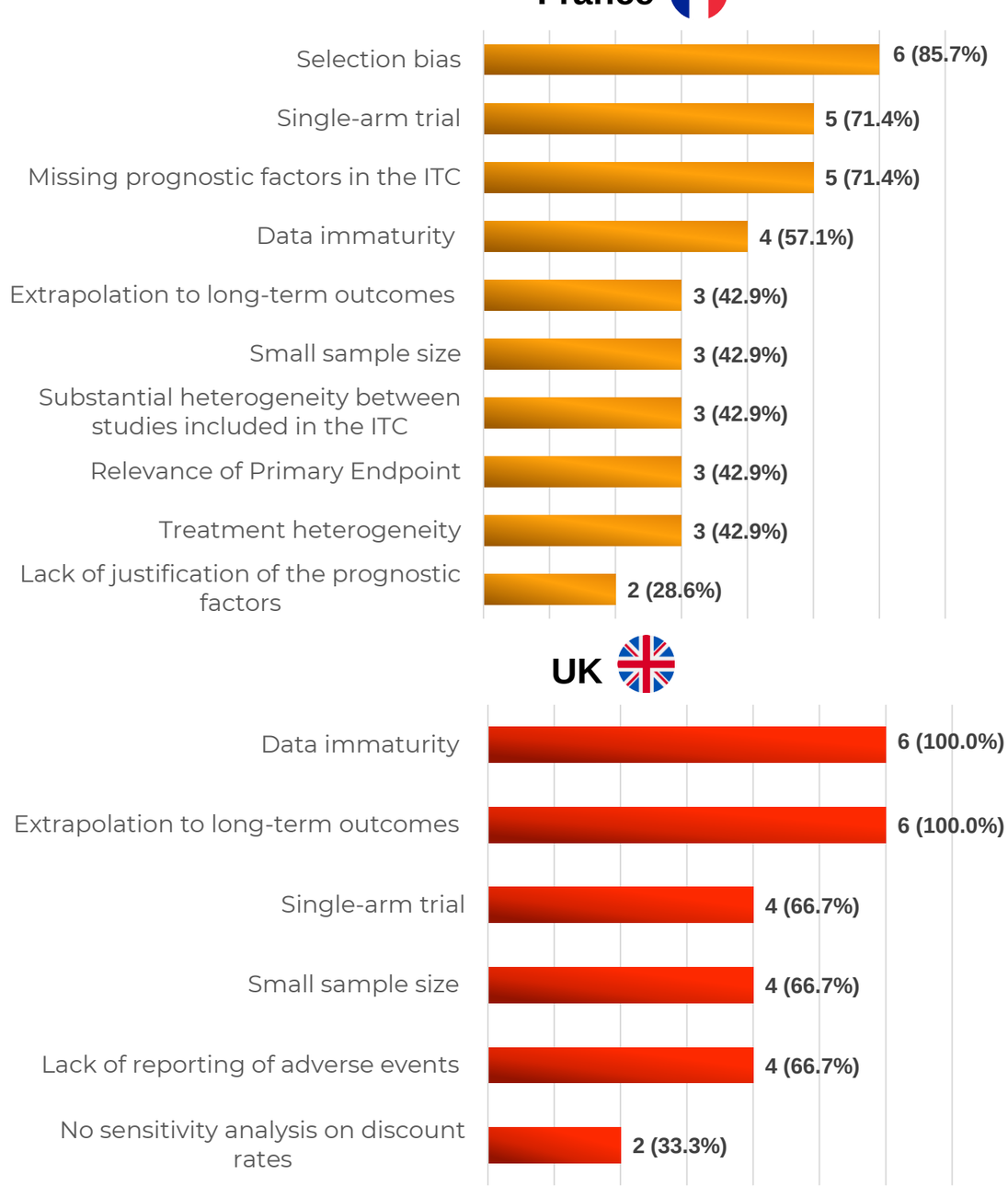
Figure 1. Number of drugs recommended for reimbursement



HTA bodies frequently cited **data immaturity** and the need to address **uncertainty in long-term extrapolations** as primary limitations when reviewing C&G therapies.

Additionally, they raised concerns about **insufficient justification** and **improper implementation of indirect treatment comparisons**.

Figure 2. Limitations mentioned by HTA bodies



Discussion

- Most criticisms mentioned by HTA bodies were related to the specificities of C&GT: the selection of patients, generally young, with higher chances of responding to treatment (selection bias); the non-comparative nature of the pivotal trial (single-arm); The data immaturity and consequently the uncertainty around long-term outcomes.
- Despite growing guidance (e.g., NICE DSU TSD 18) on unanchored ITC methods like matching-adjusted indirect comparison (MAIC), simulated treatment comparison (STC), and multilevel network meta-analysis, incorrect implementation of ITC were noted in several dossiers submitted to France's HAS.
- The limitations cited by HAS and NICE differed, suggesting each HTA body may have a distinct perspective on C&GT.
- Despite the limitations mentioned, almost all therapies were recommended for reimbursement by both HTAs, highlighting significant unmet needs in some oncology areas.
- This study may help manufacturers anticipate HTA agencies' methodological comments. Early meetings with HTA bodies are essential for identifying and addressing potential challenges.

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