Structural Uncertainty in Model-Based economic Appraisal: A Document Review of the French National Authority for Health

HTA303

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Background

Context

- In France, the reimbursement pathway involves the French health technology assessment body called the Authority for Health (*Haute autorité de santé*, *HAS*) since 2004 [1].
- Within the HAS, two commissions are carrying out the assessment of the reimbursement dossiers submitted by pharmaceutical companies [1]:
    - In case of medicines, the Transparency Commission (*Commission de la Transparence*) evaluates the clinical benefit and the clinical added benefit. This latest can range between 5 levels from "no improvement" (level V) to "major therapeutic progress" (level I). In case of medical devices, the National Committee for the Evaluation of Medical Devices and Health Technologies (*Commission nationale d'évaluation des dispositifs médicaux et technologies de santé*) evaluates the actual clinical benefit and the clinical added value (from level I to V).
    - The Commission for Economic and Public Health Evaluation (*Commission d'évaluation économique et de santé publique*, *CEESP*) evaluates the health economics part of the dossier if both the claimed clinical added value is from I to III and the new intervention might impact significantly the health insurance's expenses.
- The CEESP publishes model-based economic appraisal in which it presents in which extent the submitted dossier meets the methodological guidelines. If discrepancies occur, dossier can be qualified with minor, important, or major methodological reservations, according to the uncertainty associated to the discrepancy on the model's results [2].
- If the model-based economic appraisal includes at least one major reservation, it cannot be used for pricing negotiation, and the European price stability can be decreased below 3 years in case of first reimbursement request.
- The uncertainty can be stochastic, parametric, or structural [3]. While recommendations are rich regarding the first two, literature is scarce and old regarding this later, even if the CEESP's guidelines incorporated in 2020 some updates [2].
- Structural uncertainty is related to methodological choices about the modelling hypothesis and was categorized into 6 criteria by Bojke et al.: Data, comparator, event, health states/structure, statistical tools, other [4].

Objective

- To describe how the CEESP qualifies the structural uncertainty and how it had evolved with the guideline's updates.

Methods

Identification and selection of model-based economic appraisals

- All model-based economic appraisals published from inception until April 30th, 2025, were included.
- Model-based economic appraisals were selected from the HAS website [5].
- Model-based economic appraisals were excluded if:
    - Report was not retrieved;
    - The dossier was related to the renewal of reimbursement;
    - The dossier was an updated evaluation;
    - The dossier was not based on a model;
    - The reimbursement request was cancelled while the assessment was carried out.
- Selection of model-based economic appraisal was presented according to the PRISMA method [6].

Data extraction

- The following data was extracted for each selected model-based economic appraisal:
    - Type of investigational intervention (medicine, medical device or vaccine)
    - Investigational intervention
    - Type of reimbursement request
    - Date of evaluation by the CEESP
    - Therapeutic area
    - Indication
    - Presence of structural uncertainty according to the Bojke et al.'s criteria
    - Labelling of the structural uncertainty
    - Qualification of this structural uncertainty: absence, minor methodological reservation, important methodological reservation, major methodological reservation
    - Impact of the structural uncertainty on validation of the model-based economic appraisals

Statistical analysis

- All analysis were performed descriptively: numbers, percentages, and medians with interquartile range were reported when relevant.
- To account for the update of the CEESP's guidelines, published in July 2020, we compared figures of appraisals validated before or after July 30th, 2020 ("first" and "second" periods, respectively).
- To test for differences, the z-test or Pearson's chi-square test were performed when required. Alpha-risk was set to 5%.

Results

Identification of model-based economic appraisals

- Overall, 250 model-based economic appraisals were available from the HAS website.
- After review, 212 mode-based economic appraisals were included in the review (Figure 1).

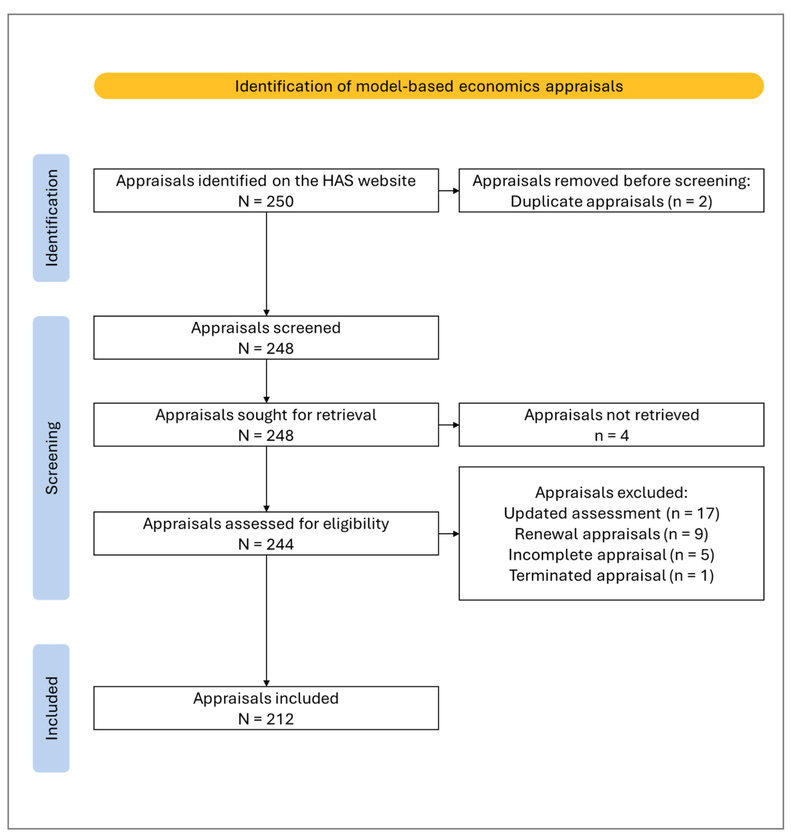

Figure 1. Identification and selection of model-based economic appraisals

HAS: Authority for Health (*Haute autorité de santé)*

Main characteristics of model-based economic appraisals

- During the first period, 112 model-based economic appraisals were evaluated, compared to the 100 evaluated during the second period. Type of reimbursement request was more frequently a first reimbursement application (n = 127, 60%) rather than an extension of reimbursement application (n = 85, 40%), regardless the period (Figure 2).

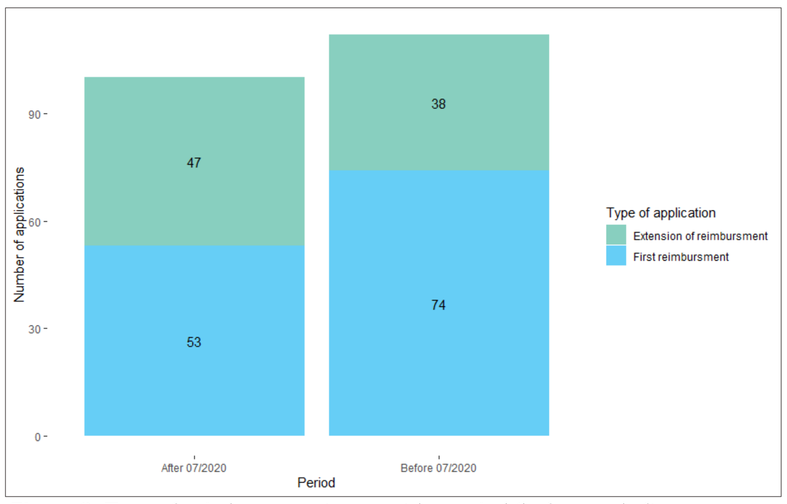

Figure 2. Type of reimbursement request by period (before and after guidelines update)

- Most of interventions were medicines (n = 191, 90%), then medical devices (n = 11, 5%) and lastly vaccines (n = 10, 5%).
- Most frequent therapeutic areas were oncology (n = 78, 37%), onco-hematology (n = 33, 16%) and rare diseases (n = 29, 14%) (Figure 3).

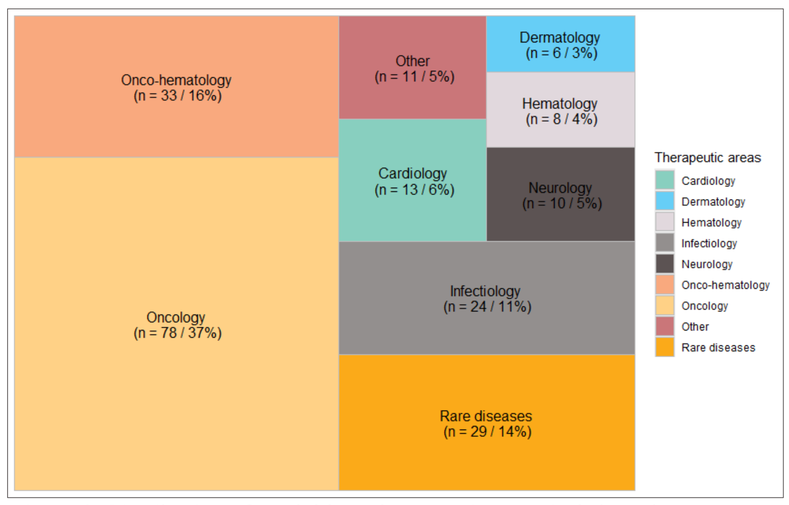

Figure 3. Distribution of model-based economic appraisals based on therapeutic areas (n = 212)

Presence of structural uncertainty

- Among the 212 model-based economic appraisals, 197 (93%) presented at least one structural uncertainty.
- A total of 725 structural uncertainties were identified among these model-based economic appraisals. Of these, 331 occurred in the first period (46%) and 394 in the second period (54%).
- Overall, most of structural uncertainties were related to the "Data" category (n = 167, 23%), followed by "Other" (n = 132, 18%), "Statistical tools" (n = 121, 17%), "Health states / structure" (n = 110, 15%), "Event" (n = 105, 14%) and "Comparator" (n = 90, 12%). The split by category and by period is presented in Figure 4.

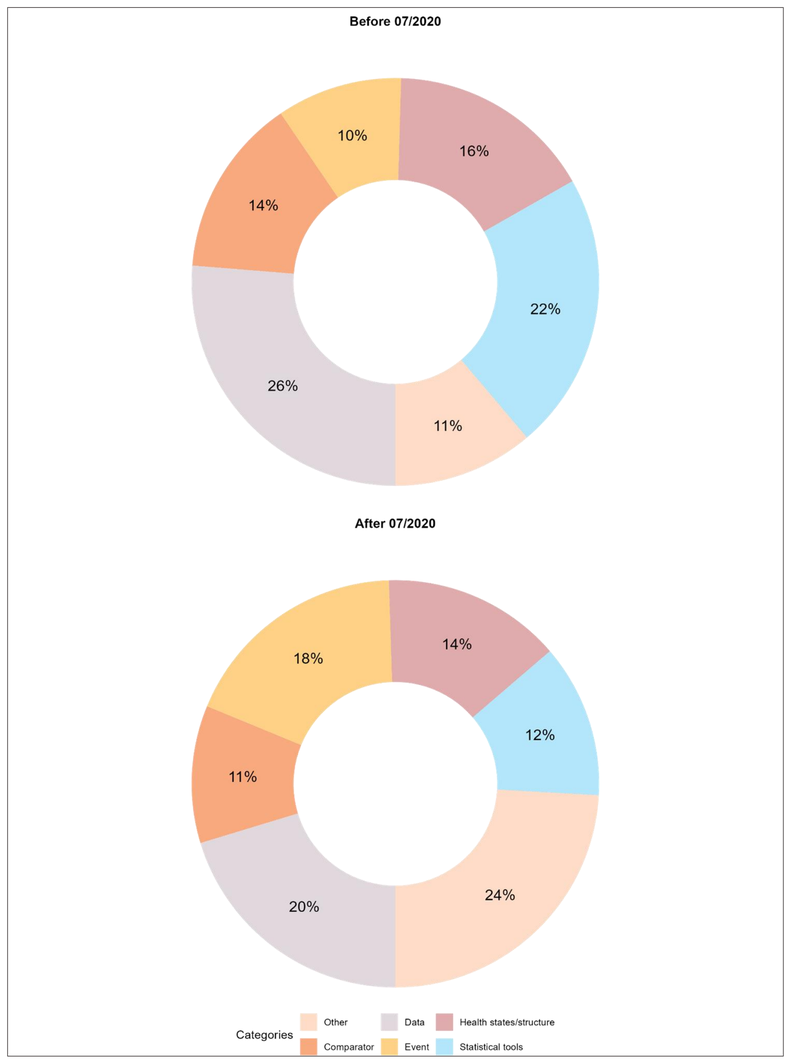

Figure 4. Repartition of structural uncertainties by categories (defined by Bojke et al.) and by period (n = 725)

Description of structural uncertainty

- Most structural uncertainty occurred when appraisals were about first reimbursement request (n = 456, 63%) rather than extension of reimbursement (n = 269, 37%).
- Overall, similarly to the repartition of model-based economic appraisals, most structural uncertainty was related to oncology (n = 220, 30%), onco-hematology (n = 113, 16%) and rare diseases (n = 100, 14%). More details regarding structural uncertainty by year and by therapeutic area is displayed in Table 1.

Table 1. Number of structural uncertainty by therapeutic area and by period

Therapeutic area	First period (N = 331)	Second period (N = 394)	Total (N = 725)
Oncology, n (%)	102 (31)	118 (30)	220 (30)
Oncohematology, n (%)	42 (13)	71 (18)	113 (16)
Rare disease, n (%)	34 (10)	66 (17)	100 (14)
Infectiology, n (%)	45 (14)	49 (12)	94 (13)
Cardiology, n (%)	38 (11)	14 (4)	52 (7)
Neurology, n (%)	21 (6)	20 (5)	41 (6)
Hematology, n (%)	13 (4)	18 (5)	31 (4)
Dermatology, n (%)	16 (5)	6 (2)	22 (3)
Endocrinology, n (%)	0 (0)	22 (6)	22 (3)
Other, n (%)	20 (6)	10 (3)	30 (4)

Evolution of structural uncertainty over time

- Overall, median number of structural uncertainty by model-based economic appraisal was 3 [2-5]. During the first period, median was 3 [2-4]. It increased during the second period (4 [3-5], p<0.002).
- Highest difference between periods was in the "Other" category.

Labelling analysis

- The labelling analysis allowed to identify "treatment waning", "time horizon", "duration of treatment" and "subsequent treatments" to be the main drivers of the between-periods difference (Figure 5).

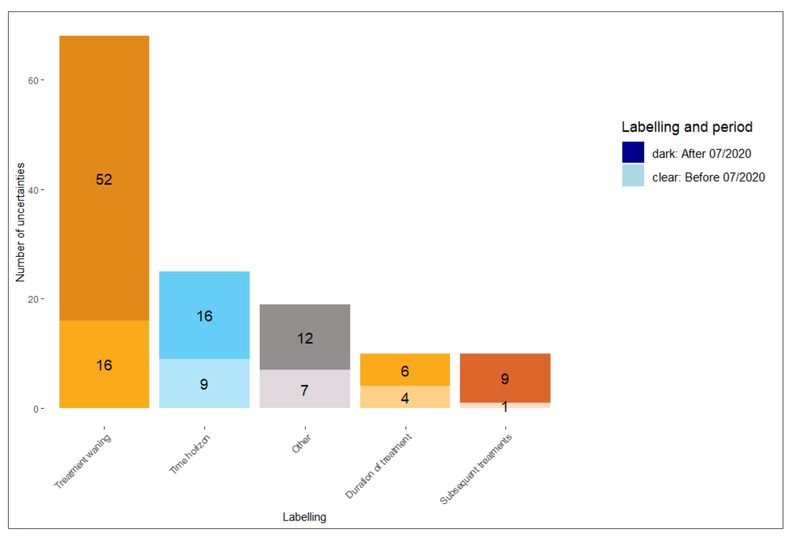

Figure 5. Labelling of structural uncertainties by period within the "Other" category (n = 132)

Qualification of structural uncertainty

- Of the 725 structural uncertainties, 571 (79%) were qualified by the CEESP with a methodological reservation.
- In the second period, structural uncertainties were more prone to by qualified with a methodological reservation (n = 333, 85%) than in the first period (n = 238, 72%) (p<0.005).
- The levels of methodological reservations by periods are presented in Table 2.

Table 2. Levels of methodological reservations overall and by periods (n = 571)

Levels of methodological reservations	Before 07/2020 (N = 238)	After 07/2020 (N = 333)	Total (N = 725)
None, n (%)	93 (28)	61 (15)	154 (21)
Minor, n (%)	98 (30)	140 (36)	238 (33)
Important, n (%)	114 (34)	169 (43)	283 (39)
Major, n (%)	26 (8)	24 (6)	50 (7)

Nota Bene: Percentages are calculated by periods, not overall

- In proportion:
    - There were less "no methodological" reservations in second period than in the first period (p<0.00006).
    - Minor and major reservations did not change significantly between periods (p=0.1, p=0.4).
    - Important reservations increased between first period and second period (p=0.02)

Impact of the structural uncertainty on validation of the model-based economic appraisals

- The 50 structural uncertainties qualified by a major methodological reservation were related to 43 different model-based economic appraisals.
- Among these 43 model-based economic appraisals, 13 had a major methodological reservation not related to structural uncertainty.
- Among the 30 model-based economics appraisal which presented a major methodological reservation only related to structural uncertainty, 15 were assessed in the first period and 15 in the second period.

Conclusions

- This is the first review to exhaustively assess how the French Health technology assessment body qualifies structural uncertainty. Structural uncertainty is deemed highly prevalent by the CEESP in model-based economic appraisals, which results in a growing number of methodological reservations. The update of the guidelines allowed the Authority for health to better qualify structural uncertainty.
- Since most of the increase in structural uncertainty was related to the "Other" category (Bojke et al.), improving its qualification would be valuable. Therefore, refining the existing Bojke et al. categories and introducing at least one related to the treatment of interest—potentially considering treatment duration and efficacy waning—would be beneficial.
- Similar research could be conducted on model-based economic appraisals published by other HTA bodies, such as the National Institute for Health and Care Excellence (NICE) in the United Kingdom.

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- All authors contributed, reviewed, and approved this poster.

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