A Review of the Quality-of-Life Data Use in French Economic and Public Health Assessment Committee's (CEESP) Efficiency Opinions for Immune-Checkpoint Inhibitors (ICIs) and Chimeric Antigen Receptor T (CAR-T cell therapies)

Gueye A[1,2], Lemasson H[2], Gaudin AF[2], Baklouti M[2]

[1] Master's degree in Health Economics and Market Access, Paris-Dauphine University, Paris, France, [2] Health Economics and Outcomes Research, Bristol Myers Squibb, Rueil-Malmaison, France

Introduction

- In several countries, health outcomes need to be measured in terms of QALYs (Quality-adjusted life years) to inform policy decisions.
- Quality of life (QoL) data such as utilities are required to produce QALYs in cost-utility analyses (CUAs).
- Use of different estimation methods, preference weights or imputation methods for missing data may lead to wide variation in utility values for the same patient in the same health state, all other things being equal.[1]
- These utility values have a substantial impact on the results of the economic evaluation. The impact of uncertainty around QoL data can be explored with probabilistic and deterministic sensitivity analyses.
- In France, the CEESP (Commission d'évaluation économique et de santé publique) is particularly vigilant about the methods used to select and integrate QoL data.
- Ensuring consistency in the methods is one of the key elements of the CEESP methodology guidance in order to enhance comparability among CUAs.
- Depending on compliance with the guidance, the CEESP exchanges with manufacturers during the technical debate and may issue reservations. A major reservation raises discrepancies in the method and invalidates the result of the CUA. 20% of methodological reservations relate to measurement of utilities integrated into models.[2]
- The large number of recent indications and EOs (efficiency opinions) for ICIs and CAR-Ts allows a comparative analysis of methodological approaches that is particularly interesting as it is limited to two therapeutic classes and similar indications.[3]

Objective

- The aim of the study was to review the methods used for valuing health states and for integrating QoL data into CUAs for ICIs and CAR-Ts since the beginning of economic evaluation in France. The second objective is to assess the extent to which the methods used by manufacturers have changed over time and to analyze how these methods are assessed by the CEESP.

Methods

Data collection

- A literature review of QoL data described in the « valuation of health states » section for all EOs related to ICIs and CAR-Ts from CEESP inception (2013) to May 31st 2022 was performed. Reservations raised by the CEESP were also reported.
- In each EO, the following data were collected for the study product and for the comparators:
  - General information on the product (nonproprietary name, therapeutic area…);
  - Health-states included in the model;
  - Sources of utility/disutility data: randomized controlled trial (RCT) used to inform the effectiveness, other RCTs, literature review;
  - Type of instruments used to describe health-states: Preference-based measure (PBM) from which prespecified utilities come or non-PBM;
  - Valuation methods: direct (standard gamble...) or indirect (PBM, non-PBM);
  - Mapping functions to estimate utilities from non-PBM outcomes or to convert outcomes from one PBM to another PBM;
  - Adjustments made to utility values: account for the impact of adverse events (AE), administration and decreasing QoL;
  - Missing data management: response rates and imputation method;
  - Sensitivity analyses conducted on QoL data;
  - Questions on QoL data during technical debate;
  - Number and type of methodological reservations: minor, important or major.

Data analysis

- Descriptive analyses for all collected data have been performed in total and by year of EO publication.

Results

General EOs description

- Among the 174 EOs available on the HAS website, 36 were related to ICIs and CAR-Ts. The first EO corresponding to our research scope was from 2015.
- 86% (N=31) of EOs were related to ICIs and 14% (N=5) of EOs were related to CAR-Ts. (Figure 1)
- 80% (N=29) of EOs were related to treatment in oncology and 20% (N=7) in treatment in onco-hematology. (Figure 1 and Figure 2)

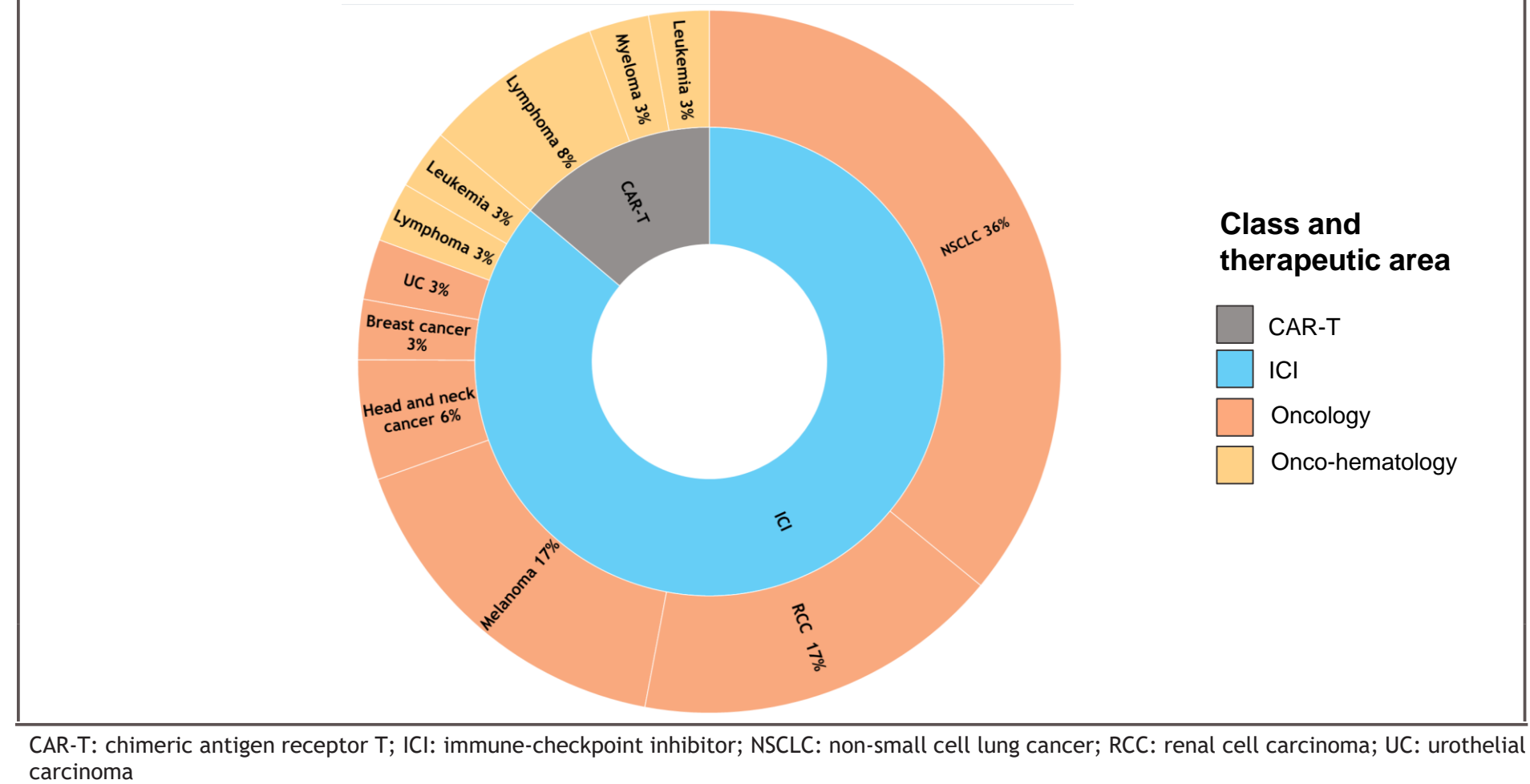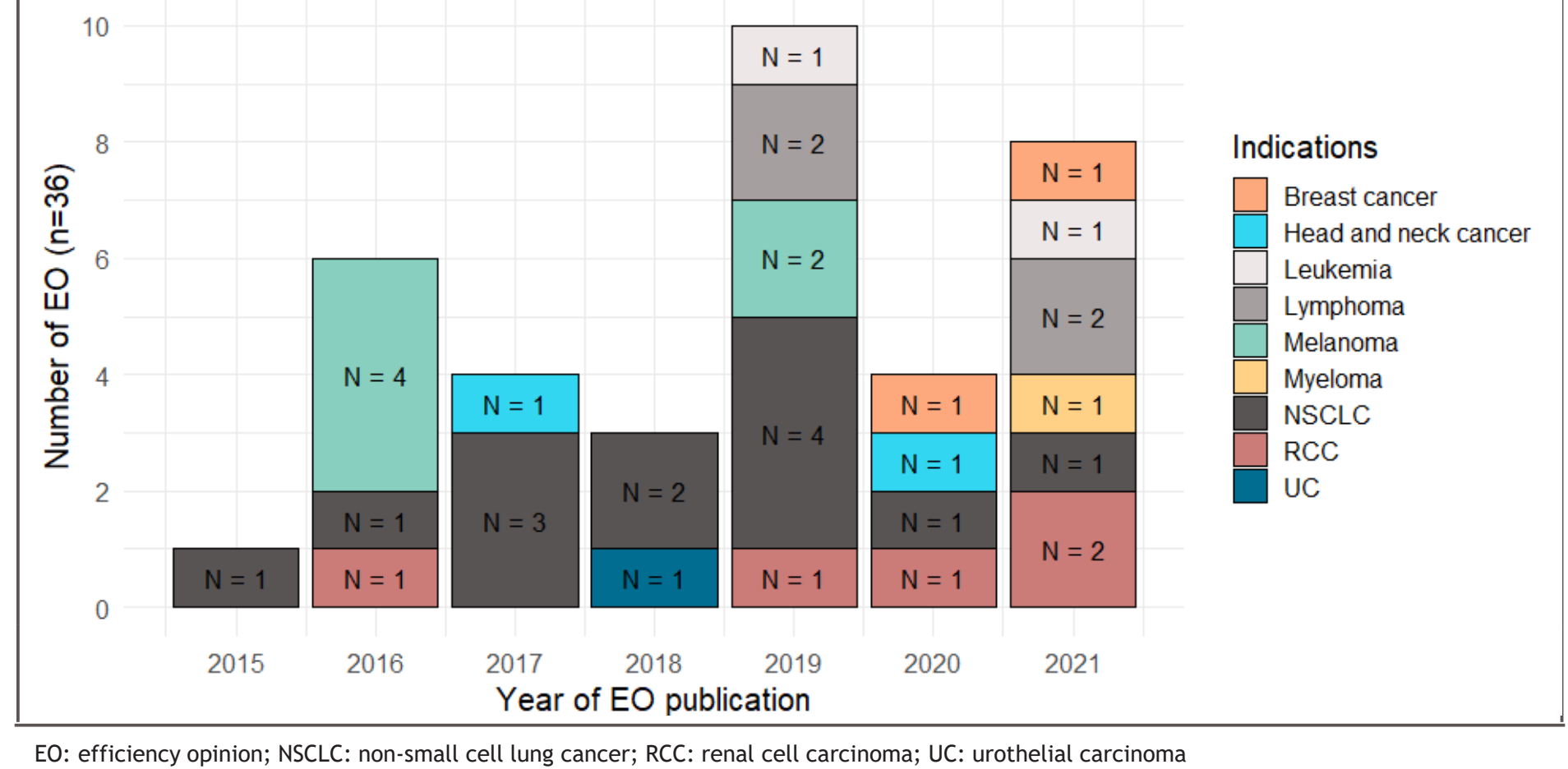**Figure 1. Distribution of EOs by class and therapeutic areas by year (N=36)**

CAR-T: chimeric antigen receptor T; ICI: immune-checkpoint inhibitor; NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma; UC: urothelial carcinoma

**Figure 2. Distribution of EOs by year of publication (N=36)**

EO: efficiency opinion; NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma; UC: urothelial carcinoma

Utilities in Economic Models

Sources

- Utility values were mostly (97%; N=35) retrieved from RCTs: in 74% (N=26/35) of EOs, the trial was open-label and in 26% (N=9/35) of EOs, it was blinded.
  - 83% (N=30) of EOs, reported the use of the RCT used to assess effectiveness as a source for utility values;
  - 11% (N=4) of EOs, reported the use of a combination of the RCT used to assess effectiveness and a de novo RCT as a source for utility values;
  - 1 EO, reported the use of a different RCT than the one used to assess effectiveness as a source for utility values
- 1 EO, reported the use of literature as a source for utility values. The method used to conduct the literature review was not reported. (Figure 3)

Figure 3. Sources of utility values
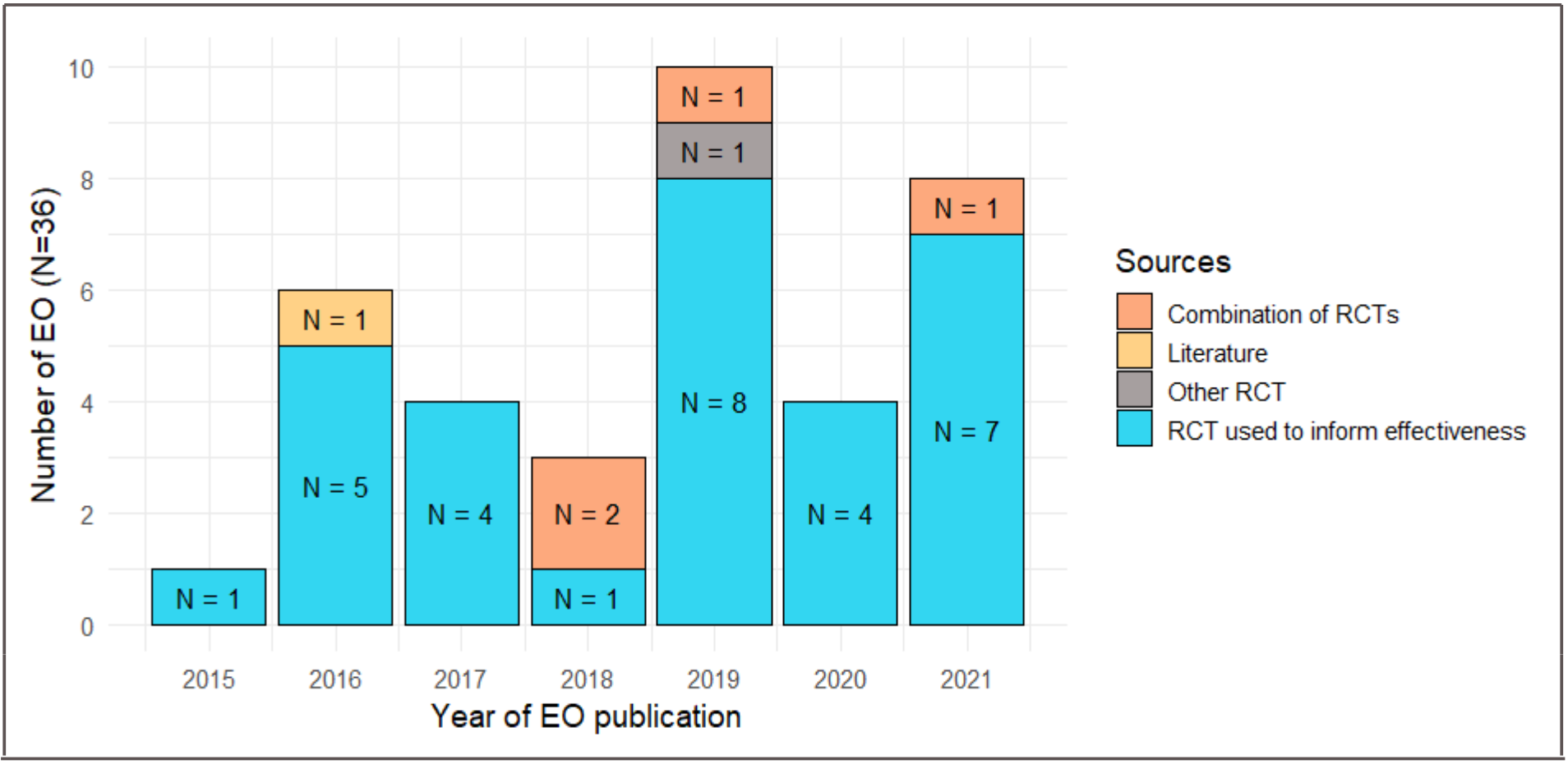
EO: efficiency opinion; RCT: randomized controlled trial

Health state description

- Most EOs reported the use of the EQ-5D instrument to describe health states (Figure 4):
  - In 47% (N=17) of EOs, the EQ-5D-3L was used;
  - In 19% (N=7) of EOs, the EQ-5D-5L was used
  - In 22% (N=8) of EOs, the type of EQ-5D used was not reported
- QLQ-C30 and SF-36 were respectively used in 2 and 1 EO.

Figure 4. Instruments used to describe health states by year of EO publication
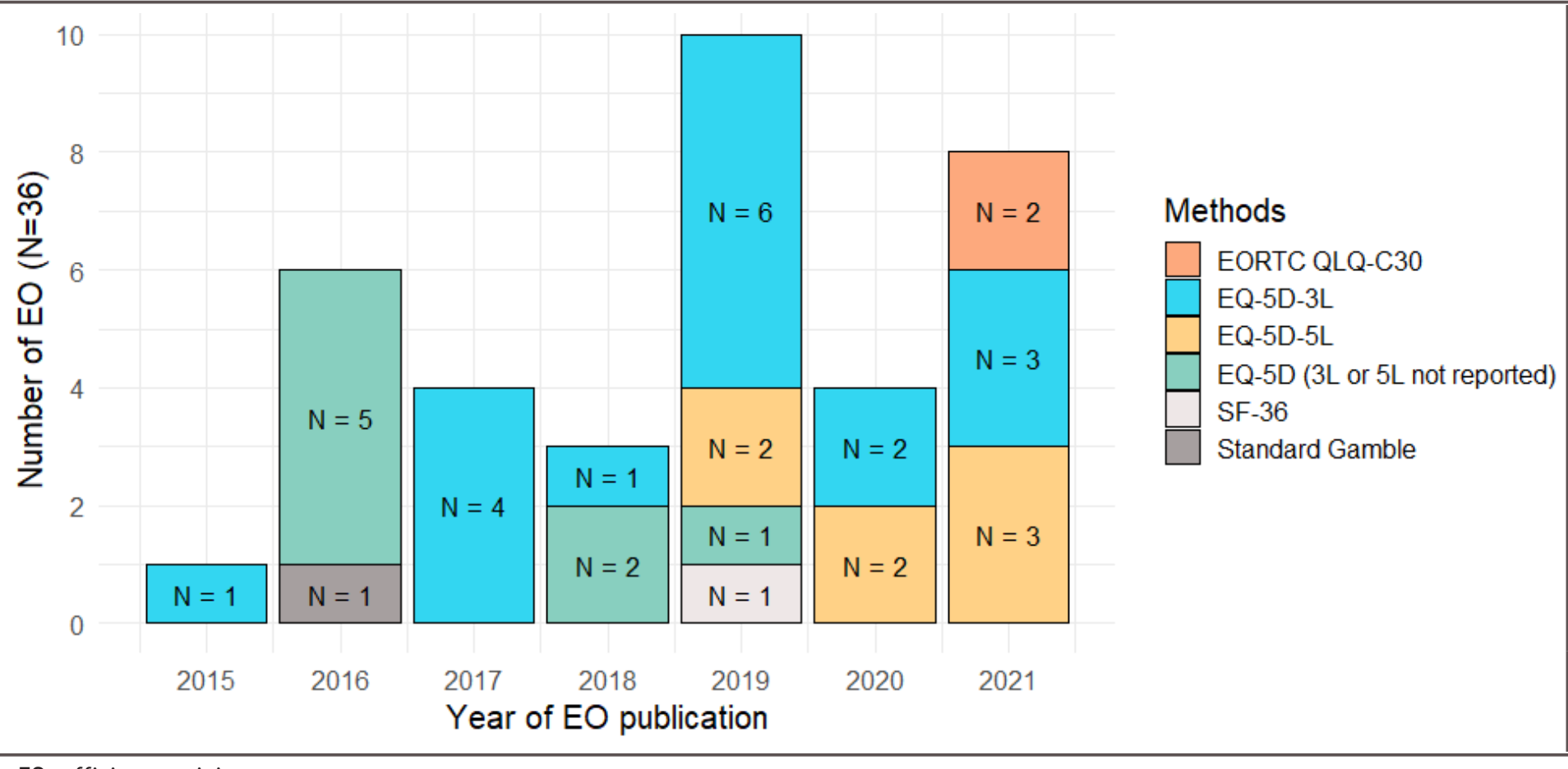
EO: efficiency opinion

Mapping function

- 86% (N=31) of EOs, integrated utilities from the same PBM used to describe health states, without the use of a mapping function.(Table 1)
- 14% (n=5) of EOs, reported the use of a mapping function:
  - 6% (N=2) of EOs, "mapped" utilities from EQ-5D-5L to EQ-5D-3L;
  - 8% (N=3) of EOs, "mapped" utilities from a non-PBM to describe health states (i.e QLQ-C30), to a PBM;
  - 60% (N=3/5) of them described the mapping function used and the statistical properties associated: The function used in 2 EOs to transform QLQ-C30 scores into EQ-5D-3L was described by Longworth et al.[4] The one used in 1 EO to transform EQ-5D-5L values into EQ-5D-3L values was described by Van Hout et al.[5]

Table 1. Mapping between health state descriptions instruments and valuation ones

	Instruments used to value health states from which utilities are integrated			
	EQ-5D (3L or 5L not reported) (N=9)	EQ-5D-3L (N=21)	EQ-5D-5L (N=5)	SG (N=1)
Instruments used to describe health states or value health states				
EQ-5D (3L or 5L not reported) (N=8)	8	NA	NA	NA
EQ-5D-3L (N=17)	NA	17	NA	NA
EQ-5D-5L (N=7)	NA	2	5	NA
QLQ-C30 (N=2)	NA	2	NA	NA
SF-36 (N=1)	1	NA	NA	NA
SG (N=1)	NA	NA	NA	1

same instrument; mapped instrument; NA: not applicable; SG: standard gamble

Health state valuation

- In the end, 97% (N=36) of EOs, reported the use of an indirect method, in which prespecified utilities are applied to patient-described health states using a PBM:
  - 58% (N=21) of EOs reported the use of the EQ-5D-3L;
  - 14% (N=5) of EOs reported the use of the EQ-5D-5L;
  - 25% (N=9) of EOs reported the use of the EQ-5D but did not report the type used.
- 1 EO reported the use of direct utility elicitation, where patients directly value their own health using an elicitation technique, it was the standard-gamble.
- Over the years, EQ-5D-3L is the most used instrument. (Figure 5)
- 1 EO used the EQ-5D-5L before the publication of its French valuation set in 2020.
- Even after 2020, the EQ-5D-3L is more used than the EQ-5D-5L.

Figure 5. Instruments used to value health states by year of EO publication (N=36)
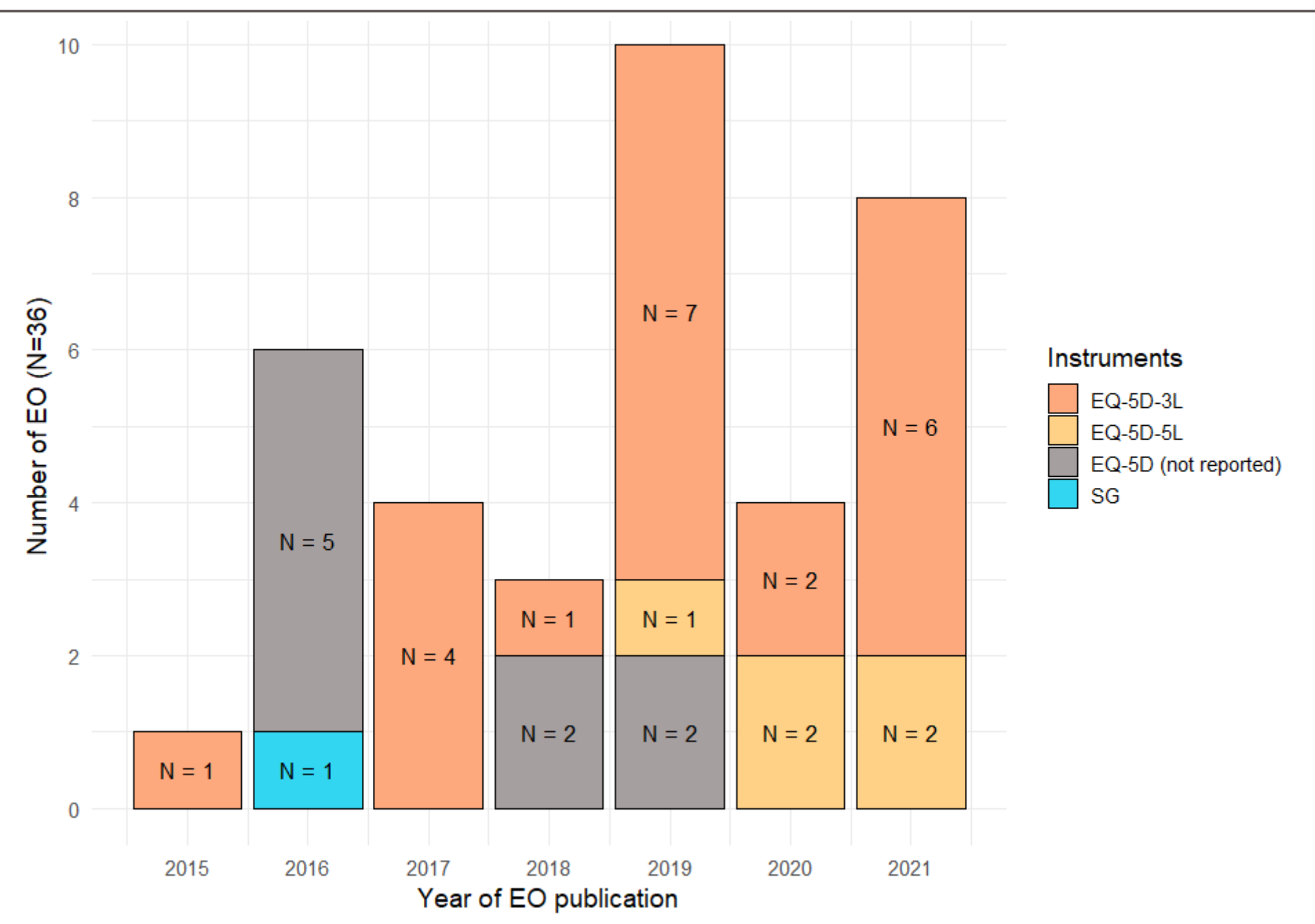
EO: efficiency opinion; SG: standard gamble

Country-specific value set

- 6% (N=2) of EOs reported the use of a non-French value set :
  - 1 EO reported the use of preferences from United-Kingdom;
  - 1 EO reported the use of a combination of preferences from United-Kingdom and Australia.
- 6% (N=2) of EOs did not report the country-specific value set used.

Response rates and missing data management

- Little information on missing data were reported as it appears in only 38% (N=14) of EOs.
- EOs did not report information on missing data such as response rates or imputation methods in a consistent way.
- 25% (N=9) of EOs reported the use of a mixed model for repeated measures (MMRM).

Integration into economic models

- 81% (N=29) of EOs, reported the use of treatment-independent utility values;
- 14% (N=5) of EOs, reported the use of a treatment-dependant utility value. In these latter, treatment-dependent values were applied only in the pre-progression state while in the post-progression state, treatment-independent values were applied;
- In 5% (N=2) of EOs, this information was not specified.
- RCTs and literature review were both used to inform treatment-related utilities and non-treatment-related utilities. In fact, open-label RCTs informed treatment-related utilities in 14% (N=5) of EOs. (Figure 6)

**Figure 6. Integration into Economic Models (N=36)**
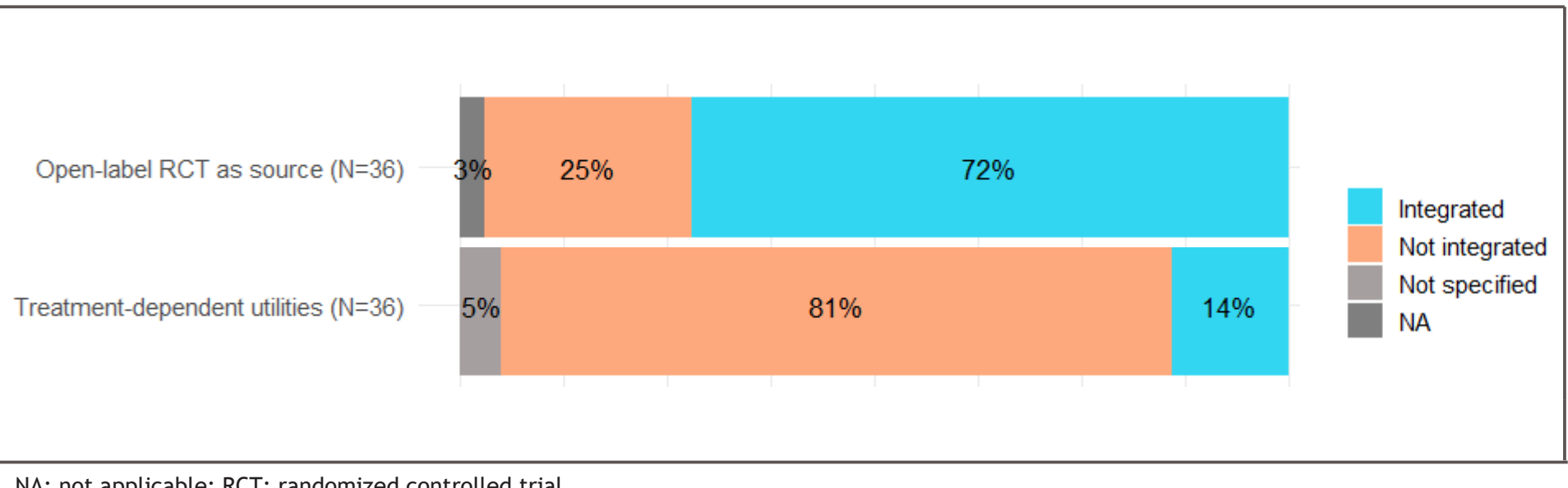
NA: not applicable; RCT: randomized controlled trial

Disutilities in Economic Models

Sources

- 89% (N=32) of EOs reported the use of disutilities (Figure 7):
  - In 33% (N=12) of EOs, disutility values were retrieved from RCTs;
  - In 56% (N=20) of EOs, disutility values were retrieved from literature (exclusively non-French or other submissions).
  - 34% (N=11) of EOs did not report the selection criteria. Same sources were used for different indications.
- When reported, the sources were the same for different indications.

Figure 7. Sources of disutility values by year of EO publication
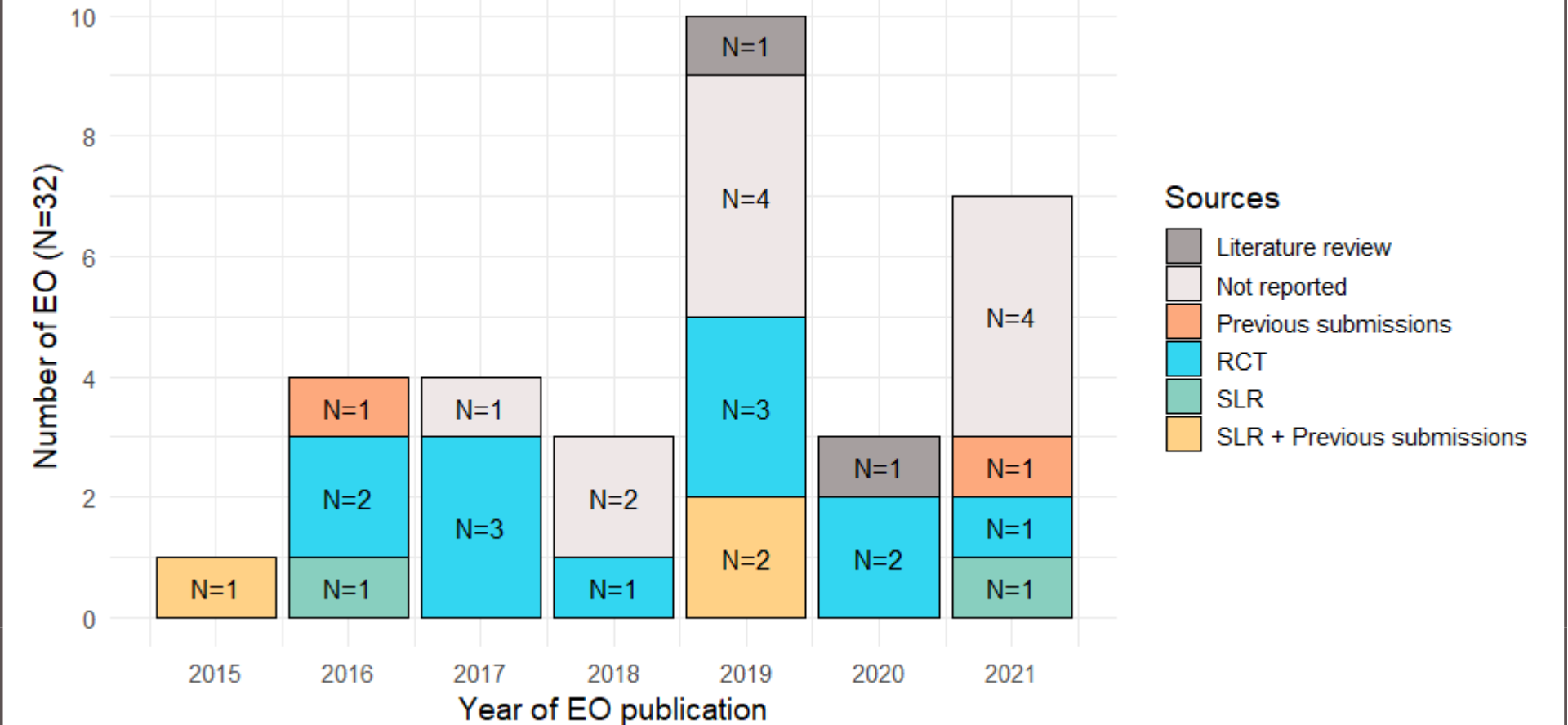
EO: efficiency opinion; RCT: randomized controlled trial; SLR: systematic literature review

- 50% (N=18) of EOs reported the use of the same sources for utilities and disutilities and 39% (N=14) reported the use of different sources. (Figure 8)

Figure 8. Relationship between sources of utility values and sources of disutility values
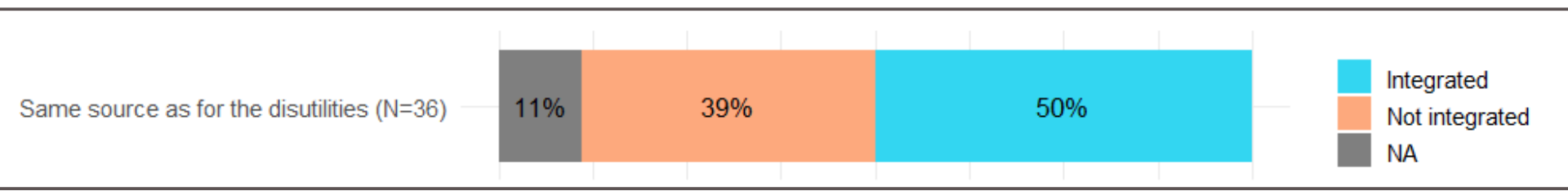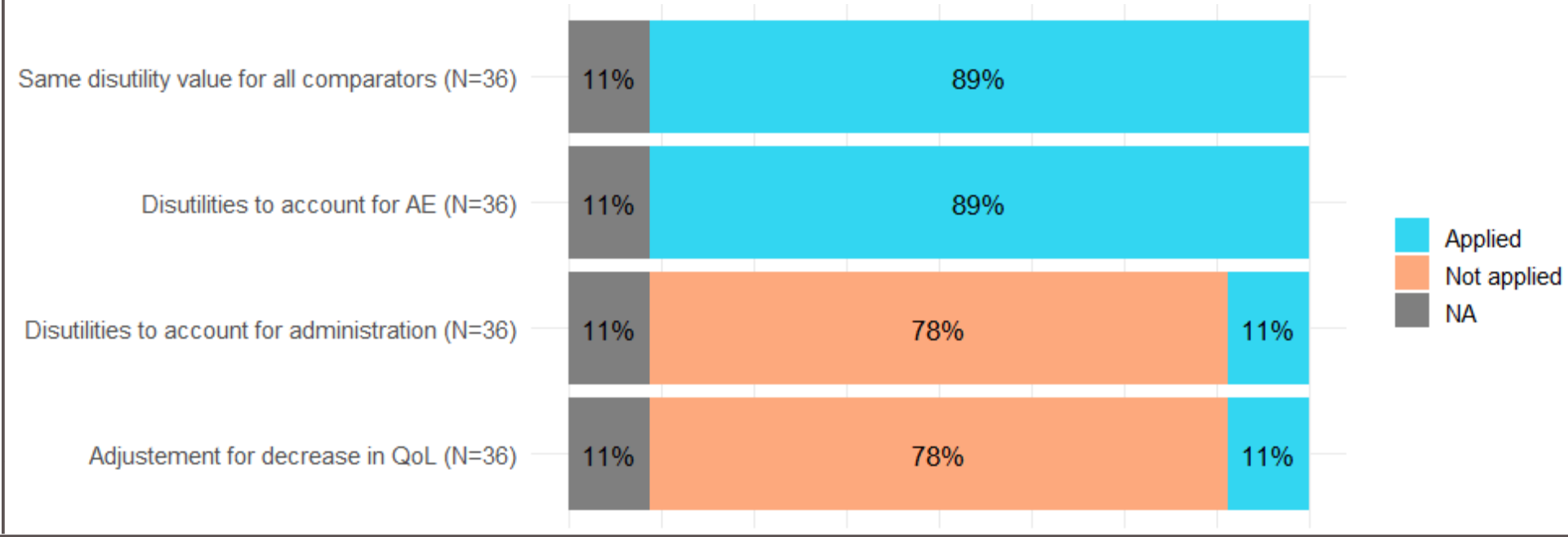

NA: not applicable

Integration of disutilities

- For 53% (N=19) of EOs, utility and disutility values were considered the same for all comparators, regardless of their difference in mechanism of action or AE. (Figure 9)
- All EOs which integrated disutilities (N=32), reported the use of disutilities to account for the impact of AEs; it was considered as a total score regardless of the type of AE in 39% (N=14) of EOs. In 39% (N=14) of EOs, disutilities reflected the expected duration of the AE.
- 12% (N=4/32) reported the use of disutilities to account for the impact of administration.

Adjustments to disutilities

- While the time horizon was on an average of 15 years for the EOs:
  - Only 12% (N=4) of EOs reported an adjustment to account for decrease in quality of life. This method appeared for the first time in 2019.
  - In 88% (N=28) of EOs, no adjustment was made (assumption of a stable quality of life). (Figure 9)
- The adjustment to account for a decrease in quality of life was never based on French data. 75% (N=3/4) of EOs reported the source behind this assumption.

Figure 9. Adjustments to account for decrease in QoL

AE: adverse event; NA: not applicable; QoL: quality of life

Sensitivity analyses

- Data reported in the section "valuation of health states" was included in the top 5 most sensitive parameters in 54% of deterministic sensitivity analyses and in the top 3 most sensitive parameters in 41% of deterministic sensitivity analyses. Utilities (value, sources, method of integration) were more likely to have an impact than disutilities.

Technical debate and methodological reservations

- Proportion of CEESP questions regarding this topic increased from 2% to 15% between 2015 and 2021. On an average, for every years, 9% of the technical debate by EO, relate to the "valuation of health states" section of the EO.(Figure 10)
- 67% (N=24) of EOs mentioned methodological reservations regarding QoL with 1 major reservation in 2021.

Figure 10. Proportion of CEESP questions on QoL data over the years
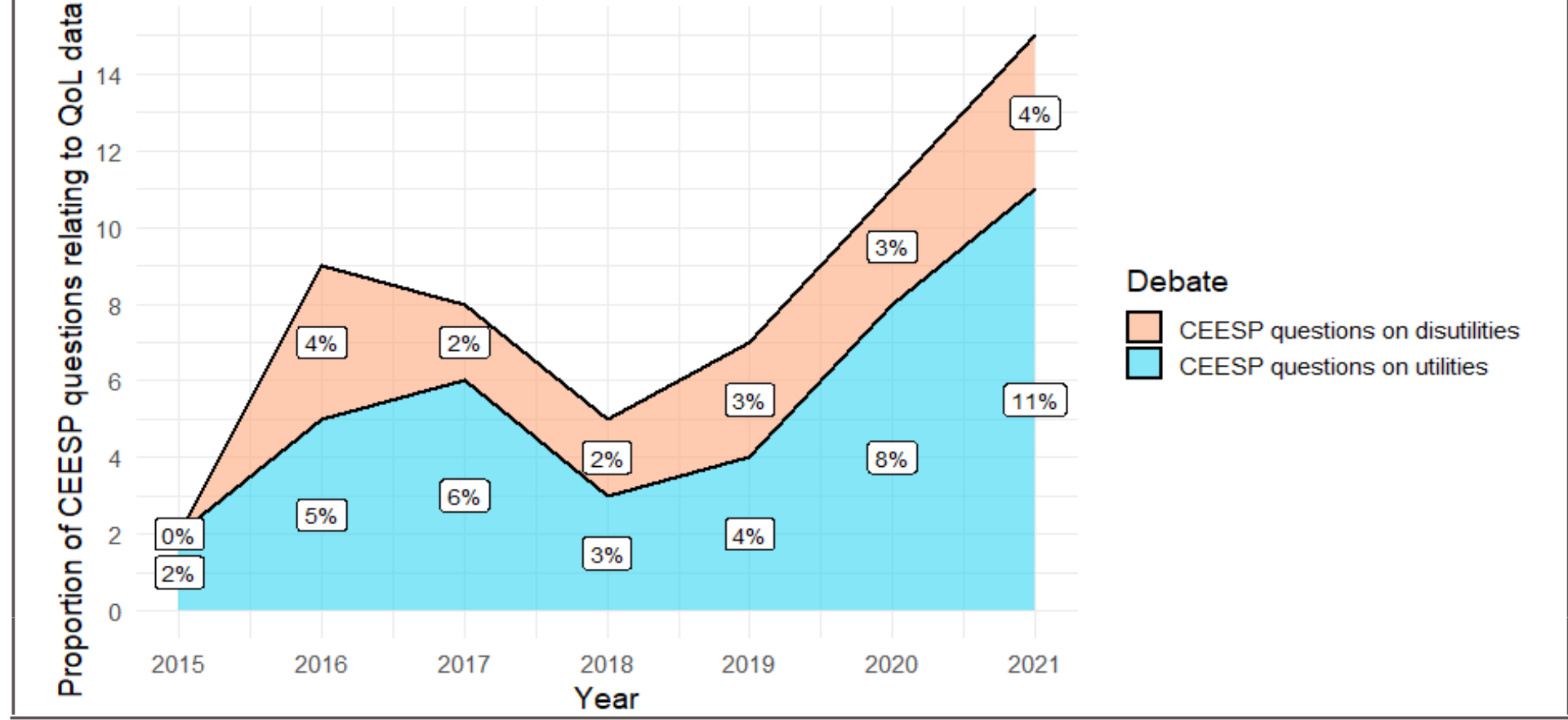
CEESP: commission d'évaluation économique et de santé publique; QoL: quality of life

Conclusions

- This study is the first review of the methods used for valuing health states and for integrating QoL data reported in French EOs for ICIs and CAR-Ts.
- Manufacturers' submissions are not public. The study is based on the information reported in EOs available on the HAS website. This is the main limitation of the study.
- The study acknowledges improved methods as well as a heterogeneity in the methods used to select and integrate utilities into models for CEESP appraisal. This impacts CUAs.
- Considering the methods for valuing health states, the EQ-5D-5L is the HAS preferred method while the EQ-5D-3L should be used as a transitional measure. However, the latter is still used. This is potentially due to the lack of available value set for the EQ-5D-5L for each country at the time of clinical development. This may evolve in the coming years.
- These results confirm other national and international findings. A study conducted on all 34 EOs issued by CEESP 2 years after its inception and a study conducted on 71 submissions to NICE 7 years after its inception highlighted a wide variety of methods used to select and incorporate utilities. Both also showed that more than 50% of submissions did not meet the HTA recommendations.[6,7]
- This subject remains an important challenge with more and more questions from CEESP during the technical debate despite an increase of manufacturers/CEESP experience.
- New French guidelines could contribute to harmonize methods and limit CEESP reservations.

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Email: aurelie.gueye@bms.com