Impact of Real-World Evidence in the HTA Process in France: Analysis of Transparency Commission Appraisals in Rare Diseases

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INTRODUCTION

- Real-world evidence (RWE) is becoming increasingly influential in healthcare decision-making, particularly in the Rare Diseases (RD) field, where clinical development may lack robust evidence[1,2].
- Given the influence of the French Health Technology Assessments (HTA) in enabling patient access to new treatment, not only in France, but also in other EU countries, this study aimed to describe the use and understand the impact of RWE studies in French HTA delivered by the Transparency Commission (TC, National Authority for Health, HAS), in the RD field, overall and according to type of sources used to generate RWE.

METHODS

- A retrospective study on French HTA TC appraisals/opinions in the RD field (RD or orphan drugs) from February 2023 (latest HAS recommendation[3]) to April 2024 was performed, focusing on initial assessments (primary indications and extensions) and reevaluations. Range extensions and PIS files were excluded.
- This study was conducted following two steps:

Step 1, Screening and description of RWE use and sources :

- Identify reference to RWE in the appraisals to support value demonstration. RWE used to illustrate unmet medical needs or epidemiology were not considered.
  - ➢ *For appraisals including multiple RWE studies/sources, the most informative one was considered for the description of use of RWE (see Figure 1).*
- Based on the main study/source of each appraisal, the type of source (e.g. studies derived from prospective/retrospective cohorts, registries, administrative databases, early access data), and the level of reported details (high, intermediate, low) were described.
  - ➢ *High: results presented in detail; Intermediate: methods provided but a few/no results detailed; Low: study mentioned without any details.*

Step 2, Assessment of impact on appraisal:

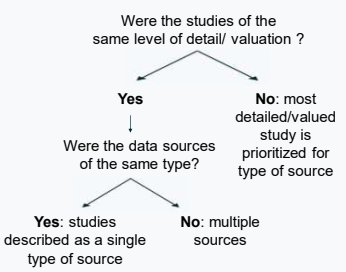
2.1 Quantitatively: Based on all available RWE studies from each identified appraisals (step one), the impact on value demonstration was assessed as:

- **a. Established**: RWE was considered to in the justification of clinical benefit clinical added value scores (SMR/ASMR), whatever levels appraised;
- **b. Supposed:** RWE was presented with detailed results, but not considered in the SMR/ASMR justification
- **c. Absent:** RWE was minimally detailed, with significant methodological criticisms being reported

2.2 Qualitatively: A summary was conducted to analyze the appraisals in which RWE had a proven impact on value demonstration..

- Descriptive statistics (frequencies, percentages) of the study findings were reported.

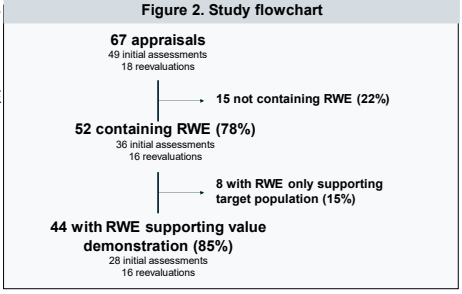
Figure 1. Identification of main study/ source leveraged in the TC opinion in case of multiple RWE studies



RESULTS

- Overall, 67 published appraisals were identified over the study period, including 73% of initial assessments (Figure 2).
- Most appraisals contained RWE studies (78%, 52/67), of which most of them supported the product value demonstration (85%, 44/67).
- Of these, 64% (28/44) were initial assessments and 36% 16/44 were reevaluations.

Figure 2. Study flowchart



Step 1: Use of RWE studies

- Among the 42/44 appraisals where a single type of source/study could be identified [a], 31% (13/42) leveraged early access programs (EAP), and 69% (29/42) leveraged research projects (RP) as main source of RWE (Figure 3).
- RP were mainly based on registries (52%,15/29) and prospective cohorts (41%, 12/29), each of them contributing to 9 and 4 indirect comparisons (ITC), respectively.
- Only one RP was based on the French nationwide claims database (SNDS), and another secondarily used data from an EAP.
- Regarding the level of details from the RWE studies, most of them had a high level of details published (Figure 4, 59% and 39% for RP and EAP, respectively).

Figure 3. Description of the type of source used for the RWE studies

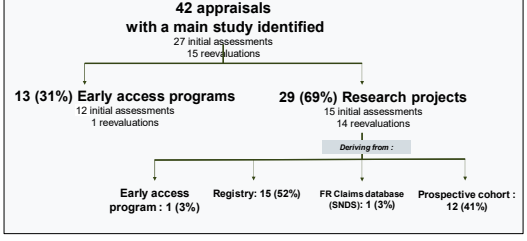
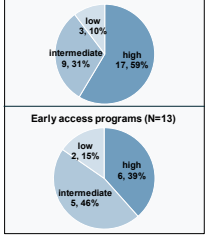


Figure 4. Level of details reported in the appraisals



[a] 2/44 appraisals did not allow the identification of a main study and were not included for the description of the use of RWE

Step 2: Assessment of impact on appraisal

- *2.1.* The quantitative analysis (Figure 5) showed that RWE studies impacted 38% of appraisals, with 20% of impact classified as *established* (9/44), and 18% as *suspected* (8/44).
- *2.2.* The qualitative analysis (Figure 6) showed that RWE studies with *established* impact all came from RP, mostly based on secondary data collections (French or foreign registries/claims database).
- For initial assessments, the main sources of RWE were all reused as external control arm in an ITC, resulting in additional comparative evidence of a benefit in a strong clinically relevant endpoint, in the context of a value demonstration gap (phase II or non-comparative clinical trials).
- For reevaluations, the main sources of RWE were mostly non-comparative studies confirming clinical trial results in routine practice.

Figure 5. Quantitative description of the impact from RWE studies on the SMR/ASMR

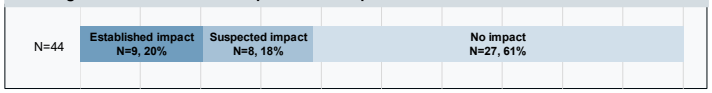


Figure 6. Qualitative description of the impact from RWE studies within cases of established impact

	Initial assessmsent (N=3)			*Reevaluations (N=6)*					
	LIVMARLI [4]	ZOKINVY [5]	EBVALLO [6]	ZOLGENSMA [7]	KYMRIAH [8]	KYMRIAH [c]	YESCARTA [10]	REVESTIVE [11]	BAVENCIO [12]
Most important clinical trial	Comp. [b] vs placebo Ph II	NC Ph II	NC Ph III	NC Ph III	NC Ph II, ITC vs clinical trials	NC Ph II, ITC vs clinical trials	NC Ph II, ITC vs clinical trials	Comp. Ph III	NC Ph II
Clinically relevant comparator	X	X	X	✓	✓	✓	✓	X	✓
Main RWE study:									
- Source	**RP:** Secondary registry (GALA)	**RP:** Secondary registry (progeria research foundation)	**RP:** Secondary registry	**RP:** Prospective cohort	**RP:** Secondary registry (DESCAR-T)	**RP:** Secondary registry (DESCAR-T)	**RP:** Secondary registry (DESCAR-T)	**RP:** Seconday registry (MUSIC 1A)	**RP:** Medical-administrative database (SNDS) and secondary registry (CARADERM)
- Comparative aspect	Comp.: ITC: clinical trials vs RWE (control group)	Comp.: ITC: clinical trials vs RWE (supportive care)	Comp.: ITC: clinical trial vs RWE (control group)	Comp.: ITC: clinical trial vs RWE (clinically relevant comparators)	Descriptive	Descriptive	Descriptive	Descriptive	Descriptive
- Main endpoints	Event-free survival	Overall survival	Overall survival	Efficacy	Effectiveness and security	Effectiveness and security	Effectiveness and security	Effectiveness and security	Overall survival
- Main limitations highlighted by the CT	Poorly reported initial differences, immortality bias, inadequately described propensity score weighting	Absence of hypothesis stated, limited choice of matching factors, unknown patient characteristics	Possible selection bias against the control group, violation of the positivity assumption	Inherent limitations of ITC; considered acceptable due to the ethical difficulties of establishing a placebo control group	Purely descriptive results and minimally informative due to the short follow-up, non-exhaustive sample of patients	Questionable applicability of these data to French practice (no French patients were included in this registry)	Registry not exhaustive, immaturity of the real-life data	Low level of evidence of studies conducted in real life setting	No quality of life and safety data, limited description of previous treatment lines, numerous missing data
Obtained level of ASMR	IV	III	IV	Maintained (III)	Maintained (IV)	Maintained (III)	Maintained (III)	Decreased (III to IV)	Increased (V to IV)

[b] NC: Non comparative; Comp.: Comparative; Ph: Phase; RP: research project; EAP: early access program

CONCLUSIONS

- This is the first published study to provide quantitative evidence that RWE studies have an impact on TC appraisals in the rare disease field in France.
- Results showed that 52% of RWE studies referenced in data packages presented in TC appraisals are reported with high level of details (60% in research projects, 40% in EAP)
- An established/supposed impact on SMR/ASMR was identified in almost 40% of appraisals including RWE studies.
- The qualitative assessment of appraisals having RWE studies which impacted SMR/ASMR suggested that it could be particularly relevant to conduct such studies in specific contexts (e.g. incomplete drug development.
- A close collaboration between pharmaceutical companies and health authorities would be helpful to maximize the impact of RWE studies in final HTA TC appraisals, especially given the specificities of RD field, where establishing a continuum of evidence generation is crucial.

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