Single-arm studies in rare diseases and statistical methods to mitigate lack of comparative data: what kind of assessment is more successful for the French HTA body?

Poster HTA174

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OBJECTIVES

Randomized controlled trials remain the 'gold standard' for health technology assessments (HTAs). However, in the context of rare diseases, **single-arm trials are often used when comparative trials are not feasible or unethical to conduct**, which can be challenging for traditional HTA. **This study aims to assess how French HTA body evaluates products in rare diseases relying on single-arm studies and which statistical methods are set up to mitigate lack of comparative data, in coherence with the new doctrine recently published in February 2023.**

CONTEXT

HAS new doctrine position to guide CTs on single-arm clinical trial assessment (figure 1)

Before new HAS doctrine published in February 2023, there was no guideline regarding the assessment of single-arm studies.

RCT
(Gold standard)

Adaptations compatible with the principles of RCT design
with high certainty of results

Uncontrolled trial (single arm) and **external comparison**

Figure 1. TC's assessment of clinical study design

> The absence of a direct comparison, **when the TC considered it feasible** = **ASMR V.**

> **Several alternatives to the traditional design** can be set up in order to accelerate the clinical development.

> **Uncontrolled trials** alone is strongly limited and be used under exceptional conditions.

> The new doctrine specifies that single-arm clinical trials with a form of indirect comparison can be used to assess the added value of a drug if these comparisons are of good methodological quality, and thus lead to a **positive valuation of the ASMR.**

Methodological points of attention HAS for the external comparison[1]

Rationale for the lack of randomisation	Adequate comparison *vs.* an external control	Performing transparent and appropriate analyses
	• Perform a systematic search • Choice regardless of study results • Pre-specification in the protocol	• Publication of filed reports, shraing of data and clinical study reports • Causal inference analysis

METHODOLOGY

Clinical opinions in rare diseases, based on single-arm studies, published from 2020 to May 2023 were identified.

The following information was extracted to estimate how the Transparency Committee (TC) used to assess these studies:

> Information on therapeutic area;

> Statistical methods developed : Adjusted indirect comparison with an historical arm ; propensity score; Exact Unilateral Binomial Test (EUBT)

> Assessment of these methods by Transparency committee (TC)

> Impact of methods set up by laboratories on TC opinions and ASMR ratings.

RESULTS

Across the extracted data (n=25), **the most represented therapeutic area** in the conduct of single-arm was **oncology (44%; n=11)** and **respiratory (16% ; n=4).**

Rationale for the lack of randomisation

> Among 25 opinions identified, **in most cases (68%, n=17), the absence of direct comparison was justified according to TC.** Even though in 9 cases, clinically relevant comparators were available.

> **When it was not justified**, **in all cases** (n=8) the TC considered that a **comparative method was feasible** (63% in oncology, 13% in respiratory and musculoskeletal disorders).

Methods to overcome the lack of comparative data (figure 2)

Among 25 opinions, **76% (n=19/25)** implemented a statistical method :

> **In 74% (n=14/19)** of cases, **indirect comparison was implemented**. The statistical method most often used was MAIC (31%).

> **In 21% (n=4/19), two methods were implemented** simultaneously: indirect comparison and setting up real-life data/register.

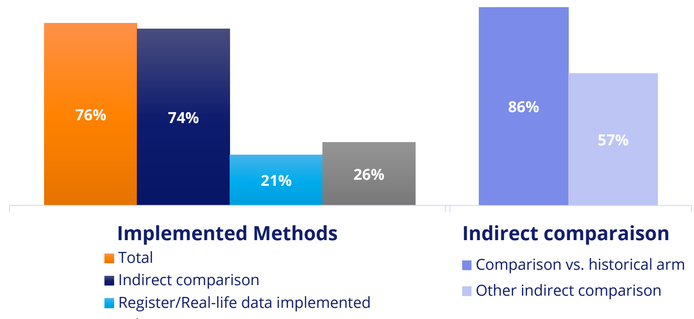


Figure 2. Methods use and their validation from TC

> Other methods implemented : other real-life studies, pooling of studies.

Validation of the method from Transparency commission

> Among 19 opinions having implemented a method, in **16% (n=3/19) of cases, the method was validated by the TC (Limeldy, Evrysdi, Tecartus).** It was indicated in different therapeutic area : metabolic deficiency, musculoskeletal disorders and oncology respectively. **In all this cases, the laboratory implemented an indirect comparison.**

> **For 84% (n=16/19), the method was unvalidated by the TC :**

- **For indirect comparisons, the main comments of the TC was :** planned a posteriori or too late, no hypothesis planned on the benefit of this type of study, heterogeneity of studies, no weighting to make patients comparable, no bias studies, small sample.
- **For registers unvalidated, the main comments of the TC was :** data still immature.
- In 18% of opinion (n=3/16) a valid method for the TC was stated.

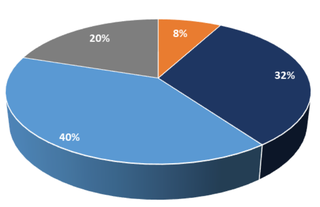
Conclusions from Transparency Commission (figure 3 and 4)

Generally, in most cases (80%), single-arm studies made it possible to obtain an ASMR level > 5.

- We observe a trend : several methods put in place (establishment of a register and an indirect comparison) can made it possible to obtain a better evaluation (ASMR > 4).
- A significant proportion of ASMR level > 5 when no method was in place highlights that **other criteria than the methods implemented to compensate the lack of comparison are important in the evaluation** of the ASMR (medical need, indication in pediatrics ...).

For example : Kalydeco and Crysvita (pediatric), Coagadex (uncovered medical need), Idefirix (no available comparotor).

Figure 3. ASMR rating



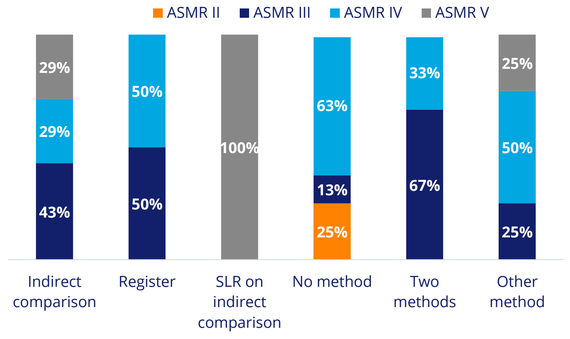


Figure 4. ASMR rating depending on the methods used

Focus on the evolution after doctrine

> Since the publication of the new doctrine, pharmaceutical companies have favored indirect comparisons only. **No method has been validated by TC**.

> We observe the same proportion of ASMR 5 (20%; n=1/5) than before doctrine, more ASMR 4 (60% ; n=3/5), less ASMR 3 (20%; n=1/5) and no AMSR 2.

> These results must be qualified by the small number of post-doctrine opinions available.

CONCLUSION

Only a **small number** of submissions from laboratories used **effective** methods. In its recently published doctrine, the TC officially approved a practice and methods that had already been suggested by experts in the industry well before it was made public. The industrial sector's capability to utilize these tools will depend on **the existence of historical data, the quality of that data, and their expertise in conducting strong MAICs**. Some limitations need to be taken into account when analyzing these results. ASMR is a **multi-factorial** criteria and depends, for example, on medical needs and existing alternatives. The large number of **pediatric** trials is also noteworthy : HAS may adapt its assessment of trials involving these populations.

HAS: Haute Autorité de Santé; TC: Transparency Commission; CRP: Clinically Relevant Comparator; SLR : Systematique littérature review

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