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INCLUSION OF ADVERSE EVENTS IN THE ECONOMIC EVALUATION OF HEALTH TECHNOLOGIES: A REVIEW OF THE MANUFACTURERS' SUBMISSIONS TO THE FRENCH NATIONAL AUTHORITY FOR HEALTH

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BACKGROUND AND OBJECTIVES

- Adequate integration of reliable safety outcomes such as adverse events (AEs) in economic evaluation of health products contributes to make efficient reimbursement and pricing negotiations decisions.
- The purpose of this pilot study was to review how AEs were included in the cost effectiveness analysis (CEA) of innovative health products submitted by the manufacturers to the French National Authority for Health (HAS).

METHODS

- A pilot review of the manufacturers' submissions to the HAS from January 2014 to April 2018 was conducted. In addition to the efficiency reports published on the HAS web site in April 2018. All the elements of the manufacturers' submissions were analyzed by the two authors: CEAs, appendices and letters of clarification.
- The analysis focused on the inclusion of the consequences of AEs on direct costs and quality of life.
- An analysis grid was developed and independently extracted by two authors:
  - the main characteristics of the products evaluated as well as the AEs criteria included in the economic decision models (Table 1).
  - disagreements were resolved through discussion.

Table 1. Criteria considered in the analysis of the inclusion of AEs in the manufacturers' submissions

Main criteria	Analysis of criteria
Characteristics of the health product (drug or medical device)	• (%) of drugs/medical devices. • (%) of therapeutic areas.
Inclusion of expected consequences of AEs on direct costs (e.g. resources induced by acute AEs, impatient care for serious infection) and loss of quality of life (e.g. disutility caused by serious infection)	• (%) of CEAs with AEs costs and/or loss of quality of life
Sub-criteria included in the estimation of direct costs and loss of quality of life related to AEs	• Data sources and their rationale. • (%) of threshold frequency of AEs enabling to consider disutilities in decision analytic models. • (%) of CEAs including severity of AEs.
Inclusion of time to onset and duration of AEs in the estimation of costs and quality of life	• Details on how occurrence and duration of AEs were modeled (i.e. cycle of model)
Sensitivity analyses including AEs parameters	• (%) of CEAs with deterministic and probabilistic sensitivity analyses. • Use of alternative data sources in the estimation of costs and quality of life.

RESULTS

- A total of 51 submissions (49 drugs and two medical devices) were reviewed. A submission may involve more than one therapeutic area. Therapeutic areas primarily concerned oncology (16/71; 23%) and infectious diseases (13/71; 18%) (Figure 1).
- For both costs and quality of life, systematic reviews were rarely done. Data sources (e.g. clinical study reports, summary of product characteristics, expert opinion) were often mentioned in a fragmented manner.
- Less than half of submissions (21/51, 41%) analyzed the consequence of AEs on both direct costs and loss of quality of life (disutilities) (Figure 2).
- Among CEAs including costs:
  - severe AEs with grade ≥ 3 were incorporated in the estimation of costs (44%, 15/34) of submissions (Figure 3),
  - occurrence of AEs was only simulated in the first cycle or first year decision models (Markov model or patient-level individual sampling) for 75% (12/16) of submissions.
- Among CEAs including disutilities:
  - severe AEs with grade ≥ 3 were incorporated in the estimation of disutilities (36%, 8/22) (Figure 4),
  - 41 % (8/22) of submissions did not mention any severity level of AEs although 82% of them included duration and/or time to onset of AEs.
- Deterministic sensitivity analyses (DSA) with AEs were performed in 47% (24/51) of submissions whereas probabilistic sensitivity analyses were done in 31% (16/51).
- Among submissions including AEs in DSA, 6% (2/33) considered alternative sources of AEs. The impact on the incremental cost-effectiveness ratio reported was minimal.

Figure 1. Percentage of CEA by therapeutic area

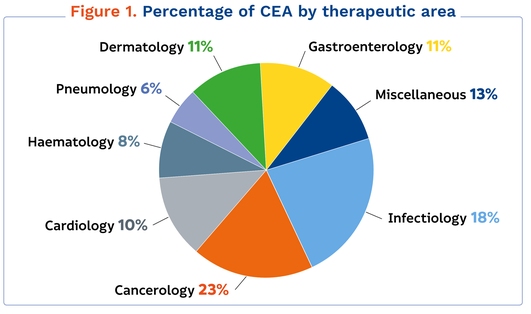


Figure 2. Inclusion of adverse events data in manufactures' submissions

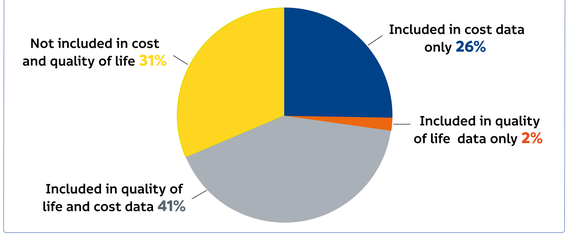
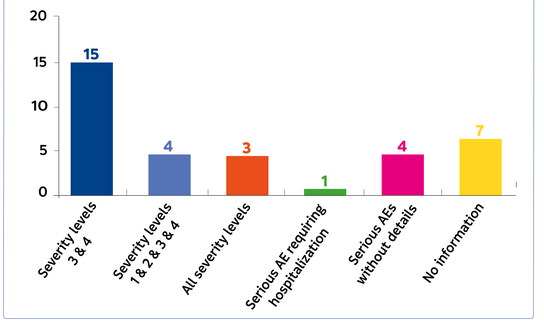


Figure 3. Level of severity of AEs considered in the cost analyses



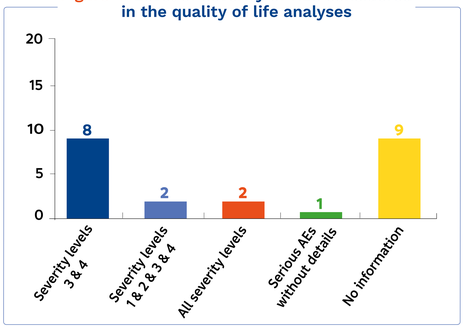
DISCUSSION

- There was substantial variation amongst the submissions in terms of the methods of extraction of AEs data sources and a lack of analysis of their consequences on costs and quality of life during the time horizon of the CEAs.
- Our results were similar to the finding of a systematic review performed on adverse drug events in economic evaluations of Anti-Tumour Necrosis Factor-Drugs for adult rheumatoid arthritis[1].
- We have only analyzed what was reported rather than what a health decision modeler should do to include the risks from drug treatment in decision analytic model.
- Our analysis-grid should be refined and applied to patients outcomes (e.g. adherence to treatment) and used to analyses a larger sample of submissions in 2020.
- The issues related to the inclusion of AEs in CEAs may not only be interpreted in terms of non-adherence of health technology assessment (HTA) guidelines :
  - current HTA guidelines of economic evaluation propose general and "fit all sizes" recommendations for the integration of AEs in economic evaluation,
  - no formal economic approach states when utilities should by (or not) adjusted on AEs[2].

CONCLUSION

- This pilot review identified a strong heterogeneity regarding AEs data sources and underlined a lack of rationale of selection of AEs types as well as the analysis of their expected consequences on either direct costs or quality of life.
- AE-specific guidance providing best practice rules for the analysis of AEs impact on cost and quality of life is required: a terminology on AEs types of interest (e.g. adverse drug event vs. adverse event), a framework distinguishing between analysis of acute and chronic AEs and aggregate and disaggregated methods for cost analysis of administrative data.

Figure 4. Level of severity of AEs considered in the quality of life analyses



1. **Heather EM, Payne K, Harrison M et al.** Including adverse drug events in economic evaluations of anti-tumour necrosis factor-drugs for adult rheumatoid arthritis: a systematic review of economic decision analytic models. Pharmacoeconomics. 2014 Feb;32(2):109-34.

2. **Hamers FF, Ghabri S, Le Gales C.** Health-state utility estimates for health technology assessment: a review of the manufacturers' submissions to the French National Authority for Health. Expert Rev Pharmacoecon Outcomes Res. 2017 Oct;17(5):489-494.