

# Identifying relevant clinical regulatory and health technology assessment (HTA) precedents via artificial intelligence (AI)

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## Introduction

- As drug developers or evaluators consider new product submissions for clinical regulatory agencies or HTAs, an effective process for all stakeholders requires understanding of regulatory precedents, including the acceptability, strengths and critiques of study designs, data sources, outcome measurements, analytical methodologies and evidence interpretations
- Human expertise is central to this process, but subject to time and resource constraints
- At the same time, relevant precedents can be challenging to identify: they span multiple therapeutic areas and evolve over time, they present as short passages within large documents, and they involve topics poorly-suited to electronic keyword searches

## Objective

- We developed and assessed AI-based approaches to identifying relevant regulatory precedents for any given topic

## Methods

### Data sources

- Public records were compiled from a variety of clinical regulatory and HTA sources (Table 1), and then cleaned and organized (“chunked”) into ~8 million semantically coherent segments of text to allow for more targeted searching and review

Table 1. Distribution of chunks across data sources

Regulatory Body	Chunks
ClinicalTrials.gov	1,102,939
EMA public assessment reports and summaries of product characteristics	2,867,309
FDA drug labels, public meeting materials and guidance	1,369,689
HAS	1,029,447
IQWiG	1,497,908

### Approach

- Documents were processed with a pre-trained embedder (PubMedBERT) and queried via a custom-built search Interface. The chunks were associated with metadata extracted from the regulatory documents such as source, title, date of publication, and therapeutic area
- Given a topic statement, the search for relevant chunks is conducted using both semantic similarity and zero-shot classification of relevance based on a large language model (LLM), OpenAI’s GPT-4.0 8k model (Figure 1)
- User feedback is collected in real-time to revise classifications of relevance, and to train an improved few-shot classifier of relevance (Figure 2)
- The search interface and underlying models were used by experts in preparing submissions for medical products to drug regulatory agencies and HTAs
- LLM prompts were refined based on feedback from users, and feedback was collected on viable use cases and the model’s utility

Figure 1. Overview of embedding and search interface

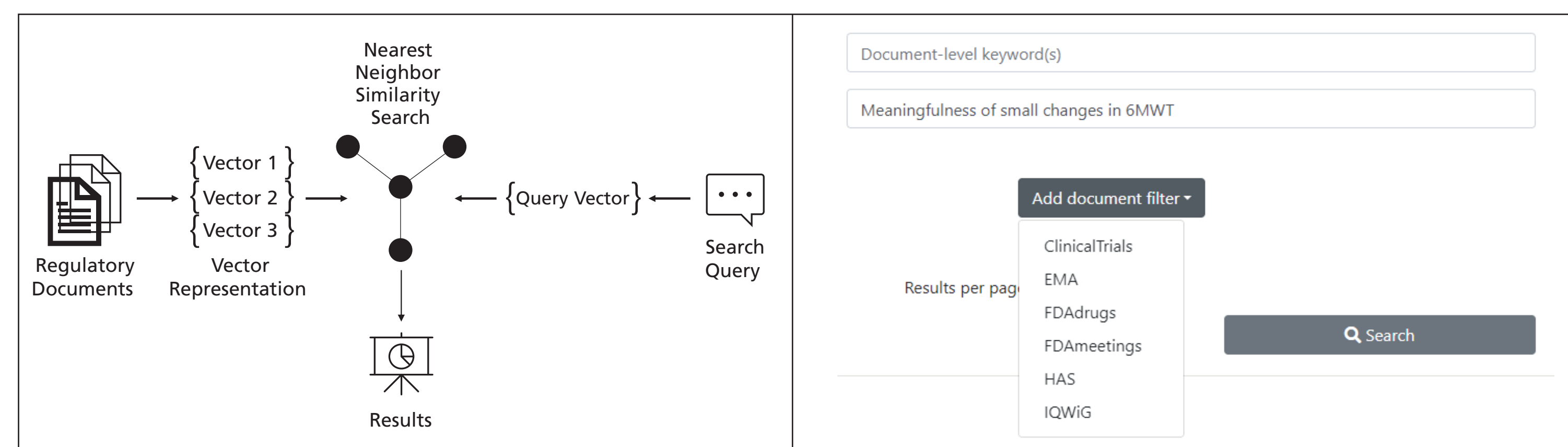
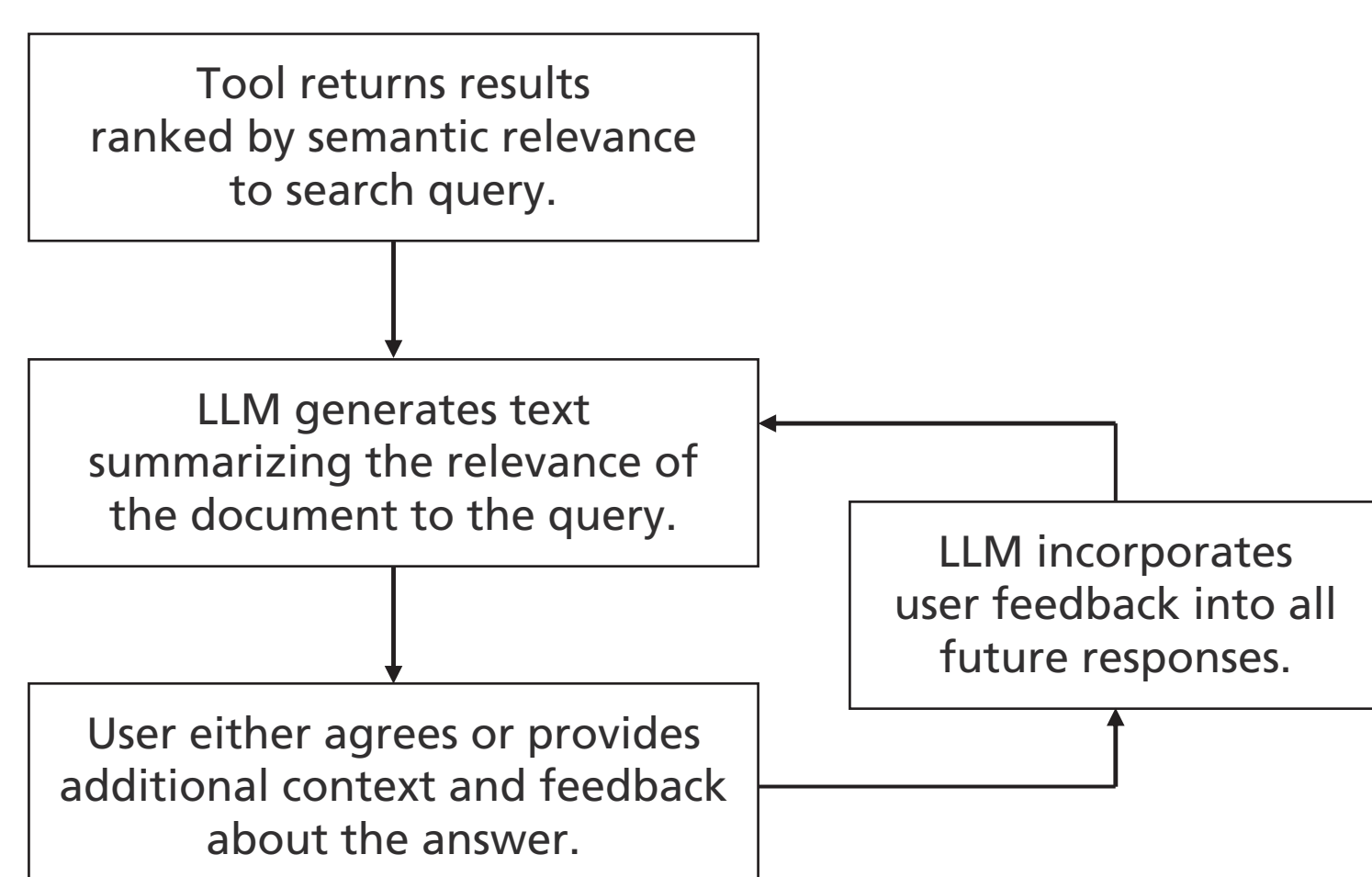


Figure 2. LLM classification workflow



## Results

- The search interface and LLM-based classifier was able to rapidly identify documents and passages of text relevant to specific topics, and to complete exhaustive searches for specific concepts; relevance or lack of relevance was well-summarized (Figures 3-5)

Figure 3. Example: meaningfulness of small changes in a functional outcome

**Source:** EMA  
**PublishedDate:** 2018-09-17T14:03:12+02:00  
**Name:** Translarna  
**Agency product number:** EMENHC/002720  
**Active substance:** Ataluren  
**Therapeutic area (MeSH):** Muscular Dystrophy, Duchenne  
**Additional monitoring:** This medicine is under additional monitoring, meaning that it is monitored even more intensively than other medicines. For more information, see Medicines under additional monitoring.  
**Conditional approval:** This medicine received a conditional marketing authorisation. This was granted in the interest of public health because the medicine addresses an unmet medical need and the benefit of immediate availability outweighs the risk from less comprehensive data than normally required. For more information, see Conditional marketing authorisation.  
**Orphan:** This medicine was designated an orphan medicine. This means that it was

**File name:** EMA-medicines-human-epar-translarna-12-translarna-h-c-2720-r-0022-eparassessment-report\_en\_ch34  
Notwithstanding Assessment report EMA CHMP 738638 2016 Page 13 21 several lines of evidence supporting the clinical relevance of a 30-meter difference in 6MWD, recent natural history studies discuss even smaller differences as being clinically meaningful for DMD patients. Delaying the time to loss of ambulation and loss of other functions is relevant for these patients since it means longer time with preserved autonomy and better quality of life QOL . The data on time to loss of ambulation and on the separate NSAA items provide some positive trends whereby these milestones may be delayed in ataluren exposed patients. Ability to climb and descend a short grouping of stairs, ability to run in short bursts or to walk a short distance unaided e.g.

**Is this text relevant to meaningfulness of small changes in 6MWT? Why?**

**Relevant**

Yes

The text is relevant to the topic “meaningfulness of small changes in 6MWT”. It discusses the clinical relevance of a 30-meter difference in 6MWD and mentions that even smaller differences can be meaningful for DMD patients. It also talks about the impact on patients’ quality of life and autonomy, which are key considerations when assessing the meaningfulness of changes in 6MWT.

**Confirm** you agree with this classification

Or, regenerate the summary based on whether the classification is **relevant** or **not-relevant**

Figure 4. Example: benefit based on patient reported outcomes in oncology

**Source:** IQWiG  
**Application field:** Cancer  
**Department/Division:** Drug Assessment  
**DocumentDate:** 2014-11-03T00:00:00.000+00:00  
**ProjectIssuingDate:** 2014-07-29T00:00:00.000+00:00  
**ProjectNumber:** A14-25  
**ProjectStatus:** Commission completed  
**ProjectTitle:** Eribulin (new therapeutic indication) - Benefit assessment according to § 35a Social Code Book V (dossier assessment)  
**ProjectType:** Dossier assessment

[Tag Document](#) [Open/Download](#)

**File name:** IQWiG-A14-25-0-a14-25\_eribulin\_extract-of-dossier-assessment\_ch214  
At most indications of an added benefit were derived for these outcomes. Mortality outcome overall survival Based on the meta-analysis of the 2 studies 301 and EMBRACE, treatment with eribulin resulted in a statistically significant prolongation of overall survival in comparison with the individual chemotherapeutic regimen with capecitabine or vinorelbine. There is therefore proof of an added benefit of eribulin for the outcome overall survival compared with the ACT individual chemotherapeutic regimen with capecitabine or vinorelbine. Morbidity outcome pain [VAS] There were no data for the relevant subpopulations on the outcome pain measured with a visual analogue scale VAS.

**Is this text relevant to evidence of added benefit based on patient-reported outcomes in oncology? Why?**

**Not Relevant**

While the text does discuss the added benefit of eribulin treatment in terms of overall survival, this is a clinical outcome and not a patient-reported outcome (PRO). PROs are typically measures of symptoms, side effects, or quality of life as reported by the patient themselves. The text mentions that there were no data for the patient-reported outcome of pain, measured with a visual analogue scale (VAS). Therefore, it does not provide evidence of added benefit based on patient-reported outcomes in oncology.

**Confirm** you agree with this classification

Or, regenerate the summary based on whether the classification is **relevant** or **not-relevant**

Figure 5. Example: use of external controls or real-world data in pediatric oncology

**Source:** FDAmeeetings  
**Document Date:** 2022-12-27T17:19:00  
**FileUrl:** https://www.fda.gov/media/162617/download  
**PageModifiedTime:** 2022-12-27T00:00:00  
**PageUrl:** https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-agenda-information-october-28-2022-meeting-oncologic-drugs-advisory-committee-meeting  
**Path:** [ “Advisory Committee Calendar”, “UPDATED AGENDA INFORMATION: October 28, 2022: Meeting of the Oncologic Drugs Advisory Committee Meeting Announcement - 10/28/2022” ]

[Tag Document](#) [Open/Download](#)

**File name:** FDAmeeetings-162617\_ch24  
Therefore, within rare diseases, an alternative option for generation of evidence is to utilize data from external control sources to create an external control arm ECA. There are very few repositories of patient-level data for neuroblastoma patients with CNS LM metastases available world-wide. An extensive search for external patient-level data was performed, including within US cooperative groups such as the Children’s Oncology Group. This led to the identification of two external control sources with sufficient patient-level data the Study Database for Neuroblastoma at the Neuroblastoma Study Center Cologne, Germany and the European International Society of Pediatric Oncology Neuroblastoma Group SIOPEN Section 4.6.

**Is this text relevant to external controls or real-world data in pediatric oncology? Why?**

**Relevant**

Sure, the text is relevant because it discusses the use of external control sources or real-world data to generate evidence for rare diseases, specifically in the context of pediatric oncology. It highlights the process of identifying and utilizing patient-level data from external sources such as the Neuroblastoma Study Center and the European International Society of Pediatric Oncology, which directly pertains to the topic of external controls or real-world data in pediatric oncology.

**Confirm** you agree with this classification

Or, regenerate the summary based on whether the classification is **relevant** or **not-relevant**

## Conclusions

- Artificial intelligence can augment human expertise to simultaneously increase the efficiency, breadth, and depth of understanding of regulatory precedents in drug development applications

## References

- Evidence Extraction to Validate Medical Claims in Fake News Detection, Deka, Pritam and Jurek-Loughrey, Anna, et al., International Conference on Health Information Science, pp. 3-15, 2022, Springer.
- GPT-4 Technical Report, OpenAI, arXiv, 2303.08774, 2023.