Ref. Ares(2025)10285804 - 25/11/2025

101191967 - GREG

Testing, improving, and co-creating Guidance and Tools for Real World Evidence Generation and Use for Decision-Making in Europe

WP1 – Evidence-based practical guidance for the use of real-world data in evidence generation for HTA and Regulatory decision-making

D1.1 Early report based on systematic review

Lead contributor	IACS, 10, Enrique Bernal-Delgado IACS, 10, Francisco Estupiñán-Romero IACS, 10, Ester Angulo-Pueyo IACS, 10, Irene Sánchez Montejo IACS, 10, Silvia Moler Zapata IACS, 10, Sofia Rodrigo Bonet IACS, 10, Wendy Nieto Gutiérrez IACS, 10, Javier González Galindo IACS, 10, Soledad Isern de Val
Other contributors	EUR, 7, Seamus Kent and EUR, 7, Maria Pyatnitskaya NICE, 4, Leonardo Koeser SYNAPSE, 3, Sharon Geerlings UOXF, 2, Annika Jodicke GALWAY, 11, Tom Melvin NOVO, 16, Lotte Husemoen SARD, 17, Juhaeri Juhaeri AMGEN, 29, Nola Tewabe MDBSI, 41, Heather Colvin GSK, 28, Rodrigo Refoios Camejo EW, 19, Rachele Busca

This project is supported by the Innovative Health Initiative Joint Undertaking (IHI JU) under grant agreement No 101191967. The JU receives support from the European Union's Horizon Europe research and innovation programme and COCIR, EFPIA, Europa Bío, MedTech Europe, and Vaccines Europe.

Due date:	31 October 2025
Delivery date:	25 November 2025
Dissemination level	Public

Contents

Document History

Version	Date	Description
V1.0	15/10/2025	First draft
V2.0	20/10/2025	Version for formal review by Annika Jödicke, Stephen Duffield and Daniel Prieto-Alhambra
V3.0	30/10/2025	Revised version for formal review by GA.
V4.0	24/11/2025	Final version

Definitions

Participants of the GREG Consortium are referred to herein according to the following codes:

1. Erasmus Universitair Medisch Centrum Rotterdam (EMC)
2. The Chancellor, Masters and Scholars of The University of Oxford (UOXF)
3. SYNAPSE Research Management Partners SL (SYNAPSE)
4. National Institute for Health and Care Excellence (NICE)
5. GETREAL Institute (GetReal)
6. Societe Europeenne De Cardiologie (ESC)
   6.1. Region Uppsala (REGION UPPSALA)
7. Erasmus Universiteit Rotterdam (EUR)
8. Stichting European Health Data and Evidence Network (EHDEN-F)
9. Stichting Eupati Foundation (EUPATI)
10. Instituto Aragones De Ciencias De La Salud (IACS)
11. University Of Galway (GALWAY)
12. The Hyve BV (THE HYVE)
13. University Of Dundee (UNIVDUN)
14. Universidade De Aveiro (UAVR)
15. Direktoratet for medisinske Produkter (NOMA)
16. Novo Nordisk A/S (NOVO)
17. Sanofi-Aventis Recherche & Developpement (SARD)
18. Bayer Aktiengesellschaft (BAYER)
19. Edwards Lifesciences Belgium BV (EW)
20. Medtronic Bakken Research Center B.V. (MDT)
21. Mölnlycke Health Care AB (MHC)
22. Institut De Recherches Internationales Servier (IRIS)
23. Pfizer Inc (PFIZER INC)
24. W. L. Gore & Associati S.R.L. (GORE S.R.L.)
    24.1. W. L. Gore et Associés S.A.R.L. (Gore S.A.R.L.)
    24.2. W. L. Gore & Associates BV (GORE BV)
25. Bristol-Myers Squibb Company Corp (BMS)
26. Boehringer Ingelheim International GmbH (BII GMBH)
27. Janssen Cilag SA (JCSPAIN)
28. GlaxoSmithKline Research & Development Limited (GSK)
29. AMGEN (AMGEN)
30. Sanofi US Services Inc. (Sanofi US Inc)
31. Sanofi-Aventis gulf F.Z.E. (SANOFI Gulf)
32. Sanofi Winthrop Industrie (SWI)
33. Sanofi Pasteur SA (Sanofi P SA)
34. Aventis Pharma Limited (Sanofi Pharma)
35. Sanofi Pasteur Limited Canada (Sanofi P L)
36. Edwards Lifesciences Sarl (EW SARL)
37. Edwards Lifesciences LLC (EW LLC)

38. Pfizer Hellas S.A. (Pfizer Hellas)
39. Pfizer AB (Pfizer AB)
40. Janssen Research & Development, LLC (JRDLLC)
41. Medical Device Business Services Inc (MDBSI)
42. Edwards Lifesciences SRL (EW SRL)
43. Edwards Lifesciences SL (EW SL)
44. Edwards Lifesciences SAS (EW SAS)
45. Edwards Lifesciences GmbH (EW GMBH)
46. Medtronic, Inc. (MDT Inc)
47. Medtronic France (MDT FR)
48. Medtronic Italia S.p.A. (MDT IT)
49. Medtronic Ltd (MDT LTD)
50. Pfizer R&D UK Limited (PFIZER R&D UK)
51. Pfizer Limited (PFIZER LTD)
52. Actelion Pharmaceuticals Ltd (ACTELION)
53. Medical Devices & Diagnostics Global Services, LLC (MDDGB)

Grant Agreement (GA)	The agreement signed between the beneficiaries and the IHI for the undertaking of the GREG project (101191967)
Project	The sum of all activities carried out in the framework of the Grant Agreement.
Consortium	The GREG consortium, comprising the above-mentioned legal entities hereby referred as Participants of the GREG consortium.
Consortium Agreement (CA)	Agreement concluded amongst GREG beneficiaries for the implementation of the Grant Agreement (GA). Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the GA.

List of abbreviations

Abbreviation	Definition
RWD	Real-World Data
RWE	Real-World Evidence
HTA	Health Technology Assessment
KB	Knowledge Base
RAG	Retrieval-Augmented Generation
LLM	Large Language Model
chatbot	Chatterbox - computer program designed to simulate human conversation through text or voice
Q&A system	Question-Answering system - computer program, often powered by artificial intelligence (AI) designed to directly answer questions posed by a human user in natural language
AI	Artificial Intelligence

Executive Summary

WP1 seeks to support the co-creation of a practical, evidence-based guidance for the use of Real-World Data (RWD) in the generation of Real-World Evidence (RWE) for HTA and Regulatory purposes.

To be practical, meaningful and sustainable, evidence-based guidance should adapt to new knowledge and users' varying needs. Traditional approaches have shown to be limited in scale and too labour-intensive for the continuous, periodic updating required to keep pace with the rapid uptake of RWE and RWD literature for HTA and regulatory purposes. Therefore, WP1 has opted for the implementation of a chatbot that will provide target-oriented recommendations for users based upon the best available knowledge.

Setting up the foundations of GREG Chatbot involves the development of a large knowledge base that can be queried, keeping it up to date within a retrieval-augmented generation (RAG) system that enables large language models (LLMs) to retrieve and incorporate new information as soon as new knowledge is made available.

To develop the ontology and knowledge base at this early stage, we conducted a literature search aimed at identifying guidance for the use of real-world data (RWD) and the generation of real-world evidence (RWE) to inform regulatory and health technology assessment (HTA) processes. In this report, we define "guidance" as any document containing explicit, actionable recommendations and/or methods related to this topic. These documents are published for or by decision-making agents, including regulators and HTA bodies, as well as international projects and initiatives. Guidance documents include guidelines, framework documents, checklist documents, articles published in scientific journals, reflection papers, position papers, reports, handbooks, and consensus statements. Our search combined a systematic search of bibliographic databases with a targeted search of the grey literature to identify records not published as journal articles. Following this approach, WP1 retrieved and selected over 109 documents for two main purposes;

1) to be the initial version of the GREG knowledge base,
2) to serve as the seed for developing the GREG Ontology, the backbone of the RAG system.

In this report, we provide details on the methods used to create version 0.0.1 (initial or first version) of the ontology. We used a mixed-methods approach. A systematic literature and grey literature scoping review was followed by the empirical derivation of the first ontology using LLM. The scope of this early report has been setting up the ontology to detect challenges, limitations and gaps in the generation of real-world evidence in HTA and Regulation, as per the needs of WP2 and WP3.

In addition, this piece of work paves the way for further developments of the ontology and subsequently the overall GREG knowledge base. Ultimately, the knowledge base will be queried, using the GREG chatbot, to respond to multiple users' needs. A minimal viable chatbot will be developed in the upcoming months to address knowledge gaps that can be covered throughout GREG use cases.

1 Introduction

1.1 Creating practical guidance for the use of real-world data in evidence generation for HTA and Regulatory decision-making

As stated in the GREG proposal, the overarching objective of WP1 is to co-create evidence-based practical guidance for the use of RWD in evidence generation through leveraging learning from the continuous assessment of existing HTA and regulatory guidelines and initiatives on the use of RWE for decision-making, including the outputs from the GREG use cases and stakeholder engagement to facilitate acceptance and implementation of advances in medicines and medical devices.

WP1 tasks are set to periodically conduct (or utilise) systematic reviews of RWD and RWE guidelines and recommendations relevant to regulatory and HTA bodies and complement those insights with those produced by all the outputs of the other WPs within the GREG including:

a) examples of previous successful or unsuccessful regulatory or HTA submissions catalogued in the WP2 and WP3 living libraries;
b) the lessons learned from the selection and implementation of GREG use case studies set to test main challenges, barriers, limitations and opportunities of research based on RWD to inform HTA and regulatory decisions providing RWE;
c) insights from the implementation of those GREG use cases selected for implementation; and
d) expert opinion and positions extracted from the discussions held within the scope of the fora facilitating the engagement with the community of health technology stakeholders, eliciting decision-makers' current and emerging needs.

Organising, extracting, classifying and summarising the key elements of the available sources of relevant information and insight requires a systematic and continuous approach aiming to iteratively build and update a common GREG Knowledge Base (KB).

The GREG KB will act as a "single source of truth" that will facilitate governance and information management, as well as enabling the development of a smart system capable of providing up-to-date, accurate, contextualised and target-oriented recommendations and guidance to a wide range of users aiming to use RWE in HTA and Regulation. Thus, instead of delivering comprehensive, fixed-in-time guidelines periodically updated throughout the duration of the project, GREG KB will support the development of a retrieval-augmented generation (RAG) system, coupled with an interactive user interface (i.e., AI chatbot), facilitating the production of directed guidance providing practical guidance specific to each user's needs. This system will also enable semantic search and context-informed access to relevant documentation within the knowledge base.

Following this approach, WP1 aims to develop, test and maintain a GREG smart application (i.e., chatbot - Q&A system), based on the RAG framework. The smart application will interpret stakeholder needs and retrieve the most relevant information from the GREG KB via large-language models (LLMs) to provide accurate answers and recommendations, where possible.

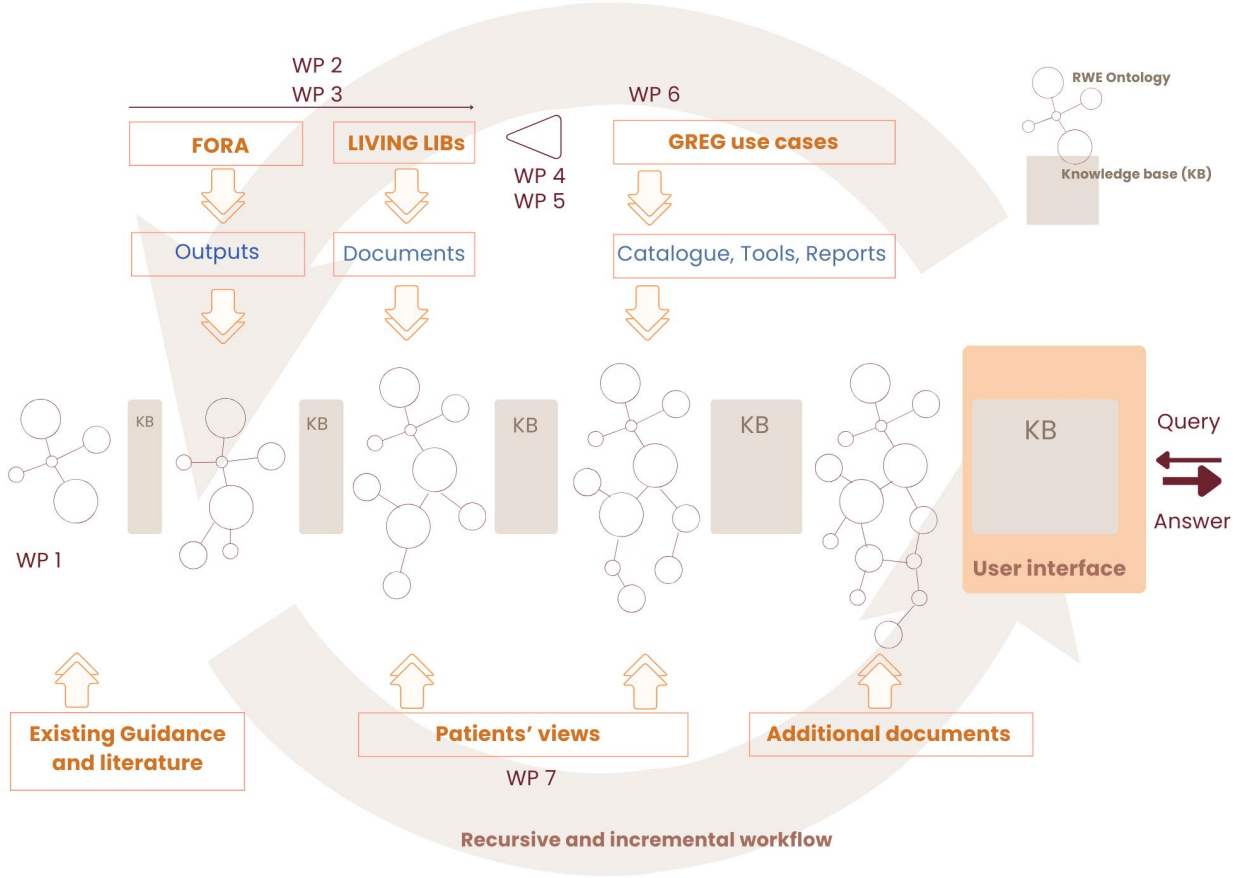

***Figure 1**: WP1's recursive, incremental workflow to build GREG KB supporting the development of the GREG chatbot (Q&A) and showcasing relevant inputs produced by GREG WPs and the GREG RWE ontology as a derived output.*

This deliverable provides details on the methods for building the first version of the GREG KB as well as presenting v.0.0.1 of the GREG ontology. In this context, an ontology is a formal, structured model defining fundamental concepts, and relationships -hierarchy- within a domain of knowledge or semantic area, which helps a system interpret user intent and structure its outputs. This GREG ontology resulted from a systematic literature review of challenges, limitations, gaps, opportunities and recommendations when generating RWE using RWD for HTA and regulatory purposes.

Specifically, this deliverable describes the methodology and processes followed while:

1. carrying out a systematic literature review and scoping review of grey literature;
2. implementing an analytical solution for the discovery of entities (concepts) regarding opportunities, gaps, challenges, limitations and recommendations for the generation of real-world evidence upon relevant documents in the literature review;
3. producing a first version of the ontology (version 0.0.1);
4. planning the validation process of this ontology.

2 Methods

2.1 Literature review methods for developing the ontology knowledge base

To develop the ontology knowledge base, we conducted a literature search aimed at identifying guidance for the use of RWD and the generation of RWE to inform regulatory and HTA processes. In this report, we define "guidance" as any document containing explicit, actionable recommendations and/or methods related to this topic. These documents are published for or by decision-making agents, including regulators and HTA bodies, as well as international projects and initiatives. Guidance documents include guidelines, framework documents, checklist documents, articles published in scientific journals, reflection papers, position papers, reports, handbooks, and consensus statements. Our search combined a systematic search of bibliographic databases with a targeted search of the grey literature to identify records not published as journal articles.

2.1.1 Systematic search

The systematic search (described in detail in **Annex I**) was conducted in May 2025 in MEDLINE (via PubMed), Embase, and the INAHTA international HTA database. The objective was to identify guidance documents that were published as journal articles. The strategy combined three concept blocks: (i) guidance terms; (ii) real-world data (RWD), real-world evidence (RWE), as well as semantic variants and related terms (e.g., electronic health records, registries, claims data, see **Annex I**), as well as adjacent concepts such as pharmacovigilance and safety monitoring; and (iii) policy terms. Searches were limited to 2015–May 2025, when the incorporation of RWD/RWE into regulatory decision-making increased substantially [1, 2].

The selection process was conducted according to the Cochrane guidance for rapid reviews as follows [3]: Before starting the formal selection process, two calibration exercises were conducted. In the first round, four reviewers independently and blindly evaluated 50 records. In the second round, approximately 20% of the remaining sample was reviewed, divided into two groups of two reviewers each. Discrepancies were resolved by discussion among all four reviewers in the first exercise and within each pair in the second. Calibration was considered adequate when at least 80% agreement among reviewers was achieved in each round. The remaining records were divided into four groups, with one reviewer assigned to each group.

The screening of records was conducted in two sequential phases, title and abstract screening followed by full-text assessment. Inclusion criteria were applied hierarchically, advancing to the next criterion only when the preceding one was satisfied. At title and abstract screening, the records were deemed eligible if they: (i) assess or include RWD or RWD related terms[1] [criterion 1] and (ii) include one of the guidance-related terms in the objectives section and referring to the provision of recommendations in the results/discussion section of the abstract [criterion 2]. From those records that passed on to the full-text stage, records were eligible if they were available in English or Spanish and addressed at least one phase in the generation of RWE (for example, data quality and curation, study design, analysis, and results reporting) [criterion 3]. Likewise, they passed on if they were addressing any stage of the technology life cycle; i.e., eligible records could pertain to the use of RWE to obtain market certification or authorization but also to inform de-implementation or disinvestment decisions [criterion 4]. Finally, out of those that passed, we selected those qualifying as the definition of a policy document - official texts published by governmental, regulatory, HTA, or

intergovernmental decision-making bodies [criterion 5]. References in the included studies were reviewed to identify other potentially relevant studies.

2.1.2 Grey Literature search

The targeted grey literature search covered records published in websites of

1) regulatory institutions, HTA agencies, and other decision-making bodies (AEMPS, AGENAS, AIFA, Anvisa, BfArM, CDA-AMC, Health Canada, Canadian Institute for Health Information, EMA, FDA, G-BA, HAS, ICER, IHI, IMI, INESSS, IQWiG, MFDS, MHRA, NICE, NMPA, PBAC, PMDA, RedETS, SFDA, SwissMedic, TFDA, TGA, WHO, and ZIN);
2) professional societies (ISPOR, ISPE, and ESMO);
3) international projects and initiatives (completed and ongoing, including EUnetHTA) funded by public institutions and included in the following websites and repositories: EU Funding & Tenders Portal, CORDIS Portal, IMI/IHI website, NIH Reporter, and HDR UK. To identify additional relevant records within the sources I and II, a snowball method was used.

The search was carried out until May 2025.

Records were selected according to source type. For regulatory bodies, HTA agencies, and other decision-making authorities as well as professional societies, we included for revision any type of publication that (i) contained at least one RWD-related term (see the full list in **Annex I**) and (ii) could be classified as "guidance". For international projects and initiatives, we included any publication when the *stated aim* of the project was to advance guidance for the generation of RWE to support regulatory or HTA processes.

2.2 Building the GREG knowledge-base

Building the GREG knowledge base (KB) is a multi-step process designed to support a Retrieval-Augmented Generation (RAG) system (see **Figure 2**). This KB is the foundation for a system that helps users to navigate through the relevant sources to find and synthesize information about the use of real-world data (RWD) in the generation of RWE for the purpose of regulatory and health technology assessment.

The first iteration of the GREG KB was built on sources (mainly documents) retrieved from the literature search described in section 2.1. All sources within the KB need to be processed to facilitate retrieval and response generation by the LLM. Processing includes

(i) parsing their contents to a common machine-readable format,
(ii) extracting and cleaning them while interpreting the source structure,
(iii) splitting (chunking) them into meaningful (i.e., semantically coherent) pieces of information,
(iv) processing these text excerpts (chunks) to elicit relationships between different annotated entities within the knowledge base. by
  (a) extracting their metadata (i.e., date, author, source, language, etc.),
  (b) generating new annotations for each chunk (e.g., entity tags)

To index relevant content, advanced RAG systems generally use semantic annotation (tagging) complemented with structured metadata. This hybrid approach optimises retrieval based on the meaning of the user's query while enabling traditional filtering and faceted searching. High-performance RAG systems complement semantic indexing through vector embedding with semantic aggregation or clustering. Vector embedding uses an embedding model (i.e., an LLM that transforms annotations into vector embeddings; see **Annex 4** on the technical details) to provide context to relevant concepts or entities extracted or annotated from the original source. Vector embedding can be considered the mathematical representation of a specific ontology arising from the layered semantic annotation of the sources included in the GREG KB and therefore serve as the backbone of the retrieval generative system. An ontology is a formal, structured model that defines the fundamental concepts (or entities) inferred from the text excerpts and the relationships between them within a specific area of knowledge.

The proposed ontology, elicited from the contextualization and semantic clustering of relevant concepts (or entities) extracted from the sources, can be manually validated to conform with users' expectation and fine-tuned to avoid ambiguity and redundancy. This validation and fine-tuning ensures the system understands the domain accurately and helps to interpret the intention of the user's questions or demands (once the user interface is ready to operate).

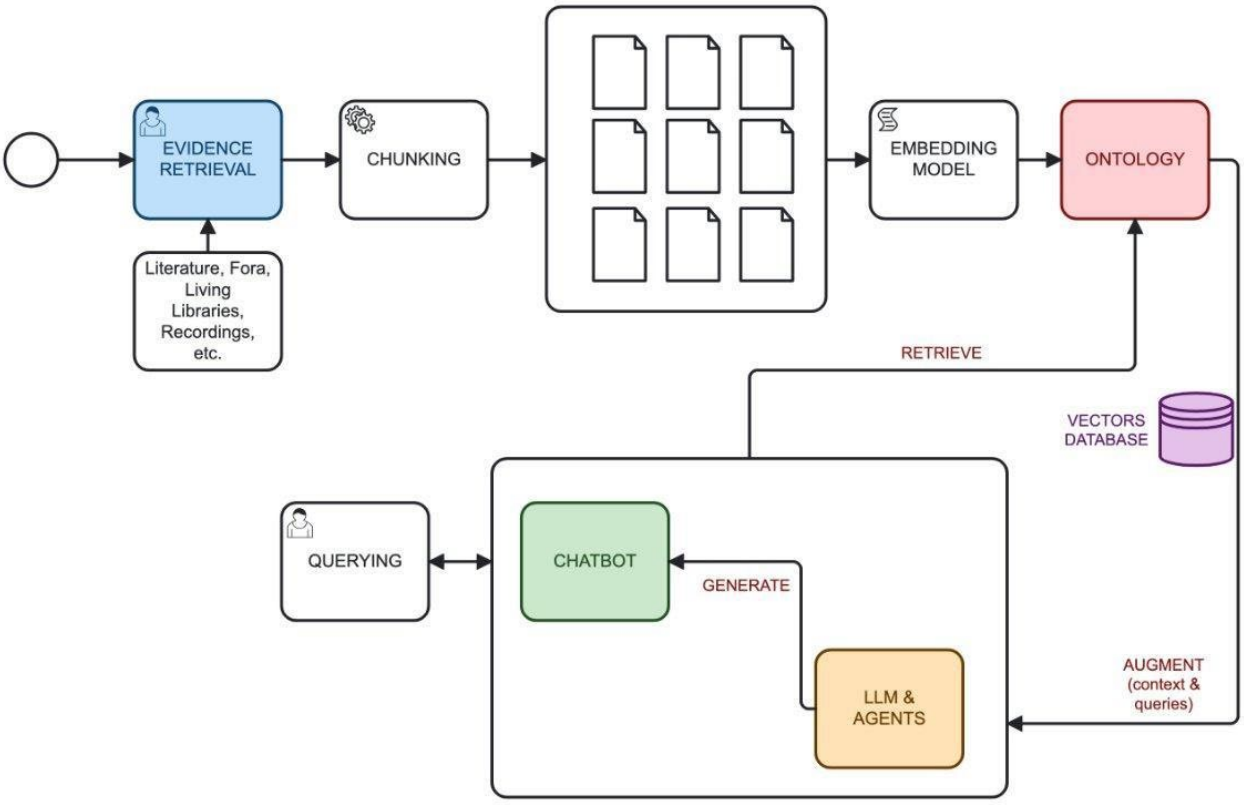

Figure 2: *Retrieval-Augmented Generative (RAG) system workflow to serve a Q&A smart system (chatbot) implementation supported by the GREG KB and GREG ontology.*

2.3 GREG ontology validation and fine-tuning

Face-validation of the ontology is a critical step to complete the GREG KB. While advanced RAG systems can automatically cluster concepts, human review ensures the elicited ontology

- aligns with the expectations of future users and the domain's real-world context, moving beyond purely statistical associations,
- ambiguity is eliminated, ensuring that a single concept is not represented by multiple, subtly different terms (synonymy),
- distinct concepts are not merged under a single dimension or category (homonymy)
- contains no redundancy and recursivity by creating a coherent hierarchical structure, and easier to query;

Thus, manual fine-tuning significantly improving the accuracy and relevance of the RAG system's responses.

WPI has implemented a human validation process for the ontology organised in two different phases attending to the hierarchical nature of the ontology, where concepts (entities) are contextualized by dimensions that are finally aggregated into categories (see structure below).

Category

|----------Dimension

|----------Concept (entity)

In this hierarchical schema, concepts (or entities) corresponding to those "terms" inferred or annotated from the semantic analysis of the text excerpts extracted from the documents added to the KB; 'Dimensions' represent the context from which the concepts have been annotated, for instance, the concept 'real world data sources' can be annotated as a "Limitation" in case the concept is inferred or annotated from an excerpt describing lack of data sources to comply with an assessment requirements or can be annotated as a "Barrier" in case it is inferred from an excerpt describing lack or difficulty of access to particular data sources; and finally, 'Categories' correspond to the aggregation of concepts and dimensions within meaningful clusters, such as 'Limitations and Barriers' in the case of the commented examples.

The first phase of the validation process consists of confronting validators (thus, voluntary participants from GREG WPs) with validation cards or fiches corresponding to all categories identified by the embedding model (i.e., the highest abstraction layer of the ontology). All dimensions included in each category are described and validators are asked to provide their expert opinion on:

A. whether the category seems to appropriately embed the dimensions attached to it (Yes/No),
B. whether the category seems useful to the purpose of contextualising the dimensions and entities inferred from the LLM, guiding users in the retrieval of relevant evidence (using a Likert scale 1 to 5 from not usable to very usable); and then
C. invited to declare any dimension that they may consider missing within the presented category; or,
D. any dimension that they may want to exclude from the category under assessment; and,

E. they are provided with a method to mark and annotate all dimensions within the category that they may consider redundant.

Results from this first phase are assessed for consistency between validators (i.e., inter-rater reliability or inter-observer agreement) and used to fine-tune the ontology confirming or discarding categories and eliminating redundancy among dimensions.

The second phase of the validation process shifts focus to coherence and refinement of the concepts derived from the initial semantic annotation. Validators are presented with validation cards for a set of concepts. These cards serve as core materials for the validation and contain all necessary information for the assessment of:

- the inferred concept or entity,
- the text excerpt (chunk) from the original source from which the concept was inferred; and,
- relevant source metadata and the dimension and category contextualizing the concept (fine-tuned in phase 1)

The validators' task is to check the coherence between the inferred concept and the text excerpt. If they find the concept ambiguous or inaccurate, they must provide a more precise alternative concept to annotate the text, always considering that multiple concepts can be inferred from a single chunk.

Since a knowledge base often generates a very large number of entities, validation must cover a meaningful sample of the entire ontology. This sample is created using a weighted-stratified sampling approach to ensure proportional representation across most relevant dimensions and categories. The total sample size is calibrated based on the available validators, aiming for a workload of 50 to 80 concepts per person, with a maximum limit of 100 concepts. The sampling is weighted according to the volume of concepts present within each dimension and category. Concept cards are distributed among validators considering a 10% overlap of identical concepts shared among them to test the consistency between validators.

A pass criterion for this phase is set as 80% of concepts reviewed marked as appropriate by the mode-value of validators. That means that for at least 80% of the sampled concepts reviewed, the agreed-upon annotation must match the mode-value of the validators' responses - the concept chosen by the majority of the expert reviewers.

Each phase of the validation process is planned to take two weeks to complete, followed by a one-week buffer to assess the results and implement the changes necessary to fine-tune the final ontology structure.

The validation is carried out using a specialised, industry-standard open source platform (see **Annex 5**) designed to support natural language processing annotation and validation.

3 Results

3.1 Literature review

The result of the literature review selection process is depicted in **Figure 3**. We identified 3,247 records through the systematic searches and 114 additional records through the grey-literature searches and citation searching. At the title-and-abstract stage, we retained 258 records from the systematic searches, 112 from grey-literature sources, and 2 from citation searching. After full-text assessment, 153 documents met the inclusion criteria: 44 from the systematic searches, 2 from citation searching, and 107 from the grey-literature searches (listed in **Annex 2**). Full-text exclusions and the corresponding reasons are detailed in **Annex 3**.

3.2 Knowledge base

Out of the 153 documents meeting inclusion criteria, 109 documents were included in the first iteration of the GREG Knowledge Base (KB) and passed through the annotation process, as some documents were excluded due to issues encountered during pre-processing and processing (i.e., parsing, cleaning, chunking and semantic annotation). The main result of this process is the first iteration GREG KB and ontology (version 0.0.1).

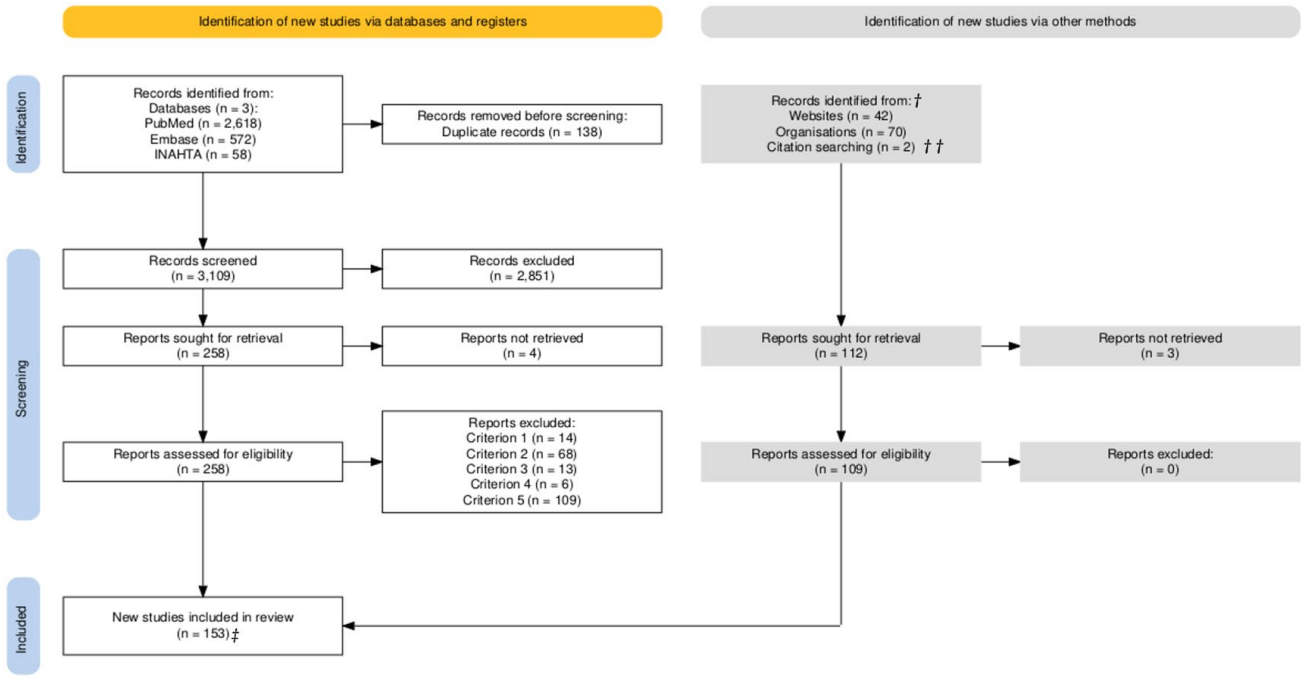

***Figure 3**: PRISMA flowchart of the study selection process of the literature search. Legend: (†) The "websites" refer to the identified initiatives (not the number of documents included per initiative). The term "organization" refers to guidance documents from regulatory bodies, HTA agencies, other decision-making institutions, and professional societies. (††) The identification of studies also included the evaluation of reference lists from prioritized studies identified in the systematic search, such as systematic reviews of RWE policies or guidelines. (‡) The total number of included studies (153) refers to: publications included in the systematic search (44), guidance documents from regulatory bodies, HTA agencies,*

other decision-making institutions, and professional societies (67), and initiatives funded by public institutions (42) - not the number of documents included per initiative.

3.3 Ontology

The GREG ontology is the structured and formal representation of the domain knowledge emerging from codifying the complex relationships inherent in the guidance on real-world data (RWD) and real-world evidence (RWE) for regulatory and health technology assessment (HTA) purposes. Structurally, the ontology is a hierarchy from over 35 thousand contextualized entities (concepts), categorized in 373 Dimensions and 10 Categories (**Figure 4** and **Figure 5**).

An interactive version of the ontology as a radial interactive tree is publicly available at this link. Categories are presented on mouse hover and can be displayed in their dimensions by clicking on each node. Dimensions within each category are sorted clockwise - starting at 9- by the number of concepts they represent, being the majority of them concentrated in the 'Limitations and challenges' category, within the 'Limitations', 'Barriers' and 'Methodological gap' dimensions; followed by the 'Governance and Ethics' category, and 'Recommendations' dimension.

In relation with the requirements of information regarding gaps, barriers, limitations, and challenges on the use of RWD and/or RWE by WP2 and WP3, the version of the ontology presented in this deliverable (v.0.0.1), currently in validation, has been able to semantically annotate 279 entities within the scope of 'Methodology and Processes' and 16936 entities considered within the scope of the category 'Limitations and Challenges'. In addition, the first version of the ontology has been able to annotate 66 entities referred to 'Documentation and references', relevant to the work planned for the Living libraries in extracting lessons from examples of successful and unsuccessful submissions to HTA and regulatory bodies.

The complete list of entities and their relationships, contextualized in dimensions (types) and linked to each text excerpt (chunk) and source document within GREG KB is available in the GREG RAG repository in GitHub as a database.

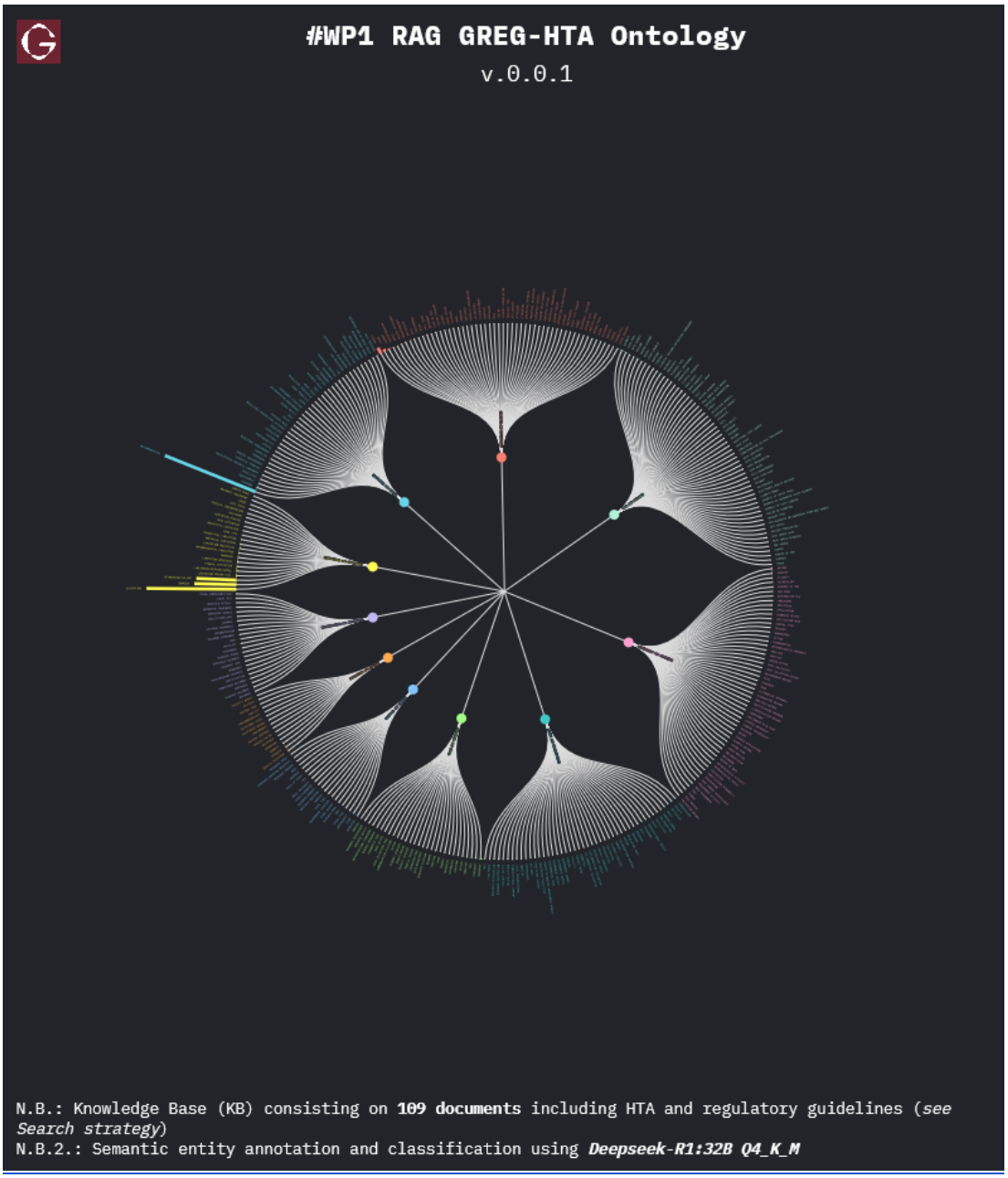

***Figure 4**: Radial hierarchical tree of the WP1 RAG GREG ontology (version 0.0.1).*

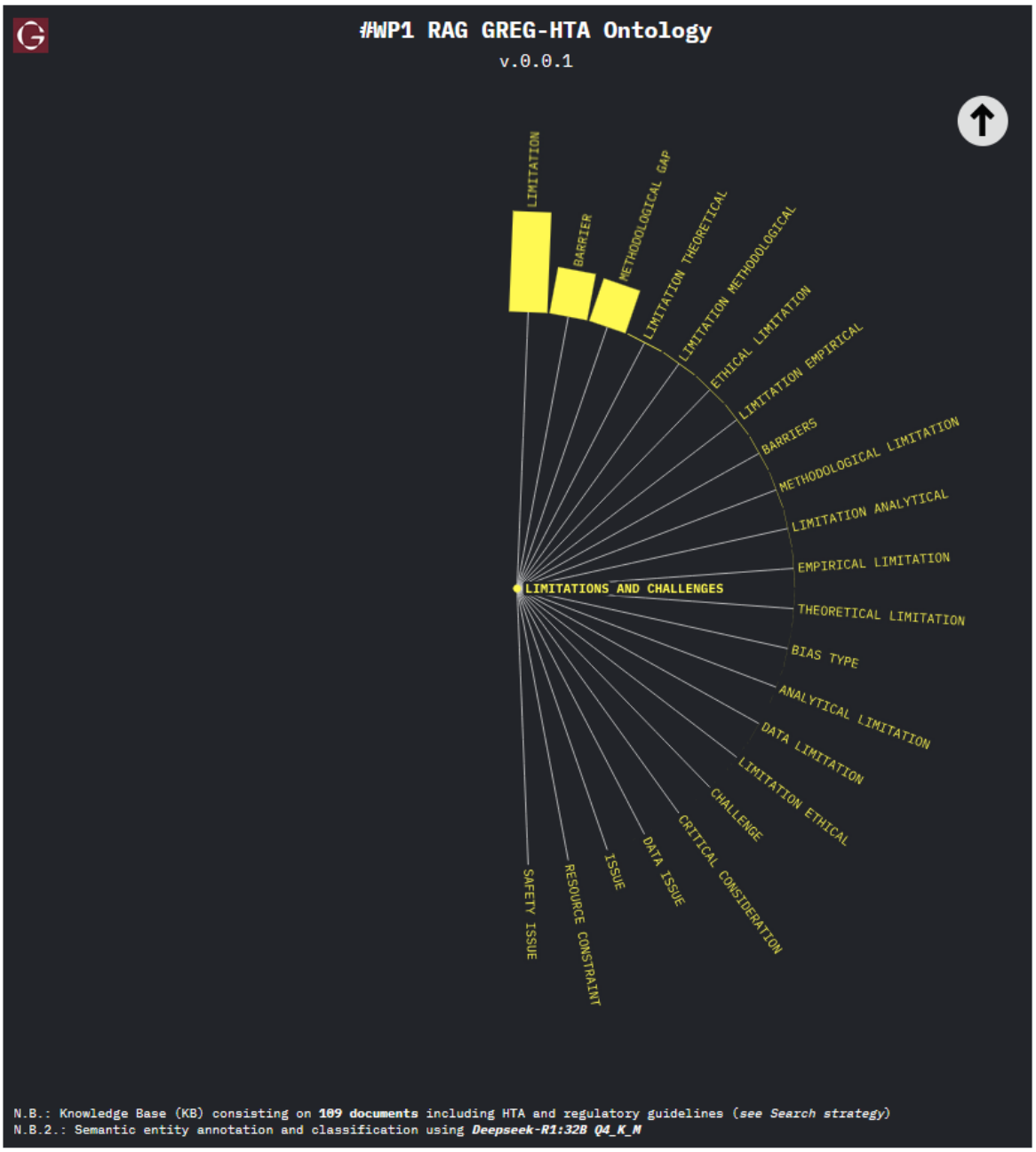

Figure 5: *Hierarchical structure (radial view) of the WP1 RAG GREG ontology (v0.0.1), detailing the specific Dimensions nested under the high-level category: 'LIMITATIONS AND CHALLENGES'.*

4 Discussion

A first systematic literature and a grey literature scoping review of guidelines related to use of RWD and RWE in regulatory and payer settings have been undertaken. As part of an Artificial Intelligence (AI)-assisted process, relevant content from these sources has been semantically annotated and organized according to a first iteration of the GREG ontology. This process is designed to be recursively executed during the project, so new literature can be periodically retrieved and analysed following similar search strategies, but also other complementary sources produced by GREG WPs can be annotated and integrated within a common GREG KB.

At least two more release versions of the ontology based on updated literature reviews are planned during 2026. These releases will also include any relevant output from other WPs, particularly lessons provided by the use cases implemented in WP6, other use cases' exemplifying successful or unsuccessful submissions collected by WP2 and 3 living libraries, outputs from discussions in the different fora and advisory boards, and other sources.

The first version of the GREG ontology (version 0.0.1) has been released with the publication of this deliverable. However, the validation process is still pending completion. This manual fine-tuning is vital to eliminate ambiguity and ensure the domain's real-world context of the insight required to produce practical guidance comparable and consistent to expert advice. The first phase of the two-phases validation process is currently underway, with the expectation that the whole process will be completed before January 2026. A fine-tuned version out of the validation (version 0.0.2 or higher) will serve as the basis for the implementation of a minimum viable product (MVP) of the GREG chatbot producing the first guidance.

The implementation and development of the GREG chatbot MVP is associated to important challenges including: a) improving the pre-processing and processing processes to include all documents retrieved and selected as relevant from the systematic search; b) processing and annotating sources in languages different from English, Spanish and Chinese (main languages supported by the LLM embedding models available open source); c) disambiguating concepts prompted by the users' queries to facilitate retrieval from GREG KB using our ontology; d) implementing robust testing and acceptable operational thresholds on the GREG chatbot and the generated responses to ensure appropriate responses and secure user interaction with the LLM model assisting the interaction; and e) other varied technical challenges derived from the integration and management of the technological stack required to run the GREG chatbot and make the whole system sustainable, by automating any processes that can be automated for keeping it up-to-date and relevant.

Finally, there are still important decisions to discuss with relevant actors in GREG; for instance, whether we should prioritise (i.e., weight differently) certain sources -for example, give more prominence to GREG outputs or institutional guidelines- or how to handle conflicting guidance from coming from different sources. WPI coordination has already introduced some of these points in the WPs debate, although the key is to start this discussion once the validation phases are completed and the GREG KB reaches a certain level of maturity as a MVP of the GREG chatbot is operational for alpha testing.

4.1 Next steps

This piece of work paves the way for further developments of the ontology and subsequently the overall GREG knowledge base. As a final output, WP1 will implement and test a GREG chatbot, that using a RAG system will enable

multiple users to query the knowledge base, synthesising the information from the sources in the knowledge base or generating specific guidance from users' demands. An outline of the activities to be developed in the next 12 months, and potential dependencies with other work-packages is found in **Table 1**.

Table 1: *Tentative WP1 planning*

Month	Activity	Dependencies
Nov'25 (M7)	[Ontology] First-step validation finalised and second version of the ontology published - (v.0.0.2)	
Dec'25 (M8)	[Ontology] Second-step validation finalised and third version of the ontology published - (v.0.0.3)	Convene a workshop to train on the validation tool to participants in this second round - invite GREG partners in WP1 to 6.
Jan'26 (M9)	[Knowledge base] Literature review update: Including relevant sources not included in the first round -e.g., grey literature in languages other than English or Spanish. Open up to scientific articles.	WP2 and WP3 provide landscape of institutions and review the search strategy
	Assessment of potential needs referred to deliverables due by month 18 in WP3.	Convening alignment meeting with WP2 and WP3
Feb'26 (M10)		
Mar'26 (M11)	First knowledge base retrieval test meant to figure out if the RAG produces evidence relevant to WP2 and WP3	Convening face validity process with WP2 and WP3
Apr'26 (M12)	Deliverable 1.2 Early report on RWE needs and Deliverable 1.3 Early report on Methodological Challenges	
May'26 (M13)	First face validity test	Convening WP
Jun'26 (M14)	Literature review update	Adding WP2 and WP3 living library outputs - due month 12
Jul'26 (M15)	Minimal viable chatbot (MVC) delivered (v.0.0.1) using latest version of the Ontology (expected v.0.1.0)	
	RWE guidance and methodological challenges identified	Convey to WP2 and WP3 for development of D3.3 and D3.4
Aug'26 (M16)		
Sep'26 (M17)	Deliverable 3.4 release for reviewers	
Oct'26		

Month	Activity	Dependencies
(M18)		
(…) Following 12 months	Towards Ontology version 1.0.0 and MVC v.1.0.0	
	Discussion on the pending challenges (e.g., weights, dealing with inconsistencies, etc)	
	Preparing for the first knowledge base retrieval test meant to figure out if the RAG produces evidence relevant to WP4 and WP5 use cases	Convening face validity process with WP4 and WP5 - due Month 38

5 Conclusion

This early report, based on a targeted systematic and scoping literature review, has set up the basis of the development of the GREG Knowledge Base and the ontology supporting the future implementation of a smart Q&A application (Chatbot).

This piece of work paves the way for further developments of the ontology and subsequently the overall GREG knowledge base. Ultimately, the knowledge base will be queried, using the GREG chatbot, to respond to multiple users' needs. A minimal viable chatbot will be developed in the upcoming months to address knowledge gaps that can be covered throughout GREG use cases.

6 Repository for primary data

Results from the processing and semantic annotation of the documents retrieved from the search described in this document and included in the GREG knowledge base are available as a queryable database at GREG RAG repository in Github: https://github.com/cienciadedatosysalud/GREG_RAG.

References

1. National Academies of Sciences, E., et al., The National Academies Collection: Reports funded by National Institutes of Health, in Examining the Impact of Real-World Evidence on Medical Product Development: Proceedings of a Workshop Series, C. Shore, et al., Editors. 2019, National Academies Press (US). Copyright 2019 by the National Academy of Sciences. All rights reserved.: Washington (DC).
2. Arondekar, B., et al., Real-World Evidence in Support of Oncology Product Registration: A Systematic Review of New Drug Application and Biologics License Application Approvals from 2015-2020. Clin Cancer Res, 2022. 28(1): p. 27-35.
3. Garritty, C., et al., Updated recommendations for the Cochrane rapid review methods guidance for rapid reviews of effectiveness. BMJ, 2024. 384: p. e076335.

Annexes

Annex I Systematic search strategy

PubMed:	#1 "real world evidence"[tiab] OR "real-world evidence"[tiab] OR "real world data"[tiab] OR "real-world data"[tiab] OR "real world study"[tiab] OR "real-world study"[tiab] OR RWE[tiab] OR RWD[tiab] OR (observational[tiab] AND (data*[tiab] OR "health data*"[tiab] OR "healthcare data*"[tiab] OR "health care data*"[tiab])) OR ((administrative[tiab] OR claim*[tiab]) AND (data*[tiab] OR "health data*"[tiab] OR "healthcare data*"[tiab] OR "health care data*"[tiab])) OR "Routinely Collected Health Data"[Mesh] OR "Electronic Health Records"[Mesh] OR "electronic health record*"[tiab] OR "electronic medical record*"[tiab] OR "electronic patient record*"[tiab] OR "Patient Generated Health Data"[Mesh] OR "Patient Health Data*"[tiab] OR "Pharmacovigilance"[Mesh] OR pharmacovigilance*[tiab] OR "safety monitoring"[tiab] #2 "Guidelines as Topic"[Mesh] OR "Policy"[Mesh] OR guidance[tiab] OR guideline*[tiab] OR position*[ti] OR framework*[tiab] OR recommend*[tiab] OR "best practice*"[ti] OR "checklist"[MeSH Terms] OR checklist*[ti] OR "check list*"[ti] OR polic*[ti] OR "good practices"[tiab] #3 "Technology Assessment, Biomedical"[Mesh] OR "Health technology assessment"[tiab] OR HTA[tiab] OR "biomedical technology assessment"[tiab] OR "health technology evaluation"[tiab] OR "Societies, Scientific"[Mesh] OR "professional society"[tiab:~2] OR "scientific society"[tiab:~2] OR "regulatory agenc*"[tiab] OR "regulatory bod*"[tiab] OR "Reimbursement"[tiab] OR "Payer*"[tiab] OR "regulatory"[tiab] #4 "letter to the editor"[tiab] OR "Letter"[Publication Type] OR "Editorial"[Publication Type] #5 #1 AND #2 AND #3 #6 #5 NOT #4 Filters applied: English, Spanish, from 2015 – 2025

Embase:	#1 'real world data'/mj OR 'real world evidence'/mj OR 'real world study'/mj OR 'real-world evidence':ti,ab OR 'real-world data':ti,ab OR 'rwe':ti,ab OR 'rwd':ti,ab OR 'real-world study':ti,ab OR (('observational study'/mj OR 'observational':ti,ab) AND ('health data'/mj OR 'health care data':ti,ab OR 'health data':ti,ab OR 'healthcare data':ti,ab OR 'data':ti,ab)) OR 'administrative health data'/mj OR 'administrative data (health)':ti,ab OR 'administrative health care data':ti,ab OR 'administrative health data':ti,ab OR 'administrative healthcare data':ti,ab OR 'health administrative data':ti,ab OR 'health care administrative data':ti,ab OR 'healthcare administrative data':ti,ab OR 'claims data'/mj OR 'routinely collected health data'/mj OR 'routinely collected health care data':ti,ab OR 'routinely collected health data':ti,ab OR 'routinely collected healthcare data':ti,ab OR 'electronic health record'/mj OR 'electronic medical record'/mj OR 'electronic healthcare database':ti,ab OR 'electronic medical record':ti,ab OR 'electronic patient record'/mj OR 'electronic patient record':ti,ab OR 'patient health data':ti,ab OR 'patient generated health data':ti,ab OR 'pharmacovigilance'/mj OR 'safety monitoring':ti,ab #2 'guideline'/mj OR 'policy'/mj OR 'policy':ti,ab OR 'guidance'/mj OR 'position'/mj OR 'position':ti OR 'framework'/mj OR 'recommendations'/mj OR 'best practice'/mj OR 'best practice':ti OR 'checklist'/mj OR 'check list':ti,ab OR 'checklist':ti,ab #3 'biomedical technology assessment'/mj OR 'biomedical technology assessment':ti,ab OR 'health technology assessment':ti,ab OR 'technology assessment, biomedical':ti,ab OR 'HTA':ti,ab OR 'regulatory agency':ti,ab OR 'regulatory agencies':ti,ab OR 'regulatory body':ti,ab OR 'regulatory bodies':ti,ab OR 'health care organization'/mj OR 'health care organisation':ti,ab OR 'health care organization':ti,ab OR 'health organisation':ti,ab OR 'health organization':ti,ab OR 'health systems agencies':ti,ab OR 'healthcare organisation':ti,ab OR 'healthcare organization':ti,ab OR 'hospital societies':ti,ab OR 'organisation, health care':ti,ab OR 'organization, health care':ti,ab OR 'pharmaceutical societies':ti,ab OR 'scientific societies':ti,ab OR 'societies, hospital':ti,ab OR 'societies, pharmaceutical':ti,ab OR 'societies, scientific':ti,ab OR 'payer':ti,ab OR 'reimbursement'/mj #4 #1 AND #2 AND #3 #5 #4 AND ('article'/it OR 'article in press'/it OR 'preprint'/it OR 'review'/it) AND ([english]/lim OR [spanish]/lim) AND [2015-2025]/py
International HTA Database (INAHTA)	(Pharmacovigilance)[mh] OR (Electronic Health Records)[mh] OR (Routinely Collected Health Data)[mh] OR (Patient Generated Health Data)[mh] OR (real world)[Title] OR (Observational)[Title] OR (Administrative)[Title] OR (claim)[Title] OR (record)[Title] OR (Pharmacovigilance)[Title] OR (safety monitoring)[Title]

Annex 2 Records retrieved from the literature search

Author	Year	Title	DOI/Link
Systematic search			
Bahri, et al.	2024	The STAR Compass to Guide Future Pharmacovigilance Based on a 10-Year Review of the Strengthened EU System	https://doi.org/doi:10.1007/s40264-024-01451-3
Balas, et al.	2015	Big Data Clinical Research: Validity, Ethics, and Regulation	https://ebooks.iospress.nl/publication/40248
Barrette, et al.	2025	Research Method, Conduct, and Reporting Considerations for Improving the Quality of Non-Hypothesis-Evaluating Treatment Effectiveness Analyses Using Real-World Data: An ISPOR Special Interest Group Report	https://doi.org/doi:10.1016/j.jval.2025.02.017.
Beck, et al.	2025	Collaborative Real-World Evidence Among Regulators: Lessons and Perspectives	https://doi.org/doi:10.1002/cpt.3457.
Berger, et al.	2017	Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making	https://doi.org/doi:10.1002/pds.4297.
C, et al.	2024	Programme for the use of real world data in health technology assessment. Potential uses for real world data in the Spanish HTA Network	https://doi.org/doi:https://doi.org/10.46994/ets_38.
Chan, et al.	2025	Development of a framework on the incorporation of real-world evidence (RWE) into cancer drug funding decisions in Canada: the Canadian Real-world Evidence for Value of Cancer Drugs (CanREValue) collaboration	https://doi.org/doi:10.1136/bmjopen-2024-096286.
Chen, et al.	2020	Using real-world evidence for pharmacovigilance and drug safety-related decision making by a resource-limited health authority: 10 years of experience in Taiwan	https://doi.org/doi:10.1002/pds.5084.
Cocoros, et al.	2021	The Certainty Framework for Assessing Real-World Data in Studies of Medical Product Safety and Effectiveness	https://doi.org/doi:10.1002/cpt.2045.
Dai, et al.	2021	Considerations for Developing a Reassessment Process: Report from the Canadian Real-World Evidence for Value of Cancer Drugs (CanREValue) Collaboration's Reassessment and Uptake Working Group	https://doi.org/doi:10.3390/curroncol28050354.
Dai, et al.	2021	Building a National Reassessment Process for Oncology Drugs: Lessons Learned by the Canadian Real-World Evidence for Value of Cancer Drugs (CanREValue) Collaboration through a Simulated Reassessment Exercise	https://doi.org/doi:10.3390/curroncol28060392.
Daubner-Bendes, et al.	2020	Quo Vadis HTA for Medical Devices in Central and Eastern Europe? Recommendations to Address Methodological Challenges	https://doi.org/doi:10.3389/fpubh.2020.612410.
Evans, et al.	2022	Engaging Patients in the Canadian Real-World Evidence for Value in Cancer Drugs (CanREValue) Initiative: Processes and Lessons Learned	https://doi.org/doi:10.3390/curroncol29080443.
Facey, et al.	2020	Real-world evidence to support Payer/HTA decisions about highly innovative technologies in the EU-actions for stakeholders	https://doi.org/doi:10.1017/s026646232000063x.
Fleurence, et al.	2024	Assessing Real-World Data From Electronic Health Records for Health Technology Assessment: The SUITABILITY Checklist: A Good Practices Report of an ISPOR Task Force	https://doi.org/doi:10.1016/j.jval.2024.01.019.
Franklin, et al.	2020	Nonrandomized Real-World Evidence to Support Regulatory Decision Making: Process for a Randomized Trial Replication Project	https://doi.org/doi:10.1002/cpt.1633.

Author	Year	Title	DOI/Link
Guerra-Júnior, et al.	2017	HEALTH TECHNOLOGY PERFORMANCE ASSESSMENT: REAL-WORLD EVIDENCE FOR PUBLIC HEALTHCARE SUSTAINABILITY	https://doi.org/doi:10.1017/s0266462317000423.
Gupta, et al.	2025	Quality in qualitative evidence: new best practice principles from NICE's real-world evidence framework	https://doi.org/doi:10.57264/cer-2025-0064.
Heininger, et al.	2017	Guide to active vaccine safety surveillance: Report of CIOMS working group on vaccine safety - executive summary	https://doi.org/doi:10.1016/j.vaccine.2017.06.033.
Hogervorst, et al.	2022	Real World Data in Health Technology Assessment of Complex Health Technologies	https://doi.org/doi:10.3389/fphar.2022.837302.
Hogervorst, et al.	2025	Analytical Methods for Comparing Uncontrolled Trials With External Controls From Real-World Data: A Systematic Literature Review and Comparison With European Regulatory and Health Technology Assessment Practice	https://doi.org/doi:10.1016/j.jval.2024.08.002.
Hussein, et al.	2024	Getting ready for the European Health Data Space (EHDS): IDERHA's plan to align with the latest EHDS requirements for the secondary use of health data	https://doi.org/doi:10.12688/openreseurope.18179.1.
Izem, et al.	2018	Sources of Safety Data and Statistical Strategies for Design and Analysis: Postmarket Surveillance	https://doi.org/doi:10.1177/2168479017741112.
Wohlhöfner, K, et al.	2021	(Good) practice organisational models using real-world evidence for public funding of high priced therapies	https://eprints.aihta.at/1329/
Kc, et al.	2023	What, Where, and How to Collect Real-World Data and Generate Real-World Evidence to Support Drug Reimbursement Decision-Making in Asia: A reflection Into the Past and A Way Forward	https://doi.org/doi:10.34172/ijhpm.2023.6858.
Klein, et al.	2022	Real-world evidence in health technology assessment of high-risk medical devices: Fit for purpose?	https://doi.org/doi:10.1002/hec.4575.
Marchenko, et al.	2018	Sources of Safety Data and Statistical Strategies for Design and Analysis: Real World Insights	https://doi.org/doi:10.1177/2168479017739270.
Meinecke, et al.	2017	Series: Pragmatic trials and real world evidence: Paper 8. Data collection and management	https://doi.org/doi:10.1016/j.jclinepi.2017.07.003.
Németh, et al.	2023	Guidance on using real-world evidence from Western Europe in Central and Eastern European health policy decision making	https://doi.org/doi:10.57264/cer-2022-0157.
O'Neill, et al.	2019	ISPOR, the FDA, and the Evolving Regulatory Science of Medical Device Products	https://doi.org/doi:10.1016/j.jval.2019.03.020.
Patel, et al.	2024	Contemporary Practice and Considerations for Real-World Data Source Identification and Feasibility Assessment	https://doi.org/doi:10.1002/pds.5862.
Peters, et al.	2021	Effective Pharmacovigilance System Development: EFPIA-IPVG Consensus Recommendations	https://doi.org/doi:10.1007/s40264-020-01008-0.
Sarntivijai, et al.	2022	eTRANSAFE: Building a sustainable framework to share reproducible drug safety knowledge with the public domain	https://doi.org/doi:10.12688/f1000research.74024.1.
Schneeweiss, et al.	2018	Real-World Data Analytics Fit for Regulatory Decision-Making	https://doi.org/doi:10.1177/0098858818789429.

Author	Year	Title	DOI/Link
Seltzer, et al.	2017	Use of endpoint adjudication to improve the quality and validity of endpoint assessment for medical device development and post marketing evaluation: Rationale and best practices. A report from the cardiac safety research consortium	https://doi.org/doi:10.1016/j.ahj.2017.05.009.
Solà-Morales, et al.	2023	Data Governance for Real-World Data Management: A Proposal for a Checklist to Support Decision Making	https://doi.org/doi:10.1016/j.jval.2023.02.012.
Tadrous, et al.	2024	Development of a Canadian Guidance for reporting real-world evidence for regulatory and health-technology assessment (HTA) decision-making	https://doi.org/doi:10.1016/j.jclinepi.2024.111545.
Takhar, et al.	2024	Application of Multi-Criteria Decision Analysis (MCDA) to Prioritize Real-World Evidence Studies for Health Technology Management: Outcomes and Lessons Learned by the Canadian Real-World Evidence for Value of Cancer Drugs (CanREValue) Collaboration	https://doi.org/doi:10.3390/curroncol31040141.
Verweij, et al.	2025	Learning from European regulator-initiated studies for regulatory decision making	https://doi.org/doi:10.1016/j.drudis.2024.104256.
Wang, et al.	2024	Adopting a Framework for Rapid Real-World Data Analyses in Safety Signal Assessment	https://doi.org/doi:10.1007/s43441-024-00694-7.
Wang, et al.	2022	HARmonized Protocol Template to Enhance Reproducibility of Hypothesis Evaluating Real-World Evidence Studies on Treatment Effects: A Good Practices Report of a Joint ISPE/ISPOR Task Force	https://doi.org/doi:10.1016/j.jval.2022.09.001.
Wisniewski, et al.	2016	Good Signal Detection Practices: Evidence from IMI PROTECT	https://doi.org/doi:10.1007/s40264-016-0405-1.
Zebachi, et al.	2025	Navigating the Real World: A Scoping Review of Structured Frameworks to Effectively Identify, Evaluate, and Select Real-World Data Sources for Fit-for-Purpose Studies	https://doi.org/doi:10.1002/cpt.3746.
Zhang, et al.	2022	Best practices in the real-world data life cycle	https://doi.org/doi:10.1371/journal.pdig.0000003
Regulatory and HTA institutions and professional societies			
FDA	2025	Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence-Enabled Device Software Functions	https://www.fda.gov/media/166704/download
FDA	2024	Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products	https://www.fda.gov/media/152503/download
FDA	2023	Examples of Real-World Evidence (RWE) Used in Medical Device Regulatory Decisions	https://www.fda.gov/media/146258/download
FDA	2023	Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices	https://www.fda.gov/media/174819/download
FDA	2023	Real-World Data: Assessing Registries To Support Regulatory Decision-Making for Drug and Biological Products	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-registries-support-regulatory-decision-making-drug-and-biological-products
FDA	2023	Data Standards for Drug and Biological Product Submissions Containing Real-World Data	https://www.fda.gov/media/153341/download
FDA	2023	Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products	https://www.fda.gov/media/171667/download
FDA	2023	Digital Health Technologies for Remote Data Acquisition in Clinical Investigations	https://becarispublishing.com/digital-content/blog-post/fda-unveils-new-

Author	Year	Title	DOI/Link
			guidance-use-digital-health-technologies-remote-data-acquisition
FDA	2022	Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-documents-using-real-world-data-and-real-world-evidence-fda-drug-and-biological-products
FDA	2018	Use of Electronic Health Records in Clinical Investigations	https://www.fda.gov/media/97567/download
FDA	2013	Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data	https://www.fda.gov/media/79922/download
FDA	2018	Framework for FDA's Real-World Evidence Program	https://www.fda.gov/media/120060/download
ICER	2018	A Framework to Guide the Optimal Development and Use of Real-World Evidence for Coverage and Formulary Decisions	https://icer.org/wp-content/uploads/2020/11/ICER-RWE-Framework-Companion-White-Paper-03282018.pdf
ICER	2018	Real World Evidence for Coverage Decisions: Opportunities and Challenges A Report from the 2017 ICER Membership Policy Summit	https://icer.org/wp-content/uploads/2020/11/ICER-Real-World-Evidence-White-Paper-03282018.pdf
ICER	2018	2020-2023 Value Assessment Framework: Considering Clinical, Real-World, and Unpublished Evidence	https://icer.org/our-approach/methods-process/considering-clinical-real-world-and-unpublished-evidence/
EMA-HMA	2025	Good Practice Guide for the use of the HMA-EMA catalogues of real-world data sources and studies	https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/good-practice-guide-use-hma-ema-catalogues-real-world-data-sources-studies_en.pdf
EMA-HMA	2023	Data Quality Framework for EU medicines regulation	https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/data-quality-framework-eu-medicines-regulation_en.pdf
EMA-HMA	2023	Real-world evidence framework to support EU regulatory decision-making	https://www.ema.europa.eu/en/documents/report/real-world-evidence-framework-support-eu-regulatory-decision-making-report-experience-gained-regulator-led-studies-september-2021-february-2023_en.pdf
EMA-HMA	2024	Real-world evidence provided by EMA Support for regulatory decision-making	https://www.ema.europa.eu/en/documents/other/guide-real-world-evidence-provided-ema-support-regulatory-decision-making_en.pdf
EMA-HMA	2025	List of metadata for the HMA-EMA Catalogues of real-world data sources and studies	https://www.ema.europa.eu/en/documents/other/list-metadata-hma-ema-catalogues-real-world-data-sources-studies_en.pdf
EMA-HMA	2024	Guideline on good pharmacovigilance practices (todos los módulos)	https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/good-pharmacovigilance-practices-gvp
EMA-HMA	2019	"Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe" Cave, Kurz and Arlett	https://doi.org/doi:10.1002/cpt.1426
EMA's CHMP	2022	Guideline on registry-based studies	https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en.pdf

Author	Year	Title	DOI/Link
EMA's CHMP	2022	European Medicines Agency post-authorisation procedural advice for users of the centralised procedure	https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-post-authorisation-procedural-advice-users-centralised-procedure_en.pdf
EMA's ENCePP	2010	Guide on Methodological Standards in Pharmacoepidemiology	https://encepp.europa.eu/document/download/f6e403a6-8033-4c22-a5ff-195ba3666299_en?filename=01.ENCePPMethodsGuideRev.11.pdf&prefLang=es
EMA's ENCePP	2018	Checklist for Study Protocols	https://catalogues.ema.europa.eu/sites/default/files/document_files/ENCePP%20Checklist%20for%20Study%20Protocols_YW.pdf
EMA-ICH*	2024	Pursuing opportunities for harmonisation in using real-world data to generate real-world evidence with a focus on the effectiveness of medicines	https://www.ema.europa.eu/en/documents/scientific-guideline/ich-reflection-paper-pursuing-opportunities-harmonisation-using-real-world-data-generate-realworld-evidence-focus-effectiveness-medicines_en.pdf
EMA-ICH*	2024	[ICH M14] General principles on planning and designing pharmacoepidemiological studies that utilize real-world data for safety assessment of a medicine	https://www.ema.europa.eu/en/documents/scientific-guideline/ich-reflection-paper-pursuing-opportunities-harmonisation-using-real-world-data-generate-realworld-evidence-focus-effectiveness-medicines_en.pdf
EMA-ICH*	2025	[ICH M11] Clinical electronic Structured Harmonised Protocol (CeSHarP)	https://database.ich.org/sites/default/files/ICH_M14_Step3_DraftGuideline_2024_0521.pdf
EMA-ICH*	2025	[ICH E6(R3)] Good Clinical Practice (GCP) on the use of RWD	https://database.ich.org/sites/default/files/ICH_M11_Technical%20Specification_Updated%20Step%202_2025_0203.pdf
EMA-ICH*	2022	[ICH E8] General Considerations for Clinical Studies	https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf
EMA-ICH*	2020	[ICH E9 (R1)] (addendum on estimands) "Statistical Principles for Clinical Trials"	https://www.ich.org/page/efficacy-guidelines
EMA-ICH*	2001	[ICH E10] Choice of Control Group and Related Issues in Clinical Trials	https://www.ich.org/page/efficacy-guidelines
European Commission	2017	Mapping of HTA methodologies in EU and Norway	https://health.ec.europa.eu/system/files/2018-01/2018_mapping_methodologies_en_0.pdf
European Commission	2024	Guidance on Validity of Clinical Studies for joint clinical assessments	https://health.ec.europa.eu/publications/guidance-validity-clinical-studies-joint-clinical-assessments_en
ESMO	2023	ESMO Guidance for Reporting Oncology Real-World evidence (GROW)	https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2823%2904018-8

Author	Year	Title	DOI/Link
ESMO	2024	Checklist for Study Protocols	https://grow.esmo.org/
IHI	2024	IHI Regulators Science Summit Report	https://www.ihi.europa.eu/sites/default/files/uploads/Documents/ProjectResources/RegulatoryScienceSummit_Feb2024_Report.pdf
EUNetHTA	2019	Final validated Standards Tool for Registries in HTA prepared	https://catalogues.ema.europa.eu/system/files/2025-02/05.01.0301%20Feasibility%20Documentation%20%20-%20Registry%20Evaluation%20and%20Quality%20Standards%20Tool%20%28REQueST%29%20_%2010-Sep-2023_Redacted.pdf
Santé Canada/ Health Canada	2019	Optimizing the Use of Real-World Evidence to Inform Regulatory Decision-Making	https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/optimizing-real-world-evidence-regulatory-decisions.html
Santé Canada/ Health Canada	2023	Health Canada's position on the CADTH Guidance for Reporting RWE to Support Decision-making	https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/health-canada-position-guidance-reporting-real-world-evidence-supporting-decision-making.html
Santé Canada/ Health Canada	2019	Elements of Real-World Data/Evidence Quality throughout the Prescription Drug Product Life Cycle	https://www.canada.ca/en/services/health/publications/drugs-health-products/real-world-data-evidence-drug-lifecycle-report.html
CADTH	2023	Guidance for reporting Real-World Evidence	https://www.cda-amc.ca/sites/default/files/RWE/MG0020/MG0020-RWE-Guidance-Report-Secured.pdf
CADTH	2023	Checklist for reporting Real-World Evidence	https://www.cda-amc.ca/guidance-reporting-real-world-evidence
HAS	2021	Real-world studies for the assessment of medicinal products and medical devices	https://www.has-sante.fr/upload/docs/application/pdf/2021-10/real-world_studies_for_the_assessment_of_medicinal_products_and_medical_devices.pdf
HAS	2021	Methodology for the Clinical Development of Medical Devices	https://www.has-sante.fr/upload/docs/application/pdf/2021-09/guide_methodology_for_the_clinical_development_of_md.pdf

Author	Year	Title	DOI/Link
HAS	2024	Can requests for real-world evidence by the French HTA body be planned? An exhaustive retrospective case–control study of medicinal products appraisals from 2016 to 2021	https://www.cambridge.org/core/journals/international-journal-of-technology-assessment-in-health-care/article/can-requests-for-realworld-evidence-by-the-french-hta-body-be-planned-an-exhaustive-retrospective-casecontrol-study-of-medicinal-products-appraisals-from-2016-to-2021/6F6C982F2F9BD35C57BCBDAD248A2430
IQWiG	2020	Concepts for the generation of routine practice data and their analysis for the benefit assessment of drugs according to §35a Social Code Book V	https://www.iqwig.de/download/a19-43_routine-practice-data-for-the-benefit-assessment-of-drugs_rapid-report_v1-0.pdf
SwissMedic	2025	Expansion of the SwissMedic position paper on real world evidence	https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/information/erweiterung-positionspapier-rwe.html
Multi-stakeholder	2024	Real World Data (RWD) quality and experience Danish national health registers	https://www.ema.europa.eu/en/documents/presentation/presentation-real-world-data-rwd-quality-and-experience-danish-national-health-registers-s-knudstrup-k-holt-nielsen-danish-health-data-authority_en.pdf
MHRA	2025	MHRA guidance on the use of real-world data in clinical studies to support regulatory decisions	https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions
MHRA	2025	MHRA guideline on randomised controlled trials using real-world data to support regulatory decisions	https://www.gov.uk/government/publications/mhra-guidance-on-the-use-of-real-world-data-in-clinical-studies-to-support-regulatory-decisions/mhra-guideline-on-randomised-controlled-trials-using-real-world-data-to-support-regulatory-decisions
NICE	2022	NICE real-world evidence framework	https://www.nice.org.uk/corporate/ecd9/resources/nice-realworld-evidence-framework-pdf-1124020816837
Therapeutic Goods Administration (TGA)	2021	Real world evidence and patient reported outcomes in the regulatory context	https://www.tga.gov.au/sites/default/files/real-world-evidence-and-patient-reported-outcomes-in-the-regulatory-context.pdf
Therapeutic Goods Administration (TGA)	2024	Clinical evidence guidelines for medical devices	https://www.tga.gov.au/resources/guidance/clinical-evidence-guidelines-medical-devices

Author	Year	Title	DOI/Link
MFDS	2022	Guidance on the application of real-world evidence (RWE) to medical devices	https://healthpolicy.duke.edu/sites/default/files/2024-04/MFDS%20Guideline%20on%20RWE%20for%20Medical%20Devices.pdf
RWD Working Group of PMDA	2024	Points to Consider When Registry Data are utilized for Partial Change Approval Applications or Revision of Electronic Package Insert for Prescription Drugs	https://www.pmda.go.jp/files/000274894.pdf
PhRMA Japan Medical AfairsCommittee Working Group	2021	Current Status, Challenges, and Future Perspectives of Real-World Data and Real-World Evidence in Japan	https://doi.org/10.1007/s40801-021-00266-3
Joint ISPE/ISPOR Task Force	2017	HARmonized Protocol Template to Enhance Reproducibility of Hypothesis Evaluating Real-World Evidence Studies on Treatment Effects: A Good Practices Report of a Joint ISPE/ISPOR Task Force	https://doi.org/doi:10.1016/j.jval.2022.09.001
Joint ISPE/ISPOR Task Force	2017	Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making	https://doi.org/doi:10.1002/pds.4297
Joint ISPE/ISPOR Task Force	2017	Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0	https://doi.org/doi10.1002/pds.4295.
Joint ISPE/ISPOR Task Force	2017	Making Real-World Evidence More Useful for Decision making	https://www.ispor.org/docs/default-source/strategic-initiatives/rwe-healthcare-decision-making-guideline.pdf?sfvrsn=56d9b92_2
Joint ISPE/ISPOR Task Force	2016	Guidelines for good pharmacoepidemiology practice (GPP)	https://doi.org/doi:10.1002/pds.3891
ISPE	2020	ISPE Statement on Real-World Evidence (RWE)	https://pharmacoepi.org/pub/136DECF1-C559-BA4F-92C4-CF6E3ED16BB6
ISPE	2020	ISPE Comments on the Framework for FDA's Real World Evidence Program (	https://pharmacoepi.org/pub/FD498949-FDC8-7D05-0866-3A7FC06C7C9A
ISPE	2020	ISPE's Comments on the Core Recommendations in the Summary of the Heads of Medicines Agencies (HMA) - EMA Joint Big Data Task Force	https://pharmacoepi.org/pub/F2B27224-B9E2-3FEB-C33B-12D38B258782
Initiatives			
TEHDAS2	2024-2026	Towards European Health Data Space 2	https://tehdas.eu/
DARWIN EU	2022	Data Analysis and Real World Interrogation Network	https://www.darwin-eu.org/
EUCAIM	2023-2026	European Federation for Cancer Images	https://www.egi.eu/project/eucaim/
IDERHA	2023-2028	Integration of Heterogeneous Data and Evidence towards Regulatory and HTA Acceptance	https://www.iderha.org/

Author	Year	Title	DOI/Link
QUANTUM	2022	The health data quality label	https://quantumproject.eu/
GDI	2022-2026	European Genomic Data Infrastructure	https://gdi.onemilliongenomes.eu/
OHDSI	2014-ongoing	Observational Health Data Sciences and Informatics	https://www.ohdsi.org/
HealthData@EU Pilot	2022-2024	European Health Data Space	https://acceptance.data.health.europa.eu/healthdata-central-platform?locale=en
TEHDAS1	2021-2023	Towards European Health Data Space	https://tehdas.eu/tehdas1/
HARMONY PLUS	2020-2024	Healthcare alliance for resourceful medicines offensive against neoplasms in hematology	https://harmony-alliance.eu/harmony-platform/
HTx project	2019-2024	Next Generation Health Technology Assessment	https://www.htx-h2020.eu/
EHDEN	2018-2024	European Health Data & Evidence Network	https://www.ehden.eu/
PIONEER	2018-2023	PIONEER	https://www.pioneer-project.eu/
BigData@Heart	2017-2023	BigData@Heart	https://www.bigdata-heart.eu/
EMIF	2013-2018	European Medical Information Framework	https://www.emif.eu/
EDiHTA	2024-ongoing	European Digital Health Technology Assessment	https://edihta-project.eu/
Sustain-HTA	2024-2027	Support Utilisation of Sustainable and TAilored INnovative methods for HTA	https://sustain-hta.org/
AD-RIDDLE	2024-ongoing	Advancing Solutions for Alzheimer's Disease	https://www.ad-riddle.org/
REALM	2023-2026	Real-world-data Enabled Assessment for heaLth regulatory decision-Making	https://realm-ai.eu/
More-Europa	2023-2027	More Effectively Using Registries to support Patient-centered Regulatory and HTA decision-making	https://www.moreproject-horizon.eu/
Real4Reg	2023-2026	Real4Reg – Unlocking Real-World Data with AI	https://www.real4reg.eu/
Reddie	2023-2026	Real-World Evidence for Decisions in Diabetes	https://www.reddie-diabetes.eu/
INSAFEDARE	2023-2026	Assessment and Assurance of Data and Synthetic Data for Regulatory Decision Support	https://www.insafedare.org/

Author	Year	Title	DOI/Link
PREDICTOM	2023-2027	Prediction of Alzheimers disease disease using an AI Driven Screening Plataform	https://www.predictom.eu/
Oncovalue	2022-2026	Implementing value-based oncology care at European cancer hospitals: An AI-based framework for assessing real-life effectiveness of novel cancer therapies in real-time	https://oncovalue.org/
EUrecca 2025	2020-2025	European Initiative for New Reimbursement and Access Approaches 2025	Not available
REALISE Working Group	2019-Ongoing	REAL World Data In ASia for HEalth Technology Assessment in Reimbursement	https://hiper.nus.edu.sg/realise-guidance/
RWE4 Decisions	2019-ongoing	RWE4Decisions: Real-World Evidence for Decisions initiative	https://rwe4decisions.com/
CCTI	2007-	Clinical Trials Transformation Initiative	https://ctti-clinicaltrials.org/
Duke-Margolis RWE group	2017-ongoing	Duke-Margolis RWE group	https://healthpolicy.duke.edu/topics/real-world-evidence
VALUE-Dx	2021-2024	The value of diagnostics to combat antimicrobial resistance by optimising antibiotic use	https://www.value-dx.eu/
ERA4TB	2020-2026	European Regimen Accelerator for Tuberculosis	https://era4tb.org/
RCT Duplicate	2019-2023	Randomized Controlled Trials Duplicated Using Prospective Longitudinal Insurance Claims: Applying Techniques of Epidemiology	https://www.rct-duplicate.org/
IMPACT HTA	2018-2021	Improved methods and actionable tools for enhancing HTA	https://www.impact-hta.eu/
ROADMAP	2016-2018	Real world outcomes across the AD spectrum for better care: multi-modal data access platform	https://www.ihi.europa.eu/projects-results/project-factsheets/roadmap
GetReal Initiative	2018-2021	Incorporating real-life clinical data into drug development	https://www.ihi.europa.eu/projects-results/project-factsheets/getreal
COMED	2018-2021	Pushing the boundaries of cost and outcome analysis of medical technologies	https://www.comedh2020.eu/index.html
REBECCA	2021-2025	REsearch on BrEast Cancer induced chronic conditions supported by Causal Analysis of multi-source data	https://rebeccaproject.eu/
CIOMS	2020-2024	Council for International Organizations of Medical Sciences: Grupo XIII	https://cioms.ch/working-groups/real-world-data-and-real-world-evidence-in-regulatory-decision-making/
PROTECT	2022	Preparing a Pre-Commercial Procurement for end-user services based on environmental observation in the area of climate change adaptation and mitigation	https://www.protect-pcp.eu/protect-project/
FACILITATE	2022	Framework for Clinical Trial Participants' Data Reutilization for a Fully Transparent and Ethical Ecosystem	https://facilitate-project.eu/

Author	Year	Title	DOI/Link
Friends of Cancer Research	Not applicable	Friends of Cancer Research	https://friendsofcancerresearch.org/

Annex 3 Excluded studies and reasons for exclusion

N°	Author	Year	Tittle	Reason of exclusion*
1	Abrahami, et al.	2021	Use of Real-World Data to Emulate a Clinical Trial and Support Regulatory Decision Making: Assessing the Impact of Temporality, Comparator Choice, and Method of Adjustment	Criterion 5
2	Adams, et al.	2024	Development of a Safety Surveillance Plan for the Academic Medicine Sponsor Performing First-in-Human Cellular Therapy Clinical Trials: A Report from the Consortium for Pediatric Cellular Immunotherapy	Criterion 5
3	Alexe, et al.	2025	Points to Consider on the Use of Medicines in Pregnancy Throughout the Product Lifecycle Based on Global Regulatory Guidance	Criterion 3
4	Anderson, et al.	2023	Real-world evidence generation from patients, their caregivers and physicians supporting clinical, regulatory and guideline decisions: an update on Disease Specific Programmes	Criterion 5
5	Annemans, et al.	2020	TRUST4RD: tool for reducing uncertainties in the evidence generation for specialised treatments for rare diseases	Criterion 5
6	Appiah, et al.	2024	Justifying the source of external comparators in single-arm oncology health technology submissions: a review of NICE and PBAC assessments	Criterion 5
7	Arora, et al.	2025	R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 19	Criterion 5
8	Arslan, et al.	2024	Towards a Regulatory Framework for Workflow Improvement in Electronic Medical Records	Criterion 2
9	Aupiais, et al.	2019	A Bayesian non-inferiority approach using experts' margin elicitation - application to the monitoring of safety events	Criterion 1
10	Babic, et al.	2025	Barriers and Facilitators for Federated Health Data Networks: Lessons Learned from a Nordic-Baltic Experience	Criterion 2
11	Babrak, et al.	2022	RWD-Cockpit: Application for Quality Assessment of Real-world Data	Criterion 5
12	Baghbanian, et al.	2025	Methods for the health technology assessment of complex interventions: A scoping review	Criterion 5
13	Bahri, et al.	2021	Systematising Pharmacovigilance Engagement of Patients, Healthcare Professionals and Regulators: A Practical Decision Guide Derived from the International Risk Governance Framework for Engagement Events and Discourse	Criterion 5
14	Bahri, et al.	2019	CIOMS Guide To Vaccine Safety Communication - Executive summary	Criterion 3
15	Balijepalli, et al.	2020	Can Standard Health Technology Assessment Approaches Help Guide the Price of Orphan Drugs in Canada? A Review of Submissions to the Canadian Agency for Drugs and Technologies in Health Common Drug Review	Criterion 1
16	Bando, et al.	2024	Appropriate Relevancy and Reliability of Real-World Data for the Utilization of Regulatory Submission	Criterion 5
17	Barberio, et al.	2024	Characterizing Fit-for-Purpose Real-World Data: An Assessment of a Mother-Infant Linkage in the Japan Medical Data Center Claims Database	Criterion 2
18	Baumfeld Andre, et al.	2020	Trial designs using real-world data: The changing landscape of the regulatory approval process	Criterion 2
19	Beaulieu-Jones, et al.	2020	Examining the Use of Real-World Evidence in the Regulatory Process	Criterion 2
20	Berry, et al.	2025	Utilizing large language models for gastroenterology research: a conceptual framework	Criterion 1
37	Betesh, et al.	2018	The Effect of Electronic Medical Record Alerts on Provider Wellness	Criterion 3
97	Betesh, et al.	2018	Using Patient Generated Health Data in an Electronic Health Record	Criterion 3
21	Beyrer, et al.	2022	A review of stakeholder recommendations for defining fit-for-purpose real-world evidence algorithms	Criterion 5
22	Blumer, et al.	2017	Wisdom within: unlocking the potential of big data for nursing regulators	Criterion 1

N°	Author	Year	Tittle	Reason of exclusion*
23	Bou-Jaoudeh, et al.	2025	Toward an Extensible Regulatory Framework for N-of-1 to N-of-Few Personalized RNA Therapy Design	Criterion 2
24	Brandes, et al.	2016	USING CLAIMS DATA FOR EVIDENCE GENERATION IN MANAGED ENTRY AGREEMENTS	Criterion 3
25	Bray, et al.	2023	R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 11	Criterion 5
26	Bray, et al.	2023	R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 12	Criterion 5
27	Bray, et al.	2023	R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 13	Criterion 5
28	Bray, et al.	2024	R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 14	Criterion 5
29	Brixner, et al.	2021	Payer perceptions of the use of real-world evidence in oncology-based decision making	Criterion 2
30	Brown, et al.	2019	Use of real-world evidence in postmarketing medicines regulation in the European Union: a systematic assessment of European Medicines Agency referrals 2013-2017	Criterion 2
31	Bucher, et al.	2025	Strengthening health technology assessment for cancer treatments in Europe by integrating causal inference and target trial emulation	Criterion 5
32	Bukovac, et al.	2023	The Regulation of Cell Therapy and Gene Therapy Products in Switzerland	Criterion 2
33	Bullement, et al.	2020	Real-world evidence use in assessments of cancer drugs by NICE	Criterion 5
34	Burcu, et al.	2022	A Framework for Extension Studies Using Real-World Data to Examine Long-Term Safety and Effectiveness	Criterion 5
35	Burns, et al.	2023	Real-world evidence for regulatory decision-making: updated guidance from around the world	Criterion 5
36	Burns, et al.	2022	Real-World Evidence for Regulatory Decision-Making: Guidance From Around the World	Criterion 5
38	Campbell, et al.	2023	SURF: A Screening Tool (for Sponsors) to Evaluate Whether Using Real-World Data to Support an Effectiveness Claim in an FDA Application Has Regulatory Feasibility	Criterion 3
39	Candore, et al.	2020	Can We Rely on Results From IQVIA Medical Research Data UK Converted to the Observational Medical Outcome Partnership Common Data Model?: A Validation Study Based on Prescribing Codeine in Children	Criterion 2
40	Capkun, et al.	2022	Can we use existing guidance to support the development of robust real-world evidence for health technology assessment/payer decision-making?	Criterion 5
41	Cars, et al.	2019	A framework for monitoring of new drugs in Sweden	Criterion 5
42	Castanon, et al.	2024	R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 15	Criterion 5
43	Castanon, et al.	2024	RWE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 16	Criterion 5
44	Chan, et al.	2020	Developing a framework to incorporate real-world evidence in cancer drug funding decisions: the Canadian Real-world Evidence for Value of Cancer Drugs (CanREValue) collaboration	Criterion 5
45	Chang, et al.	2024	Challenges and Opportunities in Interdisciplinary Research and Real-World Data for Treatment Sequences in Health Technology Assessments	Criterion 2
46	Che, et al.	2025	The Use of Real-World Data for Estimating Relative Treatment Effects in NICE Health Technology Assessment Submissions: A Review	Criterion 5
47	Che, et al.	2023	Blended Survival Curves: A New Approach to Extrapolation for Time-to-Event Outcomes from Clinical Trials in Health Technology Assessment	Criterion 1
48	Cheaib	2016	Pharmacovigilance in Clinical Trials: Current Practice and Challenges	Criterion 4
49	Chen, et al.	2025	Use of Real-World Data and Real-World Evidence in Rare Disease Drug Development: A Statistical Perspective	Criterion 5

N°	Author	Year	Tittle	Reason of exclusion*
50	Chen, et al.	2021	Evaluation of diagnostic tests for low prevalence diseases: a statistical approach for leveraging real-world data to accelerate the study	Criterion 2
51	Claire, et al.	2023	Advancing the use of real world evidence in health technology assessment: insights from a multi-stakeholder workshop	Criterion 5
52	Courcelles, et al.	2022	Solving the Evidence Interpretability Crisis in Health Technology Assessment: A Role for Mechanistic Models?	Criterion 2
53	Crane, et al.	2022	The challenges and opportunities in using real-world data to drive advances in healthcare in East Asia: expert panel recommendations	Criterion 5
54	Curtis, et al.	2023	Regulatory and HTA Considerations for Development of Real-World Data Derived External Controls	Criterion 5
55	Daigl, et al.	2024	Advancing the role of real-world evidence in comparative effectiveness research	Criterion 5
56	Dang, et al.	2023	A causal roadmap for generating high-quality real-world evidence	Criterion 5
57	de Lusignan, et al.	2015	Creating and using real-world evidence to answer questions about clinical effectiveness	Criterion 2
58	de Pouvourville, et al.	2023	Real-world data and evidence in health technology assessment: When are they complementary, substitutes, or the only sources of data compared to clinical trials?	Criterion 5
59	De, et al.	2021	Leveraging Real-World Evidence: A Paradigm Shift in Regulation	Criterion 5
60	Demuth, et al.	2025	Digital Representation of Patients as Medical Digital Twins: Data-Centric Viewpoint	Criterion 5
61	Devane, et al.	2025	Beyond the binary: integrating "real-world evidence" with randomized trials in contemporary health care	Criterion 5
62	Deverka, et al.	2020	Use of Real-World Evidence in US Payer Coverage Decision-Making for Next-Generation Sequencing-Based Tests: Challenges, Opportunities, and Potential Solutions	Criterion 3
63	Díaz, et al.	2023	Sensitivity analysis for causality in observational studies for regulatory science	Criterion 5
64	Donovan, et al.	2025	Perspective: Challenges for Personalized Nutrition in the Current United States Regulatory Framework and Future Opportunities	Criterion 3
65	Dreyer	2018	Advancing a Framework for Regulatory Use of Real-World Evidence: When Real Is Reliable	Criterion 5
66	Dreyer, et al.	2016	The GRACE Checklist: A Validated Assessment Tool for High Quality Observational Studies of Comparative Effectiveness	Criterion 5
67	Dreyer, et al.	2023	Tactical Considerations for Designing Real-World Studies: Fit-for-Purpose Designs That Bridge Research and Practice	Criterion 5
68	Dunger-Baldauf, et al.	2023	Generating the Right Evidence at the Right Time: Principles of a New Class of Flexible Augmented Clinical Trial Designs	Criterion 5
69	Ekhart, et al.	2025	Qualitative Interviews with Stakeholders in Herbal Pharmacovigilance and Recommendations for Best Practices to be Applied Worldwide	Criterion 3
70	ElZarrad, et al.	2019	The US Food and Drug Administration's Real-World Evidence Framework: A Commitment for Engagement and Transparency on Real-World Evidence	Criterion 2
71	Es-Skali, et al.	2018	Analysis of indirect treatment comparisons in national health technology assessments and requirements for industry submissions	Criterion 5
72	Facey, et al.	2021	Implementing Outcomes-Based Managed Entry Agreements for Rare Disease Treatments: Nusinersen and Tisagenlecleucel	Criterion 1
73	Facile, et al.	2022	Use of Clinical Data Interchange Standards Consortium (CDISC) Standards for Real-world Data: Expert Perspectives From a Qualitative Delphi Survey	Criterion 5
74	Fusaroli, et al.	2024	The Reporting of a Disproportionality Analysis for Drug Safety Signal Detection Using Individual Case Safety Reports in PharmacoVigilance (READUS-PV): Development and Statement	Criterion 5
75	García Martí, et al.	2023	Real-world evidence: experiences and challenges for decision making in Latin America	Criterion 2

N°	Author	Year	Tittle	Reason of exclusion*
76	Gatto, et al.	2022	The Structured Process to Identify Fit-For-Purpose Data: A Data Feasibility Assessment Framework	Criterion 5
77	Gatto, et al.	2019	A Structured Preapproval and Postapproval Comparative Study Design Framework to Generate Valid and Transparent Real-World Evidence for Regulatory Decisions	Criterion 5
78	Gatto, et al.	2023	A Structured Process to Identify Fit-for-Purpose Study Design and Data to Generate Valid and Transparent Real-World Evidence for Regulatory Uses	Criterion 5
79	Goedecke, et al.	2016	Medication Errors: New EU Good Practice Guide on Risk Minimisation and Error Prevention	Criterion 5
80	Goldstein, et al.	2023	Determinants for scalable adoption of autonomous AI in the detection of diabetic eye disease in diverse practice types: key best practices learned through collection of real-world data	Criterion 2
81	Gomes, et al.	2022	Target Trial Emulation for Transparent and Robust Estimation of Treatment Effects for Health Technology Assessment Using Real-World Data: Opportunities and Challenges	Criterion 5
82	Gomes, et al.	2024	Acceptability of Using Real-World Data to Estimate Relative Treatment Effects in Health Technology Assessments: Barriers and Future Steps	Criterion 5
83	Gray, et al.	2024	Use of quantitative bias analysis to evaluate single-arm trials with real-world data external controls	Criterion 5
84	Gray, et al.	2020	A Framework for Methodological Choice and Evidence Assessment for Studies Using External Comparators from Real-World Data	Criterion 5
85	Gruber, et al.	2023	Evaluating and improving real-world evidence with Targeted Learning	Criterion 1
86	Hamad, et al.	2023	Applying value-based strategies to accelerate access to novel cancer medications: guidance from the Oncology Health Economics Expert Panel in Qatar (Q-OHEP)	Criterion 1
87	Hampson, et al.	2018	Real-world evidence for coverage decisions: Opportunities and challenges	Criterion 4
88	Haqaish, et al.	2017	The Jordan Food and Drug Administration: Comparison of its Registration Process with Australia, Canada, Saudi Arabia and Singapore	Criterion 1
89	Heeg, et al.	2025	Defining Biological and Clinical Plausibility: The DICSA Framework for Protocolized Assessment in Survival Extrapolations Across Therapeutic Areas	Criterion 5
90	Hernandez, et al.	2025	Advancing Principled Pharmacoepidemiologic Research to Support Regulatory and Healthcare Decision Making: The Era of Real-World Evidence	Criterion 5
91	Hills, et al.	2020	An assessment of the hospital exemption landscape across European Member States: regulatory frameworks, use and impact	Criterion 2
92	Hogervorst, et al.	2023	Uncertainty management in regulatory and health technology assessment decision-making on drugs: guidance of the HTAi-DIA Working Group	Criterion 3
93	Horgan, et al.	2020	Propelling Healthcare with Advanced Therapy Medicinal Products: A Policy Discussion	Criterion 5
94	Hou, et al.	2023	Generate Analysis-Ready Data for Real-world Evidence: Tutorial for Harnessing Electronic Health Records With Advanced Informatic Technologies	Criterion 1
95	Huysentruyt, et al.	2021	Validating Intelligent Automation Systems in Pharmacovigilance: Insights from Good Manufacturing Practices	Criterion 3
96	Ishiguro, et al.	2016	The MIHARI project: establishing a new framework for pharmacoepidemiological drug safety assessments by the Pharmaceuticals and Medical Devices Agency of Japan	Criterion 2
98	Jacquemard, et al.	2021	The anatomy of electronic patient record ethics: a framework to guide design, development, implementation, and use	Criterion 5
99	Jaksa, et al.	2022	Transferability of real-world data across borders for regulatory and health technology assessment decision-making	Criterion 3
100	Jaksa, et al.	2022	A Comparison of Seven Oncology External Control Arm Case Studies: Critiques From Regulatory and Health Technology Assessment Agencies	Criterion 5
101	Jaksa, et al.	2021	Organized structure of real-world evidence best practices: moving from fragmented recommendations to comprehensive guidance	Criterion 2
102	Jiao, et al.	2020	The use of real-world evidence in ICER's scoping process and clinical evidence assessments	Criterion 2

N°	Author	Year	Tittle	Reason of exclusion*
103	Jonker, et al.	2022	Contribution of patient registries to regulatory decision making on rare diseases medicinal products in Europe	Criterion 2
104	Justo, et al.	2019	Real-World Evidence in Healthcare Decision Making: Global Trends and Case Studies From Latin America	Criterion 2
105	Kang, et al.	2022	Exploring uncertainty and use of real-world data in the National Institute for Health and Care Excellence single technology appraisals of targeted cancer therapy	Criterion 2
106	Kang, et al.	2024	Cross-sectional analysis of use of real-world data in single technology appraisals of oncological medicine by the National Institute for Health and Care Excellence in 2011-2021	Criterion 2
107	Kang, et al.	2024	Analysis of factors associated with use of real-world data in single technology appraisals of cancer drugs by the National Institute for Health and Care Excellence	Criterion 2
108	Khoo, et al.	2024	Promoting Collaboration of Regulators and Patients in Improving Drug Safety and Regulatory Decision Making	Criterion 3
109	Kirwin, et al.	2022	A Conceptual Framework for Life-Cycle Health Technology Assessment	Criterion 1
110	Klonoff	2020	The New FDA Real-World Evidence Program to Support Development of Drugs and Biologics	Criterion 2
111	Kovács, et al.	2022	Implementation of coverage with evidence development schemes for medical devices: A decision tool for late technology adopter countries	Criterion 5
112	Krause, et al.	2018	Real-World Evidence in the Real World: Beyond the FDA	Criterion 4
113	Kühne, et al.	2022	Causal evidence in health decision making: methodological approaches of causal inference and health decision science	Criterion 1
114	Kukhareva, et al.	2022	Evaluation in Life Cycle of Information Technology (ELICIT) framework: Supporting the innovation life cycle from business case assessment to summative evaluation	Criterion 5
115	Kumar, et al.	2018	Statistical Signal Process in R Language in the Pharmacovigilance Programme of India	Criterion 5
116	Lai, et al.	2022	Existing barriers and recommendations of real-world data standardisation for clinical research in China: a qualitative study	Criterion 1
117	Lambert-Obry, et al.	2022	Real-world evidence: a practical toolbox for collecting health state utilities	Criterion 5
118	Langley	2020	Value Assessment, Real World Evidence and Fundamental Measurement: Version 3.0 of the Minnesota Formulary Submission Guidelines	Criterion 5
119	Largeron, et al.	2024	Guiding Principles for Evaluating Vaccines in Joint Health Technology Assessment in the European Union: Preparing for the European Union's Regulation on Health Technology Assessment for Vaccines	Criterion 5
120	Lau, et al.	2024	Is Canada Moving towards a More Agile Regulatory Approval and Reimbursement Process with a Shifting Role for Real-World Evidence (RWE) for Oncology Drugs?	Criterion 2
121	Leahy, et al.	2020	The use of UK primary care databases in health technology assessments carried out by the National Institute for health and care excellence (NICE)	Criterion 2
122	Lee, et al.	2024	Expert survey on real-world data utilization and real-world evidence generation for regulatory decision-making in drug lifecycle in Korea	Criterion 1
123	Lentz, et al.	2020	Designing, Conducting, Monitoring, and Analyzing Data from Pragmatic Randomized Clinical Trials: Proceedings from a Multi-stakeholder Think Tank Meeting	Criterion 5
124	Levenson	2020	Regulatory-grade clinical trial design using real-world data	Criterion 5
125	Li, et al.	2023	An Improved Matching Practice for Augmenting a Randomized Clinical Trial with External Control	Criterion 5
126	Li, et al.	2023	Use of real-world evidence to support regulatory decisions on medical devices in China and a unique opportunity to gain accelerated approval in "Boao Lecheng Pilot Zone"	Criterion 5
127	Lin, et al.	2022	Incorporating propensity scores for evidence synthesis under bayesian framework: review and recommendations for clinical studies	Criterion 5
128	Lin, et al.	2023	Matching within a hybrid RCT/RWD: framework on associated causal estimands	Criterion 5

N°	Author	Year	Tittle	Reason of exclusion*
129	Lin, et al.	2022	Integrative Analysis of Randomized Clinical Trial and Observational Study Data to Inform Post-marketing Safety Decision-Making	Criterion 2
130	Liu, et al.	2023	A Proposal for Post Hoc Subgroup Analysis in Support of Regulatory Submission	Criterion 1
131	Lou, et al.	2020	Real-world data for health technology assessment for reimbursement decisions in Asia: current landscape and a way forward	Criterion 2
132	Ly, et al.	2019	Training on the Use of Technology to Collect Patient-Reported Outcome Data Electronically in Clinical Trials: Best Practice Recommendations from the ePRO Consortium	Criterion 5
133	Makady, et al.	2017	Policies for Use of Real-World Data in Health Technology Assessment (HTA): A Comparative Study of Six HTA Agencies	Criterion 2
134	Manetti, et al.	2025	A systematic literature review of real-world evidence (RWE) on post-market assessment of medical devices	Criterion 5
135	Martin	2020	Effect of pharmaceutical regulatory policy on health impact	Criterion 2
136	Mazzaglia, et al.	2018	Study Design and Evaluation of Risk Minimization Measures: A Review of Studies Submitted to the European Medicines Agency for Cardiovascular, Endocrinology, and Metabolic Drugs	Criterion 2
137	McIntosh, et al.	2017	Repeat: a framework to assess empirical reproducibility in biomedical research	Criterion 4
138	Mentz, et al.	2016	Good Clinical Practice Guidance and Pragmatic Clinical Trials: Balancing the Best of Both Worlds	Criterion 5
139	Ming, et al.	2022	Health technology assessment of medical devices: current landscape, challenges, and a way forward	Criterion 1
140	Mohetaer, et al.	2024	Drug Review and Approval Policies Based on Real-world Evidence in China and the United States: A Comparative Study	Criterion 2
141	Mordenti, et al.	2022	Remodeling an existing rare disease registry to be used in regulatory context: Lessons learned and recommendations	Criterion 5
142	Mpofu, et al.	2023	Evaluation of US oncology electronic health record real-world data to reduce uncertainty in health technology appraisals: a retrospective cohort study	Criterion 2
143	Murphy, et al.	2025	Real-world evidence to support health technology assessment and payer decision making: is it now or never?	Criterion 5
144	Nafie, et al.	2025	A Brief Report on Proposed Areas of International Harmonization of Real-World Evidence Relevance, Reliability and Quality Standards Among Medical Product Regulators	Criterion 2
145	Naik, et al.	2015	Regulatory Definitions and Good Pharmacovigilance Practices in Social Media: Challenges and Recommendations	Criterion 5
146	Nugraha, et al.	2025	Using Real-World Evidence for Health Technology Assessment in Asia: Suggested Typology and Scoping Review	Criterion 2
147	O'Donnell, et al.	2021	Evolving use of real-world evidence in the regulatory process: A focus on immuno-oncology treatment and outcomes	Criterion 1
148	Olsson, et al.	2015	Pharmacovigilance in resource-limited countries	Criterion 4
149	Oortwijn, et al.	2019	How to Deal with the Inevitable: Generating Real-World Data and Using Real-World Evidence for HTA Purposes - From Theory to Action	Criterion 5
150	Orsini, et al.	2020	Improving Transparency to Build Trust in Real-World Secondary Data Studies for Hypothesis Testing—Why, What, and How: Recommendations and a Road Map from the Real-World Evidence Transparency Initiative	Criterion 5
151	Otte, et al.	2024	Value based healthcare and Health Technology Assessment for emerging market countries: joint efforts to overcome barriers	Criterion 5
152	Parab, et al.	2020	Accelerating the Adoption of eSource in Clinical Research: A Transcelerate Point of View	Criterion 1
153	Pariente, et al.	2023	What place for intelligent automation and artificial intelligence to preserve and strengthen vigilance expertise in the face of increasing declarations?	Criterion 5

N°	Author	Year	Tittle	Reason of exclusion*
154	Patel, et al.	2020	Development and Implementation of Clinical Outcome Measures for Automated Collection Within Specialty Pharmacy Practice	Criterion 2
155	Patorno, et al.	2020	Transparency in real-world evidence (RWE) studies to build confidence for decision-making: Reporting RWE research in diabetes	Criterion 5
156	Pearson, et al.	2018	A framework to guide the optimal development and use of real-world evidence for drug coverage and formulary decisions	Criterion 5
157	Plueschke, et al.	2018	EU-funded initiatives for real world evidence: descriptive analysis of their characteristics and relevance for regulatory decision-making	Criterion 2
158	Polak, et al.	2022	Generating Evidence from Expanded Access Use of Rare Disease Medicines: Challenges and Recommendations	Criterion 5
159	Pratt, et al.	2020	Data linkage in pharmacoepidemiology: A call for rigorous evaluation and reporting	Criterion 5
160	Ramsey, et al.	2020	Using electronic health record data to identify comparator populations for comparative effectiveness research	Criterion 5
161	Rassen, et al.	2023	High-dimensional propensity scores for empirical covariate selection in secondary database studies: Planning, implementation, and reporting	Criterion 1
162	Ritchey, et al.	2020	Evaluating the Feasibility of Electronic Health Records and Claims Data Sources for Specific Research Purposes	Criterion 2
163	Rosen, et al.	2023	Can Weight of Evidence, Quantitative Bias, and Bounding Methods Evaluate Robustness of Real-world Evidence for Regulator and Health Technology Assessment Decisions on Medical Interventions?	Criterion 2
164	Ross, et al.	2021	Veridical Causal Inference using Propensity Score Methods for Comparative Effectiveness Research with Medical Claims	Criterion 5
165	Sabharwal, et al.	2015	Developing evidence that is fit for purpose: a framework for payer and research dialogue	Criterion 2
166	Sangiorgi, et al.	2024	SATURN: assessing the feasibility of utilising existing registries for real-world evidence data collection to meet patients, regulatory, health technology assessment and payer requirements	Criterion 3
167	Sarp, et al.	2022	An approach to data collection in compassionate use/managed access	Criterion 1
168	Schad, et al.	2022	Real-World Evidence-Current Developments and Perspectives	Criterion 5
169	Schwartz	2017	Real-World Evidence, Public Participation, and the FDA	Criterion 5
170	Sedrakyan, et al.	2022	Advancing the Real-World Evidence for Medical Devices through Coordinated Registry Networks	Criterion 5
171	Seidman, et al.	2024	Regulations and Funding to Create Enterprise Architecture for a Nationwide Health Data Ecosystem	Criterion 5
172	Serrano-Aguilar, et al.	2021	Postlaunch evidence-generation studies for medical devices in Spain: the RedETS approach to integrate real-world evidence into decision making	Criterion 2
173	Shah, et al.	2019	Artificial intelligence and machine learning in clinical development: a translational perspective	Criterion 5
174	Shi, et al.	2023	Benchmarking Drug Regulatory Systems for Capacity Building: An Integrative Review of Tools, Practice, and Recommendations	Criterion 1
175	Shimazawa, et al.	2016	Overcoming regulatory challenges in the development of companion diagnostics for monitoring and safety	Criterion 4
176	Sievers, et al.	2021	Real-world evidence: perspectives on challenges, value, and alignment of regulatory and national health technology assessment data collection requirements	Criterion 5
177	Simpson, et al.	2022	R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 8	Criterion 3
178	Simpson, et al.	2022	R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 4	Criterion 5

N°	Author	Year	Tittle	Reason of exclusion*
179	Singh, et al.	2023	Development and Evaluation of the Algorithm CErtaInty Tool (ACE-IT) to Assess Electronic Medical Record and Claims-based Algorithms' Fit for Purpose for Safety Outcomes	Criterion 2
180	Slattery, et al.	2020	Assessing strength of evidence for regulatory decision making in licensing: What proof do we need for observational studies of effectiveness?	Criterion 2
181	Sola-Morales, et al.	2023	Effectively Leveraging RWD for External Controls: A Systematic Literature Review of Regulatory and HTA Decisions	Criterion 5
182	Stamas, et al.	2024	Use of Healthcare Claims Data to Generate Real-World Evidence on Patients With Drug-Resistant Epilepsy: Practical Considerations for Research	Criterion 5
183	Sullivan, et al.	2022	A Structured Methodology to Assess Safety Signal Strength and Inform Causality Assessment	Criterion 2
184	Sun, et al.	2024	Leveraging real-world data to conduct externally controlled trial for rare diseases with count-type endpoints: utilizing multiple entries - a simulation study	Criterion 2
185	Tadrous, et al.	2020	Developing a Canadian Real-World Evidence Action Plan across the Drug Life Cycle	Criterion 2
186	Tang, et al.	2019	Detecting adverse drug reactions in discharge summaries of electronic medical records using Readpeer	Criterion 2
187	Thokagevistk, et al.	2024	Real-World Evidence to Reinforce Clinical Trial Evidence in Health Technology Assessment: A Critical Review of Real-World Evidence Requirements from Seven Countries and Recommendations to Improve Acceptance	Criterion 3
188	Thorlund, et al.	2020	Synthetic and External Controls in Clinical Trials - A Primer for Researchers	Criterion 2
189	Timbie, et al.	2021	Use of Real-World Evidence for Regulatory Approval and Coverage of Medical Devices: A Landscape Assessment	Criterion 5
190	Turner, et al.	2024	Transporting Comparative Effectiveness Evidence Between Countries: Considerations for Health Technology Assessments	Criterion 5
191	Varabyova, et al.	2017	The Role of Learning in Health Technology Assessments: An Empirical Assessment of Endovascular Aneurysm Repairs in German Hospitals	Criterion 1
192	Varnai, et al.	2021	The Evidence REVEAL Study: Exploring the Use of Real-World Evidence and Complex Clinical Trial Design by the European Pharmaceutical Industry	Criterion 5
193	Villeneuve, et al.	2017	The RENAPE observational registry: rationale and framework of the rare peritoneal tumors French patient registry	Criterion 2
194	Walker, et al.	2023	Pharmacovigilance in the Caribbean Countries: an Overview	Criterion 2
195	Wang, et al.	2023	Challenges and Solutions in Implementing eSource Technology for Real-World Studies in China: Qualitative Study Among Different Stakeholders	Criterion 5
196	Wang, et al.	2019	Transparent Reporting on Research Using Unstructured Electronic Health Record Data to Generate 'Real World' Evidence of Comparative Effectiveness and Safety	Criterion 5
197	Wang, et al.	2022	A Framework for Visualizing Study Designs and Data Observability in Electronic Health Record Data	Criterion 5
198	Webster-Clark, et al.	2020	Single-arm Trials With External Comparators and Confounder Misclassification: How Adjustment Can Fail	Criterion 5
199	Wehrle, et al.	2022	Implementation of a data control framework to ensure confidentiality, integrity, and availability of high-quality real-world data (RWD) in the NeuroTransData (NTD) registry	Criterion 5
200	Weininger, et al.	2017	The Need to Apply Medical Device Informatics in Developing Standards for Safe Interoperable Medical Systems	Criterion 5
201	Wheaton, et al.	2025	Use of surrogate endpoints in health technology assessment: a review of selected NICE technology appraisals in oncology	Criterion 2
202	White	2023	Building trust in real world evidence (RWE): moving transparency in RWE towards the randomized controlled trial standard	Criterion 2
203	Williamson, et al.	2023	An application of the Causal Roadmap in two safety monitoring case studies: Causal inference and outcome prediction using electronic health record data	Criterion 2

N°	Author	Year	Tittle	Reason of exclusion*
204	Wu, et al.	2020	Use of real-world evidence in regulatory decisions for rare diseases in the United States-Current status and future directions	Criterion 5
205	Xia, et al.	2019	RWE Framework: An Interactive Visual Tool to Support a Real-World Evidence Study Design	Criterion 5
206	Xoxi, et al.	2022	A Proposal for Value-Based Managed Entry Agreements in an Environment of Technological Change and Economic Challenge for Publicly Funded Healthcare Systems	Criterion 1
207	Zhu, et al.	2020	Hybrid clinical trials to generate real-world evidence: design considerations from a sponsor's perspective	Criterion 5
208	Zhu, et al.	2023	Clinical Pharmacology Applications of Real-World Data and Real-World Evidence in Drug Development and Approval-An Industry Perspective	Criterion 5
209	Zisis, et al.	2024	Real-world data: a comprehensive literature review on the barriers, challenges, and opportunities associated with their inclusion in the health technology assessment process	Criterion 5
210	Zou, et al.	2024	Real-World Data and Real-World Evidence in Healthcare in the United States and Europe Union	Criterion 5

**The criterion numbers listed as reasons for exclusion correspond to: Criterion 1. The study does not assess nor include one of the synonyms of RWD (including surveillance)[1]. Criterion 2. The study does not include one of the guideline-related terms [2] in the objective, nor in the results/discussion section of the abstract, referring to the provision of guidance or recommendations. Criterion 3. The study does not refer to any phase in the generation of RWE (i.e., from data quality to results reporting). Criterion 4. The "guidance" does not refer to any stage of the technology life cycle (e.g., RWE used to obtain certification or to inform de-implementation or disinvestment decisions). Criterion 5. The article is not a policy document [3].*

[1] RWE and RWD-related terms: RWD, real-world data, real world data, RWE, real-world evidence, real world evidence, electronic health records, pharmacoepidemiology, observational studies, registry, routine data, surveillance, safety monitoring. [2] Accepted types of "guidance" documents: guidelines, framework documents, checklist documents, articles published in scientific journals, reflection papers, position papers, reports, handbooks, and consensus statements. [3] Official texts issued by governmental, regulatory, HTA, or intergovernmental decision-making bodies

Annex 4 Technical details on the workflow for the implementation of a RAG system based on GREG KB and ontology

The GREG-HTA RAG technological stack is based on open source libraries and open source and open weights LLMs available via the HuggingFace platform (https://huggingface.co/).

RAG workflow step	Technical specification
Optical Character Recognition (OCR) / Parsing	Docling v.2.42.1 [https://www.docling.ai/]
Chunking (Hybrid)	Docling v.2.42.1 [https://www.docling.ai/]
LLM API	Ollama v.0.11.4 [https://ollama.com/] & Python library 'Ollama' v.0.5.1 [https://pypi.org/project/ollama/]
LLM	Deepseek R1:32B Q4_k_M [https://huggingface.co/deepseek-ai/DeepSeek-R1-Distill-Qwen-32B]
Annotation/Extraction format configuration (JSON schema)	Pydantic v.2.11.7 [https://docs.pydantic.dev/latest/]
Database management system (DBS) storing the semantic annotation results	DuckDB v.1.3.2 [https://duckdb.org/]

The prompt used for the semantic annotation and clustering of the documents in the GREG-HTA KB is shown below:

You are an expert ontology engineer. Your task is to analyze the following text and construct a structured ontology in JSON format, using only the information explicitly provided in the text. Do not infer or include external knowledge.

Return the output in the following JSON structure:

```
{{
"entities": [
    {{
    "entity_name": "string",              // Clear and concise name of the entity
    "entity_type": "string",              // Type of the entity: Limitation, Barrier, Recommendation, Methodological Gap
    "entity_description": "string"        // Description of the entity as stated in the text
    }}
],
"relationships": [
    {{
    "source_entity": "string",            // Name of the source entity
```

```
    "target_entity": "string",                // Name of the target entity
    "relationship_name": "string",            // e.g., addresses, leads to, relates to
    "relationship_description": "string"      // How these entities are connected, based only on the text
    }}
]
}}
```

Extract entities and relationships based on the following categories:

1. **Limitations**, classified as:
- Theoretical: limits the scope, depth, or applicability of a study.
- Methodological: limits the quality, quantity, or diversity of the data.
- Empirical: limits the representativeness, validity, or reliability of the data.
- Analytical: limits the accuracy, completeness, or significance of the findings.
- Ethical: limits the access, consent, or confidentiality of the data.

2. **Barriers**: obstacles that hinder implementation, data collection, analysis, or other stages of the research.

3. **Recommendations**: suggestions or proposals to improve or overcome challenges.

4. **Methodological Gaps**: missing or insufficient methodological aspects explicitly mentioned in the text.

Only include entities and relationships that are explicitly present in the text.

Text to analyze:
{text}

Annex 5 Technical details on the validation platform and validation process

The GREG-HTA ontology validation has been implemented in the open-source platform Argilla (https://argilla.io/). Argilla is a collaboration tool for AI engineers and domain experts to build high-quality datasets.

The validation exercise has been set on a dedicated platform within the premises of the IACS IT infrastructure, under the management of IACS Biocomputing Unit at https://argilla.bigan.eu/sign-in. Access is provided to authorised users - voluntary validators - via specific credentials provided by IACS.

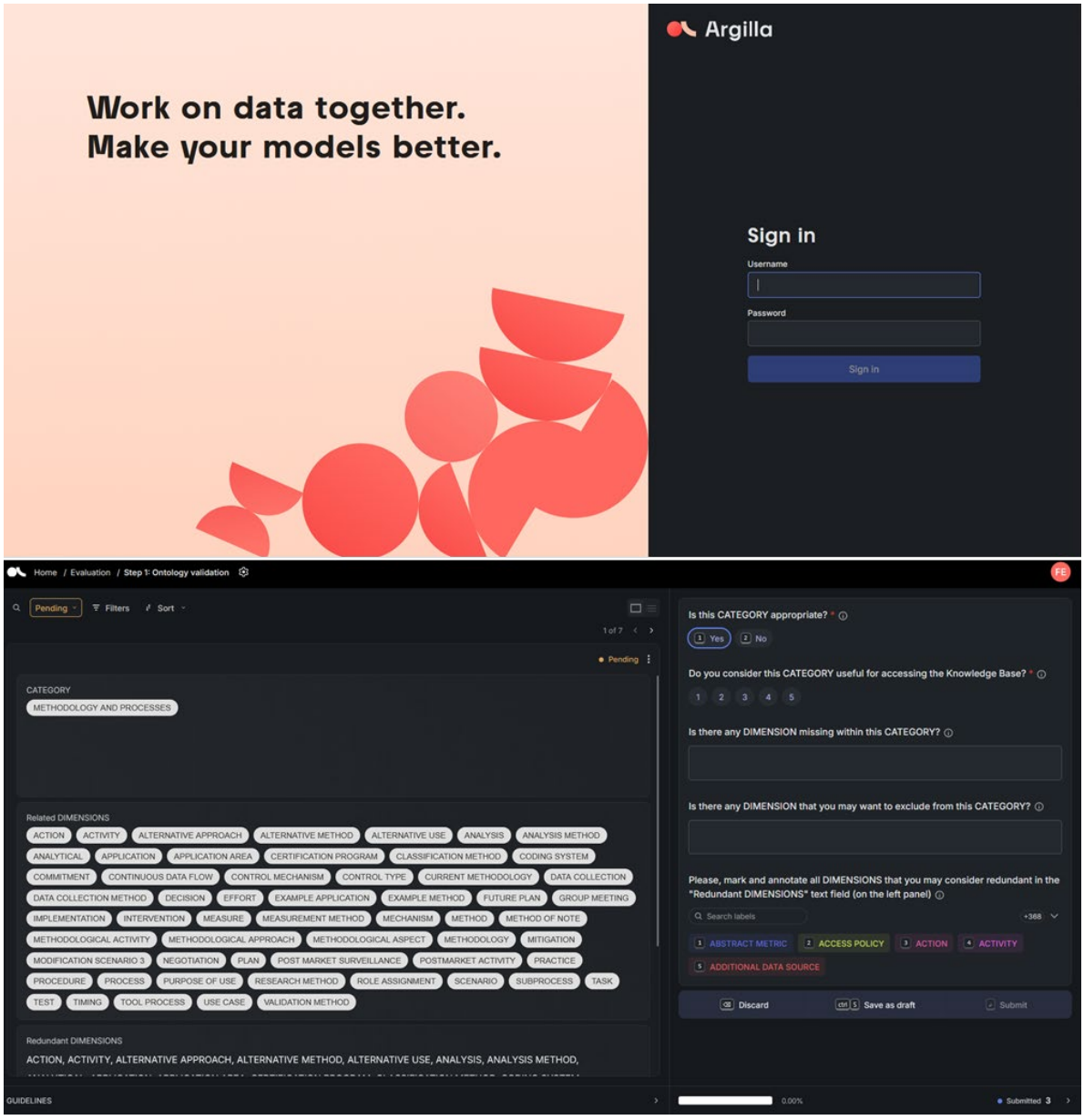

***Figure S1**: Screenshot of the user interface for the first validation phase on the categories and dimensions of the GREG-HTA ontology.*