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

D1.2 Early report on RWE needs (1)

Lead contributor	Francisco Estupiñán-Romero (10. IACS) Ester Angulo-Pueyo (10. IACS) M. Soledad Isern de Val (10. IACS) Silvia Moler Zapata (10. IACS) Wendy Nieto Gutierrez (10. IACS) Berta Olano Guillén (10. IACS) Irene Sánchez Montejo (10. IACS) Javier González-Galindo (10. IACS) Tara Srouji (16. Novo Nordisk) Helene Nordahl (16. Novo Nordisk) Enrique Bernal-Delgado (10. IACS)
Other contributors	Annika Jödicke (2. UOXF) Pall Jonsson (4. NICE) Heather Rubino (23. Pfizer) Leonardo Koeser (4. NICE) Karen Facey (2. UOXF) Seamus Kent (7. EUR) Jana Boleckova (19. EW) Maria Pyatnits (7. EUR) Lisa Naditch (17. Sanofi)
Due date:	30/04/2026
Delivery date:	22/05/2026
Dissemination level	Public

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.

Contents

Document History

Version	Date	Description
V1.0	24/04/2026	First draft for formal review by Annika Jödicke.
V2.0	08/05/2026	Revised version for review by the GA.
V3.0	14/05/2026	Revised version with comments from GA.
V4.0	22/05/2026	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)
54. The University of Edinburgh (UEDIN)

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
AI	Artificial Intelligence
ATE	Average Treatment Effect
ATT	Average Treatment Effect on the Treated
CAR-T	Chimeric Antigen Receptor T-cell (therapies)
CDM	Common Data Model
CHD	Congenital Heart Disease
EHR	Electronic Health Records
HF	Heart Failure
HFmrEF	Heart Failure with mildly reduced ejection fraction
HFpEF	Heart Failure with preserved ejection fraction
HFrEF	Heart Failure with reduced ejection fraction
HTA	Health Technology Assessment
IPD	Individual Patient Data
IPR	Intellectual Property Rights
JCA	Joint Clinical Assessment
KB	Knowledge Base
LLM	Large Language Model
LVEF	Left-Ventricular Ejection Fraction
NNH	Number Needed to Harm
NNT	Number Needed to Treat
NLP	Natural Language Processing
OMOP	Observational Medical Outcomes Partnership
PLEG	Post-Launch Evidence Generation
PPVI	Percutaneous Pulmonary Valve Implantation
PROs	Patient-Reported Outcomes

RAG	Retrieval-Augmented Generation
RVOT	Right Ventricular Outflow Tract
RWD	Real-World Data
RWE	Real-World Evidence
SGLT2i	Sodium-Glucose Co-Transporter-2 Inhibitors
SOPs	Standard Operations Procedures

Executive Summary

This report, Deliverable 1.2, presents the early findings of the IHI-GREG project regarding the needs and gaps of using Real-World Data (RWD) to support HTA and regulatory decision-making in Europe. While traditional randomised and controlled clinical trials (RCTs) remain the preferred basis for estimating comparative treatment effects, RWD –health information collected at individual-level from routine healthcare settings like electronic health records, health insurance claims, and registries- offer a powerful way to understand how medicines, medical devices and combination products work in everyday clinical practice, which provides a complementary perspective in their assessment both before market access and after being adopted and implemented as part of the regular care.

The aim of this early deliverable was to identify what decision-makers need to trust and utilise RWD and the resulting real-world evidence (RWE). To achieve this aim, we employed a several approaches, including:

a. Querying an advanced Knowledge Base containing over 25,000 semantically annotated concepts. These concepts were extracted from a selection of 652 guidelines, academic or position documents selected from a scoping search (conducted in accordance with the strategy and procedures described in D1.1),
b. Synthesising the first insights gathered from initial engagements with Regulatory stakeholders and Health Technology Assessment (HTA) experts across Europe to understand their operational 'pain points' regarding the use of RWE, and
c. Analysing and discussing early insights from an in-depth case study on a specific technology (CAR-T therapy) assessment decisions, alongside selected use cases in heart failure and medical devices targeting rare congenital disease, to determine if current guidance falls short.

Key findings

Our early analysis implies a substantial 'Implementation Gap'. While most attention is placed on the potential importance of RWD for HTA and regulatory purposes, there is a lack of practical recommendations and instructions both in the generation of RWE and for its effective use in HTA and regulatory decision-making.

Many of the current structural and operational high-level challenges center on technical issues. A primary barrier is the lack of standardized procedures for RWD access and interoperability. There is also a need to develop granular tools that help decision-makers assess the quality and applicability of Real-World Evidence (RWE). For example, these tools would help Health Technology Assessment (HTA) bodies resolve decision-relevant uncertainties. This would support development of RWE that is robust enough to meet the requirements for regulatory approval. Finally, as medical devices and AI-based technologies have more diverse evaluation and access pathways than medicines, some specific guidance needs to be developed for them.

Next steps

The GREG project will continue to identify emerging gaps and will prioritise these findings through stakeholder engagement to develop a practical toolkit to support and advance the use of RWE in HTA and regulatory decision-making. This includes a knowledge base of practical guidance, recommendations, data infrastructure (by consolidating a FAIR network of data partners) and tools to help researchers and decisions-makers turn complex real-world data into reliable evidence that improves access to safe and effective health technologies across Europe.

1 Introduction

1.1 IHI-GREG project and WP1 Objectives

Health Systems in Europe produce RWD that can support the development and evaluation of medicines and medical devices. Despite this potential, significant barriers persist restricting access to, analysis of, interpretation of, and use of RWD, and limiting its impact. Furthermore, the challenges in the practical implementation of existing guidelines for generating and using RWE further complicates the effective use of RWD in decision-making.

The GREG project aims to address these gaps by building upon insights from previous and ongoing key RWE initiatives. The GREG consortium will generate, pilot-test, and disseminate evidence-based guidance and tools to support the use of RWE in the development and evaluation of medicines, medical devices, and combination products.

The primary objective of WP1 is to develop collaboratively evidence-based practical guidance for the generation and use of RWE by drawing on continuous assessment of existing RWE guidelines and initiatives, and collating insights from key stakeholder engagement, case study analysis and practical use-case pilots to promote acceptance and implementation (Figure 1- signalling the information streams from literature, use cases, case studies and stakeholder involvement).

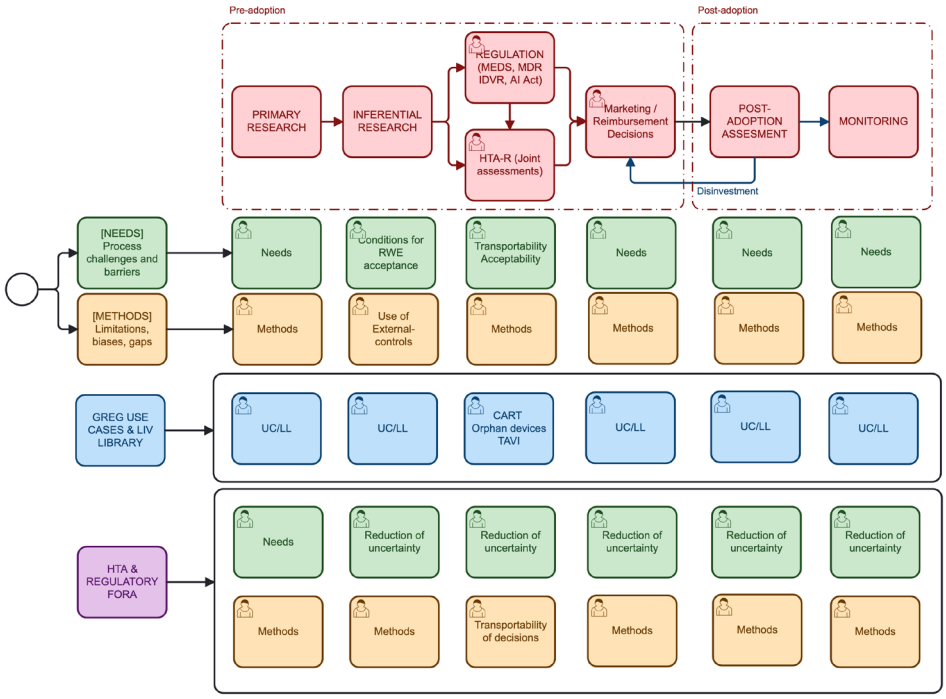

Figure 1 Conceptual framework of WP1 input streams for GREG guidance development. The scheme illustrates the flow of evidence from primary sources within GREG.

The specific objective of Task 1.2 RWE Needs and Challenges is to synthesize early insights from various sources to identify and prioritise decisions-makers' current and emerging needs.

1.2 Scope and purpose of deliverable 1.2

The scope of this early deliverable is set on Task 1.2, whose main objective is to continuously identify needs and challenges in the use of RWD and RWE faced by regulators, HTA bodies, payers and industry. Specifically, deliverable 1.2 focuses on needs and challenges at high-level structural, organisational, or process-driven aspects about the use of RWD and RWE to support decision-making across HTA and regulatory processes.

The main purpose of this early report is to compile, prioritise and present first insights on RWE needs collated from literature (both academic and grey literature) scoping search, the kick-off meetings of both the Regulatory stakeholders' (WP2) and HTA experts' fora, first case studies collected within the scope of the work on creating GREG Living Library (WP3) and expectations on practical and evidence-based recommendations provided by conducting currently selected use cases (WP4 and WP5).

Note on Scope: Although the GREG Knowledge Base (defined in D1.1) includes concepts related gaps and challenges on the interpretation of meta-analysis and Individual Participant Data (IPD) meta-analysis, which are annotated from the source materials selected as inputs, these methodologies are excluded from the present analysis, as they primarily rely on research-generated data, such as Randomised Controlled Trials (RCTs), collected in controlled experimental settings and therefore outside the report's operational definition of Real-World Data (RWD).

1.3 Foundation and links to prior Deliverables (D1.1)

This deliverable builds on the prior deliverable D1.1 (Early report based on systematic review) and should be interpreted in the context of it. Deliverable 1.1 serves as the structural and methodological bedrock for both deliverable D1.2 (Early report on RWE needs) and deliverable D1.3 (Early report on RWE methodological challenges). D1.1 describes the development of the initial GREG Knowledge Base (KB) and the core GREG ontology (v.0.0.1). This is achieved through a comprehensive scoping search of existing RWE guidelines and recommendations. D1.2 and D1.3 use the GREG KB updated after completing the GREG ontology validation (v.0.0.2). D1.2 and D1.3 leverage GREG Retrieval-Augmented Generation (RAG) capabilities to identify challenges, limitations, and gaps in generating RWE from the literature by semantically annotating key related concepts, grouped into distinct dimensions and categories.

The GREG KB is set to act as a continuously updated gathering information from trusted sources and processing it systematically to provide insights, that GREG can leverage to accurately map stakeholders' needs and methodological barriers and retrieve practical guidance on the use of RWD and RWE to support decision-making across HTA and regulatory processes.

The GREG KB is part of the RAG system set up by WP1. It can be directly queried using Cypher language [https://docs.falkordb.com/cypher/] on FalkorDB [https://www.falkordb.com/Cy] as a graph database. Alternatively, it can be accessed via a smart chatbot interface that enables inquiry-response (Q&A) interactions, powered by a generative Large Language Model (LLM).

Future versions of the GREG KB and RAG systems are expected to continuously synthesise and retrieve:

- Scoping searches of existing literature and global guidelines,
- Examples of use of RWE in regulatory and HTA submissions as catalogued by GREG Living Library,
- Methodological lessons and data reuse challenges and solutions extracted from GREG use cases for medicines and devices,
- Expert opinions elicited from summaries of Regulatory stakeholders and HTA experts' fora meetings.

The GREG KB (v0.0.2) focused on processing prioritized documents providing guidance published by decision-making agents, or international initiatives on RWE between 2015 and May 2025 (*see D1.1 to check the search strategy, selection and prioritisation criteria*).

2 Methods

Mapping the current and emerging RWE needs has required deploying several approaches, combining a scoping search with advanced AI-driven document processing, with insights from the work done in other WPs engaging regulatory stakeholders (WP2) and HTA body experts (WP3), from regulatory and HTA bodies' documented decisions (WP3 – Living Library), and from the scope and the practical challenges posed by selected use cases (WP4 & WP5) based on the reuse of RWD (WP6).

2.1 Identification and prioritization Strategy of RWE Needs and Challenges from scoping search of existing guidelines and recommendations

RWE needs and challenges were identified by querying the GREG KB (v0.0.2) to retrieve concepts within *gaps, limitations, barriers, and recommendations* dimensions, under the '*Limitations and Challenges*' category of the GREG ontology (v.0.0.2).

- Gaps: Consisting of missing or insufficient structural, procedural or other aspects explicitly cited in the guidance.
- Limitations: Factors limiting the scope, quality, validity, or applicability of RWD/RWE studies to HTA or regulatory decision-making.
- Barriers: Practical obstacles hindering the implementation, data collection, or use of RWD/RWE.
- Recommendations: Explicit suggestions proposed by decision-makers to overcome existing challenges (from which we focused on extracting the referenced challenges).

The GREG Knowledge Base and Ontology (v.0.0.2) includes 25,977 concepts, contextualised on 481 dimensions and explicitly categorised under 10 categories; semantically annotated, extracted, and aggregated from 652 processed documents. A total of 6,652 concepts is included in those dimensions under the '*Limitations and Challenges*' category. In order to end up with a usable set of RWE needs and challenges to focus on, for the purposes of D1.2 and D1.3, concepts were selected in a stepped process following several prioritization criteria:

1) Concurrency: Concepts were selected when they appeared, within the same context, in more than one source (i.e., document or guidance).
2) Frequency or density of evidence: Concepts were ranked based on their frequency of apparition within the selected dimensions (i.e., gaps, limitations, barriers, and recommendations).
3) Relevance to the assessment paradigms: Another criterion for prioritization and selection was whether the concept was specifically linked to HTA or rather to regulatory workflows and processes, thus reflecting specific operational hurdles faced by sponsors or decision-makers or whether they were general to using of RWD/RWE in this context.
4) Validation and stakeholder alignment: Top ranked concepts, in the final selection, were contrasted with RWE needs and challenges elicited from the early interaction with stakeholders (regulatory and HTA experts) and with those identified by case study analysis done for the living library, and the scope and challenges addressed by the use cases, currently selected for piloting.

2.2 Collaborative Identification Strategy of RWE Needs

While the continuous scoping search of the literature is foundational to RWE needs identification strategy, it may not be able to fully capture the nuanced, operational realities faced by decision-makers. Therefore, WP1 relies heavily on the continuous stakeholder engagement done by other WPs (GREG consortium contributors and WP leads) and on structured qualitative feedback produced from them to ensure our outputs reflect practical, emerging demands, to prioritise identified needs and to critically appraise potential knowledge gaps and unmet needs.

This identification strategy is built on collaboration with WP2 (Regulatory RWE) and WP3 (HTA) throughout the whole project, and benefits from the structured qualitative analysis of outputs (i.e., summaries and reports) from Regulatory stakeholders' fora and HTA experts' fora. Crucially, this continuous stakeholder engagement can act as a real-world validation mechanism by cross-referencing the theoretical gaps, limitations and barriers identified in the literature with those elicited by relevant stakeholders, and by ensuring that the RWE needs mapped are accurate, highly contextualised and directly actionable for the subsequent co-creation of the GREG practical guidance.

This mixed methods approach is operationalized through the integration of insights from the literature with findings derived from structured qualitative and narrative analyses of various information streams. These streams include stakeholder engagement, pilot use cases, and case studies on the use of RWD/RWE in HTA and regulatory decision-making, the latter completed as part of the Living Library. This approach ensures that WP1's identification of RWE needs remains iterative and responsive to the evolving healthcare and regulatory landscape throughout the GREG project. The analysis involves a structured interpretation of insights from each stream, categorized using the GREG ontology (v0.0.2) as a reference, followed by a narrative synthesis both within their specific contexts and the overarching scope of the GREG project.

To ensure these collaborative insights are effectively harnessed, all GREG outputs are expected to be iteratively integrated within the GREG KB, summarizing insights from all WPs into a centralized, accessible evidence base.

2.2.1 Integration with Regulatory stakeholders and HTA experts' Fora

This stream focuses on the formal collaboration with WP2 (Task 2.1: Regulatory Stakeholder Forum) and WP3 (Task 3.2: HTA Expert's Forum). Leveraging the outputs of these fora, WP1 aims to gather high-level institutional insights into the specific RWE needs and gaps perceived by decision-makers. Furthermore, the structured qualitative analysis of meeting summaries enables the identification of systemic challenges beyond the technical application of RWD/RWE.

This deliverable includes insights produced from the structured qualitative and narrative analysis of reports from:

- First Regulatory Stakeholders Forum meeting on April 2nd, 2026 (WP2), included in D2.1, and
- First HTA Experts Forum meeting on February 23rd, 2026 (WP3), included in D3.1.

2.2.2 Integration with cases studies within the Living Library (WP2 & WP3)

This stream utilizes the practical evidence generated by the Living Library (WP3), particularly on the in-depth case studies on submission experiences currently available. By analysing their results, although partial, WP1 can extract real-world insights into the methodological challenges and data quality issues encountered during the implementation of RWE in health technology assessments. The deep-dive case studies are meant to identify HTA submissions and appraisals and analyse them to identify critiques of RWE (including methods, confounding, data quality, etc.) from which draw more general conclusions about evidence requirements, and actionable insights on stakeholder needs and methodological barriers when using RWD/RWE.

Deep-dive case studies conducted as part of the Living Library can span the entire product lifecycle (from pre-authorization to post-marketing evidence generation) and can cover medicines, medical devices, and drug-device combinations across various disease areas. Analysing the use of RWE in those cases contextualised by the positive or negative result of the assessment in each regulatory environment can clarify the varying evidence standards demanded by different EU HTA bodies, while helping identify practical barriers to use RWE. More importantly, this analysis provides the necessary information to determine which specific analytical or procedural issues potentially compromising the

acceptability of the evidence. Consequently, it helps identify the underlying factors that influence HTA bodies' willingness to accept observational data.

This deliverable includes insights produced by the structured qualitative and narrative analysis of the focused research study on the evaluation of Chimeric Antigen Receptor T-cell (CAR-T) therapies, included in deliverable D3.2 Living library of HTA use cases (WP3).

2.2.3 Integration with use cases' scope and selection criteria

This collaborative strategy incorporates a last stream of feedback from the scope, methodology and technical requirements of the use cases selected for piloting in WP4 (Medicines) and WP5 (Medical Devices and Drug-device combinations), based on the reuse of RWD data accessed from Data Partners within the GREG consortium (WP6). These use cases can serve as practical examples for testing or contextualizing the future guidance developed by GREG. Their contribution to the identification of RWE needs lays on the capacity to provide direct practical insight into several high-priority methodological areas as data provenance, and fitness-for-purpose, interoperability and standardization and other technical challenges, and bias mitigation and confounding. By applying specific methodological frameworks to relevant research questions using available RWD, GREG can check where existing guidelines fail to provide actionable instructions and standard operational procedures (SOPs) covering such gaps may be needed.

This deliverable includes insights produced by the structured qualitative and narrative analysis of the protocols of the first 2 GREG use cases selected:

- Heart Failure with preserved, moderately reduced and reduced ejection fraction (WP4), and
- Transcatheter pulmonary valve bio prosthesis – Methods for Incidence and Prevalence Estimation in Orphan Medical Device Designation with Electronic Health Records (WP5).

3 Results

3.1 RWE Needs identified by the scoping search of the literature

An initial pool of 6,652 concepts across dimensions under the '*Limitations and Challenges*' category was evaluated using a multi-stage prioritisation framework to ensure actionable and highly relevant results. This framework assessed concepts based on their concurrence across multiple sources, frequency of appearance, and relevance to specific HTA or regulatory workflows. Ultimately, ranking the RWE needs, gaps, and challenges by their prevalence within the KB enabled a focus on the top 20 issues (Table 1), ensuring alignment with the main concerns identified in the literature.

Rank	Concept	Frequency (N)
1	METHODOLOGICAL GAPS	307
2	INTEROPERABILITY ISSUES	130
3	CONFOUNDING	76
4	BIAS (INFORMATION, INMORTAL TIME)	55
5	COMPARATIVE STUDIES WITHOUT RANDOMIZATION	53
6	DATA ALTRUISM	51
7	SENSITIVITY ANALYSIS	44
8	RELIABILITY	38
9	DATA COLLECTION	30
10	KNOWLEDGE GAPS	26
11	COMPLETENESS	25
12	SURROGATE ENDPOINTS	24
13	SOCIETAL PERSPECTIVE	23
14	DATA INTEGRITY	21
15	EXTERNAL VALIDITY	21
16	EVIDENCE GAPS	20
17	LACK OF STANDARDIZATION	16
18	RANDOMISED CONTROLLED TRIALS (RCTS)	14
19	IMPACT NUMBERS (NNT/NNH)	13
20	PATIENT-REPORTED OUTCOMES	13

The distribution of these RWE needs highlights a clear emphasis on methodological rigor, procedural standardization and technical infrastructure within the current regulatory and HTA landscape. These findings also suggest that while the structural aspect of data access, quality, collection, and interoperability remain a barrier or are perceived as a main limitation for the use of RWE, the primary focus of many existing guidance is the mitigation of bias and the standardization of methodologies to ensure RWE can meet the evidentiary standards required for decision-making.

Leaving aside a detailed discussion of RWE methodological issues and challenges (e.g. confounding, bias, and sensitivity analysis) representing the highest volume of mentions, which is commented in D.I.3, certain patterns can be observed

across these needs and gaps. First, a major focus on the setting of the **technical infrastructure required for the analysis of RWD**, including issues related to:

- **Data interoperability, including legal, organizational, semantic and technical interoperability**.
- **Access and availability of data**, including data collection, data accessing and the setup of schemas of data altruism enabling population to share their own health data for HTA, regulatory and research purposes.
- **Data quality and fitness-for-purpose**, encompassing the rigorous assessment of **completeness, reliability, timeliness and integrity of RWD**.
- Lack of standardization regarding the operational procedures for data accessing, management and analysis, which remains a persistent barrier to the systematic use of RWE at scale.

with a common demand reflecting the systemic lack of practical guidance on how to bridge the transition from RWD to regulatory-grade RWE, expressed as:

- **Gaps in evidence, technical knowledge, practical guidance, training and capacity** building programs focused on the specific requirements of the assessment of RWE.
- **Integration of diverse outcome measures**, specifically evolving requirements for incorporating **multiple analysis of relevant surrogate endpoints, patient-reported outcomes (PROs), and the broader societal perspective** into HTA and regulatory evaluations.

and an important concern for:

- **External validity and transportability of RWE**, focusing on the challenges of ensuring that findings from RWE studies are generalizable to the broader patient populations targeted in clinical practice.
- **Effective communication of clinical impact**, including the need for standardized reporting of impact metrics, with the translation of average treatment effects and average treatment effects on the treated to easier to communicate metrics such as numbers needed to treat (NNT) and numbers needed to harm (NNH) within RWE-based submissions, with associated uncertainty thresholds, and
- **Minimisation of knowledge gaps for certain populations RWE generation**, enabling decision-making on difficult topics such as health technologies aimed at rare diseases, or specific population subgroups, for instance those targeted by drug-device combination products or those traditionally excluded from clinical trials due to ethical or practical feasibility concerns.

Ultimately, this categorization of needs highlights that advancing the use of RWE requires a dual approach: building a resilient technical and legal infrastructure for data access and analysis, while simultaneously refining the evidentiary standards, assessment and communication tools necessary to translate complex observational data into actionable clinical and policy decisions.

3.2 Early RWE Needs in Regulatory Decision-Making

As regulatory frameworks across the EU landscape adapt to the digital transformation of healthcare, demand for RWE complementing evidence on efficacy with information on health technology adoption, effectiveness, cost effectiveness and overall impact has risen and is being partially realised by leveraging RWD analysis. The insight collated here represent a multi-stakeholder perspective on the current and emerging needs for regulatory submissions, spanning the distinct but increasingly converging pathways of human medicinal products, medical devices and drug-device combination products.

- **Data availability, access and data quality:** Despite the challenge, stakeholders are prompt to identify some major gaps for the use of RWE. First, regulatory guidance is usually high-level guidance, which does not include operational procedures or methodological approaches that could be used to produce the relevant evidence.

Second, while regulators usually have access to RWD (e.g., registries), the quality of the data is heterogeneous, and overall, there is a perception that only a limited number of data sources are available. This is particularly the case for medical devices, where routine health care data may not record any information about their use, and the data generated by some devices is not readily available for analysis as it is often collected and governed by manufactures. Regulatory stakeholders agree that availability and access to high-quality RWD is of key importance.

- **Data feasibility and fitness-for-purpose:** Related to data quality, regulatory stakeholders consider that there are still substantial challenges to identify high-quality data in a timely manner for decision-making. In particular, there is a need for standardised operational procedures for data feasibility or fitness-for-purpose assessment that include the discovery, selection and application for data access for fit-for-purpose data sources in terms of coverage, completeness, granularity and completeness of data to generate relevant evidence applicable for decision making (i.e., regulatory-grade RWE).
- **RWE on population subgroups often excluded from RCT** (e.g. pregnant or lactating women, or patients suffering from rare diseases): The exclusion of specific populations for ethical or sample size reasons from randomised controlled trials (RCTs) creates a knowledge gap at the point of market authorization; which is perceived as potentially covered by RWE. As an extension from this knowledge gap, the idealised population considered in RCTs may not adequately represent the complexity of real-world patients, including factors such as multimorbidity, etc.; and their interaction with the health care system, including barriers and facilitators for the adoption of a health technology, differences in accessibility, clinical pathways, etc. that can translate into effectiveness and safety issues.
- **Lack of standardised guidelines:** There is ample consensus on the need for more practical guidance and recommendations both on the generation of RWE from RWD and for its use in regulatory decision-making. Current available guidelines are based on high-level recommendations without enough detail to be effectively implemented in a standardised way. Regulatory stakeholders also agreed on the requirement for such practical guidance to be useful in the context of the regulatory decision framework but flexible enough in their implementation to fit different organisational and decision-making structures. Stakeholders were particularly interested in results from the empirical testing of the recommendations in real settings, sharing learnings on what works and what does not work to support the adoption of those recommendations and guidance. An example was provided considering the specific requirements on specific data formats or data sharing posed by the FDA, that might provide additional challenges for sponsors to use RWE and RWD to support their applications.

3.3 Early RWE Needs in Health Technology Assessment (HTA)

Health Technology Assessment (HTA) bodies face several high-level challenges when utilizing real-world evidence (RWE), which span data access, data quality, methodological complexities, and systemic variations both across jurisdictions and competencies and across regulatory pathways, inherently different for medicines, medical devices and combination products. This ultimately affects what evidence is available for HTA review at various stages of the product lifecycle.

- **Data availability and data access:** Accessing relevant health system data (i.e., RWD) remains a significant challenge for HTA bodies. Some HTA bodies lack access to the necessary data altogether, where others may have access to specific registries or rely on a subsidiary research network to act as a key, dedicated resource for generating real-world evidence. Even when the data exists, practical procedural challenges arise regarding who holds the data and the logistics of accessing it. In addition to this, some relevant data sources might be held or compiled exclusively by the product's owner and subject to intellectually property rights (IPR) concerns.
- **Data quality and Interoperability:** The RWD available is frequently judged to be of insufficient quality to answer complex research questions required by HTA bodies. While some HTA bodies have applied data quality frameworks, it is a priori unclear if these frameworks fully meet HTA needs until presented with a specific

question, leading to the requirement for feasibility assessments that consider fitness-for-purpose instead of fitness-for-use. Additionally, there are specific concerns regarding data interoperability, particularly concerning semantic interoperability and the potential loss of relevant data quality when mapping to standardised common data models (CDM).

- **Applicability and transportability to local contexts:** HTA bodies frequently observe that post-launch real-life outcomes in their specific jurisdictions do not match the effects demonstrated in highly selective, controlled international clinical trials. Due to the unfeasibility to conduct local RWE studies in each jurisdiction, HTA bodies must sometimes use RWE generated in other countries or regions, thus raising concerns about the validity of the data to their local context (i.e., external validity).
- **Variations in expertise and assessment capabilities:** There is notable variability in how different HTA bodies assess RWE. Many HTA bodies may currently lack the necessary internal expertise and capabilities to conduct RWD analytics, systematically assess RWE, or properly quantify the uncertainty associated with these kinds of studies.
- **Structural and regulatory differences:** HTA systems differ significantly across jurisdictions; some are integrated with payers (particularly in the case of medical devices), while others are integrated with regulators, which conform their specific evidence needs. In addition, regulatory pathways also differ widely between medicines, medical devices, and combination products, affecting what evidence is available for HTA assessment at various stages of the product lifecycle. These differences can also be enhanced by the divergence in focus between HTA bodies, usually focused on 'net health benefit', and regulators, typically focused on evaluating efficacy, making it difficult to align analytical frameworks. This is expected to persist even after the implementation of the Joint Clinical Assessments (JCAs), resulting from the European Commission regulatory effort to establish a harmonized framework for evidence requirements across the Member States.

In addition to this needs, HTA experts participating in the first forum meeting highlighted some perceived gaps for the use of RWE:

- **The need for proactive planning for RWD discovery, profiling and use in Post-Launch Evidence Generation (PLEG)** or technology adoption and effectiveness monitoring and reassessment. Experts stressed that uncertainties arising from clinical research programs should be predicted earlier so that PLEG can be planned accordingly. Currently, pre-planning is often missing, meaning late collection of RWE fails to resolve these uncertainties and delays the fulfilment of evidence needs that could have been anticipated.
- **The burden of weak clinical trials in the promotion of RWE**. Experts in the forum highlighted the apparent inverse relationship between trial strength and RWE requirements; while strong clinical trials may require vary little supplementary RWE, weak trials demand large amounts of RWE that may be actually impossible to generate or to generate with the appropriate robustness to fulfil the evidence requirements for decision-making.
- **The opportunity for artificial intelligence (AI) or natural language processing (NLP) to leverage unstructured data.** In the context of the presentation of the Living Library, experts commented on the potential for AI and PLN to produce insights from unstructured sources such as HTA assessment reports. In addition, they identified a clear need to explore those approaches and to undergo careful evaluation.
- **The need for device-specific evidence generation guidance**. Experts noted a gap in high-level guidance that adequately addresses the unique life cycle stages of medical devices compared to medicines. More so in those devices that can adapt or evolve to operational changes. Devices, typically face less stringent regulatory requirements and often take a more direct route to end users. Consequently, evidence needs for devices may occur earlier and rely more on local audits, data collection for early value assessments, and continuous monitoring.
- **The need for enhance collaboration between HTA bodies and with researchers**. While standardizing data is a widespread challenge, experts specifically pointed out that cross-border and cross-agency collaboration is essential in specialised fields, such as rare diseases, where local data alone is never sufficient

requiring a collaborative effort. Furthermore, improving the transparency of how RWE is assessed and used can help drive more consistent evaluation approaches across different HTA bodies. Finally, experts valued researchers lead initiatives on the reuse of RWD for evidence generation in bridging these gaps, testing solutions and building practical guidance.

3.4 Early RWE Needs assessed by Living Library's case study

This section presents a narrative synthesis of the high-level, structural, operational and framework-related RWE needs identified through the work done on setting up and populating the Living Library (WP3). The same process is expected to be conducted in WP2 although there are no in-depth case study outputs available at the time of writing this early report. While other integrated streams focus on gaps and emerging needs, the Living Library provides a retrospective and diagnostic view, identifying gaps through the systematic analysis of historical HTA reports in the context of in-depth case studies. Extracting the data from diverse jurisdictions and product classes, case studies in the Living Library has the potential to reveal the friction between theoretical guidance and the practical realities of RWE appraisal in HTA.

Some early gaps identified as insights from the case study on CAR-T therapy, the first case currently undergoing in-depth assessment, are:

- **Translating general principles into technical standards:** There is a critical requirement to move beyond high-level guidance toward granular, context-specific standards. This is particularly important in defining what constitutes 'sufficient' data quality, establishing data provenance reporting standards, or adopting broad consensus on which methodologies are acceptable for RWE generation for specific decision context and use cases.
- **Lack of harmonization of evaluation and reporting:** The analysis of the CAR-T case study reveals significant jurisdictional divergence in which part of the process the use of RWD is accepted (initial assessment, PLEG or reassessment), how RWE is evaluated within the assessment process, and how Post-Launch Evidence Generation (PLEG) is structured, specifically due to the complexities in the evaluation of this technology. Harmonizing these processes seems essential for predictable evidence generation and utilization pipelines across Europe.
- **Systematizing RWE impact assessment:** A major structural barrier is the inconsistency and perceived informality (i.e., varying standards) found in existing HTA reports. The lack of standardised detail in how evidence links to final decisions makes it difficult to objectively quantify the value RWE contributes to the decision-making process, and thus to assess where to focus effort on improving the evidence generation and utilization procedures.
- **Operational sustainability and process automation:** From a scalability perspective, the current reliance on manual expert-capacity driven interpretation and contrasting of RWE represents a significant operational gap in the regular and standardised use of RWE for decision-making. There is a perceived need to streamlining RWE impact assessment both in terms of acceptability for decision-making and in terms of transportability to other jurisdictions and regulatory contexts.

3.5 Early RWE Needs assessed by the first use cases

The identification of RWE needs within the GREG project is not merely a theoretical exercise but is deeply rooted in the empirical findings of ongoing use cases in WP4 and WP5, and from the work done in WP6 to facilitated access to RWD within the scope of the GREG consortium. This subsection collates early insights into the methodological, technical, and structural barriers encountered during evidence generation.

This pilot studies are meant to serve as a 'stress test' for current RWE frameworks, transitioning from high-level conceptual challenges to the granular, operational difficulties faced by data scientists and researchers in generating regulatory-ready RWE.

The insights derived from the uses cases, currently ongoing, can be categorized into two primary dimensions: a) procedural execution, producing evidence-based methodological recommendations and b) a structural definition of a 'feasibility frontier' through the application of standard selection criteria and use case feasibility assessments.

- **Procedural execution:**
  - **Data Provenance**: The development of the proposed use cases is supported by the GREG data catalogue (WP6) providing standardised information (i.e., metadata) on the data available to the GREG consortium. It sets a baseline requirement and a challenge to other research networks or RWE generation initiatives to adopt data discoverability and data management standard operational procedures produced and tested within the GREG project.
  - **Fitness-for-Purpose:** Evaluating the quality of the data, available to the GREG consortium, in terms of their fitness for specific purposes, these use cases identify potential systemic discrepancies between actual routine clinical data and documentation, and the data structures required for robust research. This includes quantifying missingness, and potential recording bias for variables and information essential to regulatory decision-making.
  - **Interoperability and Standardisation:** The transversal application of the OMOP Common Data Model (CDM) and the implementation of standard operational procedures for the landscape analysis and the feasibility analysis covering both the data accessibility and the methodological robustness, highlights the technical challenge in legal, organizational, semantic, and technological interoperability. Specifically, it surfaces the tension between data standardization and the preservation of clinical nuance during the transformation of local electronic health records (EHR) into common formats and schemas.

- **Structural definition of a 'feasibility frontier':**
  Beyond the active analysis, the criteria used to select these use cases constitute valuable insight on RWE needs and challenges. Documenting why specific datasets or clinical scenarios were deemed unsuitable, considering factors such as lack of data or of the required data granularity, insufficient longitudinally or timelines of the available data, or legal and organisational constraints to access data, use cases development help mapping the current 'feasibility frontier' of RWE.

On top of this, each use case is set to test GREG's capabilities to test and produce evidence on some specific evidence gap both in Medicines or Medical devices. A brief summary of each use case is provided in the table below with specific reference to the RWE gap or challenged addressed by each use case.

Use Case 1 (WP4 – Medicines): Chronic Heart Failure by Ejection Fraction Phenotypes

Scope: This study focuses on patients with incident chronic heart failure (HF), stratifying them by left-ventricular ejection fraction (LVEF) phenotypes: reduced (HFrEF), mildly reduced (HFmrEF), and preserved ejection fraction (HFpEF).

Aim and Primary Objectives: The overall aim is to estimate the incidence of heart failure and to characterise patient populations, treatment pathways, and outcomes across the different EF subtypes. The primary objectives are to:

1. Estimate the incidence of HF overall and by EF subtype.
2. Characterise patients with incident HF by demographics, comorbidities, healthcare utilisation, survival, and major cardiovascular outcomes, overall and by EF subtype.
3. Characterise real-world patients with incident HF who initiate treatment with Sodium-Glucose Co-Transporter-2 Inhibitors (SGLT2i) to compare their profiles and outcomes with those in registry-based clinical trials.

Methodology: Retrospective, observational cohort study utilising RWD from different databases across EU countries and USA. All databases are mapped to OMOP CDM, and the study is intended to use a federated analysis approach, running analytical code locally using OHDSI and DARWIN EU R packages without centralising patient-level data.

RWE gap or challenge addressed:

- **Gap**: **Actual representativeness of clinical trial populations of real-world utilization of SGLT2i drugs on HF patients with mild or conserved ejection fraction** – HTA bodies reviewing SGLT2i drugs use on heart failure patients noted uncertainties regarding how well clinical trial populations represent real-world patients, thus questioning the transportability of the effects across different HF phenotypes, and a lack of data on background event rates and local standards of care.
- Most existing RWE studies on heart failure fail to distinguish between EF phenotypes because data on ejection fraction is not commonly available as structure data from routine healthcare datasets.
- **Purpose**: The study aims to fill these gaps by detailing real-world standards of care, describing or characterising treatment sequencing, and evaluating the real-world applicability of major HF clinical trials (i.e., external validity).

Use Case II (WP5 – Medical devices): Orphan Medical Device Designation (Transcatheter Pulmonary Valve Bioprothesis)

Scope: This study focuses on patients with congenital heart diseases (CHD) involving right ventricular outflow tract (RVOT) dysfunction (such as Tetralogy of Fallot or common arterial trunk) who have undergone RVOT reconstruction and subsequently developed residual lesions requiring reintervention via percutaneous pulmonary valve implantation (PPVI) of a bioprothesis.

Aim and Primary Objectives: The primary aim is to compare methods for estimating incidence and prevalence of vary rare conditions using RWD to support orphan medical device designation. The primary objectives are to:

1. Estimate the incidence and prevalence of the underlying CHD population, the post-RVOT reconstruction population, and the sub-population that is ultimately eligible for PPVI.
2. Compare the RWD-based incidence and prevalence estimations with prior literature and national statistics.
3. Characterise the populations in each cohort and their drug use/treatment patterns.
4. Compare methods for combining evidence (meta-analysis, triangulation, etc.) across multiple OMOP-mapped databases to extrapolate incidence and prevalence results to the EU-27 population-level to respond to the orphan medical device designation criteria.

Methodology: Retrospective, population-level descriptive analysis, observational cohort study utilising RWD from different databases across EU countries and USA. All databases are mapped to OMOP CDM, and the study is intended to use a federated analysis approach, running analytical code locally using OHDSI and DARWIN EU R packages without centralising patient-level data. It incorporates the requirement for structured triangulation or meta-analysis for direct rate scaling of standardisation to extrapolate small event counts from various contexts to a broad EU level.

RWE gap or challenge addressed:

- **Gap: Lack of information on annual incidence or overall prevalence of rare conditions at the EU level** – To qualify for the orphan device designation in the EU, manufacturers must prove the device addresses a condition affecting fewer than 12,000 individuals per year. For complex structural cardiac indications like PPVI, the annual incidence is not routinely capture in national statistics and must be estimated using heterogeneous RWD. However, there is currently no methodological guidance on how to generate robust, regulatory-acceptable incidence or prevalence estimates from these datasets.
- **Purpose**: The study aims to develop an evidence-based methodological framework and guidance for case identification, denominator selection, heterogeneity assessment, and EU-wide extrapolation to calculate if the population complying with the device's indications meets the strict orphan device designation threshold.

4 Discussion

4.1 Gap Analysis: Comparing insights from the knowledge base vs. stakeholder's insights

This critical appraisal and gap analysis evaluates the landscape of RWE needs and gaps identified within the IHI-GREG project. We have synthesised the findings comparing where the theoretical literature meets, or fails to meet, the empirical realities of HTA bodies, regulators and researchers piloting use cases based on the reuse of RWD to generate regulatory-grade evidence.

The comparison of the insights from all streams reveals a high level of consistency regarding the core technical barriers (interoperability, quality and access to RWD). However, a significant discrepancy exists in the granularity and applicability of the existing guidance or 'Pragmatic Gap'. While literature focuses on high-level principles and infrastructure; stakeholders, experts and use cases demand specific, operational, and harmonized frameworks with tools and step-by-step instructions supporting the production of regulatory-grade evidence across the health technology life cycle.

Source	Primary Focus	Evaluated Value	Level of Consistency
Literature Scoping **(GREG KB) (WP1)**	Infrastructure & Systemic barriers (Interoperability, Data Quality)	Provides a foundational context of why RWE generation and use is difficult at scale	Highly consistent regarding technical barriers; Low consistency regarding specific application
Regulatory Stakeholders' Forum (WP2)	Technical validation, study design robustness, and criteria for regulatory-grade RWE	Essential for defining the threshold of acceptance (i.e., acceptability) for decision-making	Moderate; shifting from 'if' to 'how' to best use RWD. Highlights the opportunities and challenges of using RWD and RWE
HTA Experts' Forum (WP3)	Relative effectiveness, long-term outcomes, and economic evaluation in local context	May help resolve decision-relevant uncertainties to inform pricing and reimbursement decision but cannot replace good clinical research. Enables local evaluation of real-life value	Moderate; highlights differing national approaches, a gap in criteria for transportability, and on harmonized criteria on how to measure the uncertainty associated with RWE and, thus, how to correctly value their

Source	Primary Focus	Evaluated Value	Level of Consistency
			potential impact in decision making
Living Library case study (WP3)	Retrospective analysis of application successes and failures, apropos a particular health technology CAR-T cell therapy.	Offers relevant perspective on what RWE was used and how it has contributed to the decision-making process for a particular case. Shows high variance and capabilities across decision-makers.	Consistent with stakeholder concerns about validity and the requirement for harmonization both procedural and by application standards
Pilot Use Cases (WP4/WP5)	Actual methodological problem solving	The most granular source in terms of context; reveals the process barriers and gaps to be solved to produce relevant RWE	High discrepancy with literature; focus on uncovering methodological challenges and technical needs

Overall, this analysis identifies where existing guidance available in the literature fails to meet the needs of those performing RWD analysis for regulatory and HTA purposes and the expectations of those regulatory and HTA bodies working to include RWE into their decision-making processes. This report highlights a critical 'implementation gap' where technical availability does not equate to methodological readiness, which leads to varying standards, inconsistency in the use of RWE and low transportability across jurisdictions.

A. Infrastructure vs. Implementation
    i. Literature insights emphasise the need for technical interoperability to access RWD and the need for data standardisation and quality assessment and labelling; where pilot use cases and case study shows that the gap is not just access to data but a lack of specific guidance on how to get to a regulatory-acceptable estimate.
B. General quality vs. Specific Validity
    i. Literature insight discusses 'data quality' as a broad concept, in the sense of fitness-for-use; where stakeholder insight focuses specifically on fitness-for-purpose in the case of RWD.
    ii. In the case of RWE, literature insights focus on RWE as an instrument to fulfil particular knowledge gaps on specific subpopulations, conditions, and on the actual adoption of health technologies, while HTA bodies are more concerned with external validity and transportability, and how results from observational studies may apply to their local standard of care.
C. A 'blind spot' in Medical Devices and combination products
    i. In general, literature significantly under-represents the procedural and methodological needs of the Medical Device sector, in terms of RWD and RWE, compared to Medicines. Literature insights predominantly focus on generic guidance on RWE use for informing safety/effectiveness or even efficacy through complementing RCTs, particularly focusing on pharmaceutical products. While

advanced medicine case studies, such as the CAR-T therapy highlight the evolving RWE frameworks for complex biologics, they also underscore a stark contrast: the specific gaps, classification challenges, and fluid regulatory pathways inherent to MedTech remain largely unaddressed in current frameworks.

On the contrary, there are points of strong consistency across all sources, specifically regarding to:

A. Interoperability: All sources agree on the requirement for interoperability (legal, organisational, semantic and technical) to leverage the opportunity of RWD for health care and health policy decision-making.

B. Skills gap: Both literature and stakeholders highlight a significant variance in capabilities required to execute and evaluate complex RWE.

C. Granularity of guidance: All sources demand more granular guidance to assist in the production of RWE, and to help make sense and use it when appropriate in decision-making.

D. Standard of care: While literature and HTA experts often raise RWE needs in relation to the standard of care (i.e., external validity or for transportability), use cases pilots show that actually defining the standard of care from RWD can be a major methodological challenge that requires its own framework to ensure applicability.

4.2 Translating RWE Needs and Gaps into Practical Guidance during GREG

The translation of the RWE needs identified in this early report into actionable guidance within the GREG project follows a targeted, iterative pathway. By mapping high-frequency gaps, such as the demand for data interoperability, data access and fitness-for-purpose (or feasibility) assessments, the project can prioritise the development of standardised operating procedures (SOP) and technical benchmarks that overcome the current divide between guidance and practice. Specifically, the qualitative nuances extracted from the limitations and challenges can serve as the first step towards a structured blueprint of the practical frameworks subsequently developed by work packages. This procedure ensures that the forthcoming recommendations and guidance are grounded and offer actual settings, metrics, thresholds, instruments and tools to guide the use of RWD and RWE to impact HTA and regulatory decision-making at the scale required by the current pace of advancements in health technology.

Ultimately, this evidence-driven prioritization and gap analysis allows GREG to focus its resources on creating modular, scalable tools that address the most critical barriers to RWE adoption, transforming raw knowledge base concepts in a cohesive roadmap for regulatory and HTA excellence. In order to configure an effective first map of the RWE needs landscape, GREG can prioritize the following:

1. Move beyond 'Infrastructure', focusing on Decision-Point Guidance (e.g., what does the regulator need to minimise uncertainty in the assessment of RWD studies for integrating RWE into their decision-making process at each point in the health technology life cycle?)
2. Harmonise Definitions and Expectations among HTA and Regulatory bodies and enhance collaboration in training and capacity building, data collection and access to relevant RWD.
3. Develop MedTech-specific guidance, tracking information requirements along medical devices lifecycle and including combination products and algorithm/AI based technologies.
4. Develop Standard Operations Procedures (SOP), workflows and templates for RWD/RWE use benefiting from the integration of currently available or newly created purpose-specific tools.

5 Conclusion

The identification of divergent evidentiary needs underscores the necessity of an iterative, stakeholder-driven approach throughout the whole GREG project. While the initial landscape mapping in this early report has identified the main gaps in using RWE for decision-making, the path forward requires prioritizing efforts to transform these insights into actionable guidance. The transition from a static understanding to a dynamic support ecosystem will be driven by several strategic actions.

First, WP1is expected to update and evolve this report through two milestones:

- D1.5 (Intermediate Report): This iteration will focus on the validation and prioritization of identified gaps by updating the literature search (WP1) and cross-referencing the findings from pilot use cases (WP4/WP5), and new case studies included in the Living Library against the ongoing deliberations in the Regulatory and HTA fora (WP2/WP3), and evaluating whether the guidance produced in GREG, such as the criteria for use case selection (WP2/WP3, WP4/WP5), or the standard operations procedures for data landscaping and data feasibility assessment (WP6), adequately covers the identified needs and gaps. The goal is to move from what is missing to how stakeholders prioritise these missing pieces, ensuring GREG guidance and recommendations addresses the most impactful issues first.
- D1.9 (Final Report on RWE Needs): The final iteration will provide a longitudinal assessment of how the GREG tools and guidance have addressed the identified and prioritised needs. It will serve as a gap-closure analysis, checking any residual needs that may remain outside the project's scope, but which may be critical for the implementation of the EU regulation on HTA by 2030.

Second, WP1 acts as a central hub of the project by providing the context, awareness and requirement analysis to synthesise empirical lessons, recommendations, and practical guidance produced within other WPs into a harmonized and structured framework to accelerate the use of RWE. Its success is tethered to the technical maturation and continuous update of the GREG Retrieval-Augmented Generation (RAG) system:

- Knowledge Base enrichment: Insights from the Living Library and the HTA/Regulatory fora will be integrated and semantically annotated into the GREG KB, ensuring the RAG system does not just rely on published literature, but also incorporates consensus-built recommendations produced within the project.
- Iterative Prompt Engineering and Fine-tuning: As WP4 and WP5 pilots encounter and potentially overcome technical and methodological challenges, these lessons learned and the tools tested and proved effective will be used to refine the RAG system's response logic, facilitating proper guidance grounded in the practical reality of analysing RWD as response to users' querying.

This deliverable and its future versions will support WPI's cross-work package feedback loops, ensuring ongoing alignment with WP2, WP3, and WP6. This approach will help map tools, procedures, and templates to the high-priority gaps identified here, resulting in a functional toolkit customised to the EU regulatory and HTA landscape.

Annexes

Annex I RWE needs and challenges

Annex I contains the formatted outputs of the GREG KB querying retrieving the concepts associated with RWE needs, gaps, limitations, barriers and challenges commented in this deliverable.

It can be accessed as an Excel file: Annex I_extracted_prioritized_gaps_for_synthesis_analysis.xlsx