101191967 - GREG

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

WP2 – RWE for Regulatory Decision making

D2.1 - Regulatory Stakeholder Forum

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Contents

Document History

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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
AGES	Austrian Agency for Health and Food Safety
BfARM	Federal Institute for Drugs and Medical Devices
BSI	British Standards Institution
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
HPRA	Health Products Regulatory Agency
HTA	Heath Technology Assessment
MHRA	Medicine and Healthcare products Regulatory Agency
NB	Notified Bodies
NCA	National Competent Authorities
OMOP CDM	Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM)
RCT	Randomised Controlled Trial
RWD	Real World Data
RWE	Real World Evidence
ToR	Terms of Reference
TTE	Target Trial Emulation

Term	Definition
Living Library	A "living", public repository of cases of successful and unsuccessful submissions of RWE for regulatory decision-making across the product life cycle. The Living Library will help stakeholders understand better how RWE is used in submissions and how it was evaluated by regulators. To facilitate the set-up of the library, a common structure has been developed and the identification of cases published by regulators/academia has started. Cases published in public assessment report/reviews will be added subsequently, with some particularly interesting ones being selected for more in-depth assessment.
Use cases	"Use case" studies in GREG will be conducted to test current guidance and generate learnings and practical recommendations. They will be methodological studies, based on RWD mapped to the OMOP Common Data Model, and carried out using federated analytics without the sharing of patient-level data. As per the grant agreement, 6 categories for topics had been pre-identified, including the replication/emulation of RCTs using RWD, external comparator studies, methods for estimating population- and patient-level device utilisation and replication of previous RWE studies assessed by HTA bodies or regulators. An open call for use case suggestions was conducted within the consortium and criteria for relevant prioritisation were developed to select the first GREG use cases. Feasibility assessment of the selected use cases is ongoing. The Regulatory Stakeholder Forum will have an important role in advising/supporting the prioritisation of key topics for future (regulatory) use cases.

Executive Summary

The Stakeholder Regulatory Forum (hereafter, 'Regulatory Forum') serves as an **external advisory board** to the GREG consortium, which aims to generate practical tools and recommendations for the use of real-world evidence (RWE) across regulatory settings. Through the Regulatory Forum, GREG will engage with regulators and stakeholders to understand their current and emerging evidentiary RWE needs across the lifecycle of medicines and devices and quality requirements for RWE. The Regulatory Forum's primary responsibility is to provide advisory input during regular meetings and, upon request, to support testing processes and implementation, without direct involvement in project tasks.

In the first year of the GREG project, we have established a group consisting of 12 members from the medicines regulators i.e. National Competent Authorities (NCA), as well as the European Medicines Agency (EMA), the Medicine and Healthcare products Regulatory Agency (MHRA, UK), the U.S. Food and Drug Administration (FDA), Notified Bodies (NB), Academia and Pharmaceutical Industry to represent the Regulatory Forum. The first meeting was held on 2nd of April 2026 online.

At this first meeting, several important areas for GREG activities were identified, including both regulatory needs related to Real-World Data (RWD) (e.g. data identification, data quality, data granularity, fitness-for-purpose/feasibility assessment) as well as methodological work. The Regulatory Forum discussed topics and ideas for "use case" studies to be conducted to inform evidence-based recommendations by GREG and suggested prioritising areas where RWE is needed most (e.g. rare diseases, pregnancy, medical devices and drug-device combinations). The need for further practical recommendations on the implementation of complex methodology was suggested (e.g. target trial emulations, emulation of randomized trials in European RWD). The forum welcomed the idea of creating a "living library" comprising previous successful/unsuccessful submissions to regulators to identify areas in which RWE can be improved.

The Regulatory Forum has been established and will meet 2-4 times a year to discuss planned and ongoing GREG activities and to guide the development of recommendations, guidance, and tools for RWE on medicines and medical devices.

1 Introduction

The overarching aim of the GREG project is to generate, pilot-test, and disseminate evidence-based guidance and tools for the use of Real-World Evidence (RWE) to inform the development and evaluation of medicines, medical devices, and drug-device combinations to support and guide regulatory and Health Technology Assessment (HTA) decision-making.

To ensure GREG activities will be relevant and complement/support the work of regulators and notified bodies (NB), it was agreed that GREG would set up a "Regulatory Forum" to engage with regulators and stakeholders to understand their current and emerging evidentiary RWE needs across the lifecycle of medicines and devices, as well as their quality requirements for RWE.

While the Regulatory Forum serves as an **external advisory board** to the GREG consortium, it is led by GREG's Work Package (WP) 2 "RWE for Regulatory Decision Making". WP2 will identify barriers to the use of RWD and RWE in assessments, ascertain challenges in adoption of RWE guidance for regulatory decision-making, and develop a practical, living library of regulatory RWE use cases. The living library will comprise examples where RWE was successful and unsuccessful in informing regulatory decision-making.

The present report documents the establishment of the Regulatory Forum, from the invitation of international experts in Medicines and Medical Device Regulation to the key RWE needs, and priority areas for regulators identified in the Kick-off meeting on the 2nd of April 2026.

2 Methods

A key aim of WP2 was to establish a Regulatory Forum involving external invited experts and a WP2 community to guide the development of RWE methodological guidance and/or tools for the development and evaluation of medicines and medical devices.

The specific objectives for the Regulatory Forum in the first year of the project were to identify first RWE methodological gaps to inform future use case selection, and to identify first key regulatory needs and RWE methodological gaps for development of practical recommendations/guidance and tools.

External regulatory experts and stakeholders with experience of RWE methodological guidance for medicines and medical devices were identified by WP2 Leads and the Executive Committee, and invited to participate in the Regulatory Forum. The invited experts are leaders in their fields and were carefully selected to ensure that they have long-standing practical expertise in RWE and Regulatory Sciences for medicines and/or medical devices. The Regulatory Forum aims to be diverse and inclusive in terms of geography, sex, and background. Experts were asked to provide information on potential conflicts of interest upon joining the Regulatory Forum. While – as a European project – the focus is on RWE for decision-making in Europe, colleagues from the regulators and academia in the US are represented in the Regulatory Forum.

The aim of the Regulatory Forum is to leverage the expertise and opinions of Regulatory Forum experts in the following areas:

- Defining RWE methodological gaps for regulatory authorities through knowledge sharing and advice.
- Helping prioritise methodological gaps of highest importance to regulatory authorities.

- Providing feedback on GREG's planned and completed RWE "use case" studies to generate evidence-based recommendations
- Providing feedback on "living library" cases and their learnings.

This will inform use case proposals to be submitted during year 2 of GREG through WP4 (RWE for medicines) and WP5 (RWE for medical devices), and priority areas to inform the development of methodological recommendations in WP1.

The Forum's Terms of Reference (ToR) was developed by WP2 in line with standard terms and procedures for external advisory board. The current version used at the time of the first meeting of the Regulatory Forum is available in **Annex 1**. Regular meetings with the regulatory forum will be held 2 to 4 times a year with an agreed agenda and scope defined in advance. As agreed with the Forum members, a meeting summary will be published after each meeting.

3 Results

As of April 2026, the following experts have agreed to join the GREG Regulatory Forum (Table 1).

Table 1 Members of the Regulatory Forum

Name	Institution	Medicines/ Medical device regulation
Christoph Ziskoven	TÜV Rheinland, Germany	Medical Devices
Donal O'Connor	HPRA, Ireland	Medical Devices
Miguel Antunes	EMA	Medical Devices
Nebojsa Serafimovic	AGES, Austria	Medical Devices
Richard Holborow	BSI, UK	Medical Devices
Alison Cave	MHRA, UK	Medicines
Álmath Spooner	Abbvie, Ireland	Medicines
Britta Hänisch	BfARM, Germany	Medicines
Catherine Cohet	EMA	Medicines
Marie Bradley	FDA, US	Medicines
Peter Mol	University of Groningen, The Netherlands	Medicines
Rhea Fitzgerald	HPRA, Ireland	Medicines
Sonia Hernandez-Diaz	Harvard, US	Medicines

The Regulatory Forum's Kick-off meeting was held online via Microsoft Teams on the 2nd of April. A detailed summary is available in **Annex 2.** Briefly, the following topics were discussed in the inaugural meeting:

- Introduction to overall GREG aims, objectives and ambitions
- WP2 current activities, including the:
  - Establishment of a living library of successful/unsuccessful cases of RWE submissions
  - Planned and ongoing GREG use case studies to generate evidence-based recommendations on RWE methods
- Group discussion to identify key regulatory RWE needs

The Regulatory Forum will have a key role in supporting the identification and prioritisation of the most important gaps to help address current RWE challenges. During the Kick-off meeting, the following topics/areas were highlighted:

Availability, quality and fitness-for-purpose of RWD

One key RWE challenge/gap highlighted was **data**. While regulators and industry have access to RWD, the quality of available RWD is not always sufficient and the identification of fit-for-purpose data can be challenging. This is particularly the case for medical devices; device data is often collected by the manufacturers, but the data are not always accessible to NB, or available at the required granularity/quality that would be desirable and needed to support regulatory decision-making. Availability of data on the version of medical devices would support NB with their work on quality assurance. Drug-device combinations are another area where more work to identify and maximise use of good quality data is needed. For medicines, there are still substantial challenges to identify and access high-quality data in a timely manner.

Areas and methods for further work: Potential (future) use cases for GREG?

The Regulatory Forum welcomed the idea of use case studies to generate evidence-based recommendations. Use cases conducted through GREG will each need to have a clearly defined aim and rationale to ensure they substantially progress the field and add value to the current knowledge and recommendations. To ensure this, the WP2 and the Regulatory Forum will collaborate to identify gaps and prioritise elements of studies to test different methodological approaches.

Initial ideas/areas of regulatory interest for future use cases highlighted in the discussions included:

- Effectiveness of marketed products to support risk-benefit assessments
- Addressing quality and consistency of RWD
- RCT replication/emulation given the limited practical guidance on how to best operationalise TTE studies; replication of some RCT-DUPLICATE trials in European data sources to assess the transportability of emulation challenges and potential solutions.
- Additional work on testing different methodological approaches to evaluating effectiveness and safety in areas where RWE studies are particularly challenging to conduct and methodological limitations become apparent, e.g. in populations often excluded from randomised controlled trials (RCT) (pregnant or lactating women, rare diseases) or in scenarios where questions cannot be answered by RCT.
- Use cases on external control arms for rare diseases
- Studies assessing potential extension of indications

Note: WP2 will present these suggestions at the General Assembly (6th May 2026) and Steering Committee meetings to discuss how to both input into the development of current use cases and potentially incorporate them for future use cases.

Practical guidance, recommendations and tools

The Regulatory Forum discussed that current regulatory guidance is often high-level. This might lead to a gap between methodological theory and its practical implementation in RWE studies intended to support regulatory decisions. Therefore, a need for more practical recommendations was highlighted. Experience from other projects, however, highlighted that feeding evidence from project activities into guidance is also challenging. Training on the practical implementations of recommendations and shared learnings on "what works and doesn't work" could support the adoption of recommendations.

Learnings from successful/unsuccessful RWE submissions

The idea of creating a living library of successful/unsuccessful submissions was well-received. The Regulatory Forum briefly discussed the scope of the library, including potentially limited classes of medical devices given their complexity and range of products, as well as whether cases are restricted to European submissions or international examples should also be considered when information is limited. It was also discussed that there is less information on medical devices in the public domain compared to medicines. While the current approach for the living library is to consider a case study as unsuccessful if RWE did not help or did not make an impact on the regulator's decision, i.e. a negative decision, it was recognised that this decision might not simply be due to the inclusion of RWE, and the classification of successful and unsuccessful case studies may not be straightforward. It was acknowledged that this is indeed challenging; if RWE is not used to support regulatory decision making (unsuccessful), this is not always mentioned in the regulatory assessment, making it difficult to identify such case studies even if included in the submitted dossier.

4 Discussion

The GREG Regulatory Stakeholder Forum has been established and the first meeting highlighted important areas where GREG could contribute meaningfully. Experts actively participated, shared their topics and areas where they felt additional work would be needed, including where GREG could complement ongoing work to support RWE for regulatory decision-making.

Regular meetings – potentially focussing on specific topics such as differences in regulation for medicines and medical devices, co-creation of topics for future use cases or the discussion on methods to be tested – will be important to provide a regulatory perspective both early on (e.g. at the time of planning future use cases) and consistently throughout the lifecycle of GREG.

The first meeting of the Regulatory Forum created the following actions for GREG:

- While GREG has identified key areas where improvement in practical guidance is needed, one activity in WP1 is to identify gaps throughout the project. The Regulatory Forum welcomed the opportunity to support this activity. There will be dedicated agenda items in future meetings and liaison between WP1 and WP2 leads.
- Engaged discussions on currently selected use cases highlighted the need and opportunity for more in-depth discussion of the ongoing and future use cases from a regulatory perspective. This topic will be discussed in one of the next regulatory forum meetings. WP2 will also explore how to contribute to the development of current use cases as well as bringing areas of interest for future use cases to the General Assembly and Steering Committee meeting.
- Data quality and fitness-for-purpose was highlighted as a challenge. GREG's WP6 is currently developing a standardised process to assess feasibility based on current practices and guidance. We will facilitate a discussion on data quality and availability at one of the next Regulatory Forum meetings and invite WP6 colleagues.

5 Conclusion

The GREG Regulatory Forum has been established and successfully kicked off with their first meeting. It will have a key role in supporting the identification of RWE needs that should be prioritised by GREG and in providing a regulatory perspective throughout the lifecycle of GREG.

Annexes

Annex 1: Terms of Reference

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

Terms of Reference

Stakeholder Regulatory Forum

V3. 24/02/2026

Stakeholder Regulatory Forum: Terms of Reference

Background

GREG is an IHI-funded five-year project to test, improve and co-create guidance and tools for real-world evidence (RWE) generation, and used to support decision-makers (particularly health technology developers, regulators and health technology assessment (HTA) bodies) in Europe. It will generate, pilot-test and disseminate evidence-based RWE guidance relating to medicines, medical devices and drug-device combinations. This project will draw on past EU-funded project work relating to RWE, existing guidance from decision makers and learned societies, the literature and learnings from past use of RWE in decision-making. Guidance and tools will be developed and tested using co-creation approaches with experts, such as those who are part of the Stakeholder Regulatory Forum.

Scope of activities

The Stakeholder Regulatory Forum (hereafter, 'Regulatory Forum') serves as an **external advisory board** to the GREG consortium Steering Committee and Work Package 2 (WP2), which aims to generate harmonised guidance for use of RWE across regulatory settings. Its members will offer expertise in scientific and technical evaluation of regulatory matters. Its primary responsibility is to provide advisory input during regular meetings and upon request, and to support testing processes as well as implementation, without direct involvement in project tasks.

Initially, findings from the work to identify existing RWE guidance and case studies will be presented and the forms of guidance that would best support regulatory agencies bodies will be discussed. Later in the project draft guidance documents and tools will be presented for co-creation. Refinements of the tools will be discussed and issued for comment.

The Regulatory Forum will be provided with the most relevant information on a regular basis and will be free to feed comments at any stage of the project duration.

Broad activities of the Regulatory Forum

- To facilitate knowledge exchange between members of the consortium and key regulatory stakeholders.
- To elicit current and emerging needs for RWE across the lifecycle of medicines, devices, and drug-device combinations and quality requirements for RWE.
- To review and input on the learnings from regulatory cases studies undertaken by WP2, covering all stages of the regulatory evaluation of medicines, medical devices and drug device combinations, from pre-clinical to post-market authorization
- To examine established tools and templates being used for their suitability across stages of assessment.

The regulatory forum may be asked to engage on the following GREG deliverables:

- To advise on the design of a living library of case studies and identification and selection of use cases to be performed as part of the GREG analytical projects.
- To consider the applicability, acceptability, and completeness of existing guidance and tools available for different stages of regulatory assessment, identified by the GREG team.
- To align on a set of recommendations for the use of RWD and generation of RWE in medicines, medical device, and drug-device combination regulatory guidance.
- To advise on tool generation (for example, checklists and templates) to support the operationalisation of developed recommendations, and the evaluation of generated RWE. User-friendly interfaces for the tools will be considered ensuring they meet the needs identified with the Regulatory Forum.

Meetings

A first online set up meeting will take place in Spring 2026. Thereafter the Regulatory Forum will convene 2-4 times per year mainly for online meetings with possible face-to-face meetings (no more than one per year). The face-to-face meeting could be combined with other GREG Advisory Board Meetings (e.g. HTA) or project meetings such as the General Assembly. Reasonable travel expenses for face-to-face meetings will be fully reimbursed to Regulatory Forum members by GREG.

Composition

The Regulatory Forum will include approximately 10-12 Regulatory Professionals that are involved in assessment of RWE or work at a senior level in their organisation and wish to support development of RWE assessment. Regulatory Forum meetings will also be attended by GREG Partners from Regulatory Agencies and those leading WP2 tasks to be presented at the meeting. GREG aims to create Advisory Boards that are representative in terms of type of regulatory body (advanced/seeking support to assess RWE, geography, etc) and gender balance.

Regulatory Forum members are appointed for an initial 2-year period, with a possible renewal of the appointment afterwards.

Table 1 lists the names, institutions and expertise of the current Regulatory Forum members as of 24/02/2026.

Annex 2: GREG Regulatory Stakeholder Forum meeting: Meeting Summary (public)

Date: 2nd of April 2026

Agenda

Time	Topic	Moderator / Presenter
14:00 – 14:10	Introductions/Tour de table	Annika
14:10 – 14:25	Welcome & introduction to the GREG Mission Discussion	Annika
14:25 – 15:00	The journey so far … WP2 activities Living library Use case approach Discussion	Daniel, Birgit
15.00-15.10	Break	
15.10-15.55	Key topics/gaps and RWE needs Where do regulators feel GREG could help/complement their work? Tour de table/Discussion	All
15.55-16.00	Ways of working	
16.00	Closure	Annika

Discussion topics

1. General presentation on GREG

A general introduction to the overall aims and objectives of GREG, the generation, pilot-testing, and dissemination of evidence-based guidance and tools for the use of RWE was presented. The project structure with 9 work packages was introduced, and the importance of the Regulatory Stakeholder Forum to support the project in prioritising key needs and with the elicitation of quality requirements for RWE across medicine/device space was emphasised. GREG will use an iterative approach to the development, testing and dissemination of its recommendations, with continuing input and advice from the Regulatory Forum. The approach of federated analytics was presented, which will allow us to conduct multi-database and multinational use cases without sharing patient-level data.

The presentation was followed by a discussion and Q&A session: It was highlighted that it might be challenging to identify "big gaps" to improve by GREG given that there is already RWE guidance available. We discussed that sometimes the regulatory guidance is high-level, which does not include which method(s) could be used. While GREG has identified key areas where improvement in practical guidance is needed, one activity in WP1 is to identify gaps throughout the project. The Regulatory Forum will have a key role to support the identification and prioritisation of the most important gaps to help address current RWE challenges. One key challenge/gap subsequently highlighted was data. While regulators have access to data (e.g. registries), the quality is sometimes mixed, and overall little data is available. This is particularly the case for medical devices. The group agreed that access to high-quality RWD is of key importance. GREG has a Work Package (WP6) focusing on data identification, and a feasibility process is currently being developed based on current practices and guidance, which could be helpful provide structured approaches to evaluate what data is out there and their fitness-for-purpose. We will facilitate a discussion on data quality and availability at one of the next Regulatory Forum meetings and invite WP6 colleagues.

2. WP2 key activities

Living Library

One of the key activities of the Regulatory RWE work package is the creation of a "living", public repository of cases of successful and unsuccessful use of RWE for regulatory decision-making across the product life cycle. This living library will help understand better how RWE is used in submissions and how it was evaluated by regulators. To facilitate the set-up of the library, a common structure has been developed and the identification of cases published by regulator/academia has started. Cases published in public assessment report/reviews will be added subsequently, with some particularly interesting once being selected for more in-depth assessment.

The presentation was followed by a discussion and Q&A session: The idea of the living library was well-received. Questions were raised regarding the scope of the library, including potentially limited classes of medical devices given their complexity and range of products, as well as whether cases are restricted to European submissions. It was discussed that there is less information on medical devices in the public domain compared to medicines, which means we will have to engage with private partners to provide examples of the use of RWD, or include international examples. Currently, the included case studies are European. The aim is to find useful examples and use those to create guidance with a methodological focus. This raised the question of how "successful and unsuccessful" case studies could be defined. It was discussed that the current approach for the living library is to consider a case study as unsuccessful if RWE did not help or did not make an impact on the regulator's decision. A negative decision, however, might not be due to RWE, so this is not linked to the classification of successful and unsuccessful case studies. It was acknowledged that this is indeed challenging as sometimes if RWE was not used (unsuccessful), this is not mentioned in the review, making it difficult to identify such case studies. Unsuccessful case studies could also include RWE that was not feasible to support regulatory decision, or if there were limitations identified. It was agreed that GREG should add context or a disclaimer when the library goes live, to avoid misinterpretations.

Use case selection and prioritisation discussion

A high-level overview was presented on the (methodological) "use case" studies GREG will conduct to test current guidance and generate learnings and practical recommendations. As per the grant agreement, 6 categories for topics had been pre-identified, including the replication/emulation of RCT in RWD, external comparator studies, methods for estimating population- and patient-level device utilization and replication of previous RWE studies assessed by HTA bodies or regulators. An open call for use case suggestions was conducted within the consortium, and criteria for relevance prioritization were developed enabling the selection of the first GREG use cases. The selected use cases are currently undergoing feasibility assessment. The Regulatory Forum will have an important role to advice/support the prioritisation of key topics for future (regulatory) use cases.

The presentation was followed by a discussion and Q&A session: Questions were raised about how the selected topics/use cases would substantially progress the field and add value to the current knowledge and recommendations, e.g. in addition to ongoing projects like DARWIN or in the light of existing recommendation for ECA. This highlighted the need for a more in-depth discussion of the use cases, which will be planned for one of the next forum meetings to facilitate more detailed discussion. GREG will need to ensure that each use case adds value. To ensure this, the ideal approach will be for WP2 to review these use cases by cross-referencing with other WPs, in order to identify gaps and prioritize elements of studies to test different methodological approaches.

The Forum briefly discussed ideas/areas of regulatory interest for future use cases: effectiveness of marketed products to support risk-benefit assessments and reduce uncertainty, e.g. comparison of specific devices; addressing quality and consistency of RWD; RCT replication/emulation given limited practical guidance on how to best operationalize TTE studies; replication of some RCT-DUPLICATE trials in European data sources to assess emulation challenges.

While some of the above topics will be touched on in the current use cases (use case on medical devices in the general population aiming to characterise the granularity of data within these different data sources; replication of LEADER trial), it will be crucial for future use case waves to ensure more regulatory use cases are included and facilitate early involvement of the regulatory forum in their planning and selection. Learnings from ongoing projects, e.g. Real4Reg,

emphasising current challenges in the identification, quality, and timely access to fitness-for-purpose data will be important for GREG.

3. RWE needs from the Regulatory Experts

The regulatory forum will have a key role in supporting the identification of RWE needs that should be prioritised by GREG. Experts shared their topics and areas where they felt additional work would be needed, or where GREG could complement ongoing world to support RWE for regulatory decision making.

Data access and quality

In the medical device space, access to RWD was mentioned as one of the key challenges. RWE is important to assuring device availability is acceptable and balanced with safety, going from pre-market to post-market evidence generation. Device data is often collected by the manufacturers, but the data is not always accessible to notified bodies or available at the granularity/quality that would be desirable and needed. Plans for data collection (post market clinical follow up plans), availability of information of the version of devices, and access to data would support notified bodies with their work on quality assurance. EUDAMED is an important platform. Drug-device combinations are another area where more work would be welcomed.

For medicines, while the availability of RWD sources increased and initiatives like DARWIN EU network expanded the ability to generate RWE, there are still substantial challenges to identify and access high-quality data in a timely manner. This particularly a challenge for studies on people often excluded from RCT, e.g. pregnant or lactating women, or in the area of rare diseases. While pregnancy is a very challenging area and limitations become apparent in these studies, studies in rare diseases are as well. Additional work on testing different methodological approaches to evaluating effectiveness and safety in these populations, or in scenarios where question can be answered by a randomized trial would be welcomed. Use cases on external control arms for rare diseases were considered of interest, and studies assessing potential extension of indications would be, too. When using OMOP, more information on the impact of the mapping (balance between getting the minimum versus having more granular information) would be helpful.

Guidelines

A need for more practical recommendations was highlighted. Some guidelines are very high-level and do not provide enough detail when being (tried to) implement(ed). This might lead to a gap between methodological theory and how it is applied in studies intended to support regulatory decisions. However, ongoing projects, e.g. Real4Reg, show that collecting all the evidence from a project's activities and learnings and feeding them into guidelines is challenging. It will be important to find a balance in GREG's recommendations between being useful but flexible. Training on the practical implementations of recommendations and sharing learnings on "what works and doesn't work" could support the adoption of recommendations. Some regulators such as FDA have specific requirements on data formats or data sharing, that might provide additional challenges for sponsors to use RWE and RWD to support their applications.

4. Ways of Working

The Regulatory Forum will meet 2-4 times a year (mostly online). The Forum is a safe space for sharing thoughts and discussing challenges, aiming to facilitate knowledge exchange between members of the consortium and key regulatory stakeholders and to elicit needs and quality requirements for RWE. We will follow the Terms of Reference for the Regulatory Forum. Meeting minutes/recording will be taken (internal) to generate a meeting summary, which will be shared for review before sharing them with the consortium and making them public.

Next meeting

The next meeting will take place in early summer 2026.