Roundtable Report - 12 September 2024

Post-Launch Evidence Generation (PLEG): Learnings from Italy, Germany, and the French DESCAR-T Registry

1. Introduction

On 12th of September 2024, the RWE4Decisions multi-stakeholder Learning Network hosted a roundtable as part of a series discussing operationalisation of Post-Launch Evidence Generation (PLEG) for highly innovative medicines in Europe and Canada. Over 60 stakeholders participated, representing health technology assessment (HTA) bodies and payers, insurers, ministries of health, national public health authorities, European and international research and policy institutions, clinical teams, patient representatives, registry holders, academia, and health technology developers.

Discussions built on past RWE4Decisions work on Outcomes-Based Managed Entry Agreements (OBMEA):

- A 2017 report analysed the potential of using OBMEA for generating real-world evidence (RWE) to influence pricing and reimbursement (P&R). Findings indicated that, although several Member States had experimented with these agreements, they were unsuccessful in generating robust RWE.
- A 2021 report focused on aligning real-world data (RWD) collection post-launch for HTA/Payer purposes in two fictitious cases. The key recommendations were to:
  - Identify decision-relevant uncertainties and judge whether they can be resolved by patient-relevant outcomes collected in clinical practice
  - Link data collection with the P&R agreement, and assess feasibility of collecting sufficient RWD within a reasonable timeframe
  - Develop OBMEA data collection plans with stakeholders and publish these
  - Establish data monitoring processes during OBMEA to build quality of RWD
  - Invest in data collection infrastructures.

The 2021 report stressed the importance of horizon scanning to identify early medicines that might need OBMEA (e.g. individual treatments, an indication with high unmet need for which a number of treatments are in development, or for a type of therapy in a specific condition e.g. advanced therapies) and the value of iterative, multi-stakeholder scientific advice/consultations to plan for OBMEA and support system readiness for data collection.

After OBMEA has been completed, results should be reported in an easily accessible manner. Collaboration should be encouraged throughout the process with stakeholders, other jurisdictions and decision makers such as EMA.

2. Learnings from Italy, Germany and France

During the 12th of September roundtable meeting, three presentations from Italy, Germany and France served as case studies to showcase the operalisation of PLEG in these jurisdictions:

i. the use the Italian Medicines Agency (AIFA) registries,
ii. the German Federal Joint Committee (G-BA) routine data collection - Anwendungsbegleitende Datenerhebung (AbD),
iii. the French registry for patients with malignant haemopathies DESCAR-T.

i. Latest developments in the Italian system – use of data from the AIFA monitoring registries

A representative from the Italian Medicines Agency (AIFA) provided an overview of the AIFA monitoring registries, emphasising their pivotal role in PLEG, particularly in terms of implementing a range of different forms of OBMEA. These registries function as a national collaborative network designed to manage patient access to innovative and high-cost treatments. Built on a hierarchical, web-based platform, the system facilitates systematic data collection and analysis of RWD to support decision-making in the Italian healthcare system.

These registries monitor medicinal products for specific therapeutic indications by employing a structured approach that includes recording eligibility criteria, prescriptions, drug dispensation and treatment outcomes. Data is collected prospectively from the initiation to the conclusion of treatment, ensuring comprehensive coverage of drug usage and outcomes in real-world setting. With over 2,000 participating healthcare facilities and contributions from clinicians and pharmacists nationwide, the platform has amassed an extensive dataset, including more than 5 million treatments and 26 million prescriptions. While oncology remains the primary focus, the registries cover other therapeutic areas such as rheumatolgy, haematology and infectious diseases.

One of the system's key achievements is its ability to transform RWD into robust RWE. This is realised through:

- **Population comparisons**: The registries facilitate comparisons between patients enrolled in clinical trials and those treated in real-world settings, identifying variations in baseline characteristics, such as age and health status. For example, data from oncology registries have shown that real-world patients are generally older and have poorer health than trial populations, demonstrating the system's ability to highlight critical differences.
- **Outcome analyses**: Advanced methodologies have enabled the evaluation of treatment outcomes. In the case of COVID-19 antivirals, AIFA registry data was used to compare similar patient populations, minimising biases and delivering insights into 28-day mortality rates. Ultimately, these findings directly supported regulatory decisions.

While registries are a cornerstone of Italy's pharmaceutical management, challenges remain, particularly in modernising the ageing infrastructure and enhacing data standardisation. Ongoing efforts focus on addressing these issues, improving data completeness, expanding analytical capabilities and integrating outcomes-based managed entry agreements to ensure the system' continued relevance and utility.

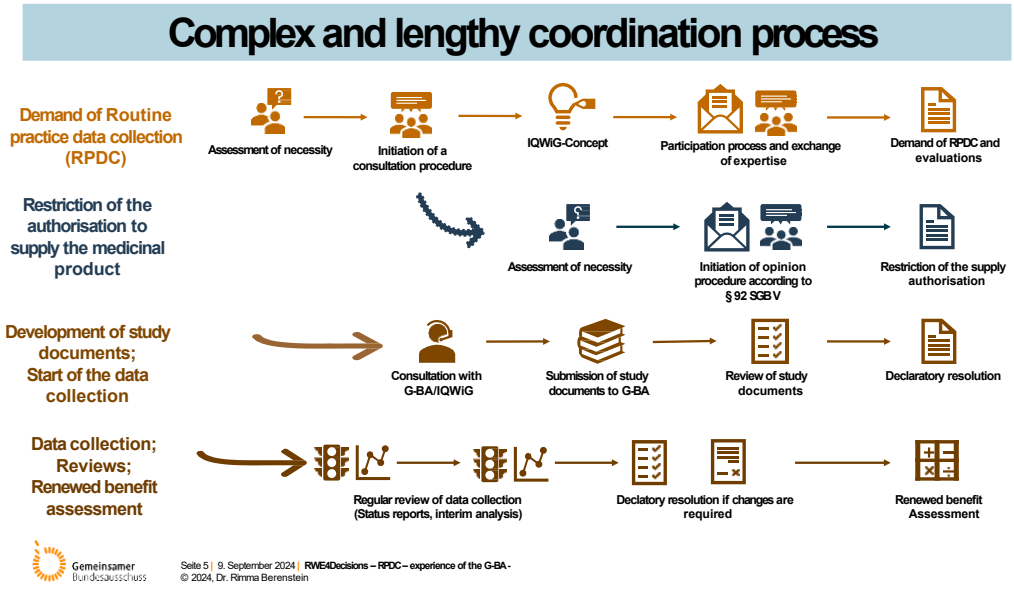
Although originally designed to ensure the appropriate use of medicinal products, the AIFA monitoring registries have evolved into a sophisticated tool for generating RWE. Their ability to provide high-quality evidence has solidified their role as an indispensable element in shaping healthcare policy and reimbursement decisions.

ii. Latest updates in the routine data collection 'AbD' and AMNOG law – the German system

A presentation from a representative of the Federal Joint Committee (G-BA) offered an overview of Germany's routine practice data collection process – 'AbD'. This procedure aims to address the need for evidence generation after marketing authorisation, with a particular focus on orphan drugs, products approved under conditional or exceptional circumstances, that do not have sufficient data for benefit

assessment. The G-BA oversees the process, including defining methodological specifications, reviewing study protocols, and ensuring compliance with timelines, though all costs are borne by the health technology developer.

The process *(see figure below)* begins with an assessment of the necessity of data collection, based on existing evidence, potential outcomes, and feasibility. This evaluation ideally occurs prior to market entry. The G-BA can also impose supply restrictions on medicinal products, requiring healthcare providers to participate in data collection. However, restrictions apply only to the intervention group, and randomised studies are excluded by law, necessitating reliance on non-randomised comparisons with confounder adjustments. The collected data undergoes periodic reviews every 18 months, culminating in a renewed benefit assessment that informs pricing negotiations. Failure to provide sufficient evidence can result in reimbursement penalties or renegotiations.



Despite the structured framework, the speaker highlighted several challenges. Germany lacks a centralised registry system, and its heterogeneous registry landscape suffers from insufficient interoperability, inadequate data quality, and limited compatibility with PLEG needs. These issues frequently necessitate significant adjustments to primary data sources, delaying data collection. Furthermore, the reliance on non-randomised comparisons, combined with strict methodological standards, demands large patient cohorts for confounder adjustment – often unfeasible in rare diseases or areas with limited therapy alternatives.

In terms of outcomes, Germany has yet to complete any benefit assessments based on data collected under this framework, with the first expected in 2027. It is therefore currently not possible to assess in how many cases the objective of quantifying the added benefit can be achieved through data collection.

While the German system has established a structured process for routine practice data collection, it remains hindered by infrastructural, legal, and methodological limitations. The speaker emphasised the urgent need for centralised registries, improved interoperability, and methodological refinements to optimise the system's ability to generate actionable evidence and support healthcare decisions.

iii. DESCAR-T: the French registry for patients with malignant hemopathies and eligible for CAR T-cell therapies

The final presentation detailed the objectives and operations of the French DESCAR-T registry – a pivotal initiative operated by LYSARC (Lymphoma Academic Research Organisation) and designed to support PLEG for patients receiving CAR T-cell therapies in France. The registry, established in 2017, aims to generate RWE on the efficacy, safety, and long-term outcomes of CAR T treatments, while addressing regulatory, clinical, and administrative needs.

DESCAR-T pursues three core objectives. Firstly, it seeks to improve the understanding of CAR T-cell therapies by evaluating their mechanisms of action, efficacy, and associated toxicities, including haematological, neurological, and emerging risks such as secondary cancers. Secondly, it assesses outcomes like overall survival, short- and long-term safety profiles, and quality of life, as mandated by the Haute Autorité de Santé (HAS), the French HTA body. Thirdly, it provides administrative support by collecting and standardising data to facilitate reimbursement processes and avoid redundancies.

The registry covers patients with haematological malignancies, such as lymphoma, leukaemia, and myeloma, treated in accredited centres across France. These centres are required to meet stringent criteria to ensure high standards of care. Patients are followed for up to 15 years, with data collected at defined intervals from the first injection and including clinical, biological, and patient-reported outcomes (PROs). Specific attention is paid to quality of life, fertility, and the impact of long-term complications, particularly for younger patients.

Collaboration is central to the registry's governance, which involves partnerships between French cooperative groups, academic institutions, and pharmaceutical companies. This governance framework ensures scientific independence while maintaining financial support from public and private sources. To date, the registry has engaged 39 hospitals and enrolled over 4,500 patients.

The DESCAR-T registry generates valuable RWE that informs national guidelines, supports treatment optimisation, and contributes to HTA evaluations. Findings are disseminated through clinical reports and publications, helping refine the understanding of CAR T-cell therapies and their application. Notably, the registry has been instrumental in addressing key gaps in comparative evidence for CAR T-cell therapies by simulating head-to-head comparisons through advanced data analysis methods, which are otherwise challenging to conduct.

Despite its success, the registry faces challenges, including financial sustainability, the burden of maintaining complete and accurate datasets, and addressing missing data, particularly in PROs. Long-term engagement campaigns are underway to ensure data quality and completeness. Yet, the registry exemplifies how robust RWD collection enhances the management of innovative therapies, improves patient outcomes, and informs healthcare decisions, including optimising treatments and shaping regulatory and clinical practices particularly in the rapidly evolving field of CAR T-cell therapies.

3. Breakout group discussions

Following the three presentations, participants were divided into multi-stakeholder breakout rooms. Discussions highlighted several key themes and challenges related to PLEG, providing insights into optimising processes, addressing barriers, and leveraging opportunities to enhance RWE generation.

- **The role of RWE in decision-making**
  - RWE is best positioned to supplement randomised clinical trials (RCT) findings, particularly for understanding baseline characteristics, confounder adjustment, and extending insights to broader populations. It should not replace RCTs but can be instrumental where RCTs are impractical, such as in rare diseases.
  - Good quality RWD and pre-specified statistical analysis plans are critical to demonstrate that the RWE produced is sufficiently robust to inform healthcare decisions. Poor-quality data, regardless of analysis, risks failing to impact outcomes.
  - Payers emphasise the need for data demonstrating patient-centred outcomes, such as quality of life, to align with reimbursement decisions. Early integration of PROs into Phase 2 and Phase 3 trials can bridge gaps in post-market evaluations.

- **Optimising data collection**
  - Effective PLEG requires early identification of potential hurdles of RWD collection in a particular jurisdiction, such as limited sample sizes due to country size or disease rarity, ability to collect the required RWD in a timely fashion, and gaps between collected and ideal datasets.
  - High-quality data is essential for meaningful analysis. Prioritising fewer but more complete outcomes, seeking to minimize missing data, and supporting efficient data collection were key recommendations.
  - Incremental data collection (instead of exhaustive upfront efforts) and early consideration of use of secondary data, including aligning informed consent for broader utility, can streamline data collection processes.
- **Addressing legal and systemic barriers**
  - Registries and data collection efforts are often siloed, hindering their effectiveness. There is a pressing need for harmonised frameworks, such as platform registries, to reduce administrative burdens and support robust PLEG systems.
  - In jurisdictions like Germany, existing legal frameworks impose rigidity that complicates PLEG. Advocating for policy changes to streamline processes and lower administrative burdens could help overcome these barriers.
- **Enhancing collaboration**
  - Collaboration among pharmaceutical companies, registry holders, HTA bodies, payers, and other stakeholders is critical to avoid duplication of efforts and to generate impactful, more robust datasets.
  - Stronger coordination at subnational, national, and cross-border levels is necessary. Initiatives like the DESCAR-T registry highlight the benefits of national-level coordination, which fosters larger, unified datasets that can be used for a range of purposes.
  - Developing common data quality standards, shared metadata frameworks, and interoperable IT solutions is essential to facilitate cross-border collaboration and ensure consistency in evidence generation.
  - Investing in interoperable systems that support routine data collection and cross-border collaboration is a priority. Leveraging systems like DARWIN EU for pharmacovigilance and adapting them for HTA purposes could yield significant benefits.
  - Wider routine data collection integrated into healthcare systems could expedite decision-making and reduce the need for standalone registries. Optimising the use of RWE for rare diseases offers opportunities to address evidence gaps efficiently.

4. Conclusion

The roundtable discussions on PLEG highlighted the diverse approaches and systems implemented in Italy, Germany, and France. The Italian AIFA monitoring system, with its extensive data collection and analysis capabilities, has evolved into a robust tool for generating RWE over nearly two decades. The German routine data collection process, overseen by the G-BA, faces challenges due to its lack of centralised registries and reliance on non-randomised comparisons. The French DESCAR-T registry, focusing on CAR T-cell therapies, exemplifies the importance of collaboration and high-quality data collection to inform healthcare decisions. These conversations underscore the need for harmonised frameworks, improved interoperability, and continuous investment in data collection infrastructures to optimise PLEG and support evidence-based decision-making in healthcare. While challenges remain, a cohesive approach across stakeholders and geographies can drive meaningful progress in generating and utilising RWE for healthcare decision-making.

RWE4Decisions is an HTA/Payer-led multi-stakeholder Learning Network, which, in 2024, developed of a set of new Stakeholder Actions to generate better real-world evidence for HTA/payer decisions about highly innovative technologies.

The work has been commissioned by the Belgian National Institute of Health and Disability Insurance (NIHDI) and is led by a multi-stakeholder Steering Group with a wider community of contributors including HTA bodies and payers, regulatory agencies, patient groups, clinical teams, industry, analytics experts and academic experts/researchers. The RWE4Decisions Secretariat is provided by FIPRA, with sponsorship by the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), AstraZeneca, Gilead, MSD, Pfizer, Roche and Takeda.

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