Co-Creating Real-World Evidence for Decision-Making

RWE4Decisions Roundtable Report – September 2023

Post Launch Evidence Generation

In September 2023, RWE4Decisions hosted a roundtable discussion to reflect on operationalization of Post Launch Evidence Generation (PLEG). Fifty-five stakeholders participated in the event, representing HTA bodies and payers, insurers, ministries of health, national public health authorities, European and international institutions, clinicians, patient representatives, registry holders, academia, and health technology developers.

The Secretariat outlined the work undertaken in the RWE4Decisions learning network in 2021 about operationalization of Coverage with Evidence Development Outcomes-Based Managed Entry Agreements (OBMEA). The recommendations from that report recommended horizon scanning to plan for post launch data collection, clear identification of uncertainties and assurance among stakeholders that relevant data could be feasibly collected and efforts would be taken to ensure high quality data capture, with transparency and rigor in planning data collection, analysis and reporting.

Participants shared potential uses of PLEG.

These were discussed and can be summarized as building evidence post-launch to:

- Manage uncertainties through financial and outcomes-based MEA in pricing and reimbursement.
- Facilitate system readiness for a complex technology.
- Determine real-life effectiveness.
- Evaluate sub-groups and special populations.
- Optimize - treatment delivery, patient outcomes, health system expenditure.

This interactive session was followed by four presentations on operationalising PLEG from representatives of the Italian Medicines Agency (AIFA), the Spanish Ministry of Health, the Dutch National Health Care Institute (ZIN) and AstraZeneca.

Evolution of AIFA Monitoring Registries, Italy

AIFA monitoring registries are built on a national collaborative network that provides patient access to innovative, high-cost treatments. In 2005, AIFA established its first national registry to collect post-authorisation data for a breast cancer treatment. It was immediately obvious that such monitoring registries would provide valuable data for medicinal products/indications. Within two years, 14 more registries for cancer treatments were established. The registry system has since evolved and in September 2023 it has 250 active registries with data entered by more than 37,000 physicians.

AIFA registries are hosted on a secure, national web-based system that uses standard forms to construct data collection schemes that may include data about patient eligibility, prescribing, dispensing, outcomes, and end of treatment. Data must be entered by clinicians and pharmacists in regional centres of the national health system before they can gain access to the medicine. Regions have access to their own data and overarching anonymised reports are provided to health technology developers.

In 2012, the AIFA registries became an official part of the Italian health information system. Furthermore, in 2014, AIFA and representatives of the Italian association of pharmaceutical industries signed a memorandum of understanding, with the pharmaceutical industry agreeing to cover the costs of the informatic development and maintenance of the registries, as well as all the costs associated with business intelligence.

AIFA has used the monitoring registries for all forms of managed entry agreements e.g. to ensure appropriate use, for a range of financial schemes and for individual OBMEA (e.g. repayment for patients that fail, or delayed payment until outcome). The registries provide a wealth of data (4,748,673 treatments, 3,732,981 patients 11,354,029 drug administrations) that can be used to explore the real world setting and improve patient care (e.g. to understand treatment sequencing).

Future plans include improvements in the technical infrastructure and continued improvements in data completeness.

Use of Post-Launch Evidence to Support Decisions, Spain

Valtermed, is an information system that aims to determine the real-life therapeutic value of medicines with a high health and economic impact. It supports real world data collection in the Spanish health system for a range of cases where there is high uncertainty about clinical outcomes, for example in clinical practice, in sub populations, when a surrogate marker has been used or when there is a high risk of bias in the pivotal efficacy trial.

As of September 2023, Valtermed includes 27 medicines (30 indications) as shown in the following table.

Medicine	**Indication(s)**
Crysvita (burosumab)	X-linked hypophosphatemic rickets in children
Veklury (remdesivir)	COVID-19
Besponsa (inotuzumab ozogamicin)	Acute lymphoblastic leukaemia
Dupixent (dupilumab)	Severe atopic dermatitis
Kymriah (tisagenlecleucel)	Acute b-cell lymphoblastic leukaemia/ large b-cell lymphoma
Yescarta (axicabtagene ciloleucel)	Large b-cell lymphoma/ primary mediastinal b-cell lymphoma
Orkambi (lumacaftor/ivacaftor)/ Symkevi (tezacaftor + ivacaftor)/ Kalydeco (symkevi +ivacaftor)	Cystic fibrosis
Alofisel (darvadstrocel)	Complex perianal fistulas in Crohn's disease
ARI-0001 (CAR-T)	Acute b-cell lymphoblastic leukaemia
Waylibra (volanesorsén)	Genetically confirmed familial chylomicronemia syndrome
Koselugo	Neurofibromatosis Type 1
Spinraza (nusinersen)*	Spinal Muscular Atropohy
Oluminat (baricitinib)	Severe atopic dermatitis
Rinvoq (upadacitinib)	Severe atopic dermatitis
Adtralza (tralokinumab)	Severe atopic dermatitis
Zolgensma (onasemnogén abeparvovec)	Spinal Muscular Atrophy
Kaftrio (ivacaftor, tezacaftor y elexacaftor)	Cystic fibrosis
Venclyxto (venetoclax)	Chronic lymphocytic leukemia
Polivy (polatuzumab vedotin + bendamustine + rituximab)	Large b-cell lymphoma
Vestronidase alfa	Mucopolysaccharidosis VII
Tecentriq (atezolizumab)	Advanced small cell lung cancer/ Triple-negative breast cancer
Luxturna (voretigene neparvovec)	Inherited retinal dystrophy
Evrysdi	Spinal Muscular Atrophy
Ultomiris	Adult patients with Paroxysmal Nocturnal Hemoglobinuria or Aypical Haemolytic Uremic Syndrome
Cibinqo	Severe atopic dermatitis

*migrated

Pricing and reimbursement discussions for a specific medicine/indication lead to a resolution that outlines uncertainties and stipulates what data must be collected, when. A pharmaco-clinical protocol is then developed by experts from the Autonomous Communities (regions) of Spain, professional societies and the health technology developer to support this. All these PLEG data collection protocols and resulting reports are publicly available here.

Examples of how the accumulating data have been used to optimize use of Dupilumab and a CAR-T were presented.

For Dupilumab in severe adult atopic dermatitis, the pricing and reimbursement agreement required data to be collected at 16, 24 and 52 weeks to determine responders according to commonly used scores in this condition. Any patient not responding was to have treatment discontinued. Beyond this individual treatment evaluation, the accumulating data have been used to understand the epidemiology of severe atopic dermatitis in Spain (incidence, prevalence, baseline severity…), to compare every new drug for atopic dermatitis to understand physicians' prescribing preferences and medicine performance, and to establish the value-based price at the time of pricing and reimbursement.

For the CAR-T, Valtermed was used to collect just four outcomes that were agreed to be key: date of leukapheresis, date of CAR-T administration, response, survival. These data are augmented with administrative data from the centralized application process about previous treatment lines and other patient selection criteria. A staggered payment plan was then agreed with part payment at time of administration (if within 30 days of leaukapheresis) and then final payment if the patient survived 18 months. The data were also used for multivariate analysis to identify which patients benefit most from therapy and to explain the relationship between response, progression and survival.

Patient Registries – Providing RWE to Support a Life Cycle Approach for HTA of High Cost Medicines From Different Perspectives

The Zorginstituut Nederland has initiated a program to explore whether national and international disease registries could provide reliable RWD for high-cost medicines for use in the initial pricing and reimbursement assessment and in reassessment after a Managed Entry Agreement, and beyond that to improve the quality of care. Registry holders were invited to propose their registries as case studies for the process and specific selection criteria were applied. The program included finally four disease registries (two oncological and two non-oncological orphan diseases) to support their development for use in HTA to provide evidence on real-world effectiveness, quality of life, cost effectiveness etc. Governance and funding requirements and ICT and methodological issues were considered, to support setting of standards for other registries.

Reflections on two of the case studies were presented, both of which specified products that received regulatory authorisation in very specific patient populations. The Dutch PLCRC registry (prospective, multi-disease) was evaluated, which collects data on adults with colorectal, small bowel and anal cancer patients from participating centres. The registry currently includes 18,000 patients and patients can consent for their data to be used for research and policy questions. In addition to clinical data, electronic patient-reported outcome measures are used and data are fed back to patients. The registry has been used to evaluate the real-life effectiveness of encorafenib in all the 166 patients treated in the Netherlands and in the sub-group that would have been excluded in the clinical trial, which showed reduced survival in that population. The first registry was for patients with colorectal cancer and assessed the use of encorafenib for adult patients with metastatic colorectal

cancer with a BRAF V600E mutation, who have received prior systemic therapy, to be used in combination with cetuximab.

Given the ultra-rarity of this disease (approximately three patients in the Netherlands) an international, disease registry was used from the MLD initiative (MLDi). This covers a range of countries in Europe and one US state. Unlike cancer, optimal outcomes for study are often unclear in rare diseases and so an important first step in this project was to undertake a delphi consensus exercise to agree a core dataset for the registry that would inform a wide range of decision makers. In HTA, the MLDi registry was used by BENELUXAI for scenario analyses on individual outcomes-based schemes (pay for performance) for children without clinical manifestations and for conditional reimbursement of symptomatic children. Autologous CD34+ cells encoding ARSA gene (Libmeldy) was approved for metachromatic leukodystrophy (MLD) in pre-symptomatic children with late infantile or early juvenile forms, and in children with the early juvenile form, with early clinical manifestations of the disease, still able to walk independently before onset of cognitive decline.

These and the other case studies are showing how disease registries can provide important information for HTA/Payers and the necessity for all stakeholders to agree a minimum dataset that is realistic for collection in clinical practice and daily life. Collecting data on quality of life, via patient-reported outcome measures is still difficult, as is connection to other health system data sources such as resource use and electronic health records. This requires better coordination of all healthcare data collection, and beyond the national setting, international collaboration is essential, particularly in ultra-rare conditions.

Reflections from health technology developers

Medicines' developers welcome the openness of HTA/payers to implement PLEG to address uncertainties related to clinical effectiveness and support optimization of care. However, currently EU Member States each have their own PLEG requirements, which creates challenges for health technology developers. It is understandable that health systems may identify different uncertainties given their different care pathways and standards of care, but moving forward it will be important to establish standardised processes and systems for post launch RWD collection and evaluation to support predictability and efficiency of medicines' development processes and reimbursement negotiations.

The national registry systems established by payers in Italy and Spain provide more predictability for health technology developers and reduce time to implementation of Managed Entry Agreements. Bespoke PLEG data collection is likely to be more expensive and, so as the Dutch case studies show, use of existing national or international disease registries may be beneficial. However, variations in data standards and quality thresholds between different registries and healthcare bodies can create challenges.

Moving forward, we need to identify the scenarios where harmonisation of post launch RWD collection is most needed, and feasible, and when we need different approaches. For example, for rare diseases, enhanced cross-country collaboration may be needed due to limited data, but this requires assessment of transferability of data from one healthcare system to another.

Furthermore, there needs to be better alignment between HTA bodies and regulators that identifies common areas of interest (e.g. long term survival) to avoid duplicative efforts.

Ideally when PLEG is needed, there should be a seamless transition from reimbursement to PLEG. This requires early and iterative dialogues among stakeholders recognizing that clinical practice changes over time and so may affect standard of care, and outcomes of importance. Such dialogues could discuss trade-offs associated with different data sources, for example does collection of more data about a range of potential confounders diminish quality of the most important outcomes. Ultimately, it will be crucial to determine if RWD collection actually impacts decisions in pricing and reimbursement re-negotiations, or will it continue to lead to the conclusions we see today with concerns about data quality meaning that RWE is not able to support HTA decisions.

Breakout room discussions

Following the four presentations, participants were divided into three multi-stakeholder groups to explore how PLEG could be operationalized. Key points arising were:

- The potential for PLEG could be discussed at horizon scanning.
- The potential for OBMEA and risk-sharing arrangements should be explored, particularly when outcomes can be clearly defined for important decision relevant uncertainties.
- PLEG has a range of purposes. Uncertainties exist for all drugs, and not only those very expensive ones with small patient populations. Evidence gaps in the determination of value are important, not only in terms of outcomes, but also in terms of population treated.
- Clear and precise questions need to be developed for PLEG with input from clinical experts, HTA bodies, payers, patients and health technology developers. Then the feasibility of collection of RWD for those questions should be determined. Active engagement of clinicians is essential to determine feasibility of assessments in clinical practice.
- Registry data are often scattered, and sometimes registry holders are reluctant to share the data. Governance and funding models for registries need to be clearly defined. A governance structure in which there is involvement from a diverse range of stakeholders increases trust.
- Need to improve secondary use of data to gain efficiencies, and support discussions about the potential of federated analyses within the European Health Data Space.
- The roles, responsibilities and support for data collection should be considered at the outset, as well as governance issues such as who can have which aspects of the data (e.g. summaries).
- HTA bodies and payers need to be clearer about whether they are willing to accept RWD to avoid wasting resources in running RWE studies that are then not used in decision making.

There were diverse opinions about when PLEG should be undertaken. Given regulators have a structured process for post marketing data collection for pharmacovigilance for ALL new chemical entities, some felt PLEG could be required for all HTAs. Several individuals from varied stakeholder groups felt this was unmanageable and raised concerns about the burden of data collection on all stakeholders given concerns about the value of the resulting RWE in re-appraisal.

The roundtable discussion concluded that PLEG may be able to play an important role in HTA/Payer re-assessments. The national based registry systems in place in Spain and Italy have required substantial investment but have proven their value. For health systems with good digitalization, standardised systems, including disease registries, could be used but investment in data capture and monitoring of data quality is needed.

RWE4Decisions is a payer-led multi-stakeholder learning network, which has developed stakeholder actions that will better enable the use of real-world evidence in HTA/payer decisions about highly innovative technologies. The work has been commissioned by the Belgian National Institute of Health and Disability Insurance (INAMI-RIZIV) and is led by a multi-stakeholder Steering Group with a wider community of contributors including HTA bodies and payers, regulatory agencies, patient groups, clinicians, industry, analytics experts and academic experts/researchers.

For further information and to see our outputs visit our website at:

https://rwe4decisions.com/about-us/

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