European Federation of Pharmaceutical Industries and Associations

# Shaping fit-for-purpose Alzheimer's Disease (AD) registries: relevance and reliability criteria for regulatory studies






Elsie L. Grace, PhD | Senior Director, Global Patient Safety, Pharmacoepidemiology | Eli Lilly

Pamela Dobay, PhD | Director, Quantitative Sciences and Development Operations | Biogen

# Disclosures

Elsie Grace is an employee of and owns stock in Eli Lilly and Company.

Pamela Dobay is an employee of and owns stock in Biogen.

# Objectives

- To raise awareness of the evidence gaps related to current and upcoming therapies that could potentially be addressed using real-world data (RWD) derived from different types of patient registries

- To go over lessons learnt and opportunities from past initiatives involving registry-based post-authorization safety studies (PASS)

- To agree on general recommendations and /or principles for defining:
    - Core data elements to be collected in registries to enable the evaluation of therapies, and the effectiveness of their risk minimisation measures
    - Key operational features of registries that are fit-for-purpose for regulatory studies: governance, quality assurance, and registry interoperability, including harmonization (e.g., use of appropriate common data model)
    - Stakeholders' collaboration to facilitate the long-term follow-up of patients using registries, and enable the generation of meaningful data for regulatory decision-making

# Registries in Alzheimer's Disease (AD) can serve a myriad of evidence-generation needs, but will one registry be able to serve them all?

*Decisions based on RWD/E from registries are associated with various levels of risk*

| Regulatory use cases | Non-regulatory use cases |
|---|---|
| Post-authorization studies | Health Technology Assessment |
| | Care pathway characterization / quality-of-care analyses |
| | Drug utilization studies |
| | Medical education / Scientific communication |
| New indication or labeling revision | Understanding natural history of disease |
| | Exploratory analyses |
| | Patient finding / recruitment |

***RWD/E needs are expected to evolve as the AD, regulatory, and technology landscape evolves***

CLINICAL DECISION SUPPORT (CDS) APPLICATIONS, SUCH AS TREATMENT DECISION-MAKING*, IS NOT CONSIDERED IN THE SCOPE OF ANTICIPATED USES OF EXISTING AD REGISTRIES

**REGULATED UNDER EU MDR (EU) / 21ST CENTURY CURES ACT*

# For regulatory studies (PASS / PAES), it is important that RWD sources are fit-for-purpose

*Decisions based on RWD/E from registries are associated with various levels of risk*

*Figure 2. Data relevancy and quality are equal components of a fit-for-purpose real-world dataset*


✓ For regulatory studies, the ability to **understand sources of confounding and bias** are critical; data quality, traceability, and transparency of data processing are extremely important

! For **safety studies, critical variables** such as lab, imaging, and immune reaction data **obtained at very specific time points** may be required: what is possible within routine clinical practice?

? Different registries have different purposes: are there existing registries whose **objectives, protocol, and core dataset are sufficiently aligned** with the planned regulatory study?

# Key relevance and reliability challenges were encountered in the registry-based study pilots*

*Past and current feasibility practices do not sufficiently de-risk registry-based studies when MAHs do not have direct access to data*

| Finding | Reliability | | | Extensiveness | | | Coherence | | | Timeli-ness |
|---|---|---|---|---|---|---|---|---|---|---|
| | Accuracy | Precision | Traceability | Complete-ness | Coverage | Format | Structural | Semantic | Uniquenes s | |
| Underreporting of SAEs | | | | ■ | | | | | | |
| MedDRA implementation issues (e.g., MedDRA was not implemented as a mandatory data entry field, or not implemented as a hierarchy) | ■ | | | ■ | | | | ■ | ■ | |
| No centralized MedDRA training or coding | ■ | | | | | | | ■ | | |
| Coding of free text to MedDRA done outside of data capture system | ■ | | ■ | | | | | | | |
| Inadequate edit checks for critical variables | ■ | | | ■ | | ■ | ■ | ■ | | |
| Minimal staff redundancy / reduced operational continuity | | | | | | | | | | ■ |
| Unavailability of critical documentation (e.g. data validation manual / data cleaning steps) | ■ | | ■ | ■ | | | | | | |

What **conclusions were drawn** from data generated in registries?
What are we **doing differently** for current / future regulatory studies?
What are **current challenges we are experiencing** in interactions with regulators?

** ALL PASS PILOTS HAD PARALLEL PRODUCT / DRUG REGISTRIES, WHERE SAFETY EVENTS ARE COLLECTED USING PRIMARY DATA COLLECTION; MARKETING AUTHORIZATION HOLDERS PROVIDED SUPPORT TO REGISTRIES TO ENHANCE SAFETY DATA COLLECTION AND FEEDBACK FOR REGISTRY IMPROVEMENT*

# What will make an AD registry fit-for-purpose across multiple evidence generation activities?

## Infrastructure

- Robust data capture system with built-in quality measures
- Adapts and scales with the needs of the field
- Linkage-ready
- Multidisciplinary expertise

## Processes

- Governance for data collection and use
- Process and training to maintain consistency and coherence
- Adequate documentation that supports analysis, prevents interpretation errors
- Consent enables linkage and secondary data use

**Well-defined objectives**

**Prioritize internal validity**

**Risk-based approach**

## Data

- Reliably-captured core data elements that support fair and meaningful comparisons
- Allows capture of data elements (e.g. imaging, biomarkers, PROs, digital measures) aligned with needs of the field and registry objectives
- Understanding of the different purposes between registries and clinical trials.
- Data elements selected for the registry purpose, not to replicate clinical trials

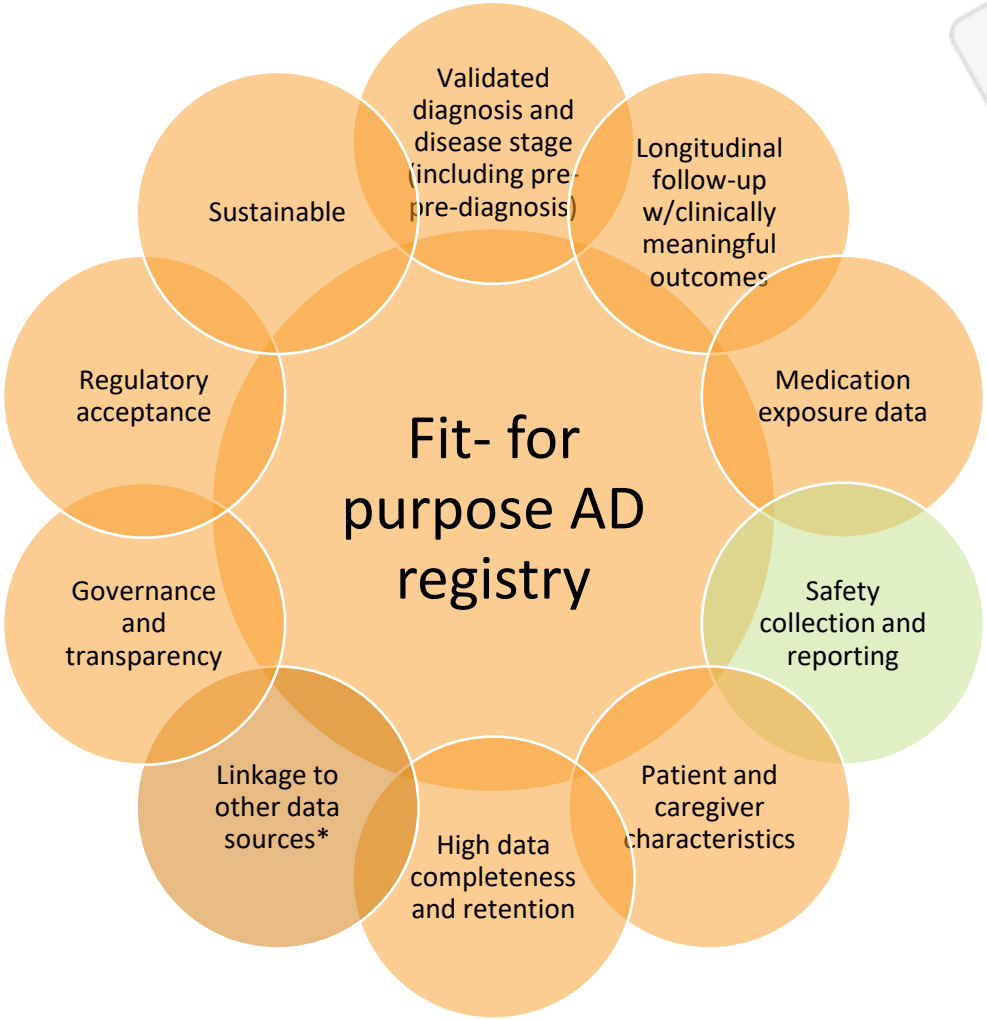
## Methods & Deliverables

- Epidemiology, statistical, and data science experts must be part of the registry team
- On the ground experts who understand site level differences and how those may affect research
- Timeliness

Reliability Relevance

# General fitness-for-purpose principles for evaluating drug safety in AD

- Well-defined objectives
- Prioritize internal validity
- Risk-based approach




*Alignment between a registry-based study's** objectives and a registry's purpose is critical for ensuring scientific validity*

*AS NEEDED

** EMA GUIDELINE ON REGISTRY-BASED STUDIES

# Practical Example: Leveraging registries for post-authorization safety studies

*A two-pronged approach covers the depth and breadth of required safety data for a **Mandatory** PASS*

Internal validity

Generalizability

*Vendor with fit-for-purpose, non-competitive registry and robust data capture system*

*Multidisciplinary team with experience developing regulatory-grade deliverables*

*Well-defined governance, data analysis and publication policy*


*Transparency through publication in the HMA-EMA data catalogues*

Comprehensive clinical, treatment, and safety data collection at specified timepoints

Process and infrastructure that support high data quality standards

Minimization of missingness and patient attrition

*Partnership with patient-centered, clinical-based AD registry*

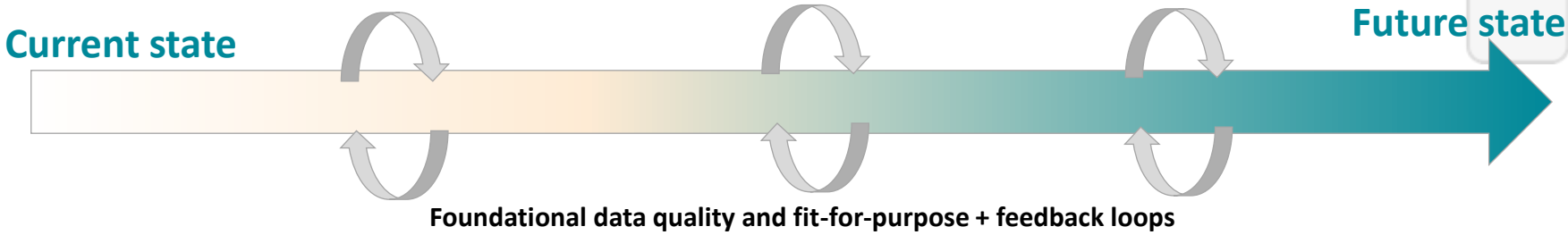
Wider patient capture to contextualize PASS study population and ARIA events

Enable the field to grow without further fragmentation

Receives funding from industry and other sources

Both approaches receive funding from industry

# We offer the following suggestions to optimise collaboration, facilitate the long-term follow-up of patients using registries, and enable the generation of meaningful data for regulatory decision-making




## Suggestion 1

**Strengthen cross-stakeholder partnership** to ensure the registry objectives and design stay aligned with evolving treatment paradigms, regulatory expectations, and data technologies.

***Registry protocol finalized after alignment is reached***

## Suggestion 2

A **risk-based approach** grounded on **fitness-for-purpose principles** should drive the choice of data for answering research questions, especially those of a regulatory nature. There is a need to pivot when registry quality or relevance threatens study objectives.

## Suggestion 3

Foundational principles of **data quality and scientific rigor**, underpinned by a **robust and scalable data capture infrastructure**, are indispensable for any registry deemed fit-for-purpose in a regulatory context.

**Learnings from previous PASS pilots should be systematically leveraged to drive continuous improvement and enhance quality in AD registries* that will be used in future regulatory studies (PASS / PAES)**

* EXISTING AND PLANNED REGISTRIES ARE IN SCOPE