

# GETREAL CONFERENCE 2026

## ABSTRACTS | POSTER BOOK

GetReal Conference 2026:  
Selection of accepted posters

**29-30 June 2026** | Utrecht, The Netherlands

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Introduction of Research Abstracts and Posters

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# RESEARCH ABSTRACTS AND POSTERS



As part of the 2026 conference programme, the GetReal Institute continued its call for research abstracts, building on the success of the previous year and providing further opportunities to showcase the breadth of activity across the real-world evidence (RWE) community. Submissions spanned applied case studies, pilot projects and methodological developments, reflecting the diversity of approaches used to generate and apply RWE. The initiative supports the Institute's commitment to advancing best practice, encouraging dialogue and providing a platform for researchers and practitioners to share their work with the wider RWE community.

## Fostering Cross-Sector Collaboration

The abstracts and poster track provided a forum for exchange between researchers, regulators, HTA bodies, patient representatives and industry stakeholders. Contributors shared experiences, research findings and practical approaches from different perspectives, supporting greater cross-stakeholder understanding of the generation and use of RWE.

## Highlighting Innovation and Best Practice

The submitted abstracts reflected innovative concepts, practical applications and emerging methodologies relevant to regulatory, HTA and broader healthcare decision making. The selected contributions demonstrated how approaches to generating and using RWE continue to evolve in response to methodological, policy and decision-making challenges.

## Supporting Early-Career Engagement

Building on the success of the previous year's poster track, the 2026 conference continued to provide opportunities for early-career professionals and students to present their work, engage with experienced experts and expand their professional networks. This forms part of the Institute's wider commitment to supporting the development of the next generation of RWE researchers and practitioners.

# REVIEW & SELECTION PROCESS

All submitted abstracts were reviewed and scored by the GetReal Institute Abstract Committee, comprising representatives from across the Institute's membership. Abstracts were assessed against predefined criteria, including relevance, methodological quality, innovation and contribution to the field. Following the review process, three abstracts were selected for oral presentation at the 2026 conference:

- Contribution of Real-World Evidence for the Orphan Medicines Approvals in the European Union between 2000 and 2025 | Lisbon University
- Automated Study Feasibility Using Agentic Artificial Intelligence to Rapidly Identify Fit-for-Purpose Secondary Data | ThermoFisher Scientific
- From Trials to Routine Care: Evaluating CPMS Identifier Recording in UK Primary Care EHRs | Medicines & Healthcare products Regulatory Agency

## POSTER SESSION

A moderated poster presentation and networking session was held on Day 2 of the conference, alongside the poster gallery. The session provided authors with an opportunity to present their work, receive feedback and engage in discussion with conference participants.



# POSTERS

## GetReal Conference 2026: A Selection of Abstracts and Posters

- Initiation with GLP-1 Receptor Agonists treatment for obesity in patients with mental health conditions - A Real World Data Retrospective Study
- Validation of Composite Mortality Data in Electronic Health Records-Derived Data in Germany: Comparison to a German Cancer Registry
- Contribution of Real-World Evidence for the Orphan Medicines approvals in the European Union between 2000 and 2025
- Large-scale early access programs, limited data capture for regulatory decision-making: learnings from orphan medicines approved in the European Union (2000-2025)
- Hybrid retrospective-prospective studies in rare diseases: review of [clinicaltrials.gov](https://clinicaltrials.gov) studies
- TARGET-EU: Strategies to handle a clinically favorable intercurrent event for a clinically unfavorable outcome in an oncology target trial emulation
- The importance of describing treatment trajectories before applying the prevalent new user design in complex settings: the case of sacubitril – valsartan in heart failure
- Long-term follow-up requirements of approved in-vivo gene therapies in Europe
- Bridging Real-World Evidence and Practice Through Implementation Science: Challenges and Recommendations for Hybrid Effectiveness-Implementation Studies in Pharmaceutical Drug Development
- Automated study feasibility using agentic artificial intelligence to rapidly identify fit-for-purpose secondary data
- Development and Implementation of a Dynamic Framework for Assessment and Improvement of Registries' Data Quality
- Enabling Real-World Evidence Through Linkage of National Health Service Business Services Authority (NHS BSA) Dispensing in England to the Clinical Practice Research Datalink (CPRD) primary care data
- CONTEXT-AWARE GENERATIVE AI FOR EVIDENCE GENERATION, ANALOG-DRIVEN ENROLLMENT FORECASTING, AND OPERATIONAL RISK MANAGEMENT IN ONCOLOGY TRIALS
- From Trials to Routine Care: Evaluating CPMS Identifier Recording in UK Primary Care EHRs
- Unmet Needs and Disease Burden: Perspectives from Adults with Psoriasis and Clinicians Treating Psoriasis in the United States
- From Real-World Evidence to Trial Emulation: The EMA's Shift Toward Target Trial and Estimand Frameworks

# Initiation of GLP-1 Receptor Agonist Treatment for Obesity in Patients With Mental Health Conditions

## A Real World Data Retrospective Study

Or Shaked, MD MPH<sup>1</sup>, April Chan, MD MBA<sup>1</sup>, Yana Gaskin, MD<sup>1</sup>, Talia Tron, PhD<sup>1</sup>, Izhar Laufer<sup>2</sup>, Gabriel Chodick, PhD<sup>3</sup>  
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Schedule  
a Demo



### Objectives

Glucagon-like peptide-1 receptor agonists (GLP-1s) have demonstrated substantial and sustained weight loss in obese patients and are increasingly used. Beyond metabolic outcomes, GLP-1s have been associated in large observational studies with neutral or beneficial effects on mood, emotional-eating, and quality-of-life. Nevertheless, concerns regarding psychiatric safety - including depression, anxiety, and suicidal behavior - have been raised in post-marketing studies. Such concerns may influence prescribing behavior or patient acceptance, particularly among patients with mental health conditions (PwMHC). Understanding real-world treatment initiation patterns in this population is critical for informing clinical practice, health policy, and market-access decisions. This study evaluated GLP-1 initiation rates among patients with and without mental health conditions as a real-world indicator of potential treatment hesitancy, among physicians or patients.

### Methods

This retrospective cohort study used electronic health records (EHR) data from a large, state-mandated healthcare provider in Israel (Leumit Health Services). Data curation, harmonization, analysis and graphics were done in Briya AIRE platform. Adults with documented obesity (BMI≥30 kg/m<sup>2</sup> or ICD diagnosis of obesity) and no diagnosis of type-2 diabetes were included. Mental health conditions were identified based on documented ICD diagnoses of depressive disorders, anxiety disorders, and indicators of suicidality. GLP-1 (Semaglutide, Wegovy) initiation rates during 2025 were compared between patients with and without documented mental health conditions. Patients with implausible BMI were excluded (N=72).

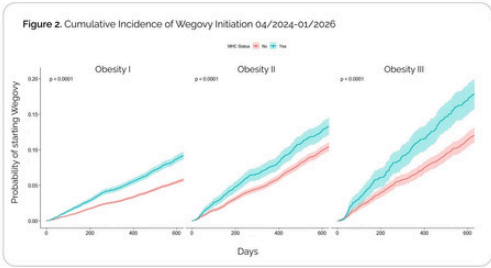
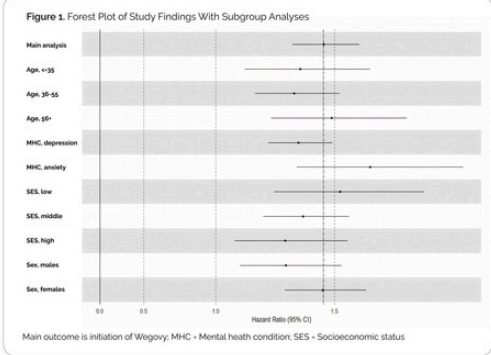
### Results

The study included 64,717 adults with obesity, of whom 5494 (8.5%) initiated GLP-1 therapy between April 2024 and January 2026. The highest initiation rate was observed among patients aged 45-54 years (11%). Compared with patients without documented mental health conditions, PwMHC were more likely to initiate GLP-1 therapy (11%) compared to non-MHC (7.6%), with an adjusted HR of 1.46 (95%CI: 1.38 - 1.55), with little variation across subgroups.

**Table 1.** Study Population and Initiation Rates of Weight Reduction GLP-1 Initiation Therapy, Israel 04/2024-01/2026

| Characteristic          | No<br>N = 59,223 <sup>1</sup> | Yes<br>N = 5,494 <sup>1</sup> | p-value <sup>2</sup> |
|-------------------------|-------------------------------|-------------------------------|----------------------|
| Age                     | 43 (31, 56)                   | 44 (33, 54)                   | 0.8                  |
| Age Category            |                               |                               | <0.001               |
| <25                     | 6,469 (93%)                   | 464 (6.7%)                    |                      |
| 25-34                   | 12,356 (92%)                  | 1,037 (7.7%)                  |                      |
| 35-44                   | 11,987 (90%)                  | 1,292 (9.7%)                  |                      |
| 45-54                   | 11,560 (89%)                  | 1,373 (11%)                   |                      |
| 55-64                   | 9,639 (91%)                   | 914 (8.7%)                    |                      |
| 65-74                   | 6,739 (94%)                   | 399 (5.6%)                    |                      |
| 75+                     | 473 (97%)                     | 15 (3.1%)                     |                      |
| Sex                     |                               |                               | <0.001               |
| Female                  | 30,637 (90%)                  | 3,491 (10%)                   |                      |
| Male                    | 28,586 (93%)                  | 2,003 (6.5%)                  |                      |
| BMI, kg/m <sup>2</sup>  | 32.5 (30.9, 35.2)             | 33.9 (31.6, 37.2)             | <0.001               |
| BMI Category            |                               |                               | <0.001               |
| Obesity I <sup>1</sup>  | 43,364 (93%)                  | 3,248 (7.0%)                  |                      |
| Obesity II              | 11,407 (88%)                  | 1,513 (12%)                   |                      |
| Obesity III             | 4,452 (86%)                   | 733 (14%)                     |                      |
| Mental Health Condition |                               |                               | <0.001               |
| No MHC                  | 45,010 (92%)                  | 3,715 (7.6%)                  |                      |
| Depression              | 12,356 (89%)                  | 1,509 (11%)                   |                      |
| Anxiety                 | 1,857 (87%)                   | 270 (13%)                     |                      |
| Any MHC                 | 14,240 (89%)                  | 1,784 (11%)                   | <0.001               |
| Sector                  |                               |                               | <0.001               |
| Arab                    | 17,795 (94%)                  | 1,088 (5.8%)                  |                      |
| Jewish                  |                               |                               |                      |
| Ultraorthodox           | 13,551 (92%)                  | 1,142 (7.8%)                  |                      |
| Jewish Religious        | 2,106 (93%)                   | 170 (7.5%)                    |                      |
| Jewish                  | 25,771 (89%)                  | 3,094 (11%)                   |                      |
| Socioeconomic Status    |                               |                               | <0.001               |
| Low                     | 21,553 (94%)                  | 1,343 (5.9%)                  |                      |
| Middle                  | 28,574 (91%)                  | 2,797 (8.9%)                  |                      |
| High                    | 9,066 (87%)                   | 1,351 (13%)                   |                      |

<sup>1</sup> Median (Q1, Q3); n (%)  
<sup>2</sup> Wilcoxon rank sum test; Pearson's Chi-squared test  
<sup>3</sup> According to WHO adult BMI categories: Obesity I patients include obesity ICD diagnosis



### Conclusions

In this large real-world cohort, PwMHC were more likely to initiate GLP-1 therapy for obesity than those without such conditions. These findings support equitable access to GLP-1 therapy across mental health subgroups and provide important real-world evidence for clinicians, payers, and policymakers evaluating the safety, uptake, and value of advanced obesity treatments.

# Validation of a Composite Mortality Variable in EHR-Derived Data in Germany

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Scan to learn more

## Introduction

- **Accurate mortality ascertainment is fundamental for real-world evidence (RWE) generation in oncology**, particularly for overall survival (OS) analyses used in comparative effectiveness research and regulatory submissions<sup>1</sup>
- **EHR data alone face challenges with incomplete death capture** due to patients being deceased outside healthcare systems, care transitions, or loss to follow-up<sup>1,2,3</sup>
- To counter this challenge, the electronic health record (EHR)-derived **Germany Flatiron Health Research Database (FHRD) composite mortality (CM) variable integrates multiple data sources**
- **Investigating the validity of the CM variable against a reference standard** supports establishing to what extent this composite endpoint is fit-for-purpose for real-world OS analyses

## Methods

### Study Design

- **Mortality validation study** of completeness and date accuracy comparing the **Germany FHRD CM variable** to **German Cancer Registry (CR)** data as reference
- Study cohort: **1280 patients across 7 cancer types from one partner site with available CR linkage**
- Study period: 01/01/2018 to 12/31/2024

### Composite Mortality Variable Components

- **Sourced from structured and unstructured EHR data** (i.e., clinical notes, hospice reports, technology-enabled data processing by clinical experts)
- **Externally sourced mortality information** from postal service records and linked national cancer registries (available for some sites)

### Validation Metrics

- **Sensitivity:** Proportion of CR deaths correctly identified by composite variable  
$$\frac{\text{True Positives (TP)}}{\text{TP} + \text{False Negatives (FN)}}$$
- **Specificity:** Proportion of CR living patients correctly identified as non-deceased  
$$\frac{\text{True Negatives (TN)}}{\text{TN} + \text{False Positives (FP)}}$$
- **Temporal accuracy:** Percentage of death dates matching CR within  $\pm 30$  days and exact match

## Results

Table 1. Study Cohort Composition by Cancer Type

| Cancer Type, n (%)            | N = 1280 |
|-------------------------------|----------|
| Non-small cell lung cancer    | 394 (31) |
| Colorectal cancer             | 333 (26) |
| Breast cancer                 | 274 (21) |
| Small-cell lung cancer        | 81 (6)   |
| Multiple myeloma              | 80 (6)   |
| Prostate cancer               | 78 (6)   |
| Diffuse large B-cell lymphoma | 40 (3)   |

→ Multi-cancer validation cohort ensures generalizability across tumor types

Table 2. Validation Metrics for the Mortality Variable

| FHRD CM Variable | Cancer Reg: Deceased | Cancer Reg: Alive |
|------------------|----------------------|-------------------|
| Deceased         | TP = 508             | FP = 58           |
| Alive            | FN = 71              | TN = 643          |

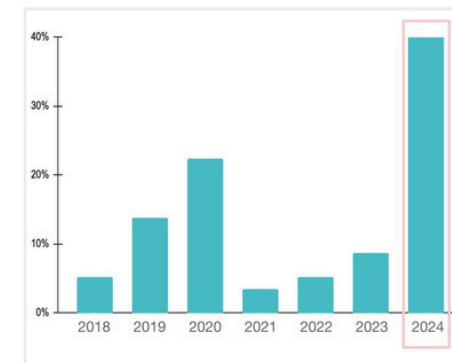
### Performance metrics

**Sensitivity: 87.7% (508/579)**  
**Specificity: 91.7% (643/701)**

Table 3. Agreement Between the FHRD CM Variable and Cancer Registry Death Dates

| Agreement Window     | Patients, n (%) | Interpretation                       |
|----------------------|-----------------|--------------------------------------|
| Exact date match     | 431/508 (84.8)  | High precision for survival analyses |
| Within $\pm 30$ days | 502/508 (98.8)  | Minimal impact on survival estimates |
| CM date before CR    | 12%             | Possible faster EHR capture          |
| CM date after CR     | 3%              | Rare delayed reporting               |

Figure 1. Proportional Distribution of False Positives by Year of Death



The **majority of apparently false positively captured mortality events fall into 2024**, the episode that is close to the CR cutoff date

→ **When accounting for CR reporting lag** (using December 31, 2023 cutoff), **specificity improves from 91.7% to 95.0%**

This study provides evidence that the **Germany Flatiron Health mortality endpoint is highly accurate** and fit-for-purpose for RWE studies

## References

1. Zhang et al (2021), doi: 10.1111/1475-6773.13669
2. Curtis et al (2018), doi: 10.1111/1475-6773.12872
3. Adamson et al (2026), doi: 10.1186/s12885-026-15548-8

**Acknowledgments:** Data first presented at Krebs Kongress in Berlin, Germany, February 18-21, 2026

**Disclosures:** This study was sponsored by Flatiron Health, Inc.—an independent member of the Roche Group. During the study period, SS, BA, CK, SBW, CB, JH, JM, EH, QZ, and KSR reported employment with Flatiron Health, Inc. and stock ownership in Roche.

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## Discussion

- **High sensitivity** demonstrates robust death capture; **Strong specificity** indicates minimal false positives
- **High temporal accuracy** is critical for time-to-event analyses
- Validity measures **align closely with those of the US Flatiron Health Research Database** (sensitivity: 83.9%-91.5%, specificity: 93.5%-99.7%,  $\pm 30$ -day temporal agreement: 96.3-97.9%)<sup>1</sup>
- False positive patterns suggest **cancer registry reporting delays** rather than composite variable errors
- **A multi-source integration strategy enhances completeness** of mortality information, qualifying its use for generating impactful RWE to inform clinical practice and healthcare policy in Germany

# Contribution of Real-World Evidence for the Orphan Medicines Approvals in the European Union between 2000 and 2025

Luísa Bouwman<sup>1,2</sup> · Diogo Almeida<sup>1,2</sup> · Carla Jonker<sup>3</sup> · Hubert Leufkens<sup>1,4</sup> · Bruno Sepodes<sup>1,2</sup> · Carla Torre<sup>1,2</sup>



<sup>1</sup>Faculdade de Farmácia, Universidade de Lisboa, Portugal | <sup>2</sup>Research Institute for Medicines (iMED.Ulisboa), Portugal | <sup>3</sup>Medicines Evaluation Board, Utrecht (The Netherlands) | <sup>4</sup>Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands.

## BACKGROUND

Orphan medicinal products (OMPs) face challenges aligning with traditional randomized control trials (RCT) pathways. RWD/RWE can provide critical complementary evidence — yet their systematic contribution to EU OMP approvals over 25 years had not been comprehensively characterised.

## OBJECTIVE

Assess the contribution, role and temporal trends of RWD/RWE in regulatory decision-making for OMP marketing authorisation approvals in the EU (2000–2025), across both pre- and post-authorisation phases.

## METHODS

**Population:** All 311 orphan medicinal products (OMPs) approved by EC (Jan 2000–Dec 2025)

**Data source:** European Public Assessment Reports (EPARs) from the EMA website

**Pre-authorization screening:** Keyword search per EPAR; RWD classified as 'main', 'supportive', or 'not known'

**Post-authorization screening:** PAMs in Annex II conditions, SOBs, and RMP category 1–3 activities screened for RWD/RWE

**Extraction:** Data source type, study design, main objective, and role in benefit-risk assessment

**QC:** 25% random sample checked by second author; full check for critical variables; consensus by 3 researchers

## KEY FINDINGS AT A GLANCE

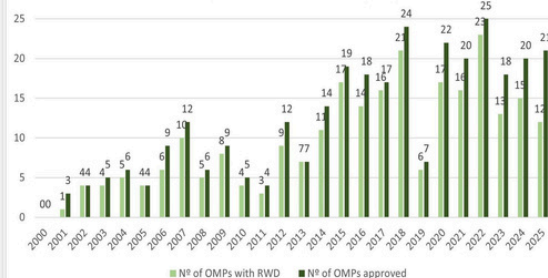
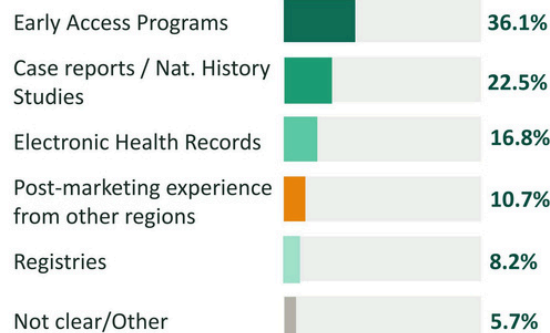


Figure 1. Annual OMPs approved (dark green) and OMPs with RWD identified in pre- or post-authorisation phase (light green), EU 2000–2025. In 2000 no OMPs have been approved.

## Pre-authorization RWD sources (N=280)



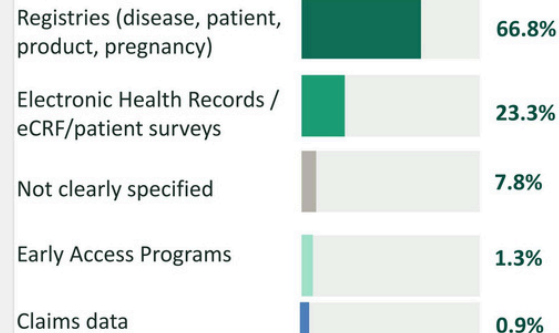
## Role of RWD in Pre-authorization



Corresponding to 41 OMPs  
73% Non-oncological indications  
56% Non-small molecules  
59% Conditional MA/approval under exceptional circumstances

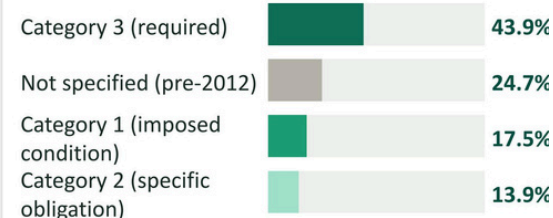
53% of main-evidence RWD sources were **external controls** — primarily from EHRs (n=16), natural history studies (n=6) and patient registries (n=5).

## Post-authorization RWD sources (N=232)



## POST-AUTHORISATION STUDIES (N=232)

- Additional Pharmacovigilance Activities in the Risk Management Plan (RMP)  
N= 223; 96%



- Post-authorisation Efficacy Studies  
N= 9; 4%

## CONCLUSIONS

>80% of OMP MAAs contain RWD/RWE — confirming it as an **essential component** of OMP regulatory evaluation

68% of pre-auth RWD is **supportive**; main evidence RWD particularly relevant for ATMPs and non-standard MAs

**Early Access Programs** most common **pre-auth** RWD source (36%), yet data collection remains largely unstructured

**Registries** dominate **post-auth** phase (67%); prospective cohorts most common study design (93.5%)

**Lack of Harmonisation** standardised EPAR **terminology** and documentation needed to improve RWE interpretability

# Large-scale Early Access Programs, Limited Data Capture for Regulatory Decision-Making: Learnings from Orphan Medicines Approved in the EU (2000–2025)

Luísa Bouwman<sup>1,2</sup> · Diogo Almeida<sup>1,2</sup> · Carla Jonker<sup>3</sup> · Hubert Leufkens<sup>1,4</sup> · Bruno Sepodes<sup>1,2</sup> · Carla Torre<sup>1,2</sup>

<sup>1</sup>Faculdade de Farmácia, Universidade de Lisboa, Portugal | <sup>2</sup>Research Institute for Medicines (iMED.Ulisboa), Portugal | <sup>3</sup>Medicines Evaluation Board, Utrecht (The Netherlands) | <sup>4</sup>Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands.



## BACKGROUND

**Early Access Programs (EAPs)** — comprising **Compassionate Use (CUP)** and **Named Patient Programs (NPP)** — enable patients with serious conditions to access unauthorised treatments outside clinical trials.

EAPs have been recognised as potential sources of Real-World Data (RWD), yet their specific contribution to EU orphan medicine regulatory assessments remains insufficiently characterised.

## OBJECTIVES

- 1 Describe **prevalence** and role of EAP-derived RWD in EU OMP regulatory assessments
- 2 Explore **temporal trends** across 2000–2025
- 3 Identify **countries** involved and variability across OMP characteristics

## METHODS

**Population:** All 311 orphan medicinal products (OMPs) approved by EC (Jan 2000–Dec 2025)

**Data source:** European Public Assessment Reports (EPARs) from the EMA website

**Screening:** Structured keyword search per EPAR ("compassionate use", "named patient", "real-world data", "managed access", "expanded access")

**Classification:** Role of EAP data: pivotal, supportive safety/efficacy, both, 'not clear', or 'not relevant'

## KEY FINDINGS AT A GLANCE



FIGURE 1 — ANNUAL OMP APPROVALS VS. EPARs MENTIONING EAPs (2000–2025)

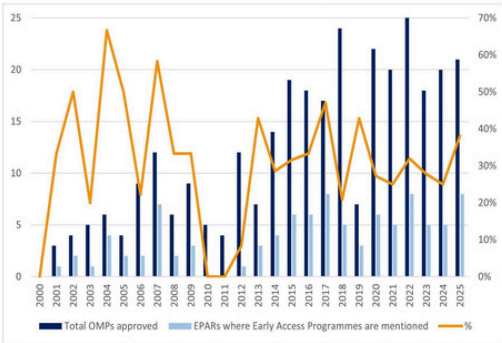
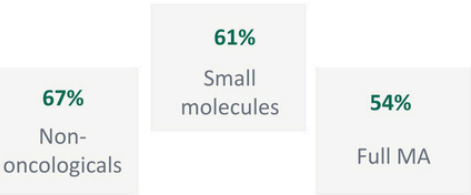
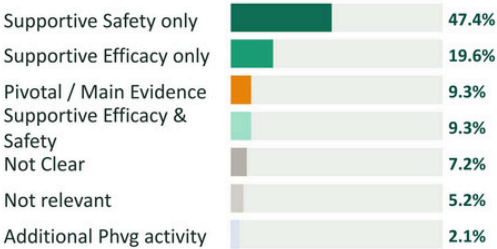


Figure 1. Annual number of OMPs approved (dark bars) and EPARs with EAP references (light bars), EU 2000–2025. Prevalence ranged from 0% (2010–2011) to 67% (2004); mean 31.2%. In 2000 no OMPs have been approved.

## PRODUCT CHARACTERISTICS (N=97 WITH EAPs)



## ROLE OF EAP DATA IN REGULATORY ASSESSMENT (N=97)



9 OMPs had EAP data considered **pivotal**, including nitisinone (global CUP with standardised collection & long-term follow-up) and cholic acid (compassionate treatment studies as main clinical evidence).

## GEOGRAPHIC DISTRIBUTION OF EAPs

| Country / Region           | N (%)        |
|----------------------------|--------------|
| Not specified in EPAR      | 44 (45.4%)   |
| France                     | 13 (13.4%)   |
| France + other countries   | 11 (11.3%)   |
| EU countries (unspecified) | 9 (9.3%)     |
| Unites States (US)         | 9 (9.3%)     |
| EU (unspecified) + US      | 4 (4.1%)     |
| Germany                    | 2 (2.1%)     |
| Netherlands/UK/Other       | 1(1.0%) each |

France's prominence reflects its structured ATU/AAP framework mandating data collection protocols (ANSM) — making EAP data more likely to be considered by regulators.

## CONCLUSIONS

- 31% of EPARs mention EAPs; often, EAP patient populations exceed pivotal trial sizes
- 48% of cases: EAP data support safety assessment only; contribution to efficacy remains very limited
- 9 OMPs relied on EAP data as pivotal/main evidence, with considerable variability in study design
- Missed opportunity: absence of structured protocols limits use for robust efficacy assessment
- Lack of Harmonised EU framework: coordinated by EMA could transform EAPs into a robust RWD source for rare diseases

## POLICY IMPLICATIONS

**Proposed approach:** Non-interventional monitoring protocols (e.g. EMA-approved registry-based studies) implemented by sponsors across all Member States where the medicine is administered — whether individually or to patient cohorts.



**A centralised EU framework** would reduce administrative burden, promote equitable access, and generate **regulatory-grade RWD** — particularly valuable in rare diseases where clinical trial populations are inherently small.

# Hybrid Retrospective-Prospective Studies in Rare Diseases: Review of ClinicalTrials.gov Studies

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ABS-06

## Background

- Real-world evidence can support regulatory decision-making at different stages of the drug product life cycle, especially in the context of rare diseases.
- In this context, there are three important options for study design: retrospective, prospective, and hybrid.
- Because of the smaller number of patients impacted by each rare disease, retrospective or prospective designs alone may not be sufficient or fit for purpose, especially for comparative purposes supporting regulatory evidentiary needs. Rather, a hybrid design, in which primary data collection in a prospective study is supplemented with retrospectively collected data from chart reviews, registries, or electronic medical record databases, offers the same patients or for a different set of patients and can deliver the right information.
- In this study, we describe how hybrid studies are being conducted in clinical development programs for rare diseases.

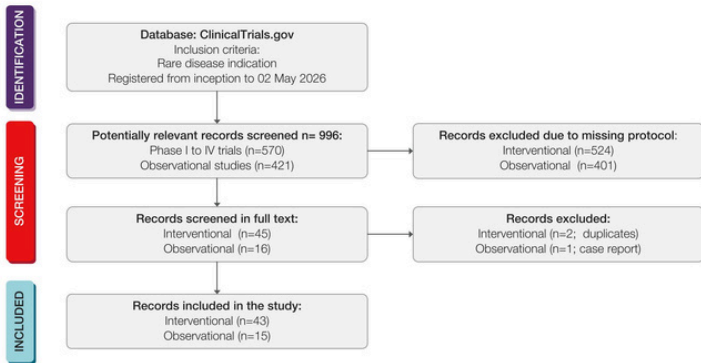
## Methods

- A cross-sectional descriptive analysis was conducted of all studies with a rare disease indication and a protocol registered in ClinicalTrials.gov as of 02 May 2026.
- The search was based on explicit keywords and eligibility criteria. Peer-reviewed, full-text protocols meeting the eligibility criteria were screened by a single researcher. Data of interest were extracted from eligible protocols into a bespoke spreadsheet.

## Results

- A total of 996 studies were registered in ClinicalTrials.gov from inception to 02 May 2026 for rare disease indications. Of those, 570 were classified as interventional (Phase I to IV) and 421 as observational studies. Very few of these studies had available protocol documents (n=61, 6.1%): 45 were interventional and 16 observational studies. After removing two duplicate interventional studies and one case report study, 43 (7.5%) interventional and 15 (3.6%) observational studies were included in this review (Figure 1).

Figure 1. Study Search and Screening Flow Diagram

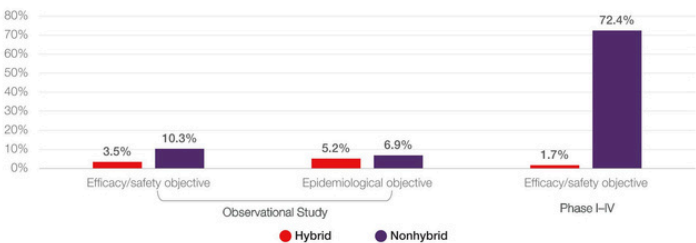


Only 10% of all identified studies in rare disease indications were hybrid, and most of them (83%) were observational in nature.

- Among the 58 studies selected for this study, we identified six hybrid studies (6/58, 10.3%): one (1/58, 1.7%) was a hybrid Phase I to II trial and five (5/58, 8.6%) were hybrid observational and epidemiological studies. In contrast, all except one of the 52 nonhybrid studies used a purely prospective longitudinal design: 42 were conducted as Phase I to IV trials (42/58, 72.4%), and the remainder were observational studies (eight prospective and one retrospective) (Figure 2).

## Results (continued)

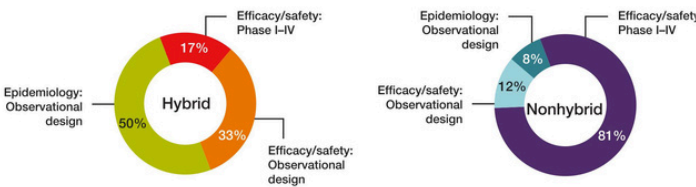
Figure 2. Distribution of Hybrid and Nonhybrid Studies by Study Type



Only 2% interventional studies seeking regulatory approval used a hybrid design; the remaining 98% used a prospective design.

- With regard to the study aim, the main focus of hybrid designs was either the estimation of safety and efficacy (3/6, 50.0%) or epidemiological parameters of the disease (3/6, 50.0%). In contrast, nonhybrid prospective studies were mainly concerned with safety and efficacy endpoints to support applications for marketing authorization of a new drug (48/52, 92.3%) (Figure 3). Overall, only one (2.3%) of the 43 interventional studies seeking regulatory approval used a hybrid design compared with 42 (97.7%) that followed a prospective design.

Figure 3. Distribution of Hybrid and Nonhybrid Studies by Objective



Hybrid designs were used as a viable way to accrue a sufficiently large sample size to evaluate study objectives, including to support regulatory evidentiary needs.

- All six hybrid studies identified in this study relied on existing historical and concurrently collected real-world registry data to supplement a new prospective data collection. The rationale for using a hybrid design was to accrue a sufficiently large sample size to evaluate comparison in Phase I to IV studies and trends and outcomes in epidemiological studies.
- The six studies used a combination of both a hybrid "mixed patient" design, in which retrospective and prospective data are collected from different sets of patients, and a hybrid "same-patient," or ambispective, design, in which prospective and retrospective data are collected on the same set of patients.

Hybrid study protocols lacked methodological detail, especially observational protocols.

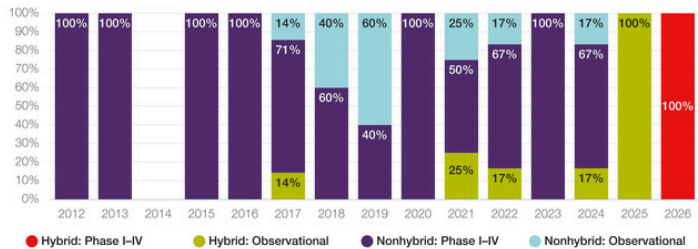
- Among the three hybrid studies that focused on efficacy and safety endpoints, two used an active-controlled design. One was a natural history observational study relying on existing historical and concurrently collected registry data. The other study was a Phase I to II trial that merged real-world historical and concurrent randomized trial data.

- These hybrid studies used different methods to control for bias. The observational study used propensity score methods to control for differences in key prognostic factors across comparison groups, but not for differences between populations with retrospectively versus prospectively accrued data. The hybrid Phase I to II trial used the Bayesian hierarchical model to combine information from historical drug users and concurrent trial participants, giving historical data lower weight (discounted) compared with internal trial information.
- Overall, the level of methodological detail provided in the protocols was limited, especially among observational studies, which often lacked a critical rationale for methodological choice and acknowledgment of study limitations.

Although still of limited scope, hybrid designs are on the rise.

- The hybrid study design was more likely to be used after 2020 (5/6, 83.0%) compared with nonhybrid studies (17/52 [32.7%]). The only hybrid study registered for regulatory purposes dated 2026 (Figure 4).
- Half of the hybrid studies (50.0%, n=3) were conducted in the EU, whereas nonhybrid studies were more often conducted in the US (43.0% vs. 36.0% for US- vs. EU-based studies).

Figure 4. Trends Over Time on Type of Studies for the Rare Disease Indication



## Conclusions

- The findings of this study are consistent with the rarity of hybrid designs among external comparator designs reported in the literature. However, the study findings suggest that the hybrid design will be increasingly leveraged to support drug development in rare diseases.
- Because retrospective and prospective combined data may differ in availability and quality, these designs present unique challenges. Studies intended for regulatory submission considered the heterogeneity of measurements and outcomes between prospective and retrospective patient populations when combining these patients into comparator arms. However, no clear criteria for data combinability were presented in the hybrid study protocol. Overall, the level of methodological detail in observational studies was limited, particularly regarding approaches to minimize potential bias arising from differences in attributes in retrospectively and prospectively collected data. As adoption of hybrid designs increases, guidance on their use to support regulatory approval is needed.
- Only 6.1% of eligible studies registered in ClinicalTrials.gov had a protocol available for review, which voided the assessment of most studies and therefore may limit the representativeness of the study results.

### Disclosures

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# TARGET-EU: Strategies to handle a clinically favorable intercurrent event for a clinically unfavorable outcome in an oncology target trial emulation

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## INTRODUCTION

Clinical trial results cannot always be generalized to clinical practice due to strict selection criteria. Target trial emulation (TTE), using real-world data (RWD), has been proposed as a framework to provide insights into therapeutic benefits of patients not included in clinical trials. Within this framework, it is important to clearly define the estimand, and that requires rational strategies on how to handle intercurrent events (IEs). Several strategies can be applied:

- Principal stratum
- Hypothetical
- While-on treatment
- Treatment policy
- Composite

## AIM

The aim of the TARGET-EU project is to assess the robustness of applying the TTE and estimand framework using RWD. In one of the specific TARGET-EU case studies, the added value of bevacizumab in the first-line treatment of metastatic colorectal cancer (mCRC) is assessed.

Strategies to handle a clinically favorable IE considering a clinically unfavorable outcome are discussed.

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## METHODS

We designed a TTE to compare progression-free survival (PFS) of mCRC patients treated with a capecitabine-oxaliplatin (CapOx) regimen with versus without bevacizumab (B). PFS was defined as the time to first occurrence of disease progression or death.

Local treatment of metastases was considered a clinically favorable IE (it can only be applied if systemic treatment causes tumor shrinkage). Local treatment can consist of:

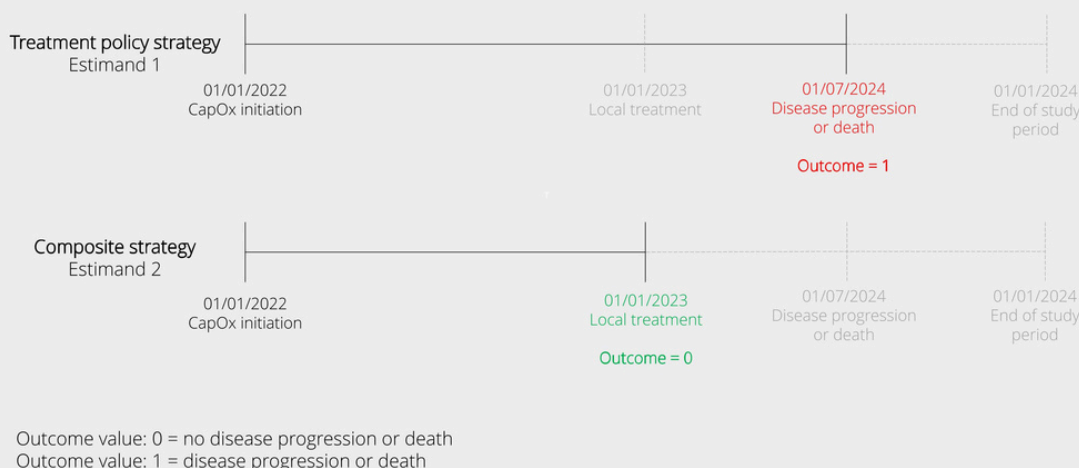
- Surgery
- Radiotherapy
- Ablation
- Other local treatments (e.g. embolization or hyperthermic intraperitoneal chemotherapy).

The following strategies to handle IEs were considered:

- Principal stratum: targets the subgroup of individuals who would not receive local treatment under either the intervention or the control.
- Hypothetical: reflects a hypothetical scenario in which local treatment would not have occurred.
- While-on-treatment: only includes outcomes up until the occurrence of local treatment.
- Treatment policy: regards the occurrence of local treatment as part of the treatment condition.
- Composite: takes the occurrence of local treatment into the outcome definition.

We defined two estimands that handle the IE local treatment most appropriately (Figure 1). Estimand 1 applies the treatment policy strategy, in which local treatment is ignored and the patient is followed up until the outcome. Estimand 2 applies the composite strategy, in which local treatment indicates a clinically favorable outcome. The patient is no longer at risk of disease progression or death (i.e. patient is censored).

**Figure 1. Visual example of how the treatment policy strategy vs the composite strategy handle a clinically favorable intercurrent event (local treatment) considering a clinically unfavorable outcome (disease progression or death).**



## DISCUSSION

We discussed several strategies to handle a clinically favorable IE considering a clinically unfavorable outcome. Different strategies to handle IEs reflect different research questions. It should be kept in mind that the treatment can affect the possibility to undergo local treatment, and undergoing local treatment can affect the occurrence of the outcome.

- The treatment policy strategy is most suitable for an estimand that evaluates bevacizumab's effectiveness within clinical practice. The interest lies in the treatment effect, given that the exposure can lead to local treatment.
- The composite strategy is most suitable for an estimand that ensures that local treatment is not represented as a clinically unfavorable outcome. An estimand applying this strategy changes the interpretation of the endpoint, which should remain clinically relevant.
- The principal stratum strategy is less suitable because it relies on the assumption that the treatment itself has no causal effect on whether someone receives local treatment.
- The hypothetical strategy is less suitable because it does not account for the fact that local treatment is not randomly allocated.
- The while-on-treatment strategy is less suitable because it would truncate follow-up at the occurrence of local treatment, eventually leading to overrepresentation of poor outcomes.



# The importance of describing treatment trajectories before applying the prevalent new user design in complex settings: the case of sacubitril – valsartan in heart failure

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## INTRODUCTION

- The prevalent new user (PNU) design focuses on patients switching from an old to a new drug
- It matches switchers to continuing users of the old drug with comparable prior treatment trajectory
- Currently defined switcher trajectories are insufficiently detailed for accurate matching in complex settings

## AIM

To illustrate how complex treatment histories can be characterized and incorporated into the PNU matching algorithm using the example of heart failure (HF):

- Patients can switch to a new drug (sacubitril – valsartan; SV) from their old therapy:
  - angiotensin – converting enzyme inhibitors (ACEIs) or
  - angiotensin – II receptor blockers (ARBs)
- SV switchers can be direct or delayed (Figure 1)

## METHODS

- ✓ Descriptive study
- ✓ Clinical Practice Research Datalink Aurum linked with Hospital Episode Statistics
- ✓ Patients with an incident HF diagnosis (≥2 years of primary care history) and an SV prescription between January 2014 and March 2023
- ✓ Assessment of ACEI/ARB treatment 2 years before incident HF diagnosis until SV initiation
- ✓ Comparison of the identified treatment history patterns to those in PNU
- ✓ Incorporation of additional patterns into the matching algorithm

## RESULTS

- We included 20,081 patients and identified 6 treatment history patterns (Figure 1).
- In a real-world study comparing SV with ACEIs, each SV user will be matched to an ACEI user:
- on pattern 1-6
  - total number of ACEI/ARB prescriptions from base cohort entry to index SV/ACEI prescription
  - calendar year of index SV/ACEI prescription
  - gap between last ACEI/ARB and index SV/ACEI prescription (0-60, 61 – 180, > 180 days)
  - time-conditional propensity score

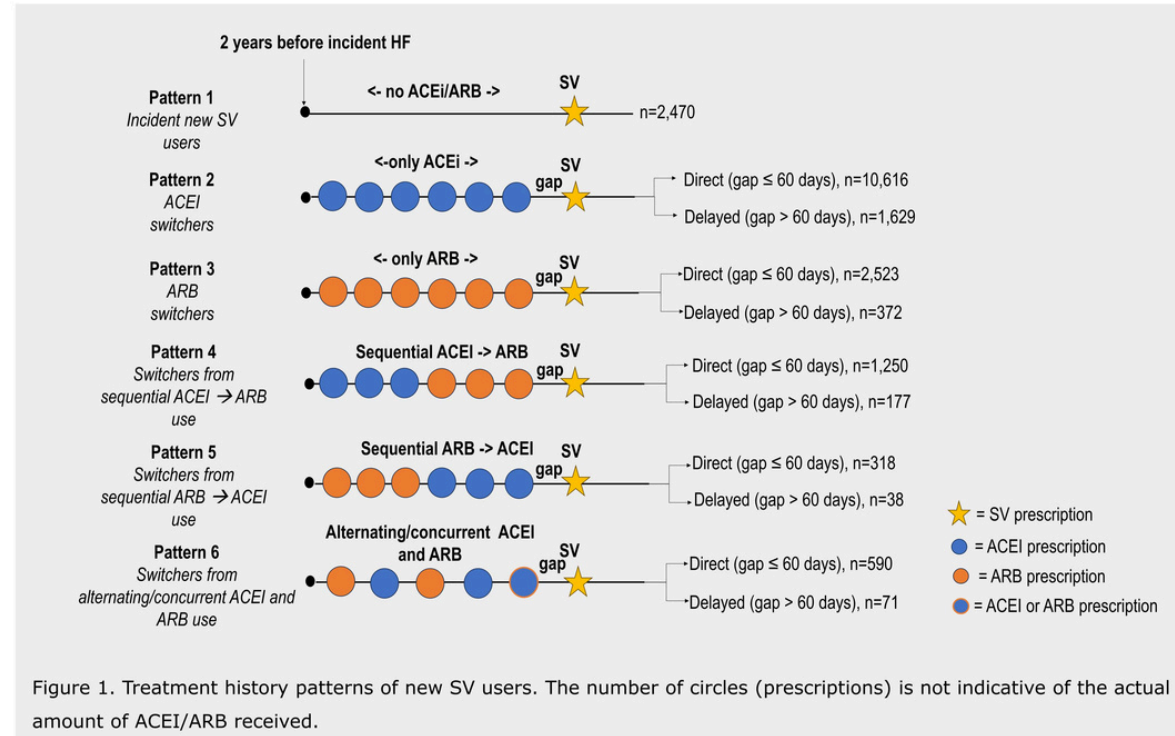


Figure 1. Treatment history patterns of new SV users. The number of circles (prescriptions) is not indicative of the actual amount of ACEI/ARB received.

## CONCLUSION

The prevalent new user (PNU) design can be optimally implemented in complex settings by following a data-driven approach where the relevant treatment history patterns prior to the new drug initiation are elucidated and used to define an accurate matching algorithm. A balance should be maintained between a granular but feasible matching algorithm.

## AFFILIATIONS

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# Long-term Follow-up Requirements of Approved In Vivo Gene Therapies in Europe

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ABS-09

## Background

- The increasing number of approved in vivo gene therapies in Europe has prompted greater regulatory focus on the long-term monitoring of safety and effectiveness following marketing authorisation.<sup>1</sup>
- Unlike conventional medicinal products, gene therapies may produce durable or potentially lifelong biological effects, while clinical development programmes are often based on relatively small patient populations and limited follow-up periods.
- As a result, important uncertainties may remain at the time of approval regarding long-term efficacy, durability of treatment response, delayed adverse events, and potential risks associated with vector persistence or genomic integration.
- To address these uncertainties, the EMA frequently requires post-authorisation studies and long-term follow-up (LTFU) activities as part of the benefit-risk assessment framework.
- Understanding the nature and frequency of these regulatory requirements is essential for stakeholders involved in the development, regulatory evaluation, and lifecycle management of gene therapies.

## Objectives

- To provide an overview of key design characteristics of post-marketing commitment studies requested for in-vivo gene therapies approved in Europe.

## Methods

- We reviewed European Public Assessment Reports (EPARs) for the eight in vivo gene therapies approved by the EMA (identified via the EMA website in the list of approved advanced therapies) to characterise the types of observational LTFU studies, as well as observational post-authorisation safety (PASS) and efficacy (PAES) requirements imposed by regulators.
- The eight in vivo gene therapies with their indications are summarised in Table 1.

Table 1. The Eight EMA-approved In Vivo Gene Therapies

| Name – /VV(Marketing Authorisation Holder)            | Indication                                                                                             | Therapeutic Area     | EMA Market Approval Date |
|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------|----------------------|--------------------------|
| Imlygic® – talimogene laherparepvec (Amgen)           | Treatment of melanoma that cannot be surgically removed and that has spread to other parts of the body | Oncology             | Dec 2015                 |
| Luxturna® – voretigene neparovec (Novartis)           | Vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations           | Ophthalmology        | Nov 2018                 |
| Zolgensma® – onasemnogene APOB10 transgene (Novartis) | Spinal muscular atrophy                                                                                | Neurology            | May 2020                 |
| Upstaza® – eladociclovir (PTC Therapeutics)           | Severe aromatic L-amino acid decarboxylase (AADC) deficiency with a genetically confirmed diagnosis    | Neurology            | Jul 2022                 |
| Roctavian® – valoctocogene roxaparvovec (BioMarin)    | Severe haemophilia A                                                                                   | Haematology          | Aug 2022                 |
| Ebvallo® – talemeciclovir (Pierre Fabre)              | Treatment of Epstein-Barr virus positive post-transplant lymphoproliferative disease                   | Haematology/Oncology | Dec 2022                 |
| Hemgenix® – etranacogene dezaparvovec (CSL Behring)   | Severe and moderately severe haemophilia B                                                             | Haematology          | Feb 2023                 |
| Vyjuvek® – beremagene geperpavec (Krystal biotech)    | Treatment of wounds in patients with dystrophic epidermolysis bullosa                                  | Dermatology          | Apr 2025                 |

Abbreviations: AADC = aromatic L-amino acid decarboxylase; INN = international nonproprietary name; RPE65 = retinal pigment epithelium-specific 65 kDa protein gene

## Reference

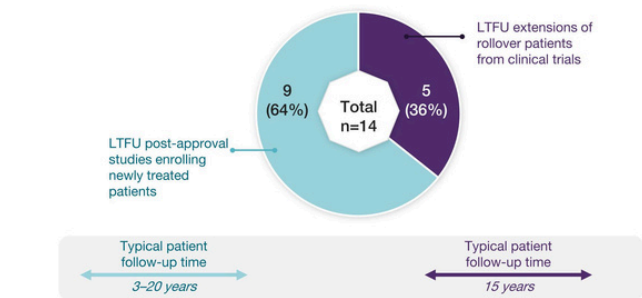
- European Medicines Agency. Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products - Scientific guideline. <https://www.ema.europa.eu/en/guideline-safety-efficacy-follow-risk-management-advanced-therapy-medicinal-products-scientific-guideline>.

## Results

### Types of Long-term Observational Studies

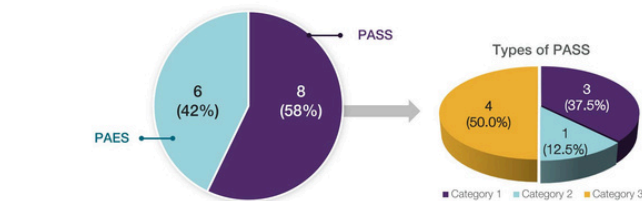
- Long-term observational study designs were consistently outlined in the risk management plans, in line with regulatory requirements for cell and gene therapies, with a median (min-max) of 1.5 (1.0–3.0) observational studies per approved therapy.

Figure 1. Types of Long-term Observational Study Designs



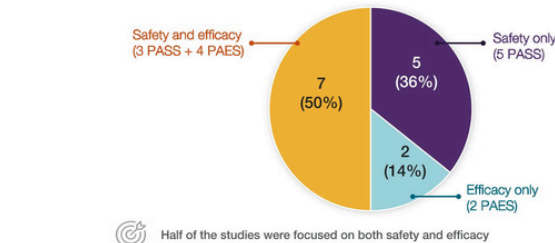
Abbreviation: LTFU = long-term follow-up

Figure 2. Types of Post-marketing Commitments



Abbreviations: PAES = post-authorisation efficacy studies; PASS = post-authorisation safety studies

Figure 3. Main Objectives of the Post-marketing Requirements



Abbreviations: PAES = post-authorisation efficacy studies; PASS = post-authorisation safety studies

## Disclosures

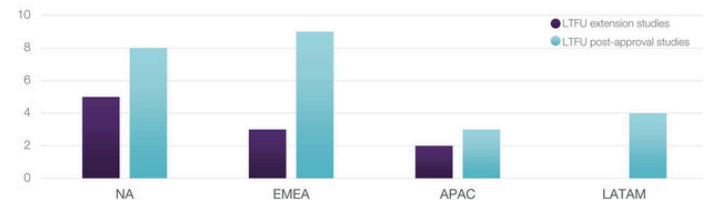
SR and AR are employees of PPD™ Observational Studies, Thermo Fisher Scientific. Funding provided by Thermo Fisher Scientific. Editorial and graphic design support were provided by Karissa Calara and Kawthar Nakayima of Thermo Fisher Scientific.

Figure 4. Types of Data Sources for LTFU PAS (n=9)



Abbreviations: LTFU = long-term follow-up; PAS = post-authorisation study

Figure 5. Regional Location Where LTFU PAS and LTFU Extension Studies are Conducted (Number of Studies per Region)



Abbreviations: APAC = Asia-Pacific; EMEA = Europe, Middle East and Africa; LATAM = Latin America; LTFU = long-term follow-up; PAS = post-authorisation study

## Limitations

- This review was restricted to in vivo gene therapies and did not include ex vivo approaches, in which patient cells are genetically modified outside the body before reinfusion (e.g., chimeric antigen receptor T-cell [CAR-T] cell therapies).
- The analysis was limited to information publicly available in EPARs and associated regulatory documents; additional details on study implementation and rationale may not be publicly disclosed.
- The small number of approved in vivo gene therapies in Europe at the time of review limits the generalisability of findings and may not reflect future regulatory expectations as the field evolves.
- The study assessed planned post-authorisation commitments rather than their execution, completion, or impact on regulatory decision-making.
- The review focused exclusively on EMA-approved products and therefore does not capture potential differences in LTFU requirements across other regulatory jurisdictions.

## Conclusions

- Approved in vivo gene therapies in Europe are consistently subject to long-term observational follow-up requirements, reflecting regulatory emphasis on ongoing safety and effectiveness monitoring.
- Regulatory commitments combine extended follow-up of clinical trial participants with post-approval studies in real-world populations, often over periods of up to 15 to 20 years.
- Most post-approval studies rely on primary data collection, highlighting the continued need for robust long-term data infrastructure beyond existing patient registries.
- These findings demonstrate the central role of real-world evidence in supporting long-term benefit-risk assessment and informing regulatory decision-making for advanced therapy medicinal products.

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# Bridging Real-World Evidence and Practice Through Implementation Science: Challenges and Recommendations for Hybrid Effectiveness–Implementation Studies in Pharmaceutical Drug Development

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## Background

- Implementation science (IS) bridges the gap between research and practice, helping evidence-based interventions reach patients and improve outcomes.
- Real-world evidence (RWE) complements IS by showing how interventions perform in routine care and across diverse patient populations.
- Hybrid effectiveness–implementation studies combine these approaches, evaluating both clinical effectiveness and implementation in real-world settings to accelerate adoption and long-term sustainability.

## Objectives

- To highlight key challenges in applying hybrid studies in pharmaceutical drug development and offer practical recommendations to address them

## Methods

- Researchers who have been involved in hybrid studies and have experience as reviewers, principal investigators, scientific project managers, and research associates identified challenges encountered across past and ongoing studies.
- The challenges identified were organized into themes, and recommendations were developed from collective lessons learned and practical implementation experience.

## Conclusions

- Limited familiarity with IS methods and terminology remains a barrier to broader adoption within pharmaceutical drug development.
- Hybrid studies provide an efficient approach for integrating clinical and IS objectives into a single trial while generating RWE on intervention performance in routine practice.
- Building IS capacity and supporting stakeholders in such studies can enhance study success and accelerate the adoption, implementation, and sustainability of evidence-based interventions.

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## Disclosures

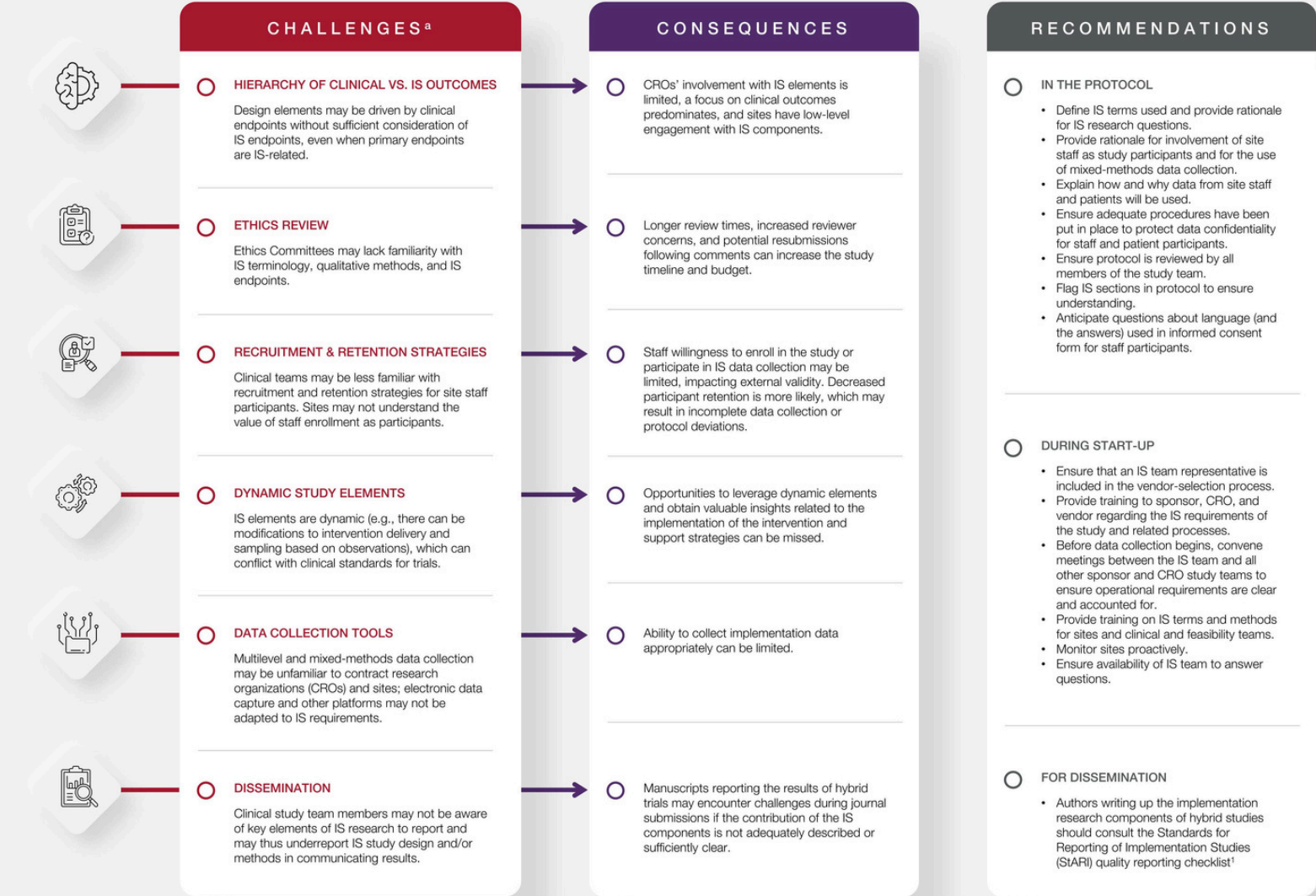
The authors are employees of PPD™ Evidera™ Patient-Centered Research, Thermo Fisher Scientific.

## Acknowledgments

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## Findings



<sup>a</sup> Note that some challenges are not unique to hybrid studies

# Automated Study Feasibility: Leveraging Agentic AI to Rapidly Identify Right Fit Secondary Data

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ABS-12

## Background

- Identifying appropriate data sources for real-world evidence is increasingly challenging as research questions demand granular clinical, temporal, and biomarker data. At the same time, the number and diversity of available real-world data (RWD) sources, across electronic health records, registries, claims, and linked datasets, has expanded rapidly across regions.
- The Professional Society for Health Economics and Outcomes Research (ISPOR) task force guidance emphasizes transparent, reproducible evaluation of data source suitability; however, feasibility assessments often rely on manual processes and fragmented institutional knowledge. There remains a need for scalable approaches that can operationalize ISPOR principles in a consistent and practical way across diverse data sources.
- This approach aligns with ISPOR principles of transparency, reproducibility, and fitness-for-purpose in real-world data selection.

## Objectives

- This poster describes the development of a structured metadata catalogue and explores the use of an agentic artificial intelligence (AI) interface to operationalize transparent, reproducible data source selection.

## Framework Development and Insights

- Data source catalogue development followed a reproducible workflow using a unified data element grid (DEG) template, harmonized from internal knowledge and EMA catalogue metadata. For initial development, 100 commonly used claims and electronic health record (EHR) databases were prioritized. DEGs were curated by subject-matter experts using a structured extraction process, with independent review by a second knowledgeable reviewer.
- This structured metadata foundation enables systematic and reproducible interrogation of data sources and forms the basis for AI-assisted querying.
- Adding an AI-assisted querying layer to curated metadata enables a more standardized, efficient, and reproducible approach to identifying fit-for-purpose data sources. The process for framework development is outlined in **Figure 1**.

## AI-Powered Data Source Recommendations

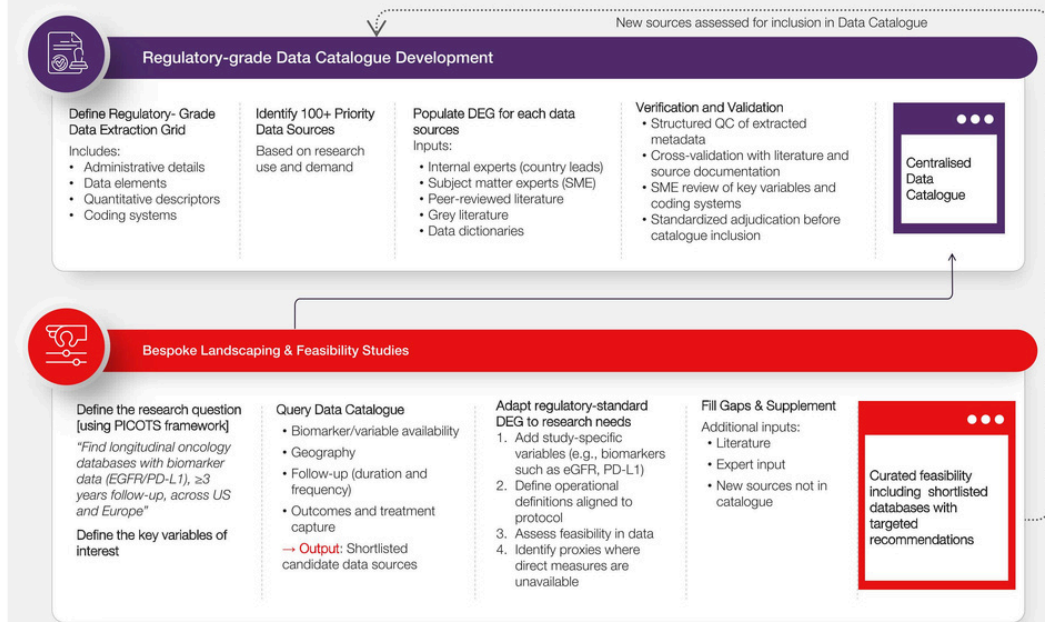
- An AI agent-based interface is under development to interpret study requirements in line with ISPOR-ISPE good practice for real-world data studies, align them with catalogue metadata, and generate standardized, transparent recommendations for data source suitability. The AI does not generate knowledge; it operationalizes expert-curated metadata.

- The planned front-end interface will allow non expert users to enter study requirements in free-text form, which are then cross checked against catalogued metadata to present data recommendations to the user. A prototype is illustrated in **Figure 2**.
- While this approach shows clear potential, development and early prototyping identified several practical challenges around standardization, accounting for complex study designs and data heterogeneity, usability, and automation.
- These findings are directly informing refinement of the metadata catalogue and highlighting where additional standardization and training data are needed to improve performance.

## Conclusions

- A harmonized metadata foundation combined with an AI-driven interface provides a scalable approach to operationalizing ISPOR principles for data source selection supporting greater transparency, reproducibility, and confidence in real-world evidence studies.
- As the field continues to evolve, high-quality background data remain critical. The model will improve with further refinement and expanded data, but human expertise remains essential to guide interpretation and appropriate use.
- Ongoing work focuses on improving classification of complex data sources, expanding catalogue coverage, and evaluating the impact of AI-assisted feasibility assessments on study planning efficiency and decision quality.

Figure 1. Framework for Systematic Data Catalogue Development and Bespoke Landscaping



Abbreviations: DEG = data extraction grid; EGFR = epidermal growth factor receptor; HRD = homologous recombination deficiency; PD-L1 = programmed death ligand 1; PICOTS = population, intervention, comparator, outcome, time, and setting; rwpfs = real-world progression free survival; QC = quality control; SME = subject matter expert.

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## Disclosures

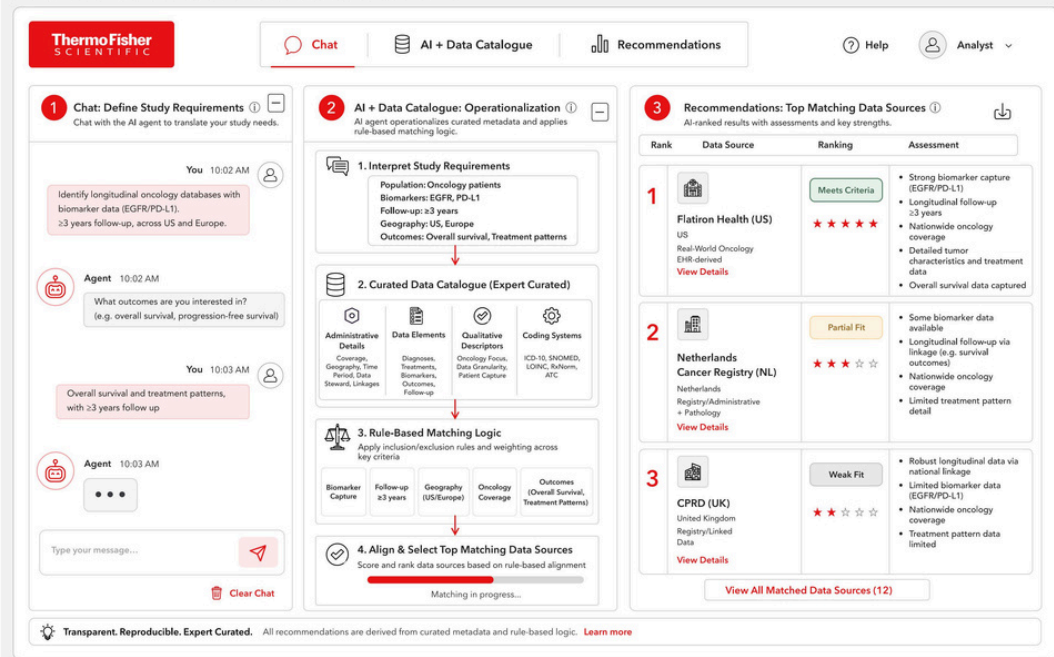
The authors are employees of PPD™ Evidera™ Real-World Data & Scientific Solutions, Thermo Fisher Scientific, and report no other relevant financial relationships.

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Figure 2. AI Agent-Enabled Study Recommendations



Abbreviations: AI = artificial intelligence; ATC = Anatomical Therapeutic Chemical; CPDR = Clinical Practice Research Datalink; EGFR = epidermal growth factor receptor; ICD-10 = International Classification of Diseases, 10th Revision; LOINC = Logical Observation Identifiers, Names, and Codes; NL = Netherlands; PD-L1 = programmed death ligand 1; SNOMED CT = Systematized Nomenclature of Medicine—Clinical Terms.

# Development and Implementation of a Dynamic Framework for Assessment and Improvement of Registries' Data Quality

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## Background

- According to the EMA Guideline on registry-based studies<sup>1</sup>, quality management should be continuous and regularly assessed throughout the registry's lifetime. Uncertainties in data quality can undermine confidence in the evidence generated. The EMA data quality framework<sup>1</sup> provides guidelines for ensuring data quality for regulatory decision-making, applicable to any data source. A current long-term study using multiple SMA registries offers an ideal opportunity to adopt EMA guidance, which can be applied to registries in other therapeutic areas.

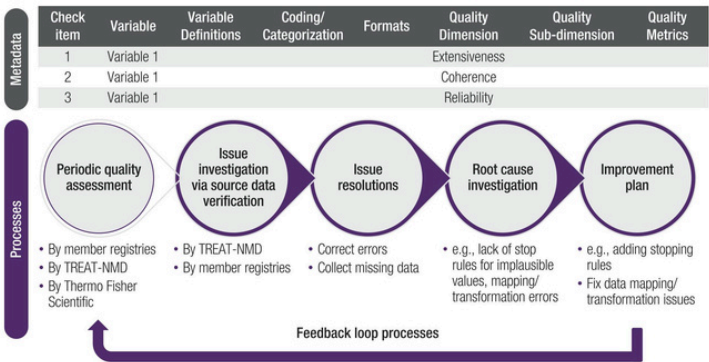
## Objectives

- To develop a dynamic framework for assessing and improving registry data reliability, extensiveness, and coherence and to implement it across six TREAT-NMD registries (BNMDR [Belgium], Neuromuscular Disease Registries in Bulgaria, Georgia, and Latvia, ReaDy [Czechia] and Ukrainian SMA Registry) to support a study in SMA.

## Methods

- A data quality framework and improvement process (DQF&IP) was developed based on EMA guidance and Findable, Accessible, Interoperable, and Reusable (FAIR<sup>2,3</sup>) principles, and implemented across registries taking part in an ongoing study. This framework includes different data-quality dimensions and subdimensions, as well as their characterization and related metrics to make reliable assessments.
- The DQF&IP (Figure 1) is composed of metadata (variable definitions, coding, formats, dimensions, quality metrics) and processes, which include periodic quality assessment, issue investigation, root-cause analysis, and improvement planning, which is implemented iteratively in a continuous feedback loop.

Figure 1. Data quality framework and improvement process



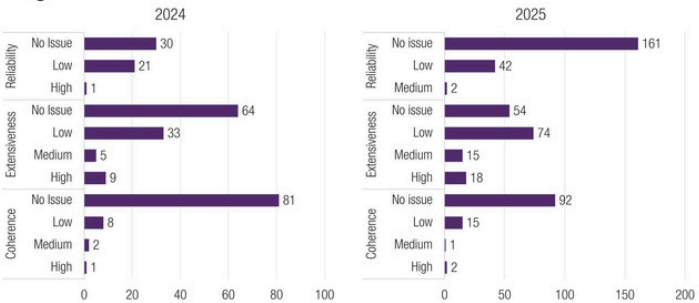
Note: TREAT-NMD provided the data for the study, and Thermo Fisher Scientific conducted the analysis.

- Variables included in the metadata were checked for quality across three dimensions: extensiveness, coherence, and reliability, along with subdimensions such as completeness, conformance (format coherence and structural coherence), plausibility, and uniqueness. Key performance indicators were implemented, including thresholds for missingness proportions and implausible values (e.g., age, weight, height, maximum scores, etc.). Data quality was assessed periodically by TREAT-NMD and Thermo Fisher Scientific, and investigated by the member registries using the DQF at two different time points (2024 and 2025). Queries were categorized into "no issue", "low" (<25%), "medium" (<50%), and "high" (>50%) categories based on the proportions of issues identified. Findings from the periodic quality assessment triggered issue investigations via source data verification, root cause investigation, and improvement planning.

## Results

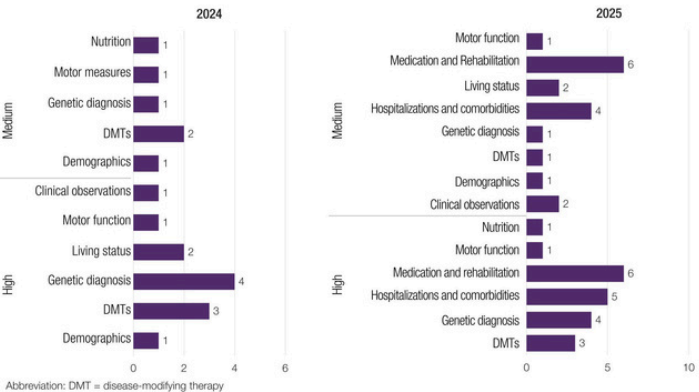
- Data from approximately 400 patients across six TREAT-NMD registries were assessed. In the 2024 data cut, the metadata included 255 unique check items across 96 unique variables and three dimensions (coherence: 36.1%, extensiveness: 43.5%, reliability: 20.4%). In 2025, the list of unique check items was expanded, the metadata increased to 476 check items across 153 unique variables and three dimensions (coherence: 23.1%, extensiveness: 33.8%, reliability: 43.1%).
- Across both 2024 and 2025, most cases fell into the "no issue" category (Figure 2). When errors occurred, they were mostly categorized as "low", with few cases classified as "medium" or "high". In the reliability dimension, most cases reported no issues. The extensiveness dimension showed relatively more spread across categories. While "no issue" remained common, there were noticeable "low" and "medium" cases, and even some "high" cases, specifically in 2025. For coherence, most cases were recorded as "no issue," with very few "low", "medium", or "high" cases. High frequencies were mostly related to missingness.

Figure 2. Distribution and number of unique data checks by dimensions and issue categorization



- In the TREAT-NMD case report form (CRF), items are organized into modules. Among the "medium" category in 2024, the most common queries related to the DMTs module, while the "high" category had the highest frequency of queries in the genetic diagnosis module (Figure 3). In 2025, medication and rehabilitation had the highest frequency in both the "medium" and "high" categories.

Figure 3. Distribution of data quality issues by group of variables



- Among the queries identified over the last few years, Table 1 below provides insight into the top key issues, their root causes, and the improvement plans that have been discussed or are currently being discussed.

Table 1. Key issues, root causes, and improvement plans for identified queries

| Key Issue                                                                                                                       | Root Cause                                                                                                                                                             | Improvement Plan                                                                                                            |
|---------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| The variable "motor ability observed in clinic" appeared missing for a three registries, raising concern about outcome validity | Two registries only report results for those observed in clinic; one indicated that all information from a certain period should be marked as being observed in clinic | Ongoing discussions with the registries with the aim to update the dataset to ensure completeness and avoid future flagging |
| Conflicting information between "status" variables (e.g., current ventilation) and date/episode variables (start and end date)  | Delay in updating status variable despite start/end dates being recorded                                                                                               | Where possible, registries will update the "status" variable at the same time when recording dates                          |
| Absence of timely updates for variables that require regular updating                                                           | Ongoing status (e.g., symptomatic status) and dates not consistently recorded unless there is a change; registries typically update only when changes occur            | Where possible, registries to record information even if the status hasn't changed                                          |

## Limitations

- The missingness examined as part of the quality-control process was based on the absence of expected information indicated by other variables. It was not possible to determine if the entire entry was missing (e.g., a treatment was given, however, neither the treatment name nor date was recorded).
- Additionally, while beneficial, the registry may retrospectively update data previously entered, including between data cuts. Consequently, data-quality issues that were not present in one data cut may be newly introduced and identified in subsequent data cuts.
- Most registries map their data to the TREAT-NMD conceptual disease model. While developing the DQF&IP, it was observed that this mapping process removed the dependence between variables, making it challenging to quantify true missingness.

## Conclusions

- The prospective data collection in clinical registries allows for adaptability and quality improvement throughout the data lifecycle. Our study's DQF&IP highlights the importance of having a clear and dynamic framework to continuously assess and enhance the quality of registry data. This supports research sustainability and benefits the patient community. Additionally, this flexible framework can be adapted to registry data for other indications.

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## Acknowledgments

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## Medicines & Healthcare products Regulatory Agency

### INTRODUCTION

#### Background

Primary care electronic health records, such as CPRD Aurum, capture prescribed medications but do not confirm whether these medicines are dispensed, limiting accurate assessment of medication exposure in real-world evidence (RWE) studies.

The NHS Business Services Authority (NHSBSA) Medicines Dispensed in Primary Care dataset contains item-level records of dispensed medicines in England.

Linking these data to CPRD Aurum primary care records enables more complete characterisation of medication use across the prescribing–dispensing pathway.

#### Objectives

To describe the completeness, coverage, and key characteristics of the newly linked NHSBSA dispensing data within CPRD Aurum and its utility for real-world evidence generation.

### METHODS

#### Study period

1 April 2018 to 1 April 2024

#### Descriptive characterisation assessed:

- Structural completeness of key identifiers
- Completeness of medication coding (BNF, dm+d)
- Demographic distributions (age, sex)
- Exemption status
- Annual dispensing patterns over time

### RESULTS



**~28.1  
million**  
CPRD Aurum  
patients linked  
to NHSBSA data



**1491**  
contributing  
practices



**3.22  
billion**  
dispensed items

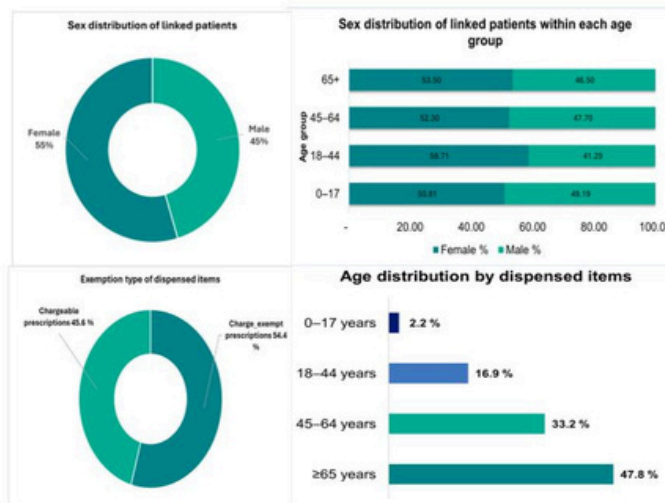


**~100%**  
complete medication  
coding (BNF/dm+d)

## Enabling Real-World Evidence Through Linkage of National Health Service Business Services Authority (NHSBSA) Dispensing in England to the Clinical Practice Research Datalink (CPRD) primary care data

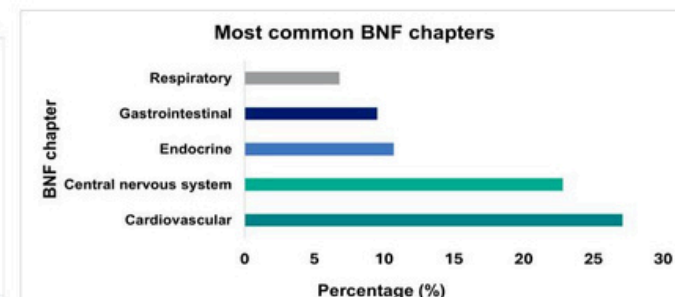
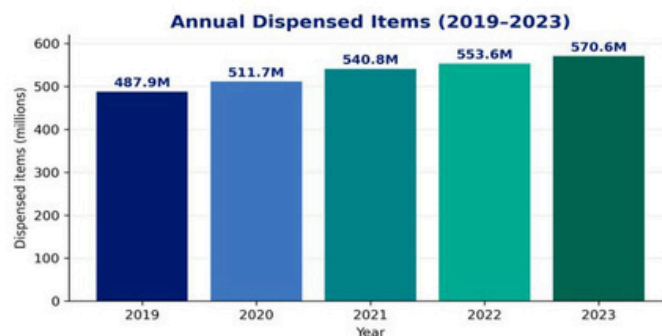
Zainab Khalaf, Justin Chan, Jennifer Campbell, Susan Hodgson

Medicines and Healthcare products Regulatory Agency, CPRD data services, Canary Wharf, London E14 4PU, UK (MHRA)



#### Key takeaway

- Females accounted for ~55 % of linked patients.
- Patients aged  $\geq 65$  years accounted for the largest proportion of the dispensed items (48%).
- 54.4% of dispensed items were issued under prescription charge exemption.
- Annual dispensing increased steadily from 487.9 million items in 2019 to 570.6 million items in 2023.
- Cardiovascular medicines were the most frequently dispensed category.



### CONCLUSIONS

- The CPRD Aurum NHSBSA linkage provides a large-scale resource of dispensed medicines, enabling confirmation of medication exposure beyond prescribing records alone.
- The linked dataset demonstrates excellent coverage and coding completeness, containing 3.22 billion dispensed items from 28.1 million patients across 1,491 practices.
- Dispensing was concentrated among older adults, with patients aged  $\geq 65$  years accounting for the largest proportion of dispensed items, while cardiovascular and central nervous system medicines were the most frequently dispensed therapeutic categories.
- This resource enhances opportunities for real-world evidence generation, supporting research on medication utilisation, adherence, effectiveness, safety, and healthcare policy.

### ACKNOWLEDGEMENTS

We acknowledge the contribution of Rhys Barnett and the CPRD Health Data Services team in processing and delivering the linked NHSBSA Dispensing data.

This study is based on data from the Clinical Practice Research Datalink (CPRD); the data is provided by patients and collected by the NHS as part of their care and support. BSA Dispensing Data are subject to Crown copyright (2026), reused with the permission of The Health and Social Care Information Centre, all

# Context-aware Generative AI for Evidence Generation, Analog-driven Enrollment Forecasting, and Operational Risk Management in Oncology Trials

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## Background

- Clinical trial feasibility planning depends on identifying historical trials with similar design and patient populations ("analogs").<sup>1</sup>
- Traditional analog selection is often manual, subjective, and difficult to scale, which can reduce reproducibility and consistency in feasibility assessments.<sup>2</sup>
- Public resources such as ClinicalTrials.gov contain rich trial information, but much of it is unstructured and not readily comparable across studies.<sup>1</sup>
- Advances in natural language processing and machine learning enable transformation of unstructured clinical trial text into standardized, structured features for systematic comparison.<sup>3,4</sup>
- Recent large language model approaches further demonstrate the value of artificial intelligence (AI) for extracting and matching clinical trial information from complex free text.<sup>5</sup>
- There remains a need for context-aware, reproducible frameworks that translate trial similarity into quantitative enrollment benchmarks and operational insights.<sup>2,6</sup>

## Objectives

- Develop a context-aware GenAI workflow to identify oncology trials with matched study designs
- Extract enrollment performance and operational difficulty signals
- Generate explainable recommendations for enrollment rates in planned trials
- Establish a scalable pipeline to support future machine learning applications

## Methods

### Data and Study Selection

- Completed interventional oncology trials were identified from a structured clinical trial dataset. Key study attributes included trial phase, design, eligibility criteria, enrollment, and geographic footprint. Enrollment performance was quantified as patients per site per month (PPSM).

### GenAI-based Trial Characterization

- A context-aware generative AI model was used to extract standardized features from unstructured trial text, including study title, conditions, interventions, and summaries. Each trial was represented as a structured "trial fingerprint," capturing key clinical and operational attributes such as indication, stage/line, biomarker requirements, comparator class, eligibility complexity, trial burden, and geographic footprint (Table 1).

Table 1. Trial Features Used for Similarity Assessment

| Feature                | Description                                |
|------------------------|--------------------------------------------|
| Indication             | Extracted disease category from trial text |
| Stage/Line             | Disease stage (early, metastatic, etc.)    |
| Phase                  | Clinical trial phase                       |
| Biomarker Required     | Whether enrollment requires biomarker      |
| Comparator Class       | Trial design comparator type               |
| Trial Burden           | Intensity of procedures and visits         |
| Eligibility Complexity | Restrictiveness of inclusion criteria      |
| Geographic Footprint   | Distribution of trial sites                |

### Similarity and Analog Identification

- Trial fingerprints were converted into vector representations and compared using embedding-based similarity. Candidate analog trials were restricted to those with matching trial phase and stage/line, ensuring clinical comparability (Figure 1 and Figure 2).
- Similarity scores were further refined using rule-based adjustments for exact matches on key attributes, and top-ranked analog trials were selected for each target study.

### Enrollment Benchmarking

- Enrollment rates from selected analog trials were summarized using median, interquartile range, minimum and maximum values, and similarity-weighted mean PPSM. These metrics were used to generate data-driven enrollment expectations.

## Methods (continued)

Figure 1. Analog Identification and Enrollment Benchmarking Framework

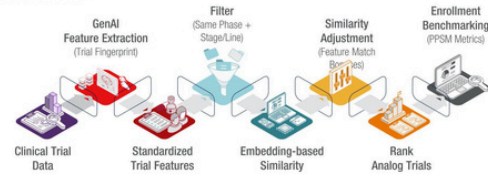
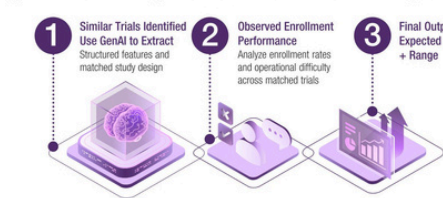


Figure 2. How Analog Trials Can Inform Enrollment Expectations



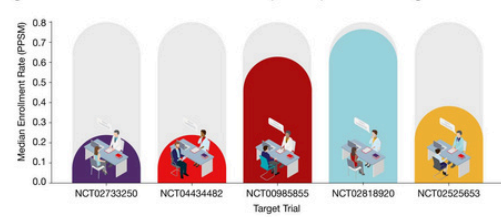
### Explainability and Study Design

- The framework generated qualitative insights describing factors expected to influence enrollment performance, including biomarker requirements, eligibility complexity, comparator design, and trial burden.
- Five completed oncology trials were treated as target studies, each matched to up to 10 analog trials.

## Results

- Across five target oncology trials, the framework identified clinically relevant analog cohorts and generated enrollment benchmarks based on analog trial performance. Each target trial was matched to 4 to 10 analog trials, with analogs aligned on key design features including phase, stage/line, and indication.
- Median enrollment rates ranged from 0.24 to 0.77 PPSM, while similarity-weighted mean enrollment rates ranged from 0.34 to 0.75 PPSM (Figure 3). Across targets, enrollment performance varied substantially, indicating that even clinically similar trials can have meaningfully different recruitment patterns.

Figure 3. Median Enrollment Rates (PPSM) Across Target Trials



Abbreviation: PPSM = patients per site per month

- Enrollment benchmarks derived from analog trials showed meaningful variation across clinical settings.
- Median PPSM ranged from 0.24 to 0.77; weighted mean PPSM ranged from 0.34 to 0.75.

## Results (continued)

- The overall enrollment range across analogs is 0.03 to 2.93 PPSM.
- These findings indicate that even among clinically similar trials, enrollment performance can vary substantially, highlighting the importance of capturing both central tendency and variability.

### Cross-target Comparison of Enrollment Performance

- Clear differences in expected enrollment were observed across trial settings:
  - Neoadjuvant non-small cell lung cancer (NSCLC) (NCT02818920) demonstrated the highest enrollment performance, with a median PPSM of 0.77 and a weighted mean of 0.75, suggesting favorable recruitment conditions in earlier-stage disease settings.
  - Locally advanced lung cancer (NCT00985855) showed moderate enrollment performance, with a median PPSM of 0.63, reflecting a balance between clinical complexity and patient availability.
  - Metastatic NSCLC and small cell lung cancer targets (NCT02733250 and NCT04434482) demonstrated the lowest enrollment rates, both with a median PPSM of 0.24, suggesting greater recruitment challenges in advanced disease settings.
- These results highlight that trial context (stage/line and disease setting) is a key determinant of enrollment performance.

### Variability in Analog Trial Performance

- Despite high similarity between target and analog trials, substantial variability in enrollment performance was observed within analog cohorts. The most notable example was NCT02525653 (metastatic lung cancer); median PPSM was 0.38, and the interquartile range was 0.09 to 0.99 (Table 3).
- The full range was 0.03 to 2.93, and the weighted mean was 0.69. This represents nearly a 100-fold difference between the lowest and highest performing analog trials, even within a highly similar cohort.
- This finding reinforces that single-trial comparisons are insufficient. Distribution-based benchmarking is necessary for realistic planning.

### Role of Similarity Weighting

- Similarity-weighted mean PPSM values were generally higher than median PPSM across targets, indicating that closer-matching analog trials tend to exhibit stronger enrollment performance.
- For example:
  - NCT02525653: median 0.38 versus weighted mean 0.69
  - NCT02733250: median 0.24 versus weighted mean 0.34
- This demonstrates that similarity weighting helps prioritize more relevant analog evidence, improving the interpretability of enrollment estimates.

### Operational Insights and Explainability

- In addition to quantitative benchmarks, the framework generated qualitative insights explaining observed enrollment patterns (Table 4):
  - High procedure burden and restrictive eligibility criteria were associated with reduced enrollment or increased variability.
  - Comparator design (e.g., active control or standard-of-care arms) influenced patient willingness to participate.
  - Randomized designs introduced additional recruitment challenges in certain settings.
  - Targets without major complexity signals demonstrated more stable enrollment performance, suggesting that operational simplicity contributes to improved recruitment outcomes.

Table 3. Summary of Enrollment Performance (PPSM) Across Target Trials Based on Matched Analog Cohorts

| Target Trial | Indication   | Stage/Line       | Phase     | N Analogs | Median PPSM | Q1-Q3 PPSM | Min-Max PPSM | Weighted Mean PPSM | Key Insight                   |
|--------------|--------------|------------------|-----------|-----------|-------------|------------|--------------|--------------------|-------------------------------|
| NCT02733250  | NSCLC        | metastatic       | Phase 1/2 | 8         | 0.24        | 0.16-0.54  | 0.06-0.76    | 0.34               | Stable, moderate variability  |
| NCT04434482  | SCLC         | metastatic       | Phase 1/2 | 8         | 0.24        | 0.17-0.54  | 0.13-0.76    | 0.35               | Higher procedure burden       |
| NCT00985855  | Lung (other) | locally advanced | Phase 2   | 5         | 0.63        | 0.18-0.90  | 0.15-1.07    | 0.59               | Comparator + burden effects   |
| NCT02818920  | NSCLC        | neoadjuvant      | Phase 2   | 4         | 0.77        | 0.54-0.97  | 0.36-1.10    | 0.75               | Favorable recruitment setting |
| NCT02525653  | Lung (other) | metastatic       | Phase 2   | 10        | 0.38        | 0.09-0.99  | 0.03-2.93    | 0.69               | High variability              |

Abbreviations: NSCLC = non-small cell lung cancer; PPSM = patients per site per month; SCLC = small-cell lung cancer

Table 4. Factors Associated With Enrollment Performance

|                     | Observed In                  | Key factors                                                                                                                          |
|---------------------|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Lower Enrollment    | Metastatic NSCLC and SCLC    | • High procedure/visit burden<br>• Complex eligibility criteria<br>• Comparator design (active control)<br>• Randomized study design |
| Moderate Enrollment | Locally advanced lung cancer | • Balanced clinical complexity<br>• Moderate operational burden<br>• Mixed enrollment constraints                                    |
| Higher Enrollment   | Neoadjuvant NSCLC            | • Earlier-stage disease setting<br>• Lower operational complexity<br>• Fewer enrollment constraints                                  |

Abbreviations: NSCLC = non-small cell lung cancer; SCLC = small-cell lung cancer

## Strengths and Limitations

- This study demonstrates a context-aware framework that integrates generative AI with structured trial data to identify clinically relevant analog trials and generate enrollment benchmarks. The approach enables transformation of unstructured trial text into standardized, interpretable features, supporting consistent comparison across studies. By combining similarity-based ranking with distribution-based enrollment metrics, the framework provides both realistic expectations and insight into variability, while maintaining transparency through explainable feature contributions.
- However, several limitations should be considered. The demonstration is based on a limited number of target trials and may not capture the full range of variability across oncology studies. The accuracy of extracted features depends on the completeness and quality of source trial descriptions, and similarity adjustments rely on predefined rules rather than learned optimization. Additionally, substantial variability in enrollment performance persists even among highly similar trials, reflecting unmeasured operational and real-world factors not fully captured by the current framework.

## Conclusions

- This study demonstrates that a context-aware GenAI framework can systematically identify clinically relevant analog trials and generate data-driven enrollment benchmarks for clinical trial planning.
- By combining similarity-based analog selection with distribution-based performance metrics, the approach provides both an expected enrollment rate and a realistic range of outcomes, addressing limitations of single-trial comparisons.
- The integration of quantitative outputs with qualitative explanations enhances interpretability and supports more informed feasibility decision-making.
- With further scaling, this framework has the potential to enable large-scale evidence generation and machine learning-based prediction of clinical trial performance.

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### Disclosures

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# From Trials to Routine Care: Evaluating CPMS Identifier Recording in UK Primary Care EHRs

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## INTRODUCTION

Longitudinal electronic health records (EHRs) are used to support healthcare decision making. Clinical Practice Research Datalink (CPRD) contains UK-wide coded, pseudonymised primary care EHRs and currently supports two clinical trials with recruitment and safety monitoring. One challenge is identifying RCT participation and linking trial cohorts to routine care for post-trial follow up. In UK primary care, SNOMED codes capture research activity, while the Central Portfolio Management System, a national portfolio recruitment system, assigns unique portfolio study identifiers (CPMS IDs). If CPMS IDs are reliably recorded in routine care, alongside trial participation codes, this could enable study specific linkage in CPRD and support follow up beyond trial end. We assessed the completeness of CPMS IDs recorded in CPRD for two studies with known enrolment.

**Objective:** To assess the completeness of CPMS ID recording in CPRD for two pragmatic trials with known enrolment.

## METHODS

We assessed recording of trial participation in CPRD data for two UK pragmatic trials: DaRe2THINK (cardiovascular) and Asymptomatic (respiratory).

Using the March 2026 Aurum build of CPRD data we extracted records with SNOMED codes indicating any trial activity (e.g. consent, invitation). We then identified records containing trial-specific CPMS IDs, and restricted analyses to codes corresponding to participation-related pathway milestones only (e.g. enrolment, follow-up). Observed counts were then compared with known enrolment totals for each trial.



## RESULTS

When examining overall representation of CPMS IDs in CPRD data, compared to the reference period of 2016- November 2025, CPRD CPMS IDs represented 32.8% of the 18,912 trials reported by the CPMS system.<sup>1</sup>

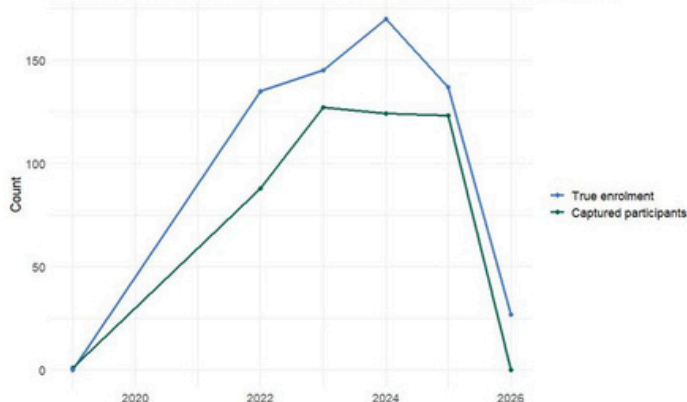
### Completeness of DaRe2THINK and Asymptomatic CPMS ID recording in CPRD Data

| Study        | Known enrolled | CPMS ID recorded | % completeness |
|--------------|----------------|------------------|----------------|
| Asymptomatic | 614            | 455              | 74%            |
| DaRe2THINK   | 1,313          | 813              | 62%            |

### Most frequent SNOMED Participation Events

|                                                          |      |
|----------------------------------------------------------|------|
| Participant in research study                            | 24%  |
| Patient entered into trial                               | 19%  |
| Consent given to participate in research study           | 18%  |
| Patient consented to clinical trial                      | 16%  |
| Referral for participation in clinical trial             | 6%   |
| Consent given to review medical record in research study | 5.5% |

Asymptomatic: Trends in Captured Participants vs True Enrolment

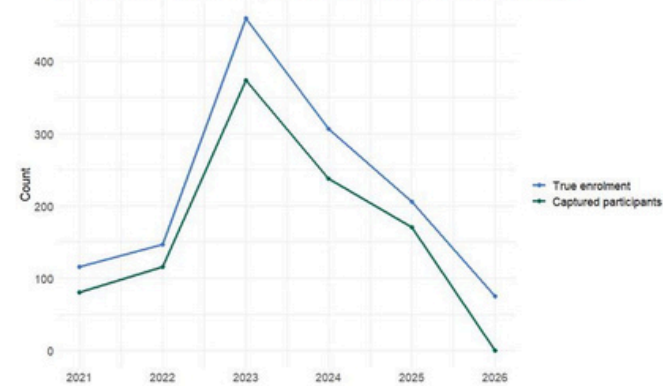


## CONCLUSIONS

Completeness of CPMS ID recording in CPRD primary care was variable across the studies examined. While study-level linkage and extended follow-up are feasible when CPMS IDs are available, overall sensitivity may be enhanced by jointly leveraging SNOMED codes alongside CPMS identifiers. The observed variability in recording is likely multifactorial. Differences in study teams and their operational practices may influence how consistently CPMS IDs are captured and entered into primary care records. In addition, variation in patient populations may play an important role: for example, studies involving more vulnerable populations may have closer clinical oversight and more diligent documentation in primary care, leading to higher completeness of recording. However, the use of CPMS identifiers and SNOMED codes for post-trial follow-up may also raise governance challenges, particularly around whether such identifiers can be routinely used for secondary follow-up beyond the original trial context, and how this aligns with consent, data access permissions, and regulatory approvals. Standardising CPMS recording practices across studies and settings could therefore strengthen the utility of EHR data for post-trial follow-up and improve the assessment of longer-term safety outcomes.

<sup>1</sup> (UK Clinical Research Delivery key performance indicators: data to November 2025 (data tables))

DaRe2Think: Trends in Captured Participants vs True Enrolment



# Unmet Needs and Disease Burden: Perspectives from Adults with Psoriasis and Clinicians Treating Psoriasis in the US

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## Synopsis

- Psoriasis (PsO) affects approximately eight million people in the US and more than 125 million people worldwide.<sup>1,2</sup>
- Understanding patient and healthcare provider (HCP) perspectives is critical to optimize PsO care.
- This analysis represents the US dataset from the global ENCOMPASS study conducted across 11 countries, to evaluate clinical profiles, disease burden, treatment preferences and goals, and the impact of PsO on patient quality of life (QoL).

## Objectives

- To characterize the treatment experiences of US HCPs and adult patients who are candidates for systemic therapy, with the goal of informing patient-centered treatment strategies and disease management approaches.
- To quantify unmet needs and current treatment preferences in the US.

## Results

Figure 1. Sociodemographic Data for Patients and HCPs

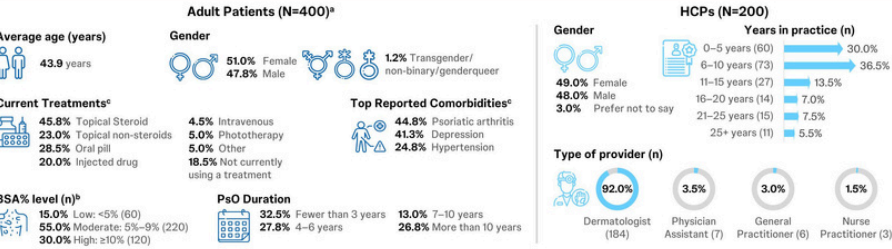


Figure 2. Adult Patient Top Reported Body Areas<sup>a</sup> and Level of Being Bothered by PsO Location

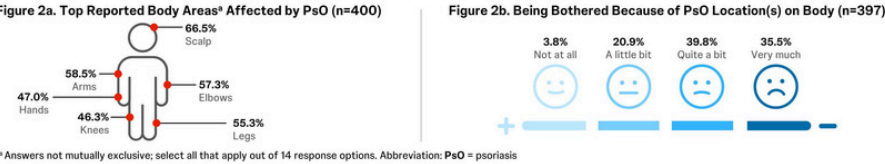
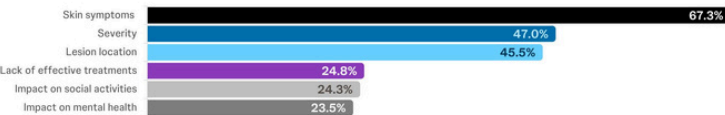


Figure 3. Adult Patient Reported Top PsO Symptoms<sup>a</sup> and Itch-related Impacts during the Past Month



Figure 4. Most Important Factors Contributing to Disease Burden for Adult Patients (n=400)<sup>a</sup>



## Methods

- A web-based US survey (ENCOMPASS) conducted between March and May 2025 among the following groups:
  - Patients:** US adult patients (≥18 years old) with a diagnosis of PsO eligible for systemic therapy, as defined by one or more of the following three categories specified in the International Psoriasis Council guidelines:
    - PsO lesions on ≥10% of body surface area (BSA)
    - PsO lesions on high-impact sites of the body, e.g., hands/feet, face, genitals, scalp, or nails
    - Topical therapy that failed to control PsO symptoms
  - HCPs:** US dermatologists and advanced practice providers working in dermatology practices, who dedicated at least 50% of their practice to medical dermatology, and treated PsO cases in the past year.
- The Dermatology Life Quality Index (DLQI) was included only for adults to measure the impact of PsO on their QoL.
- This was a sequential, mixed-methods, non-interventional study employing quantitative surveys and qualitative interviews, with a purposive and quota-based sampling strategy to ensure robust representation of targeted adult PsO patients.

## Conclusions

- ✓ PsO burden extends beyond skin. Itch, sleep disruption, concentration difficulties, and high DLQI scores highlight the profound quality of life impact from PsO, which is compounded by comorbidities such as psoriatic arthritis and depression.
- ✓ Patients prioritize clear skin, itch relief, and long-term control for treatment goals, while HCPs emphasize effectiveness of treatment, potential side effects, and long-term safety.
- ✓ Patients and HCPs prefer oral therapies, and >90% of patients currently on injectables would be willing to switch to a safe and equally effective oral treatment, pointing to an unmet need.

Figure 5. Overall Treatment Preference: Patients and HCPs<sup>a</sup>

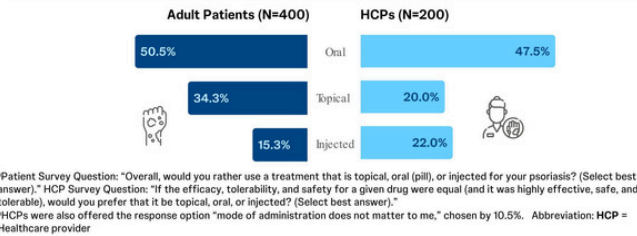


Figure 7. HCP Top Three Factors for Consideration When Selecting Treatment for Adult Patients (n=200)<sup>a</sup>

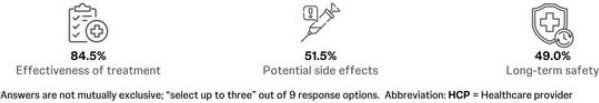


Figure 9. HCP-reported Top Three Concerns Regarding Injectables (n=200)<sup>a</sup>

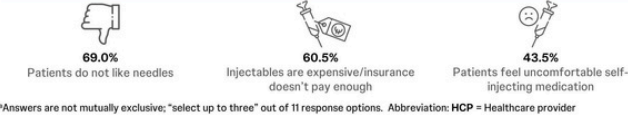


Figure 11. Adult Patient-reported Key Reasons<sup>a</sup> for Discontinuing Past Treatment: Injectables vs. Oral<sup>b</sup>



## Limitations

- A purposive, and quota-based sampling strategy was used to ensure adequate representation of adult patients with significant BSA involvement (BSA>5%). Therefore, the findings may not reflect the experiences of the broader US PsO populations, especially adolescents or individuals with mild BSA involvement.
- This poster included only participants from the US; treatment experiences and unmet needs may differ among adult patients and HCPs in other countries.

# EMA's shift Toward Target Trial and Estimand Frameworks in Regulatory-Grade Real World Evidence

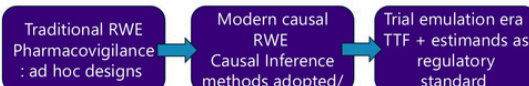
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## BACKGROUND

Regulatory use of real-world evidence (RWE) has historically been fragmented, primarily focused on pharmacovigilance, and methodologically inconsistent. Growing demand for decision-grade observational evidence is driving a paradigm shift at the European Medicines Agency (EMA).

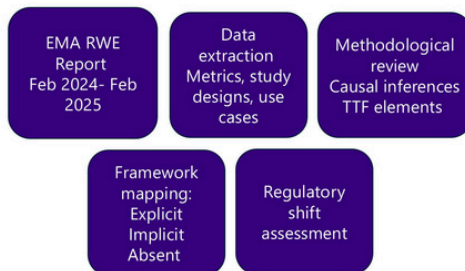
The EMA is now transitioning toward structured, reproducible, causal inference-driven RWE, operationalised through the target trial framework (TTF) and the estimands framework, via the TARGET-EU and DARWIN EU initiatives.



## OBJECTIVE & METHODS

To examine the EMA's evolving approach to RWE and assess the emerging role of the TTF and estimand frameworks as standards for regulatory-grade observational studies.

**Data sources:** EMA's 3rd Annual RWE Experience Report (February 2024–February 2025); DARWIN EU network portfolio; TARGET-EU initiative documentation.



| Assessment domain | What we examined                    |
|-------------------|-------------------------------------|
| Study scale       | Volume of regulator-led RWE studies |
| Efficiency        | Median study completion timelines   |
| Feasibility       | Feasibility study success rate      |
| Use cases         | Regulatory application contexts     |
| TTF adoption      | Target trial components per study   |
| Estimand use      | Explicit estimand specification     |

TTF assessment used AI-assisted extraction validated by primary reviewer. The reviewer then classified studies as explicit (direct TTF reference), implicit/partial (key components present without explicit reference), or not aligned.

## RWE APPLIED ACROSS REGULATORY CONTEXTS

**Marketing authorisation**  
RWE supporting MAA submissions

**HTA joint assessment**  
EU Reg. 2021/2282 evaluations

**Public health policy**  
Pandemic preparedness; medicines shortages

**Pharmacovigilance**  
Safety signal investigation (continuing)

## TTF ASSESSMENT ACROSS STUDIES IN 3RD REPORT

| Study Type      | Explicit | Implicit/partial | None | Total |
|-----------------|----------|------------------|------|-------|
| Comparative     | 2        | 3                | 0    | 5     |
| Non-comparative | 0        | 4                | 18   | 22    |
| Total           | 2        | 6                | 19   | 27    |

There are 31 studies in the EMA report, but 4 have not yet been published; therefore, we included 27 studies.

6/27 studies show implicit TTF alignment – 2 are comparative studies, and 4 are non-comparative studies.

## SUMMARY OF TTF ALIGNMENT IN 3RD REPORT STUDIES

| Study           | Topic                                                                                                  | TTF      |
|-----------------|--------------------------------------------------------------------------------------------------------|----------|
| EUPAS1000000481 | Brand-specific influenza vaccine effectiveness in the Nordic countries                                 | Explicit |
| EUPAS1000000539 | Comparative effectiveness and safety studies using the target trial emulation and estimand frameworks* | Explicit |
| EUPAS1000000351 | Incidence of myoclonus in heart failure: sacubitril/valsartan vs other treatments                      | Implicit |
| EUPAS1000000443 | Association of VTE with NSAID use in women 15–49 years using hormonal contraceptives                   | None     |
| EUPAS1000000599 | Eye disorders in women with breast cancer treated with anastrozole, letrozole or tamoxifen             | None     |

\*An additional 10 Target-EU studies are planned under the EMA 3rd Annual RWE Report and are expected to be published in due course, reflecting ongoing development of target trial framework applications.

## METHODOLOGICAL SHIFT

### TRADITIONAL APPROACH

- Retrospective comparisons
- Ad hoc matching strategies
- Passive RWE acceptance
- No pre-specification required
- Pharmacovigilance-centric

### EMA EMERGING STANDARD

- Target trial defined upfront
- RCT infeasibility justified
- Estimands pre-specified
- Time-zero + exposure aligned
- Protocol pre-registered

## EMA's TTF REQUIREMENTS

The TARGET-EU initiative signals a shift from voluntary best practice to active methodological standard-setting. EMA now requires sponsor to address:

- ✓ Target trial definition
- ✓ Exposure definition
- ✓ RCT infeasibility
- ✓ Eligibility criteria
- ✓ Estimand specification
- ✓ Protocol pre-registration
- ✓ Time zero alignment

## CONCLUSIONS

- 1 TTF and estimand framework are **transitioning from methodological options to regulatory expectations** for decision-grade RWE at EMA
- 2 DARWIN EU is enabling scalable RWE, but TTF formal adoption remains nascent which may be due to how feasibility is assessed
- 3 TTF alignment currently occurs only in comparative studies; no non-comparative study demonstrated TTF components

## CAPABILITY REQUIREMENTS

### CAUSAL INFERENCE EXPERTISE

Investment in trial emulation methodology and biostatisticians experienced in TTF

### DATA PARTNERSHIPS

Longitudinal, linkable, federated data compatible with DARWIN EU standards

### PRE-SPECIFICATION GOVERNANCE

Processes to commit design decisions before data access-not retrospectively

### PROACTIVE REGULATORY ENGAGEMENT

Frame observational evidence within trial paradigms at pre-submission stage

### Bottom line

EMA's 3rd Annual RWE Report signals an emerging shift toward structured, causal inference-driven evidence standards. TTF and estimand frameworks are gaining traction in comparative studies, yet formal adoption remains limited, suggesting that regulatory expectations are directionally clear but not yet uniformly operationalised across the EMA RWE portfolio.

The earlier version of this work was presented at ISPOR US 2026