
# Generating High Quality Real-World Evidence for Regulatory Decision Making in Europe

HEOR THEATER

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# Relevant financial disclosures



- Nothing to disclose.

"For evidence-based decision making, there is a need for a good understanding of the quality of the data that underpins these decisions, which translates into a need for a European Data Quality Framework."

**—Emer Cooke, EMA Executive Director**

# Considerations



## Coverage & Representativeness

- Measures the amount of information available referring to the data accessibility:
  - what exists in the real world?
  - is it inside the capture process?
  - is it in the data format ?
- Cannot be easily measured, as the total information may not be definable or accessible.
- Example: Whether a set of individuals present in a dataset is representative of a population under study.

## Completeness

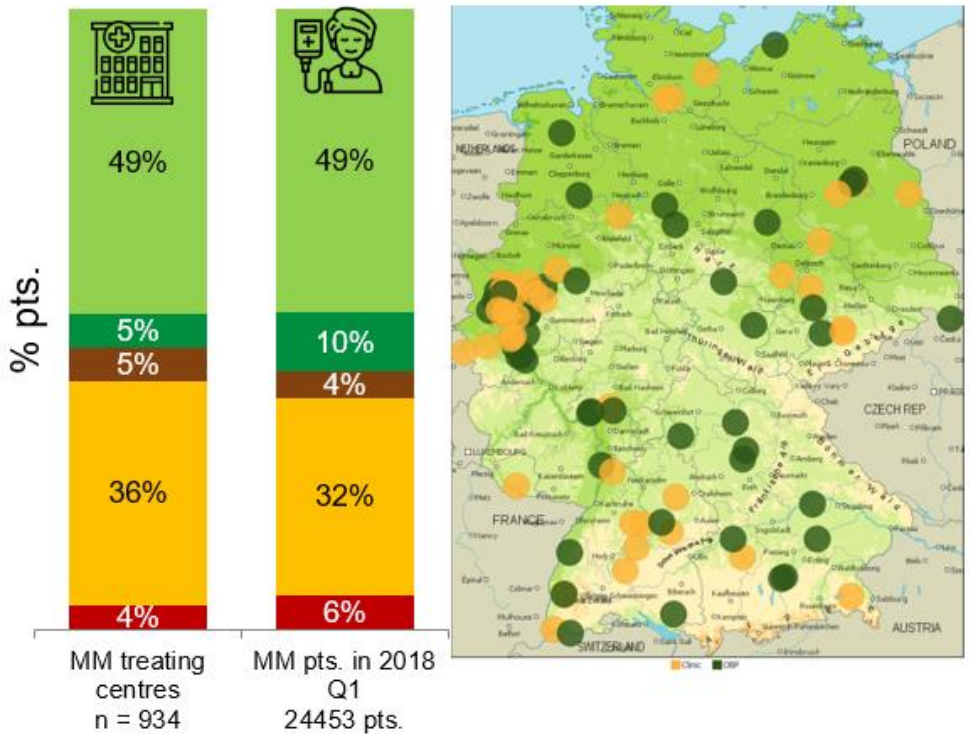
- Measures the  amount of information available referring to the data quality:
  - total information given the data capture process
  - Structure of the data
  - data format (!)
- Data unavailable in the dataset are called “missing”.
- Example: Cytogenetic testing rate in Multiple Myeloma (clinical reality) versus RWD requirements

European Medicines Agency, Heads of Medicines Agencies; Data Analytics and Methods Task Force, *Data Quality Framework for EU medicines regulation”, Draft, 30-Sep-2022,* **https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/data-quality-framework-eu-medicines-regulation_en.pdf**

# Considerations



## Coverage & Representativeness

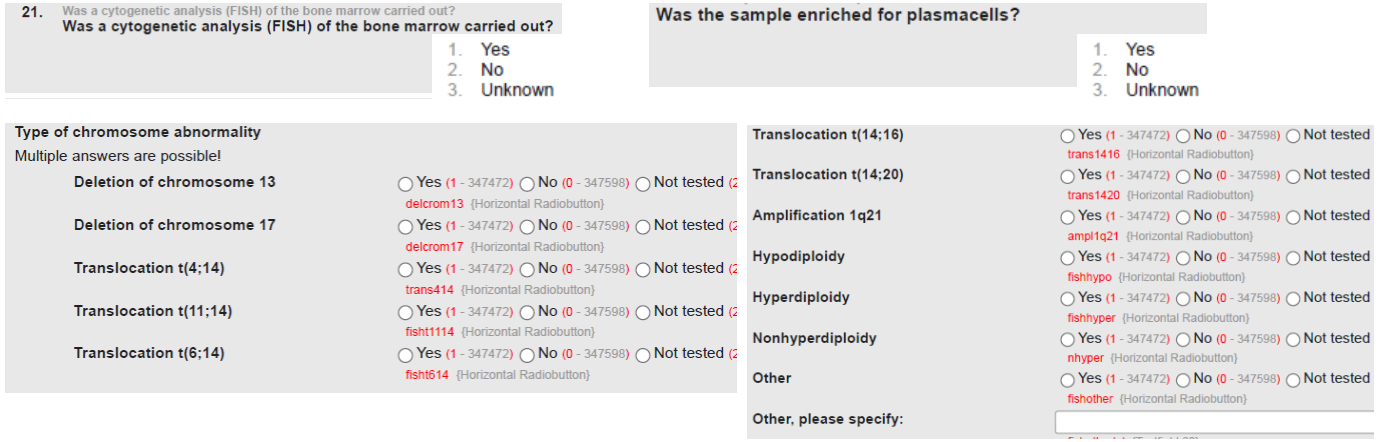



## Completeness

***Deriving R-ISS in TherapieMonitor Data Source***

R-ISS was not directly available as a covariate within the TherapieMonitor eCRF maintained by the OncologyInformationService. For the TherapieMonitor Cohort R-ISS was defined as follows:

- If ISS=1 and LDH low and no cytogenetic abnormalities/not tested, then R-ISS=1
- If ISS=1 and LDH missing and no cytogenetic abnormalities/not tested, then R-ISS=1
- If ISS=3 and (LDH high or cytogenetic abnormalities), then R-ISS=3
- If ISS=3 and (LDH missing and no cytogenetic abnormalities/not tested), then R-ISS=3
- Else R-ISS=2

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# Meeting challengers on European level



## EMA Recommendations

**Federated models** are gaining rapid traction, using the data while keeping them behind the firewalls of their originating organizations. This model requires

- a standardization and systematic quality management that can be applied to such distributed systems
- A large number of participating HCOs

EUROPEAN MEDICINES AGENCY

**Proactive external communication to promote framework adoption**

+

**Establish a data quality framework for regulatory use of big data sources with associated data quality metrics**

+

**Expansion of qualification advice process to establish renewable certification of datasets and big data methods and strategies**

**"Real-world data (RWD) and real-world evidence (RWE) are already used in the regulation of the development, authorization, and supervision of medicines in the European Union. "…We see learning from what we do as a central part of this work and the review in this edition, showing 40% of marketing authorization applications to the EMA in 2018–2019 contained RWE, is an important example of this."***

European Medicines Agency, Heads of Medicines Agencies; Data Analytics and Methods Task Force, *Data Quality Framework for EU medicines regulation", Draft, 30-Sep-2022,* **https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/data-quality-framework-eu-medicines-regulation_en.pdf**

*Peter Arlett et al.: Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value PHARMACOLOGY & THERAPEUTICS | VOLUME 111 NUMBER 1 | January 2022

# Meeting challengers on European level



## Unmet needs and barriers

- Operational level:
  - Regulatory Fragmentation on country or even regional level
  - Insecurity around Application of Legal Provisions (e.g., GDPR)
  - Data Availability & Costs owing to the different levels of digitalization of health care and health care system itself
- Technical level:
  - Lack of Semantic and Technical Interoperability (incl. Common Data Standards) impeding Integration & Generation of larger RWD-Ecosystems
  - Data Access in different health care sectors, esp. outside university hospitals
- Methodological level:
  - Limited Guidance on, and Inconsistent use of appropriate Methods for Data Collection & Analysis

**Essential factors to consider include:**
**information available in the data source, quality and validity of this information, design of the data collection, statistical analytical plan supporting data analysis and interpretation, and the likelihood of bias due to the unblinded, uncontrolled, or non-randomized treatment allocation.***

*Franklin, J.M., Glynn, R.J., Martin, D. & Schneeweiss, S. Evaluating the use of nonrandomized real-world data analyses for regulatory decision making. *Clin. Pharmacol. Ther.* 105, 867–877 (2019).

# Recent examples



| Value Dossier / Use Case | Problem / Challenge |
| --- | --- |
| Additional benefit of monotherapy with **amivantamab** in adult patients with advanced NSCLC compared to the appropriate comparator therapy. | The two registries used **lacked data on the expression of very important patient characteristics** (health status, disease severity, type of their prior treatment). In addition, the registries **did not contain data on important endpoints**. |

In a Rapid Report, the German Institute for Quality and Efficiency in Health Care (IQWiG) provided manufacturers and registry operators with specific recommendations for care-related data collection.

"[…] we have to state that the manufacturers do not interpret the requirements we defined for data collection close to the point of care in the way we would like"

*—Thomas Kaiser, Head of IQWiG's Drug Evaluation Department*

"However, the place of RWE in that decision making, its evidentiary value, remains a subject of debate. This is particularly true in the demonstration of efficacy when a product is first approved compared with further explorations of established effects once the medicine is approved.

We believe that the binary discussion between clinical trials and RWE is unhelpful as each approach brings its own strengths and weaknesses.

Whereas the randomized clinical trial remains the gold standard for of the initial demonstration of efficacy, there is a place for RWE through the different regulatory touchpoints of a medicine's lifecycle."

***Peter Arlett et al: Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value***
***CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 111 NUMBER 1 | January 2022***

# Recent examples



| Value Dossier / Use Case | Problem / Challenge |
|---|---|
| Additional benefit of monotherapy with **Amivantamab** in adult patients with advanced NSCLC compared to the appropriate comparator therapy. | From the perspective of IQWIG:<br>• Some existing RWD sources were neglected<br>• Non-sufficient completeness of data esp. in the identified confounders<br>The two registries used **lacked data on the expression of major confounders** (health status, disease severity, type of their prior treatment). The effect of amivantamab in RWD may be caused by the confounders. |
| Withdrawal of **Teclistamab** launch application to GBA | The decision not to launch Tecvali in Germany was attributed to "the anti-innovation design of early benefit assessment."<br><br>GBA was criticized for inflexibility in its dossier requirements for drugs that are conditionally approved based on small-scale studies.<br><br>"Outdated methodological regulations in the German benefit assessment system would not be able to capture the added value of the therapy with the data currently available."<br><br>The company notes that AMNOG would not recognise the evidence from its Phase I/II study. |

This decision based on a binary discussion of RWE and RCT creates a barrier of access to new and innovative medicines for patients in need.

# How do we meet the challenges?



- **Early Detection**
  - Leveraging the TriNetX federated network combined with extensive epidemiological research enables detection and identification of applicable patient profiles early in the protocol development process.
- **Early Discussion / Planning**
  - Decades of experience allow for engaging in consulting and planning activities among all stakeholders as early as possible to establish the best approach to meet specific research objectives.
- **Fit-For-Purpose Approach**
  - The highly flexible methodological approach driven by state-of-the-art technology enables a custom-tailored and regulatory accepted approach towards definition of the target population, data components, variable richness and representativity from a regional and health care sector standpoint.
- **Potential for rapid Adjustments & Amendments**
  - Changes to variable requirements and information need can be implemented on-the-fly and collected for the whole target population back to the baseline

**After Market Authorization, representative Real-World Data is the closest approach to randomization in an RCT. The database must reflect the quantitative and qualitative variables compared to the preceding clinical trials as well as ensure longitudinality.**

# Our potential



## The standard approach

- Our trusted methodology applied in TherapyMonitor, a multi-year, indication-specific, longitudinal chart review project based on a consortium model allowed for a RWD Comparator Arm to the results of a US-based trial:
- "Adjusted Comparison of Outcomes between Patients from CARTITUDE-1 versus Multiple Myeloma Patients with Prior Exposure to PI, Imid and Anti-CD-38 from a German Registry"*

## Extending the potential

- Enablement of specific and exclusive research protocol deployment for each consortium member:
- Flexible approach in retrospective data collection and analysis for each individual use-case
- Increase in requirements is met by adhering to the principles on a continuous basis within the longitudinal chart review process:
  - Early Detection
  - Early Discussion / Planning
  - Fit-For-Purpose Approach
  - Potential for rapid Adjustments & Amendments

*Merz, M.; Goldschmidt, H.; Hari, P.; Agha, M.; Diels, J.; Ghilotti, F.; Perualila, N.J.; Cabrieto, J.; Haefliger, B.; Sliwka, H.; Schecter, J.M.; Jackson, C.C.; Olyslager, Y.; Akram, M.; Nesheiwat, T.; Kellermann, L.; Jagannath, S. Adjusted Comparison of Outcomes between Patients from CARTITUDE-1 versus Multiple Myeloma Patients with Prior Exposure to PI, Imid and Anti-CD-38 from a German Registry. Cancers 2021, 13, 5996. https://doi.org/10.3390/cancers13235996

# EMA requirements: Our approach



**Proactive external communication to promote framework adoption**

TriNetX Oncology is a member in various federated data partnerships such as EHDEN and HONEUR, actively promoting and conducting sponsored, as well as investigator-initiated research projects.

The continuous transfer of knowledge, expertise and requirements shape the adoption of regulatory and scientific requirements.

**Establish a data quality framework for regulatory use of big data sources with associated data quality metrics**

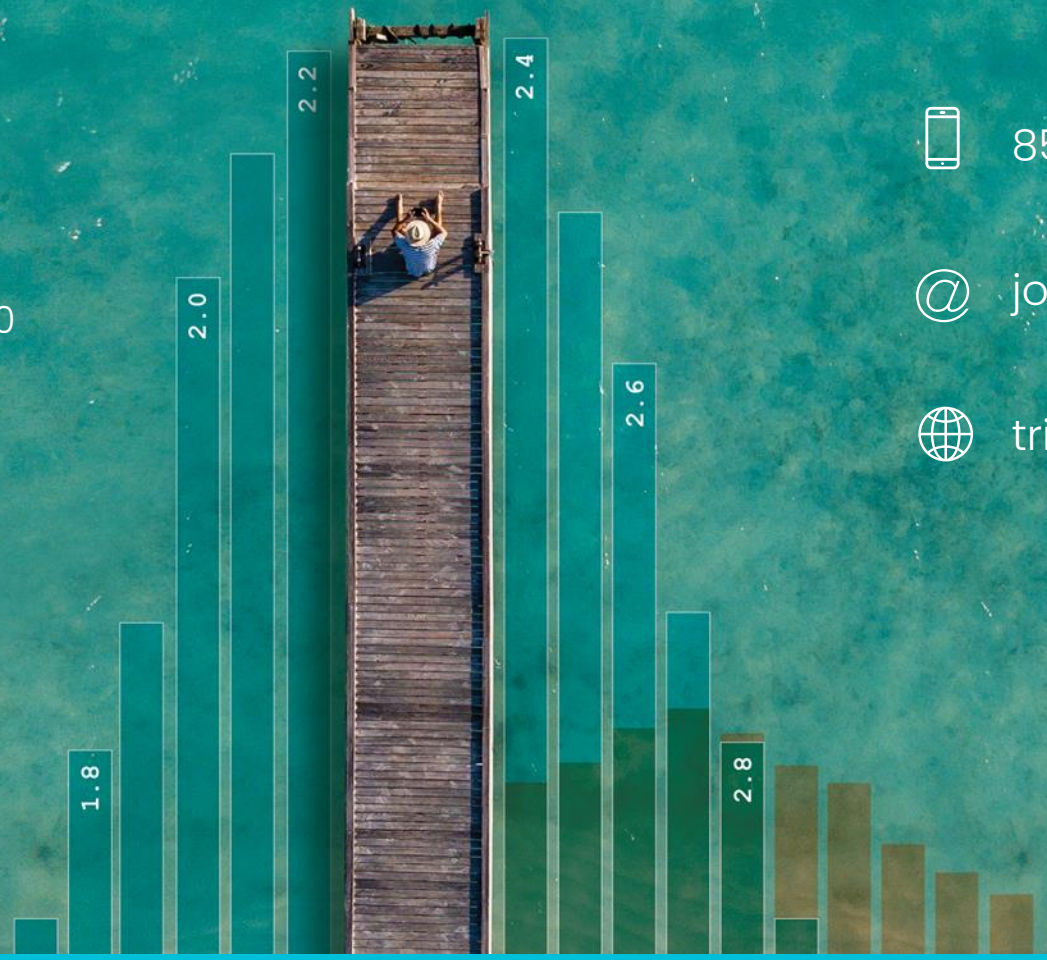
Positioned as a front-runner on procedural, regulatory and methodological aspects of RWD to RWE transformation.

Elaborate and flexible strategies in the collection, harmonization, integration and analysis of relevant data based on qualitative, quantitative and timely representativity enable adherence to changing data quality metrics.

**Expansion of qualification advice process to establish renewable certification of datasets and big data methods and strategies**

Owing to the highest grade of flexibility in our state-of-the-art methodology, we are set to support and facilitate all aspects and requirements towards qualification, methodological developments and strategies leveraging RWD towards better treatment options and outcomes for cancer patients.

# Thank You!

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