HTA Conference

Health Technology Assessment:
Better Methods, Better Evidence, Better Decisions

RWE as complement to RCTs to strengthen evidence packages

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SPOTLIGHT SESSION
USING REAL-WORLD EVIDENCE TO INFORM HEALTHCARE DECISION-MAKING

Conflicts of interest

- **None**

What is real-world evidence (RWE)?

RWE is clinical evidence regarding the use and potential benefit or risks of a medical product, derived from analysis of real-world data (RWD)[1–4]

RWD relate to patient health and/or delivery of healthcare routinely collected from a variety of sources and study designs, e.g.:[1–4]

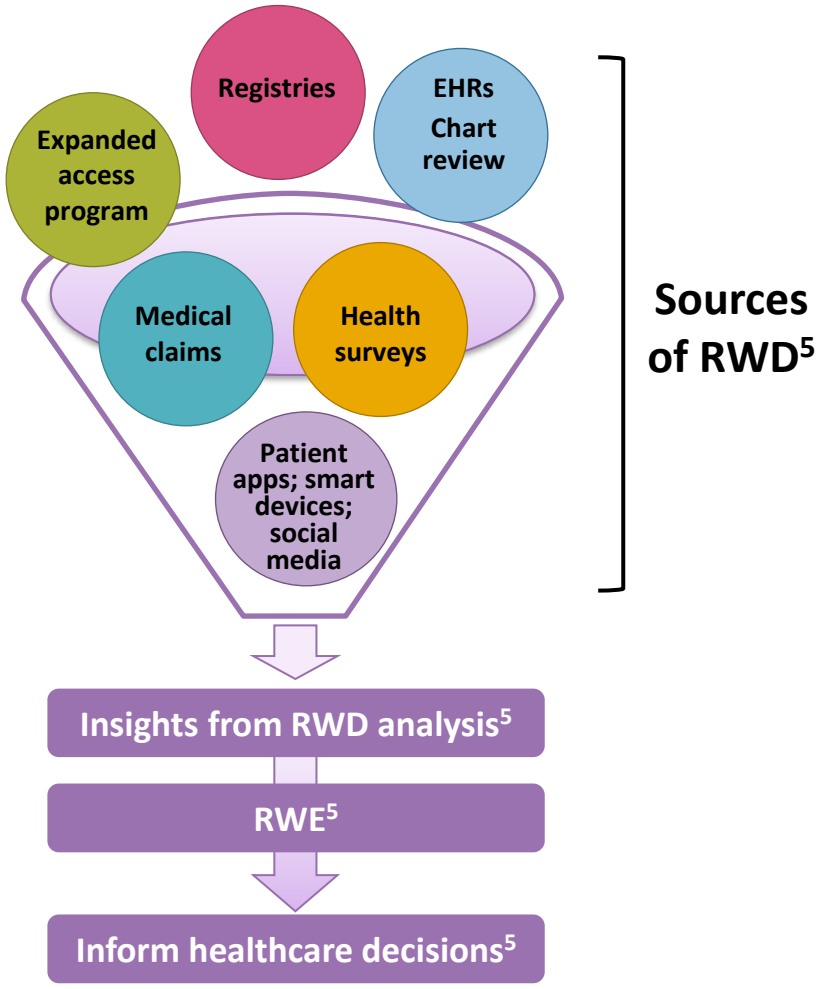
Data sources:

- Local/national clinical registries
- Electronic health/medical records (EHR/EMR)
- Billing or insurance claims databases

Observational (non-interventional) study designs:

- Cross-sectional
- Prospective/retrospective cohort
- Case-control studies
- Surveys

RWE is generated, outside of randomized controlled trials, in standard clinical practice via observational studies[1,3]



EHR, electronic health record; EMR, electronic medical record; RWD, real- world data; RWE, real-world evidence

1. Berger M, et al. Pharmacoepidemiol Drug Saf 2017;20:1003–8; 2. Garrison LP, et al. Value Health 2007;10:326–35; 3. Makady A, et al. Value Health 2017;20:858–65; 4. Breckenridge AM, et al. Br J Clin Pharmacol 2019;85:1874–77; 5. Adapted from: Framework for FDA's real-world evidence program 2018. Available at: https://www.fda.gov/media/120060/download

The importance of real-world evidence for clinical decision-making

RWE is important for understanding evolving treatment practices and therapeutic outcomes in the real-world setting[1]

- This is of particular relevance in the setting of disease treatment, due to the rapidly expanding range of approved therapeutic options and the increasing complexity of treatment

In recent years, significant improvements in efficacy have been demonstrated in RCTs[2]

- RWE is important for determining whether these improvements are reflected in real-world practice, which is not always the case due to a range of factors
- Up to 43.5% of real-world patients may not be eligible for RCTs based on standard eligibility criteria[3]

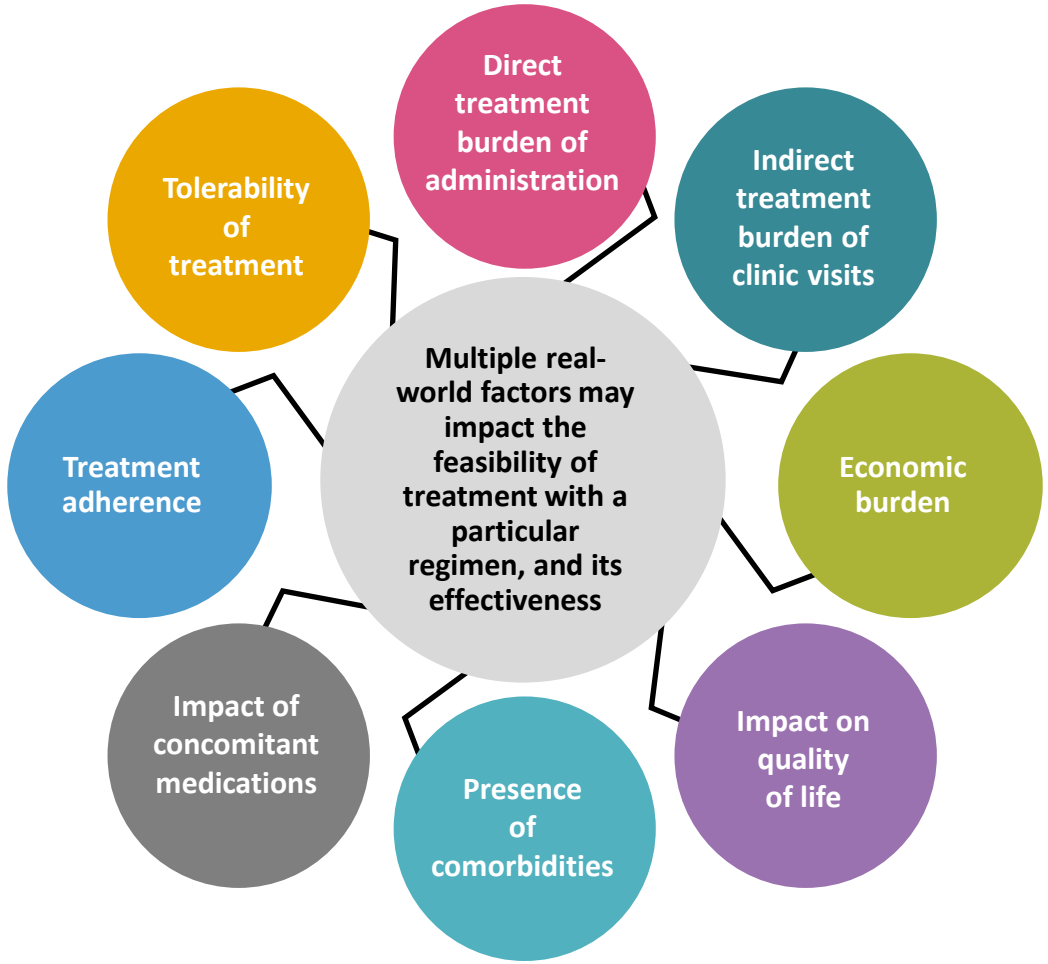
RWE is also important for capturing practical treatment considerations[1]

- These include treatment tolerability and convenience, and the practicality of therapy
- These aspects are not always captured adequately within RCTs

MM, multiple myeloma; RCT, randomized controlled trial; RWE, real-world evidence

1. Costello C, et al. Future Oncol 2019;15:1379–85;
2. Richardson PG, et al. Blood Cancer J 2018;8:109;
3. Wagner LI, et al. Blood 2019;134(Suppl 1): Abstract 1843

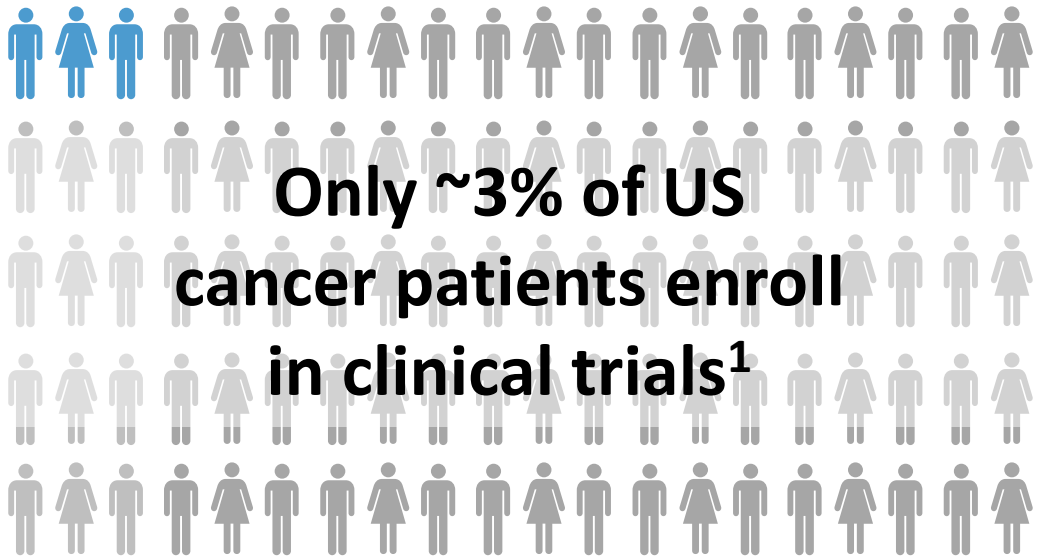
Real-world considerations: Factors impacting on the feasibility and effectiveness of treatment



Richardson PG, et al. Blood Cancer J 2018;8:109;
Richardson PG, et al. Blood 2017;130(Suppl 1):3149

Representation of real-world populations in randomized clinical trials

RCT populations are not reflective of real-world patient populations



A number of patient populations are typically under-represented in clinical trials

- Patients with comorbidities[2] or advanced disease[2,3]
- Elderly, frail patients[2,3]
- Patients from lower socio-economic backgrounds[4]
- Ethnic or racial minorities[2,3,5]

These characteristics are linked to worse outcomes to treatment[2–5]

Advanced age, functional decline, and comorbidities represent components of frailty that are predictive of mortality and toxicity risk[6]

1. Institute of Medicine Forum on Drug Discovery, Development, and Translation: https://www.ncbi.nlm.nih.gov/books/NBK50895/ (accessed Aug 2020);
2. Shah JJ, et al. Clin Lymphoma Myeloma Leuk 2017;17:575–83;
3. Costa L, et al. Leuk Lymphoma 2016;57:2827–32;
4. Ganguly S, et al. Am Soc Clin Oncol Ed Book 2019;39:519–29;
5. Pulte E, et al. Blood Advances 2018;2:116–9;
6. Richardson PG, et al. Blood Cancer J 2018;8:109

MM, multiple myeloma; RCT, randomized clinical trial

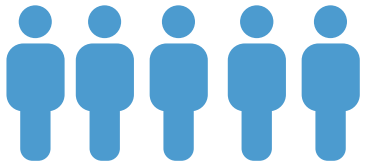
The efficacy vs effectiveness gap

Efficacy

- **Performance of an intervention under ideal controlled circumstances** – RCTs[1–3]
- **Provides robust evidence that a treatment "works" in a select** homogeneous patient population in specialized clinical settings to maximize ability to find treatment effects without dilution by factors unrelated to treatment while protecting patient safety[2,3]

Efficacy: "Can it work?"

- Performance of an intervention under ideal controlled circumstances (RCTs)[2,3]
- Uses: Regulatory approval, evidence-based guidelines, physicians and other HCPs, and patients/caregivers[2,3]



Effectiveness

- **Performance of an intervention under real-world conditions** (observational studies)[1–3]
- **Robustly conducted "real-world"/observational research** can assess generalizability of findings from RCTs, i.e., the true benefit of an intervention in routine clinical practice in a heterogeneous patient population treated in a variety of clinical settings[2]

Effectiveness: "Does it work?"

- Performance of an intervention under real-world conditions (observational studies)[2,3]
- Uses:[1,3,4] Increasing regulatory agency interest, payers and health technology assessment authorities, physicians and other HCPs, and patients/caregivers

1. Berger M, et al. Pharmacoepidemiol Drug Saf 2017;20:1003–8;
2. Garrison LP, et al. Value Health 2007;10:326–35;
3. Makady A, et al. Value Health 2017;20:858–65;
4. Makady A, et al. Value Health 2017;20:520–32

HCP, healthcare provider; RCT, randomized controlled trial

Differences between real-world evidence and randomized clinical trials: Factors potentially contributing to differences in outcomes/duration of therapy

Clinical trial factors

- Patient selection – elderly and comorbid patients and patients from lower socioeconomic backgrounds are under-represented
- Under-representation of community centers
- Stringent inclusion/exclusion criteria
- Protocol-driven dose modification may lead to better tolerability and longer duration of therapy

Real-world factors

- Higher/cumulative toxicity burden among trial-ineligible patients; e.g. elderly patients and patients with more comorbidities
- Patient and physician preference and motivation
- Different distribution of academic vs community centers
- Healthcare access issues
- Tolerability/convenience factors contributing to premature discontinuation, e.g. mobility, patient distance from hospital, number of visits required during treatment
- Direct/indirect costs

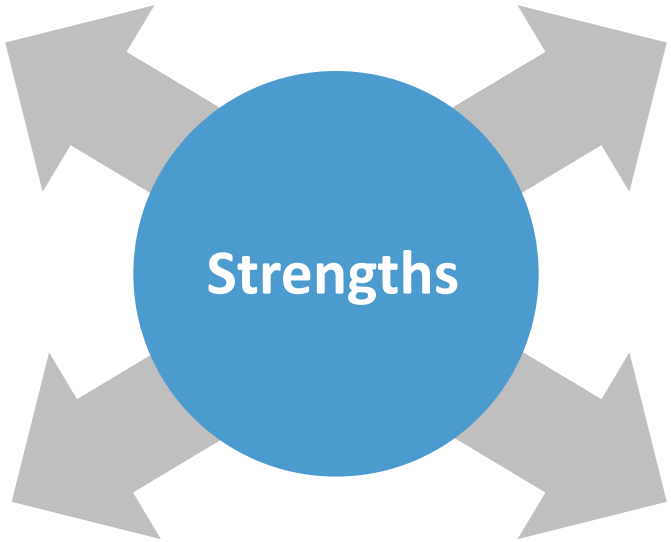
These factors make interpretation of data from clinical trials and real-world analyses highly complex

Richardson PG, et al. Blood Cancer J 2018;8:109

Strengths of real-world evidence

RWE has broader generalizability vs RCTs,[1] reflecting the heterogeneity of patients treated in real-world clinical practice,[2,3] including patients with:

- Comorbidities
- Advanced age
- Reduced performance status



Data can validate/complement evidence from RCTs in real-world clinical practice:[1,2]

- Efficacy
- Tolerability
- Safety profile

RWE provides information on real-world treatment patterns[1,3]

- Dosing
- Treatment duration
- Resource use

RWE studies are more time-/cost-efficient[1]

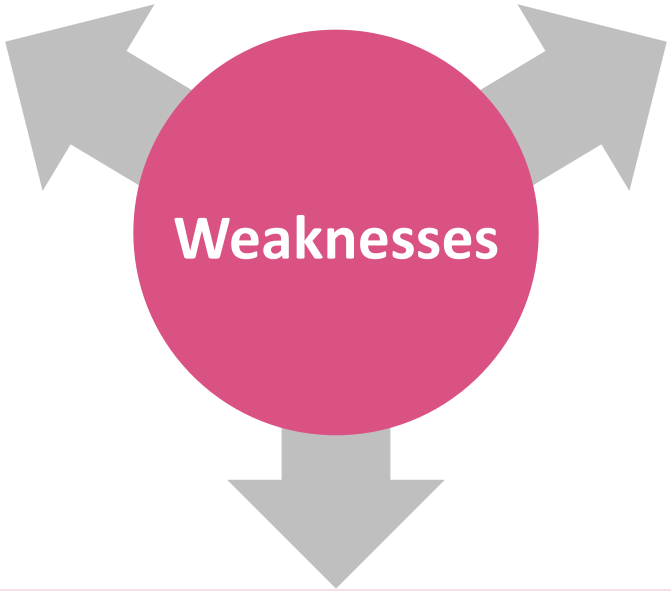
RCT, randomized controlled trial; RWE, real-world evidence

1. Blonde L, et al. Adv Ther 2018;35:1763–74;
2. Costello C, et al. Future Oncol 2019;15:1379–85;
3. Richardson PG, et al. Blood Cancer J 2018;8:109

Weaknesses of real-world evidence

Heterogeneous datasets

- Arising from heterogeneous clinical practice and documentation[1]



Findings limited to data that are randomly available – susceptible to selection bias[1,2]

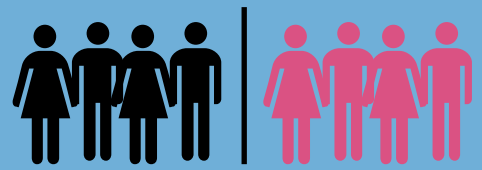
- Potential incompatibility of data from different sources
- Less scrutiny, and less uniformity in reporting or data processing/collection[1]

Real-world data do not constitute a uniform assessment of efficacy under controlled conditions:

- Lack of well-characterized, balanced groups of patients in treatment arms[1]
- Not blinded or randomized[1]
- Potential lack of formal, defined endpoints (e.g. use of time to next therapy as a proxy for progression-free survival due to data availability)[3]

1. Blonde L, et al. Adv Ther 2018;35:1763–74;
2. Kim H-S, et al. J Korean Med Sci 2018;33:e213;
3. Richardson PG, et al. Blood Cancer J 2018;8:109

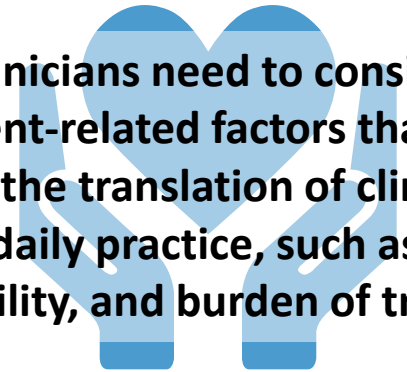
Both clinical trials and observational studies provide complementary information for decision making



Clinical trials evaluate treatment efficacy in selected patient populations and have good internal validity[1]

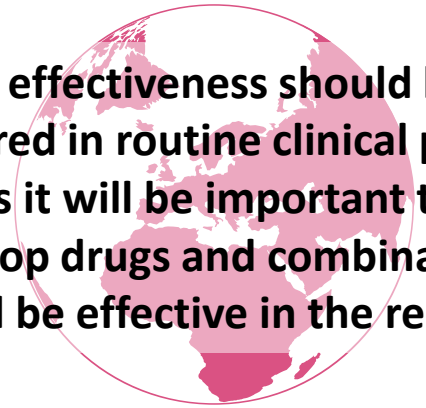
Observational studies provide insights into treatment effectiveness in heterogeneous patient populations[1]

Patient-related factors[1]



Clinicians need to consider patient-related factors that may impact the translation of clinical trial outcomes to daily practice, such as quality of life, tolerability, and burden of treatment

Real-world effectiveness[1]



Real-world effectiveness should be a metric considered in routine clinical practice, as it will be important to develop drugs and combinations that will be effective in the real world

RWE can be used to complement data from RCTs to gain a more complete picture of the advantages and disadvantages of medications as they are used in practice[2]

RCT, randomized controlled trial; RWE, real-world evidence

1. Richardson PG, et al. Blood Cancer J 2018;8:109;
2. Blonde L, et al. Adv Ther 2018;35:1763–74

Interpretation of “time-to-event” endpoints

- **PFS (**Duration from start of the treatment to disease progression or death **)**
  - May be the most common time-to-event endpoint reported from both clinical studies and real-world evidence
  - Requires rigorous and uniform monitoring of patients to ensure accuracy[1]
  - Caution should therefore be used if comparing PFS from real-world datasets to data from more rigorous, well-defined, prospective clinical trials
- **TTNT (**Start of index line of therapy to the start of the next line of therapy /death**)**
  - Likely a suitable endpoint for real-world analyses due to limited ambiguity and rigor required
  - TTNT does however require uniform criteria for defining start of next treatment both within and across treatment arms[1]
- **OS (**Time to death of any cause from e.g. start of treatment line or from time of diagnosis**)**
  - Considered a reliable cancer endpoint and is easily and precisely measured[2]
  - Requires long-term follow-up for data to mature[2]
  - May be affected by switch from control to treatment or subsequent therapies[2]

OS, overall survival; PFS, progression-free survival; TTNT: time to next treatment

1. Rajkumar SV, et al. Blood 2011;117:4691–5;
2. FDA: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry 2018. https://www.fda.gov/media/71195/download. Accessed 14 June 2021

Regulatory viewpoints on real-world evidence: US FDA

The US FDA uses RWD and RWE to monitor post-marketing safety and adverse events and to make regulatory decisions[1]

21st Century Cures Act

Passed in 2016, the Act places additional focus on the use of these types of data to support regulatory decision-making, including approval of new indications for approved drugs[1]

The US Congress defined RWE as data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials; the FDA has expanded on this definition[1]

Guidance documents available covering:

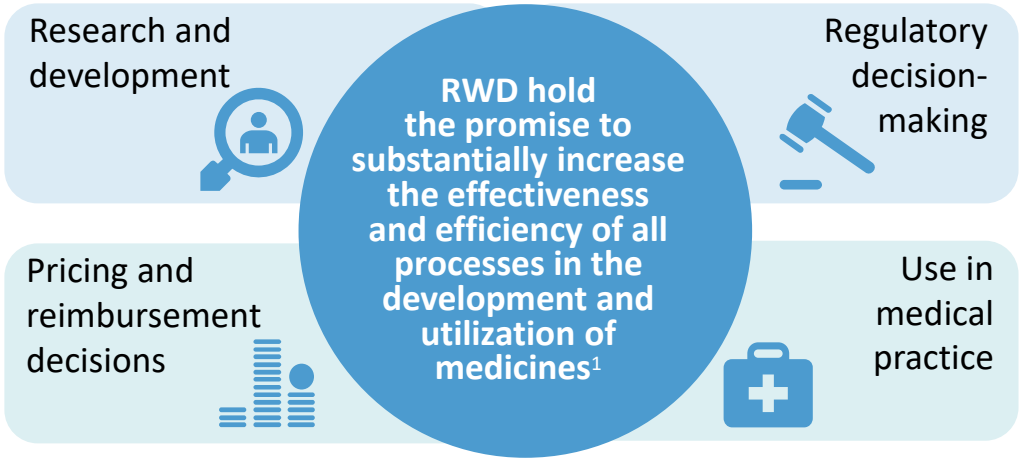
- Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics[2]
- Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices[3]
- Use of Electronic Health Record Data in Clinical Investigations Guidance for Industry[4]

The FDA has also published the Framework for its Real-World Evidence Program, including a Framework for Evaluating RWD/RWE for Use in Regulatory Decisions[5]

1. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence;
2. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-documents-using-real-world-data-and-real-world-evidence-fda-drugs-and-biologics-guidance;
3. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices;
4. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-electronic-health-record-data-clinical-investigations-guidance-industry;
5. https://www.fda.gov/media/120060/download (all accessed Aug 2020)

FDA, Food and Drug Administration; RWD, real-world data; RWE, real-world evidence

Regulatory viewpoints on real-world evidence: EMA



There are currently no formal guidelines or frameworks published by the EMA

The EMA Executive Director and Senior Medical Officer, as well as heads of three national EU agencies, and academia, payer, and Organization for Economic Co-operation and Development (OECD) representatives, stressed in a paper that a "learning healthcare system" will be needed to fully realize the potential of RWE[2]

> *A **learning healthcare system**, based on electronic health records and other routinely collected healthcare data, would allow RWD to be continuously fed into the system, ensuring that with every new patient treated, we know more overall about the practice of medicine.*

Presentations available covering:

- Real-world evidence (RWE) – an introduction; how is it relevant for the medicines regulatory system?[3]
- Real-world evidence – what have we learned recently at EMA?[4]
- Use of real-world data pre-authorization –what can it answer?[5]

EMA, European Medicines Agency;
EU, European Union;
RWD, real-world data; RWE, real-world evidence

1. https://www.ema.europa.eu/en/news/harnessing-potential-real-world-data-through-learning-healthcare-system (accessed Aug 2020);
2. Eichler H-G, et al. Clin Pharmacol Ther 2018;105:912–22;
3. https://www.ema.europa.eu/en/documents/presentation/presentation-real-world-evidence-rwe-introduction-how-it-relevant-medicines-regulatory-system-emas_en.pdf;
4. https://www.ema.europa.eu/en/documents/presentation/presentation-real-world-evidence-rwe-what-have-we-learned-recently-ema-emas-pcwp-hcpwp-joint-meeting_en.pdf;
5. https://www.ema.europa.eu/en/documents/presentation/presentation-session-1-use-real-world-data-pre-authorisation-what-can-it-answer-peter-mol_en.pdf;
(all accessed Aug 2020)

Summary

Importance of real-world evidence

- RWE is clinical evidence derived from RWD on the use and potential benefit or risks of a medical product [1–4]
  - RWE is generated, outside of RCTs, in standard clinical practice via observational studies[1,3–4]
  - RWE is important for understanding evolving treatment practices and therapeutic outcomes in the real-world setting, including practical treatment considerations[5]
- RWD provide estimates of effectiveness, rather than efficacy, in a variety of typical practice settings[2]
- Interpretation of data between clinical trials and real-world analyses is highly complex, with a multitude of factors confounding interpretation of efficacy and effectiveness between regimens[6]
- RWE can be used to complement data from RCTs to gain a more complete picture of the advantages and disadvantages of medications as they are used in practice[7]
  - Regulatory authorities have implemented a range of initiatives to optimize the use of RWE and advance RWD in regulatory decision making[8–10]

1. Berger M, et al. Pharmacoepidemiol Drug Saf 2017;20:1003–8; / 2. Garrison LP, et al. Value Health 2007;10:326–35;/ 3. Makady A, et al. Value Health 2017;20:858–65; / 4. Breckenridge AM, et al. Br J Clin Pharmacol 2019;85:1874–77;/ 5. Costello C, et al. Future Oncol 2019;15:1379–85;/ 6. Richardson PG, et al. Blood Cancer J 2018;8:109; / 7. Blonde L, et al. Adv Ther 2018;35:1763–74;/ 8. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence (accessed Aug 2020)/ 9. https://www.ema.europa.eu/en/news/harnessing-potential-real-world-data-through-learning-healthcare-system (accessed Aug 2020)/ 10. https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices/strengthening-use-real-world-evidence-drugs.htm (accessed Aug 2020)/ 11. Moreau P, et al. N Engl J Med 2016;374:1621–34; / 12. van Beurden-Tan CHY, et al. J Clin Oncol 2017;35:1312–20; / 13. Hajek R, et al. Future Oncol 2021;17:2499–2512

Σας ευχαριστώ!