Multi-stakeholder workshop on Real World Data (RWD) quality and Real-World Evidence (RWE) use.

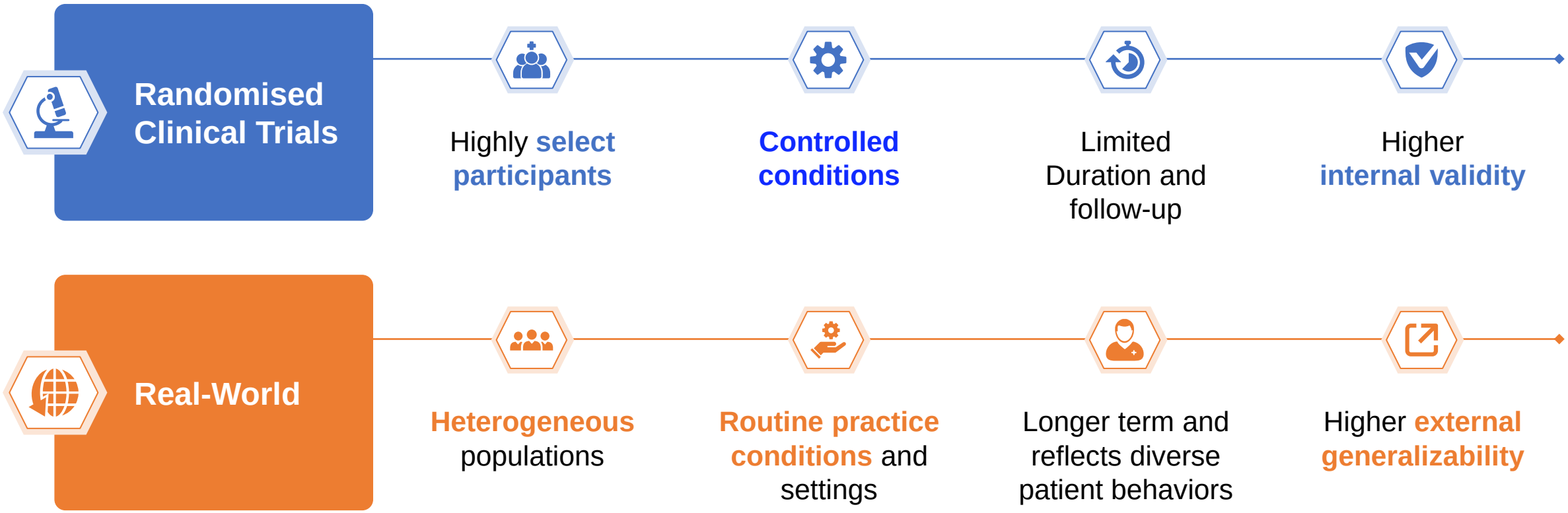
Use of RWE in medicines development and regulatory submissions – an industry perspective

Álmath Spooner PhD, Regulatory Policy and Intelligence, AbbVie.

Chair EFPIA's Integrated Evidence Generation and Use Group (IEGU WG).

EMA, Amsterdam, June 27th, 2023

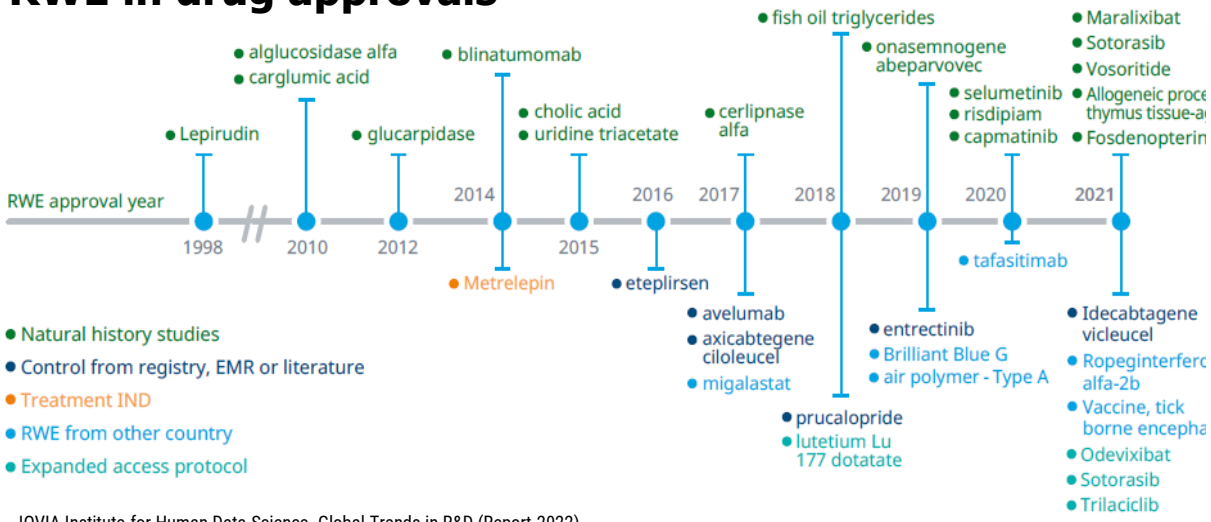
To meet evidence requirements, we use complementary data streams



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

Fit-for-purpose RWE is Changing Medical Product Development

RWE in drug approvals



IQVIA Institute for Human Data Science. Global Trends in R&D (Report 2022).

Paradigm with RWE

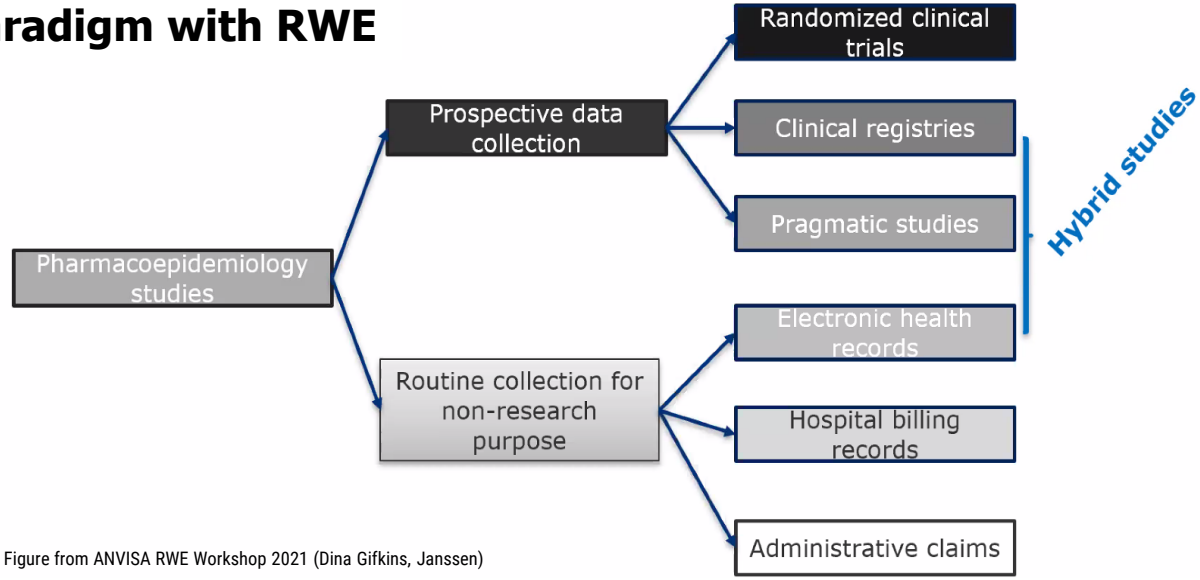


Figure from ANVISA RWE Workshop 2021 (Dina Gifkins, Janssen)

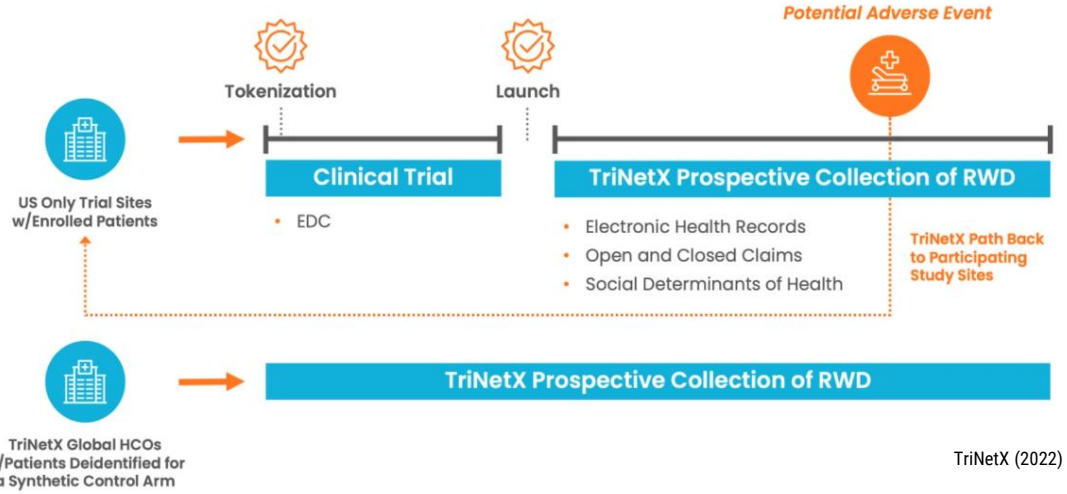
RWE external control arms

Drug development *~14 years*

Accelerated scenarios
~6 years after phase 3
~4 years after phase 2 (oncology)

Figure is hypothetical for illustrative purposes only. (Alex Liede, AbbVie, 2019)

Follow similar patients in RWE alongside trial



TriNetX (2022)

Regulatory recognition of the value of broader application of RWE

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

"These data have the ability to significantly contribute to the way the benefit-risk balance of medicines is assessed over their entire life cycle"

– EMA 2016 Annual report

FDA

"Key to understanding the usefulness of real-world evidence is an appreciation of its potential for complementing the knowledge gained from traditional clinical trials"

– FDA Leadership,
Sherman R, et al.

N Engl J Med 2016;375:2293–7

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

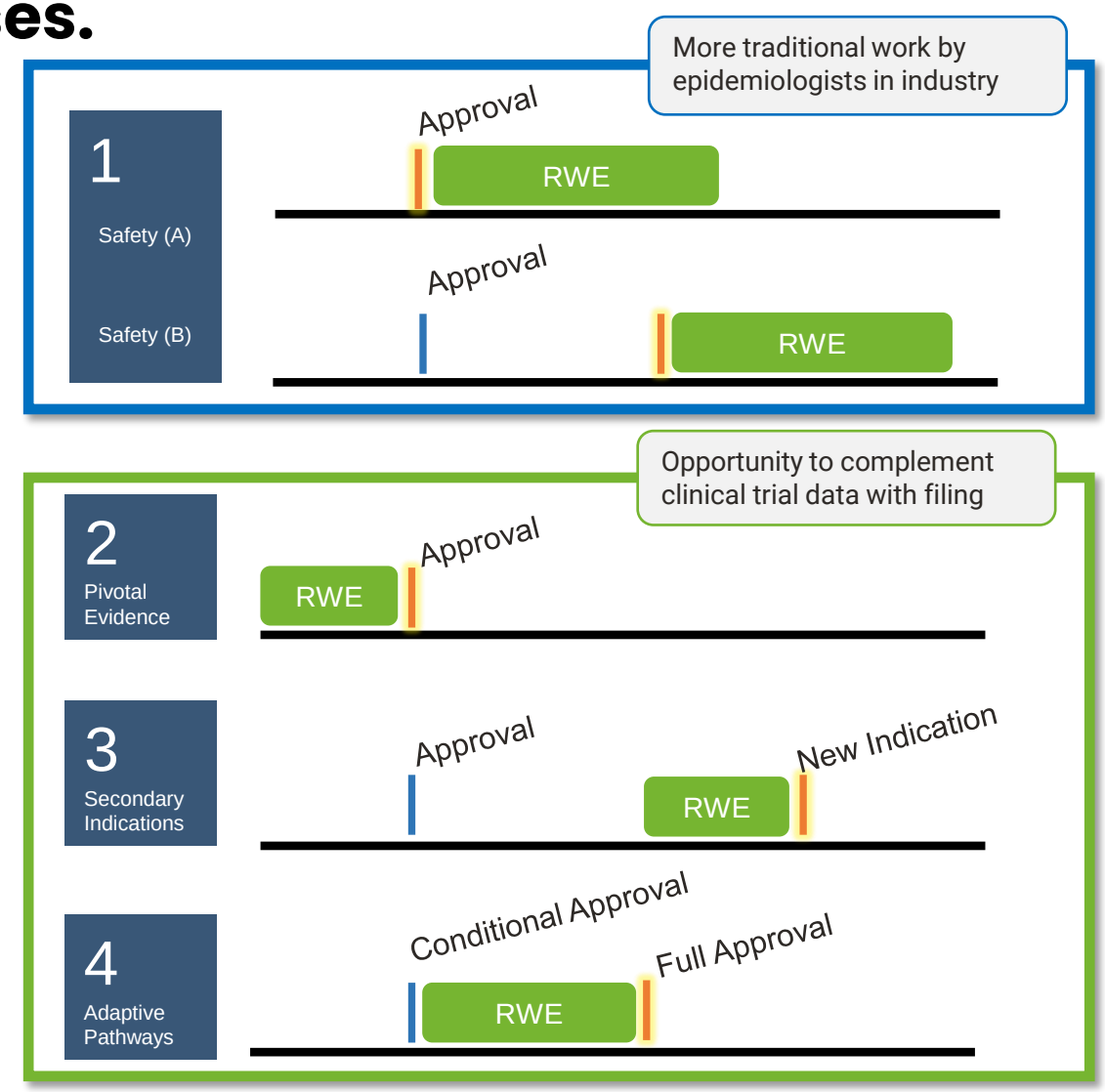
Health Canada

FDA U.S. FOOD & DRUG ADMINISTRATION

ICMRA

Role for Fit for Purpose RWE incrementally evolving beyond traditional use cases.

1. **Long-term Safety (and Effectiveness)**
   - Comparator for single arm extension trial or registry
2. **New Approval**
   - To compare disease trajectory to interventional single arm trial of new medication when traditional RCT is not operationally feasible
     - Rare disease or subtype (oncology)
     - Identify eligible patients exposed to an approved alternative or no treatment
     - Well defined indication, outcomes, and predictable clinical course can be identified and measured in existing RWD
3. **Secondary Indications**
   - Effectiveness of new therapy for expanded population (e.g., pediatrics) or new indication (e.g., oncology)
4. **Confirmatory Evidence with Accelerated Approval**
   - In the scenario where RCT is not feasible (rare disease or subtype, or unethical) or to supplement for relevant outcomes



Franklin J et al. Evaluating the use of non-randomized real-world data analyses for regulatory decision making. Clin Pharm Ther. 2019;105(4). Doi:10.1002/cpt1351

RWE supported the assessment of efficacy for COVID-19 vaccines

Features		Key Learnings
Rationale/ Commitment regarding RWE use	• Limited data from RCTs on the efficacy of COVID-19 vaccines in people over 60. Data on sub-population of older people in the original trials were not available when countries initiated COVID-19 vaccination programs for people over 60 (January 2021) [5]	***RWE provided a timely mechanism to address uncertainties from RCTs in specific subpopulations.*** ***RWE was particularly important during the pandemic, given the need for fast access to vaccine/treatment.***
Therapy area / Product	• COVID-19 / COVID-19 mRNA vaccine (Comirnaty®) and COVID-19 vaccine (Vaxzevria®)	
Stakeholder(s)	• Payers and regulators: NHS Scotland, STIKO (Germany), EMA	
Key Study objective(s)	• To estimate the effectiveness of COVID-19 mRNA vaccine (Comirnaty®) and COVID-19 vaccine (Vaxzevria®) at the population level in "real world" settings [1]	
Source data	• Electronic Healthcare Records and vaccination data	
Study Type / Study Design	• Non-interventional, prospective study[1]	
Decision – Impact (including limitations)	• Due to the emergency of the pandemic, it was not feasible to run additional RCT. RWE was used to complement RCT findings to prove efficacy in older people [1] • The study showed vaccine effects were 91% for the mRNA vaccine (Comirnaty®) and 88% for the COVID-19 vaccine (Vaxzevria®) against COVID-19 hospital admissions at 28–34 days after vaccination for people over 60 [1] • NHS Scotland COVID-19 Vaccine Deployment Plan 2021 used RWE study [1] as the evidence on vaccine safety and efficacy in lowering hospitalisation rates in sub-population over 60 [3] • EMA decision that COVID-19 vaccine (Vaxzevria®) was effective in over 60 years old patient group used data from non-interventional study [6] • Germany initially had a negative perspective at approving the vaccine for those aged 65 and over due to efficacy concerns. Based on EMA's recommendation, which was supported by RWE, Germany's STIKO decided to reverse the previous decision and allowed COVID-19 vaccine (Vaxzevria®) use in people over 65 years old [4]	
Country(ies) scope	• The study took place in Scotland[1] but used in Germany and the EU decision making (the study was referenced by EMA in the document "AstraZeneca's COVID-19 vaccine: benefits and risks in context") [2]	

1. *Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, Bedston S, Beggs J, Bradley D, Chuter A, de Lusignan S, Docherty AB, Ford D, Hobbs FR, Joy M, Katikireddi SV, Marple J, McCowan C, McGagh D, McMenamin J, Moore E, Murray JL, Pan J, Ritchie L, Shah SA, Stock S, Torabi F, Tsang RS, Wood R, Woolhouse M, Robertson C, Sheikh A. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. Lancet. 2021 May 1;397(10285):1646-1657. doi: 10.1016/S0140-6736(21)00677-2. Epub 2021 Apr 23. PMID: 33901420; PMCID: PMC8064669.*
2. *EMA (April 2021) AstraZeneca's COVID-19 vaccine: benefits and risks in context; available at https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-benefits-risks-context*
3. *NHS Scotland Scotland's COVID-19 Vaccine Deployment Plan 2021 Update – March 2021; available at https://www.gov.scot/binaries/content/documents/govscot/publications/strategy-plan/2021/03/coronavirus-covid-19-vaccine-deployment-plan-update-march-2021/documents/coronavirus-covid-19-vaccine-deployment-plan-update---march-2021/coronavirus-covid-19-vaccine-deployment-plan-update---march-2021/govscot%3Adocument/COVID-19%2Bvaccine%2Bdeployment%2Bplan%2B-%2Bupdate%2B-%2B24%2BMarch%2B2021.pdf*
4. *Discussion of new data on AstraZeneca vaccine AZD1222 available at https://www.sciencemediacenter.de/alle-angebote/press-briefing/details/news/diskussion-neuer-daten-zum-astrazeneca-impfstoff-azd1222/*
5. *Bloomberg (January 2021) Germany Excludes Seniors From AstraZeneca Covid Shot Approval; available at https://www.bloomberg.com/news/articles/2021-01-29/germany-excludes-seniors-from-astrazeneca-covid-shot-approval*
6. *EMA assessment report Vaxzevria, available at https://www.ema.europa.eu/en/documents/referral/use-vaxzevria-prevent-covid-19-article-53-procedure-assessment-report_en.pdf*

AstraZeneca, Pfizer
EFPIA IEGU WG Case study finalised: February 2021

Use of RWD for an external control arm – PRIME, SAWP

Features		*Key Learnings*
Rationale/Commitment for RWE use	New Product Approval - need for an external control arm to establish the magnitude of the benefit, and contextualize single-arm clinical study (MM 001) results.	***Early engagement with EMA through PRIME scheme and scientific advice offered the opportunity to discuss with regulators the use of an external control arm to provide context for the magnitude of benefit and address the limitations of the registrational single-arm trial approach***
Therapy area / Product	Abecma (idecabtagene vicleucel) - CAR T-cell therapy for the treatment of Relapse and Refractory Multiple Myeloma (RR MM) (Advanced Therapy / Haematology)	
Stakeholder(s)	EMA	
Key Study objective(s)	• Describe demographic and selected clinical characteristics of RW subjects with RRMM who received at least 3 prior myeloma regimens (RRMM cohort) • Describe demographics, disease characteristics, treatment patterns, and **clinical outcomes (primary endpoint ORR)** of the above RW subjects and for the cohort of RW subjects who met eligibility criteria for Study MM 001 (Eligible RRMM cohort)	
Source data	Clinical sites, registries, research databases collated in a single data model: subject-level data were collected on 1949 RW subjects. 190 subjects were selected as having similar characteristics to the MM-001 population	
Study Type / Study Design	Non-Interventional, Retrospective, multi-center study to generate an external comparison arm for the registrational single-arm study MM-001	
Decision – Impact (including limitations)	The adjusted indirect comparisons to the external control arm (NDS-MM-003 study) demonstrated a clinically relevant and statistically significant benefit for ide-cel across all pre-defined efficacy endpoints. The comparisons were limited by the long time period allowed for the collection of baseline data, the overlapping recruitment periods for the RW Study and the MM-001 at the same centers, the large proportion of missing data (up to 30%) for some co-variates of the PS model. Still, despite the limitations, the results indicated that treatment with Abecma was associated with responses well above standard of care. As a result, the product was granted a Conditional marketing Authorization.	
Country(ies) scope	Global RWE study. EU Approval.	
Abecma; INN-idecabtagene vicleucel (europa.eu)		

BMS, Study Case finalised: June 2021

RWD Studies Accelerate a Regulatory Approval Decision

Features		*Key Learnings*
Rationale/Commitment for RWE use	RWD in the form of historical data was used to complement a single-arm clinical trial for regulatory submission to compare novel therapies for R/R ALL. The study was necessary to help accelerate regulatory approval of blinatumomab for adults with R/R ALL by the FDA, EMA, and other regulatory agencies.	***RWD in combination with a single-arm clinical trial can accelerate a regulatory approval in situations where a disease is rare, prognosis is very poor, and/or there are limited therapeutic options available***
Therapy area / Product	Relapsed/Refractory (R/R) Acute Lymphoblastic Leukaemia (ALL)/Blinatumomab	
Stakeholder(s)	US FDA, EMA	
Key Study objective(s)	To evaluate complete remission (CR) and overall survival (OS) with standard of care salvage chemotherapy in adults with Ph-negative, B-precursor R/R ALL	
Source data	Historical data sets were pooled from European national study groups and large individual sites from Europe, UK, and the United States	
Study Type / Study Design	Observational; Single-arm trial contextualized with historical comparator data	
Decision – Impact (including limitations)	The results provided from this study provided critical evidence that helped accelerate the approval of blinatumomab for adults R/R ALL by the FDA and EMA where blinatumomab was granted accelerated/conditional marketing authorization for adults with Ph-negative, B-precursor ALL.	
Country(ies) scope	USA, Europe	

N Gökbuget, et al. Blinatumomab vs historical standard therapy of adult relapsed/refractory acute lymphoblastic leukemia. Blood Cancer Journal; 2016 Sep 23; 6(9):e473

Amgen

Study Case published: 2016

Complementing single-arm trial data with external control data based on RWD

Features		*Key Learnings*
Rationale/Commitment for RWE use	To properly contextualize and interpret the outcomes of the Phase II single-arm trial of avelumab in patients with distant metastatic Merkel Cell Carcinoma (mMCC) who had previously received 2 lines or later lines of treatment (rare indication without available Standard of Care (SoC) at that time), by conducting an external control cohort study	***Despite known limitations when assessing outcomes in oncology by using RWD as external controls, the limited sample size linked to the ultra rare indication, and the lack of SoC (absence of consensus on the most appropriate chemotherapy), some RA have accepted the data coming from the real-world setting as supportive information to get regulatory approval based on their "openness" to RWD, when others not***
Therapy area / Product	Merkel Cell Carcinoma / Avelumab	
Stakeholder(s)	Regulatory authorities (RA)	
Key Study objective(s)	To assess patient responses to second-line and later (2L+) chemotherapy	
Source data	Electronic Health Records from community oncology practices across the USA (incl. over 1000 physicians in practices across 19 states)	
Study Type / Study Design	Non-Interventional Study	
Decision – Impact (including limitations)	14 patients were qualified for primary analysis. In the 2L+ primary analysis population, ORR was 28.6%, median DOR was 1.7 months and median progression-free survival was 2.2 months Acceptance of the data coming from the real-world setting has been perceived as supportive information to get regulatory approval in several geographies, but not all	
Country(ies) scope	US data used during interactions with RA in multiple geographies	

Reference: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-avelumab-merkel-cell-carcinoma-transcript.
CL Cowey, L Mahnke, J Espirito, C Helwig, D Oksen, M Bharmal. Real-world treatment outcomes in patients with metastatic Merkel cell carcinoma treated with chemotherapy in the USA. Future Oncol. 2017 Aug;13(19):1699-1710.

Merck KGaA

Study Case published: December 2021

Global Regulatory Authorities are at varying stages of Evaluating, Developing and Implementing Policies for RWE

UK MHRA

Guideline on use of RWD in Clinical Studies to support regulatory decisions.
Guideline on RCTs using RWD to support regulatory decisions

Health Canada

Projects aim to use of real-world evidence to support regulatory decisions across a product's life cycle for both drugs and medical devices. Issued several guidance on this topic

US-FDA

PDUFA VI, 21st Century Cures Act
Label Expansion
Fulfilling PMR/C
PDUFA VII- Pilots, Guidance, Workshops

Potential Future Initiatives:

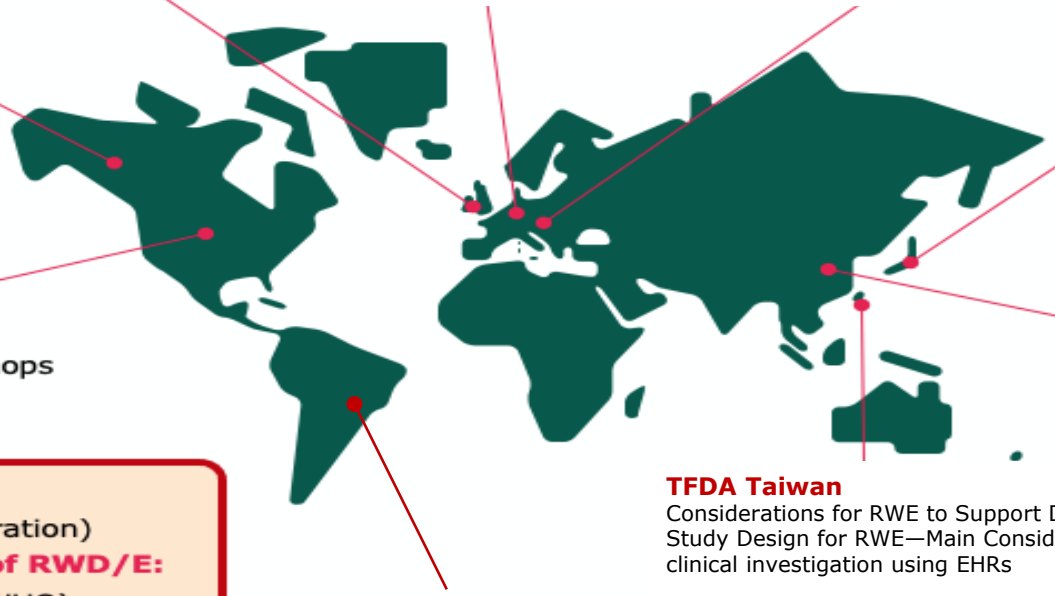
- ICH (selected topics under consideration)

Others discussing regulatory use of RWD/E:

- South Korea
- Brazil
- CIOMS (WHO)
- ICMRA

EMA European Union[1]

EMA Regulatory Science Strategy 2025
HMA/EMA Networks Strategy to 2025
EMA PAES and registry guidelines
EHDS & DARWIN EU



Swissmedic

Addressing the real-world approach for drugs is integrated in Swissmedic Strategic Objectives 2019-2022 & have a position paper on RWE use

PMDA Japan

Policy and guidelines on use of RWD for pharmacovigilance, such as electronic medical records and data of patient registries for drug safety assessment. Points to Consider for Ensuring Reliability when using Registry Data for Approval Applications

NMPA China

Several guidances on the use of RWD to support regulatory decision-making across product lifecycle

TFDA Taiwan

Considerations for RWE to Support Drug Research and development, Guidelines Study Design for RWE—Main Considerations for Pragmatic Clinical Trial and for clinical investigation using EHRs

ANVISA Brazil

First perspectives from the Brazilian Health Regulatory Agency (ANVISA) shared in November 2020,[4] Workshops, draft guidance for industry review in September 2022.

1. EMA: European Medicines Agency. Update on Real World Evidence Data Collection. https://ec.europa.eu/health/sites/default/files/files/committee/stamp/2016-03_stamp4/4_real_world_evidence_ema_presentation.pdf

"Good Science Principles" for the conduct of Non Interventional Studies

OP 1	Appropriate research design for the research question considered
OP 2	The study protocol is the cornerstone of the research process
OP 3	Valid, 'Fit for purpose' traceable data and transformations
OP 4	Validated and well described analytical methods
OP 5	Reducing bias and confounding
OP 6	Transparency for the conduct and reporting of NIS

Adapted from Acha et al. Principles for good practice in the conduct of non-interventional studies: the view of industry researchers. Accepted for publication by TIRS.

Conclusions

1

Key driver for selection of evidence stream and research methodology is the research question.

CTs and RWE require robust research practices & value depends on fitness to address question.

2

Different dimensions of uncertainty have different levels of relevance depending on context.

Meeting expectations for evidence generation requires early and iterative dialogue and greater predictability on relevance and acceptability of RWE.

3

Evolving health data ecosystem and advancements in data science and technology offer opportunities for clinical evidence generation.

Policy direction is towards increasing regulatory capacity to analyse and use RWE.

4

Critical to build alignment on fitness for purpose of data, methodologies and analytical approaches.

Greater predictability for sponsors will be facilitated by guidance development (e.g. ICH M14 as a starting point).

Medical Product Development is a global effort - increasing international convergence on acceptability of RWE will be a key enabler for predictability and uptake.