Harnessing Real-world data for regulatory use

Report on the joint HMA/EMA Big Data Steering Group workshop on Real-world evidence (RWE) methods

14 June 2024

Contents

Executive summary

This one-day hybrid HMA/EMA Big Data Steering Group (BDSG) workshop organised by the Heads of Medicines (HMA) and the European Medicines Agency (EMA) in the context of the joint HMA-EMA Big Data Steering Group plan 2023-2025 took place on 14 June 2024 to gather perspectives on the draft RWE reflection paper (RF) discuss priorities for future regulatory Real-world evidence (RWE) guidance development and collaboration, and engage stakeholders regarding methods to be used to generate RWE in the context of regulatory decision making. The workshop also provided an introduction to the Methodology Working Party (MWP) and the MWP Roadmap for the development of RWE guidance as part of the draft MWP Workplan.

The workshop was chaired by Peter Arlett (EMA, BDSG co-chair) and Jeppe Larsen (Danish Medicines Agency, BDSG co-chair).

During the workshop, participants from patient organisations, academia, registry holders, health technology assessment (HTA) bodies, industry (pharmaceutical and medical devices), the European Commission and medicine regulators exchanged experiences, views and ideas on how to further strengthen and futureproof the use real-world data (RWD) for regulatory purposes. Key challenges were identified, and suggestions were made by participants, setting the stage for future improvements to enhance the use of RWE in medicines regulation.

The workshop marked an important milestone in advancing the discussion around RWE in healthcare, with all materials, including the agenda, presentations, and a recording, available on the EMA event page for the Joint HMA/EMA Big Data Steering Group workshop on RWE methods.

This report summarizes the discussions held throughout the day.

Objectives and Agenda

The workshop had the following objectives:

To hear the views of stakeholders and experts:

- on the draft Real-world evidence reflection paper,
- on priorities for future regulatory guidance development and collaboration beyond the reflection paper.

To engage with the stakeholders on RWE methods in regulatory decision making.

The workshop was divided in different sessions, including a welcome session. Each session was followed by panel discussions that included industry and patient representatives, academic researchers, regulatory authorities, and healthcare professionals.

Welcome

- Opening remarks from EMA by Emer Cooke (EMA Executive Director)
- Opening remarks from BDSG by Jeppe Larsen (HMA BDSG co-chair)
- Scene-setting and goals of the workshop by Patrice Verpillat (EMA, Head of TDA-RWE)
- Data-driven approaches in health research & innovation by Tomasz Dylag (European Commission, DG Research and Innovation)

Session 1: Presentation and discussion of the draft RWE reflection paper - chaired by Kit Roes (MWP Chair) and Mencía de Lemus Belmonte (CAT member.

- Presentation of the RWE reflection paper by Xavier Kurz (ESEC RWE)
- Panel discussion with invited stakeholders:
    - Pharmaceutical Industry: Almath Spooner
    - Academia: Helga Gardarsdottir
    - Patients: Bettina Ryll
    - HCP: Holger Schunemann
    - Moderator: Olaf Klungel

Session 2a: Target Trial Emulation and estimand frameworks for non-interventional studies with causal objectives - chaired by Harald Enzmann (CHMP Chair) and Daniel Morales (EMA).

- Introduction to regulatory-grade causal inference by Xabier García de Albéniz (RTI Barcelona)
- Use of Estimands in Target Trial Emulation by Juan Jose Abellan Andres (EMA, TDA-RWE)

- Target trial emulation in a DARWIN EU vaccine effectiveness study by Daniel Prieto-Alhambra (DARWIN EU Coordination Center)
- Target trial and estimand in post-market safety studies by Rima Izem (Novartis)
- Panel discussion with invited stakeholders:
    - Pharmaceutical industry: Helene Nordahl
    - Academia: Anthony Matthews
    - Regulator: Rhea Fitzgerald

Session 2b: RWD-derived external controls in clinical trials - chaired by Carla Torre (CHMP) and Marcia Rueckbeil (EMA).

- RWD-derived external controls in regulatory context by Elina Asikanius (SAWP, MWP)
- The use of RWD derived External Control Arm to assess the Benefit of New Therapies by Maurille Feudjo Tepie (UCB)
- Externally controlled trials in oncology by Donna Rivera (US FDA)
- RWD-derived external controls case study: Abecma by Andrea Buzzi (EMA) + Theodor Framke (EMA)
- Panel discussion with invited stakeholders:
    - Pharmaceutical industry: Mehmet Burcu
    - Academia: Denis Lacombe
    - HCP: Jan Cornelissen
    - Regulator: Bruno Delafont

Session 3: The next three years: roadmap for RWE guidance - chaired by Jeppe Larsen (BDSG co-chair) and Kit Roes (MWP Chair).

- Introduction to Methodology Working Party by Kit Roes (MWP Chair)
- MWP Roadmap for the development of RWE guidance by Olaf Klungel (MWP Member)
- Panel discussion with invited stakeholders:
    - Pharmaceutical industry: Marieke Schoonen
    - Academia: Viviana Giannuzzi
    - Patients: George Paliouras
    - HCP: Ioana Agache

Summary of the workshop and conclusion

- Concluding remarks by Peter Arlett (EMA, BDSG co-chair)

Welcome and setting the scene

Summary of opening session

Opening messages

- The workshop commenced with Peter Arlett welcoming all participants, both in person and online.
- This was followed by opening remarks from Emer Cooke, the Executive Director of the European Medicines Agency, and Jeppe Larsen, co-chair of the HMA BDSG.
- Patrice Verpillat, head of the EMA RWE Workstream, then set the scene and outlined the objectives of the workshop.
- Finally, Tomasz Dylag from the Directorate-General (DG) for Research and Innovation provided additional European context.

Summary opening remarks Emer Cooke (EMA Executive Director)

Real-world evidence is becoming increasingly important in the regulation of medicines, offering valuable insights, particularly in post-marketing surveillance and in situations where randomised controlled trials (RCTs) are not feasible. While clinical trials remain the gold standard, RWE complements them by providing additional evidence that can enhance decision-making. The European Medicines Agency and the Heads of Medicines Agencies are actively integrating RWE into their regulatory processes through initiatives like the "Data Analysis and Real World Interogation Network" (DARWIN EU®).

To support this integration, the EMA has developed tools such as a metadata list used in the catalogues of RWD sources and studies, and a Data Quality Framework. These resources help ensure that RWE is reliable and can be effectively used in regulatory decision-making. The Big Data Steering Group and the Methodology Working Party are instrumental in guiding how RWE is incorporated into the EMA's processes.

Workshops and stakeholder engagements organised by these groups are crucial for discussing the practical application of RWE methodologies. The outcomes of these discussions shape further guidance, ensuring that RWE can be used confidently for regulatory purposes. This commitment to leveraging high-quality data and robust methods signifies a progressive step towards improved healthcare outcomes through more informed regulatory decisions.

Summary opening remarks Jeppe Larsen (HMA BDSG co-chair)

Over the past few years, HMA/EMA has been diligently working to leverage the potential of real-world data and evidence through the Big Data Steering Group and the Methodology Working Party. The anticipation surrounding the benefits of RWD is high across various sectors, including academia, industry, regulatory bodies, and healthcare.

The challenge now is to meet these high expectations and effectively harness these benefits. To address this, HMA/EMA has been developing essential knowledge and tools to ensure to deliver on these promises. Furthermore, while medical devices have not traditionally been a primary focus, they are gaining increasing attention due to the merging of technologies, which calls for a more consistent approach to clinical evidence across both fields.

Moving forward, it is crucial to expand our knowledge and maintain a robust dialogue and active participation to advance our understanding and application of RWD and RWE.

Joint HMA/EMA Big Data Steering Group workshop on RWE methods: setting the scene

Summary presentation of Patrice Verpillat (Regulator – EMA)

The workshop explores the pivotal role of RWD and RWE in regulatory decision making, with a particular emphasis on the European regulatory framework and international harmonisation efforts, particularly under the International Council for Harmonisation (ICH) M14 framework.

The workshop discussions include detailed examination of the RWE draft reflection paper, targeted sessions on specific methodologies such as target trial emulation and the use of external controls, and a look at the MWP's three-year work plan to guide future regulatory guidance and collaborative efforts. Each of the RWE methods will be discussed in the context of their application, strengths, and limitations. Key challenges such as data quality, ethical considerations regarding privacy and data sharing, and the need for methodological rigor are acknowledged, highlighting the importance of broad collaboration among researchers, clinicians, policymakers, and other stakeholders.

By engaging a diverse group of stakeholders, the workshop aims to foster in-depth discussions and gather valuable input to shape the future integration of RWD and RWE in regulatory decision-making, ultimately enhancing the robustness and relevance of evidence used in regulatory contexts.

Data-driven approaches in health research & innovation

Summary presentation of Tomasz Dylag (Policy and funding – European Commission, DG Research and Innovation)

The European health sector is experiencing a significant evolution through a series of legislative, research, and collaborative initiatives aimed at enhancing health data utilisation and innovation. At the forefront of this transformation is the European Health Data Space (EHDS), a landmark piece of legislation designed to streamline the exchange and application of health data across EU member states. Scheduled for adoption by early 2025, the EHDS regulation is set to boost the use and reuse of health data by establishing frameworks for both primary use, which pertains to direct healthcare delivery, and secondary use, which covers applications in research, innovation, policy-making, and regulatory processes.

Complementing this legislative effort are the research initiatives funded under Horizon Europe and the Innovative Health Initiative (IHI). These initiatives are at the cutting edge of developing methodologies for RWD analysis, with a notable example being the MetReal cluster of six projects. This cluster is working to establish robust evidentiary standards and machine learning methods for regulatory and HTA processes. Among these projects, The Real4Reg stands out for its focus on utilising AI and machine learning to enhance the analysis of RWE for decision-making, particularly in areas such as breast cancer and amyotrophic lateral sclerosis (ALS). Public-private partnerships further amplify these efforts, with the Innovative Medicines Initiative (IMI) and IHI fostering collaboration across various health industry sectors. Noteworthy projects in this arena include EHDEN, which aims to standardize health data to improve interoperability and accelerate evidence generation through a massive collaboration involving 187 partners and over 850 million records. Another significant project, IDERHA (Interrogation of Heterogeneous Data and Evidence towards Regulatory and HTA Acceptance), focuses on integrating health data

from diverse sources, including wearables and digital applications, to enable real-time data analysis for decision-making, with a specific focus on lung cancer. Additionally, the IMPROVE project is enhancing value-based healthcare by integrating patient-reported outcomes and real-world data from wearables, with applications across ophthalmology, oncology, and cardiovascular conditions.

Regulatory advancements are also being driven by events like the Regulatory Science Summit held by the IHI in February 2024, which provided a platform for discussing cutting-edge topics such as rare diseases, pediatrics, regulatory sandboxes, Artificial Intelligence (AI) in healthcare, and the use of real-world data. The summit highlighted the importance of generating evidence from diverse sources and integrating them into regulatory frameworks, addressing the need for predictability and understanding in the acceptance of RWE.

Presentation and discussion of RWE reflection paper

Summary of session 1

Key messages

- EMA has published a draft RWE reflection paper (RP) that offers guidance on the use of real-world data in non-interventional studies (NIS) to generate real-world evidence for regulatory purposes. The development of this paper is part of the Methodology Working Party Workplan 2022-2024 and the joint HMA-EMA Big Data Steering Group plan 2023-2025.
- Interested partners and stakeholders involved in the planning, conduct and analysis of non-interventional studies are invited to provide feedback on the draft reflection paper during a public consultation round. The public consultation process is aimed to further refine and enhance the guidance, ensuring that stakeholders' perspectives are incorporated to strengthen the methodological rigor and transparency in this important area of research.
- This initiative by the EMA not only highlights the importance of incorporating RWD into regulatory decision-making but also sets a framework for methodological rigor and transparency in non-interventional studies.

Use of real-world data in non-interventional studies to generate real-world evidence: draft reflection paper

Summary presentation of Xavier Kurz (Expert - ESEC)

The presentation described the development and content of the draft RWE reflection paper on the use of RWD in regulatory processes, specifically for generating RWE. The RP has gone through several iterations and was reviewed by key EMA Committees and approved for public consultation by the Committee for Medicinal Products for Human Use (CHMP) in April 2024 and was published in May 2024, with a consultation period open until the end of August 2024.

The paper offers a comprehensive framework for integrating RWD and RWE into the regulatory process, in the context of NIS. It carefully defines RWD as data that describe patient characteristics (including treatment utilisation and outcomes) in routine clinical practice. RWE is evidence derived from the analysis of RWD. One of the central themes of the paper is the emphasis on the quality and reliability of data, stressing the need to minimise bias and ensure that the evidence generated is reliable enough to support regulatory decisions. The paper advocates for a proactive and collaborative approach, encouraging early and ongoing dialogue between stakeholders and regulators to optimize the use of RWD. It also emphasises that the appropriateness of using RWD should be assessed on a case-by-case basis, recognizing that not all data are suitable for all regulatory purposes.

Methodologically, the paper highlights the importance of employing reliable frameworks, such as target trial emulation and estimand frameworks, to improve study design, reduce biases, and enhance the credibility of the findings. These frameworks help align non-interventional study designs with the standards of randomised controlled trials, thereby increasing the validity of RWD in regulatory decision-making. Additionally, the paper addresses critical issues related to

data governance, transparency, and the need for meticulous documentation of data sources. This ensures that the reliability and relevance of the data can be confirmed, which is crucial for its acceptance in regulatory contexts. The paper also underscores the importance of statistical analysis in the generation of RWE, particularly the need to focus on estimation and clinical relevance rather than mere statistical significance, especially when dealing with large datasets. This approach ensures that the conclusions drawn from the analysis are not only statistically sound but also meaningful and applicable in real-world clinical settings. Furthermore, the paper acknowledges the challenges inherent in working with RWD, such as potential biases and the need for high-quality data, and provides guidance on how to address these issues to produce valid and reliable evidence.

Overall, the reflection paper provides a framework for using RWD in regulatory assessments, stressing the importance of methodological rigor, transparency, and the case-by-case evaluation of RWD's suitability for answering specific regulatory questions.

Feedback from panel discussion

- The multi-stakeholder discussion highlighted several key themes that align with the points covered in the draft reflection paper. One participant emphasised the importance of developing a fit-for-purpose framework for evaluating RWE, noting the need for clarity on methodologies and consistent criteria to enhance the applicability and reliability of non-interventional studies. This included the significance of defining terminology and addressing ambiguities in the reflection paper to foster better dialogue among stakeholders. Another contributor praised the reflection paper for its structured guidance and focus on feasibility assessments, which were seen as critical for avoiding low impact studies and improving methodological transparency. The value of target trial emulation was highlighted for its rigorous approach to mimicking clinical trials, which can enhance trust in RWE. A representative of patient interests brought an important perspective on the practical impact of research methodologies on patient outcomes. They urged a sharper focus on the positive potential of methodologies to address underrepresentation of some populations and biases in clinical trials, advocating for methods that genuinely reflect patient realities and improve accessibility to novel therapies. A further perspective supported the paper's emphasis on causal inference and stressed the importance of addressing methodological gaps, such as handling treatment switching and loss to follow-up through evidence synthesis. The need to adapt study designs and methods to ensure the clinical relevance of findings was also underscored.
- The discussion pointed out the need for further clarification and development in certain areas. Firstly, the purpose of the RP needs to be defined more clearly to ensure that all stakeholders have a common understanding of the objectives and goals of the research. Secondly, there is a call for a greater emphasis on analytical bias. This involves a deeper examination of how the same dataset can lead to varying results, depending on the analytical methods used. The definition of NIS was another area identified as requiring a more precise explanation to avoid any ambiguity in interpretation. Lastly, the stakeholders suggested that the RP should explicitly address the applicability of its text to both primary and secondary research, ensuring that the findings and recommendations are relevant and useful across different research contexts.

Target Trial Emulation (TTE) and estimand frameworks for non-interventional studies with casual objectives

Summary of session 2a

Key messages

- Target trial emulation (TTE) and the estimand frameworks represent sophisticated approaches to causal inference in observational research. TTE involves simulating a hypothetical (randomised) trial using real-world data to address causal questions, ensuring that study designs closely mirror the rigor of randomised trials. Meanwhile, the estimand framework focuses on clearly defining and managing treatment effects amidst real-world complexities, including intercurrent events and varying treatment conditions.
- Together, these methodologies enhance the precision of causal estimates and align non-interventional (observational) studies more closely with the standards of clinical trials, improving the reliability and interpretability of findings in real-world evidence.

Introduction to regulatory-grade causal inference

Summary presentation of Xabier García de Albéniz (RTI Health Solutions)

Xabier García-Albéniz highlighted that the target trial emulation in causal inference covers several important concepts and methodologies that are essential for estimating causal effects using RWD.

It begins by defining key terminology, distinguishing between the causal estimand, which represents the true effect intended to be measured, and the statistical estimand, which depicts the statistical methodology to estimate this causal effect using the available data. The estimation process involves data analysis and the assumptions made during modelling.

The concept of target trial emulation is central to the discussion, with the goal being to frame a causal question by specifying a hypothetical randomised trial that would answer that question. This process requires defining the trial components, such as eligibility criteria and treatment strategies, and then emulating these components with the available data. A crucial aspect discussed is aligning "Time 0", the starting point for outcome measurement, which needs to be aligned with eligibility and exposure assignment to avoid bias, a task considered as being more complex in RWD than in randomised trials.

The presentation also explored the classification of treatment strategies, including accounting for grace periods, managing varying treatment durations, and addressing dynamic strategies based on specific conditions. When estimating treatment effects, the focus should be on complete adherence, particularly in safety studies, and on evaluating comprehensive treatment strategies rather than just drug intake. Additionally, post-baseline events such as changes in treatment, competing events, and follow-up losses are addressed to ensure appropriate causal effect estimation.

The presentation concluded by emphasising the importance of identifying relevant populations for decision-making, comparing comprehensive treatment strategies, aligning Time 0 with exposure and eligibility, and clearly stating all assumptions within the emulation framework.

Use of estimands in target trial emulation

Summary presentation of Juan Jose Abellan Andres (Regulator – EMA)

Juan Jose Abellan Andres provided a comprehensive presentation on the estimand framework. This framework represents an evolution from the traditional Population, Intervention, Comparison, Outcome, and Time (PICOT) approach, which has long been used to structure clinical trial research questions in RWD studies. When considering the TTE, the use of the estimands framework to specify the target trial would be more aligned with current regulatory guidance in clinical trials.

At its core, the estimand framework described in ICH E9(R1) emphasises the importance of clearly defining the treatment effect of interest in a given study through its attributes, which include specifying the population of interest, the outcome or variable being measured from each individual, the treatment conditions being compared, and the summary measure used to quantify the treatment effect. This structured definition is crucial for ensuring that the research question is addressed with precision and that the results are interpreted in a meaningful way.

Additionally, the framework addresses the challenge posed by the occurrence of intercurrent events—such as use of rescue medication, treatment discontinuation, treatment switches or death—that can occur after the initiation of treatment and affect the outcome or prevent its existence. By explicitly incorporating strategies to manage these intercurrent events, such as treatment policy, hypothetical, composite, or principal-stratum approaches, the estimand framework helps researchers specify more effectively how the occurrence of the identified intercurrent events inform the treatment effect and whether data after the intercurrent event are relevant. These strategies ensure that the treatment effect is assessed accurately despite the occurrence of events that might otherwise confound the results. For example, a treatment policy approach might evaluate the effect of treatment regardless of the occurrence of intercurrent events, while a hypothetical approach might consider the treatment effect in a scenario where such events would not occur. By clearly specifying these strategies upfront during the study design phase, rather than making ad-hoc adjustments during analysis, researchers can avoid discrepancies in the treatment effect targeted by a study and consequently ensure a more accurate interpretation of the treatment effect. Furthermore, the estimand framework clarifies the role of sensitivity analyses, which should aim at assessing the robustness of results against variations in assumptions made in the primary analysis. In contrast, changes in the definition of exposure or outcome lead to different estimands, i.e. different research questions.

Ultimately, the integration of the estimand framework into target trial emulation enhances the precision and clarity of causal questions, bridging the gap between traditional clinical trial methodologies and RWD studies. By advancing the way treatment effects are defined and analysed, this framework contributes to more reliable and actionable insights in health research, aligning RWE with regulatory standards of clinical trials and improving the overall quality of causal inferences drawn from RWD.

Target trial emulation in a DARWIN EU vaccine effectiveness study

Summary presentation of Daniel Prieto-Alhambra (Academia – DARWIN EU)

Daniel Alhambra Prieto discussed the ongoing study within DARWIN EU which is designed to evaluate the effectiveness of HPV vaccination in preventing severe disease outcomes, specifically invasive cervical cancer and high-grade cervical lesions such as CIN 2 and CIN 3, as well as related surgical interventions (i.e. conisation). This research spans three European countries: Norway, Spain, and the UK, and seeks to answer two main research objectives. The primary objective is to assess the vaccine's effectiveness in reducing the incidence of these severe outcomes. The secondary objective is to compare the effectiveness across different brands and vaccine schedules, provided sufficient data is available.

To minimise biases and enhance baseline exchangeability, the study design incorporates a comprehensive matching process. The population under study includes women who were eligible for HPV vaccination, focusing on those born from 1995 onwards and within the age range of 9 to 15 years at the time of vaccination. Participants are matched based on a variety of factors including geographic region, General Practitioners (GP) practice, year of birth, and propensity scores, which reflect the conditional probability of vaccination based on baseline characteristics. This approach aims to align the vaccinated and unvaccinated groups as closely as possible to ensure comparability.

To handle intercurrent events, the study employs a rigorous analytical strategy. This includes censoring unvaccinated individuals if they later receive the vaccine, a rare event due to the nature of the vaccination programs, while vaccinated individuals are only censored if they receive additional doses beyond the initial regimen. Methods such as propensity score matching and negative control outcomes are used to assess the impact of confounding. Additionally, the study examines testing rates over time to ensure that screening is balanced across vaccination statuses.

The integration of both the estimand framework and the target trial emulation approach is instrumental in strengthening the study's causal inference capabilities. These frameworks aid in defining the timing of outcomes and managing intercurrent events, thereby reinforcing the validity and robustness of the study conclusions.

Target trial emulation and estimand in post-market safety studies

Summary presentation of Rima Izem (Industry – Novartis)

The presentation focused on the importance of clearly defining the target causal estimate in post-marketing safety studies and demonstrated how the target trial emulation and estimand framework can aid in this process. Specifying the target causal estimate is crucial for aligning the study design, data sources, and analytical methods with its causal objective. By doing so, it clarifies the purpose of the study for all stakeholders and guides planning and interpretation.

These concepts were illustrated by using a hypothetical case study of a biologic drug, NovD, which was approved for treating patients with a chronic indication by repeated exposure. The complexities of defining comparators and handling intercurrent events - factors that can significantly influence the study results – were discussed. The presentation outlined practical considerations related to the timing of information, noting that the knowledge gap and relevant information can evolve from the time of drug approval to the final analysis. This evolution necessitates a flexible approach in defining and refining the causal estimate.

The presentation highlighted that while the initial pre-specification of the analysis plan is important, it should be done cautiously and with an understanding that more descriptive data may become available over time. It was also pointed out that real-world treatment practices are

by nature dynamic, which can affect study outcomes and should be accounted for in the analysis.

In that respect, the target trial emulation and estimate frameworks are invaluable tools for ensuring that post-market safety studies are well-aligned with their causal objectives and adaptable to new information as it emerges.

Feedback from panel discussion

- The multi-stakeholder discussion underscored the significant potential of TTE in enhancing the use of RWD in clinical research, emphasising its complementary role to, rather than replacement of, RCTs. It was noted that TTE can bridge the gap between RWD and clinical development, provided it is applied thoughtfully to address specific research questions and design studies that complement existing RCTs. The TTE framework was recognized for its ability to help clearly define causal questions in comparative effectiveness or safety studies of medicines and specify treatment strategies, which improves the interpretability and quality of non-interventional studies. However, it was stressed that TTE should be approached as a three-step process: (1) specifying an target trial ideally using the estimands framework, (2) adapting it iteratively to RWD, and (3) validating whether the non-interventional study that emulated trial addresses the intended question. Another key point raised was the application of TTE in post-market safety monitoring. While TTE holds promise in this area, it must be applied cautiously due to challenges such as generalisability and data completeness. Addressing these issues will require comprehensive and granular data sets and advanced statistical methods.
- The session called for rigorous standards and clear guidance to ensure the effective integration of TTE into regulatory decision-making, allowing for meaningful comparisons with RCTs. Additionally, the discussion highlighted the importance of collaboration and communication between trial investigators and researchers to leverage TTE effectively and improve the quality of evidence in clinical research.

RWD derived external controls in clinical trials

Summary of session 2b

Key messages

- The integration of RWD into clinical trials as external controls presents a nuanced landscape of benefits and challenges. However, integrating RWD as an external control also introduces unique complexities and uncertainties, including potential biases and data quality issues, which must be carefully managed to ensure robust and reliable conclusions.
- The EMA emphasises the critical understanding of the limitations and appropriate contextual use of RWD as external controls in clinical trials.
- As the industry moves forward, it is essential to recognise these complexities and develop robust methodologies that can leverage the strengths of studies based on RWD and RCTs to inform regulatory decisions effectively.

RWD-derived external controls in regulatory context

Summary of presentation of Elina Asikanius (Regulator – MWP)

The presentation provided a detailed examination of the challenges and considerations associated with using external controls from RWD in clinical trials, particularly in the context of regulatory decision-making. She explained that external controls, which compare treatment effects observed in clinical trials against data from outside those trials, can offer valuable insights but also introduce significant uncertainty. This uncertainty arises because RWD and clinical trial data are fundamentally different in their collection methods, patient populations, and treatment conditions. She pointed out that while RCTs are the gold standard due to their rigorous design and comprehensive data on multiple endpoints, external controls often focus narrowly on a single primary endpoint, potentially overlooking other critical aspects such as secondary endpoints, safety, tolerability, and patient adherence. This limitation makes it challenging to draw robust comparisons and assess the full spectrum of treatment effects.

She emphasised that distinguishing between the effects of the treatment and the effects related to the data source is a major hurdle. RWD can introduce biases and variability that are not present in the more controlled setting of RCTs. She also addressed the issue of comparing treatment effects using external controls, noting that such comparisons require careful consideration of exchangeability—the concept that the external data should be comparable to the trial data in terms of population characteristics, clinical practice, and other factors. This complexity often makes it difficult to ensure that the comparisons are truly valid.

Differences between external controls and single-arm trials were further discussed, noting that single-arm studies sometimes receive regulatory approval based on endpoints that can isolate the drug effect, such as absolute treatment responses in oncology. In contrast, external controls involve comparing treatment effects across different sources, which demands a higher level of scrutiny to ensure their exchange ability.

Finally, while external controls have their place, they are rarely the best option due to the added uncertainty they bring. The scientific community should focus on identifying scenarios where external controls can genuinely complement existing evidence rather than merely adding complexity. The final message was a call for ongoing discussion about how to effectively integrate external controls into the evidence base in a way that addresses these challenges and enhances the robustness of regulatory assessments.

The use of RWD derived external control arm to assess the benefit of new therapies

Summary of presentation of Maurille Feudjo Tepie (Industry – UCB)

The presentation provided detailed information on a case study where an external control arm was used for regulatory interactions. The goal was to illustrate how an external control can help provide additional context to a single-arm trial, potentially reducing, rather than adding, uncertainty. The presenter discussed the specific condition under investigation, which was a rare mitochondrial disorder called Thymidine kinase 2 deficiency (TK2d), characterised by severe muscle weakness and high mortality rates.

The condition, first described in 2001, affects fewer than two people per million, and there is no approved treatment available, with current management limited to supportive care. The investigational drug, referred to as dCT, showed promising results in reducing mortality and was granted orphan designation and later eligibility for the priority medicines (PRIME) program. Despite these promising results, the difficulty of conducting a conventional trial due to the rarity of the condition and the lack of existing registries was emphasised.

To address these challenges, a new data repository was built using retrospective data, supplemented by a systematic literature review and collaboration with investigators to gather individual patient data. The external control group was composed of patients from the investigational trial and those receiving the drug through a compassionate use program. Key analytical considerations included ensuring that the outcome measures were relevant to clinical practice, such as survival, and addressing potential biases. Efforts were made to achieve comparability between the external control and the trial data, including considerations for immortal time bias and employing various analytical methods such as Cox proportional hazards analysis and exact conditional logistic regression.

The presentation concluded with a discussion of the critical questions faced during this process, particularly regarding the adequacy of the external control and the clarity of the initial regulatory interactions.

Externally controlled trials in oncology

Summary of presentation of Donna Rivera (Regulator – US FDA)

Donna Rivera delivered a comprehensive presentation on the use of externally controlled trials (ECT) in oncology. Her talk was structured into three main areas: guidance on ECTs, methodological challenges, and a case study of a recent approval using an ECT. She began by outlining the FDA's guidance on ECT design, emphasising that such trials measure the outcomes of a new treatment against outcomes from external, non-trial sources. The guidance highlights that ECTs are often considered when randomisation is not feasible due to ethical or practical constraints. The importance of thorough upfront planning and consulting with relevant review divisions to assess the appropriateness of an ECT was highlighted, noting that these trials are typically used in scenarios such as rare diseases or high unmet medical needs.

She addressed the methodological challenges associated with ECTs, including issues related to data source comparability, completeness of data capture, and potential biases such as selection and immortal time bias. Despite their utility, ECTs often face limitations compared to RCTs and are generally used as supportive evidence rather than primary evidence. The FDA's recent approval of Eflornithine (DFMO) for neuroblastoma was used as an example to explain how an ECT can be used to demonstrate efficacy. In this case, the external control data came from a well-matched and robustly analysed source, overcoming many of the typical challenges associated with ECTs.

The presentation concluded by reaffirming the FDA's preference for RCTs due to their rigorous design, but acknowledged the practical and ethical limitations that sometimes necessitate the use of ECTs. The importance of careful design and thorough evaluation when using external controls was again emphasised to ensure valid and reliable evidence.

RWD-derived external controls case study

Summary of presentation of Adrea Buzzi and Theodor Framke (Regulator - EMA)

The presentation began with an introduction to ABECMA, a CAR T-cell therapy developed by Bristol Myers Squibb, which was granted conditional marketing authorisation by the European Commission on August 18, 2021. ABECMA, also known as Idecabtagene vicleucel, was the first CAR T-cell product approved for treating relapsed and refractory multiple myeloma in adult patients who had received at least three prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody. The approval was based on the pivotal MM-001 (KarMMa-1) study, a Phase 2 open-label trial that assessed the therapy's efficacy and safety, focusing on endpoints such as overall response rate (ORR) and complete response rate (CRR). In addition to the KarMMa-1 study, supportive evidence was drawn from the CRB-401 dose-escalation study and from the NDS-MM-003 study, a global non-interventional retrospective study using historical control data which provided real-world insights into patients with similar profiles who had relapsed and refractory multiple myeloma.

Then the methodology used in the external control study was detailed. This study aimed to complement the single-arm KarMMa-1 trial by using data from clinical sites, registries, and research databases. The study employed inverse probability of treatment weighting (IPTW) to adjust for differences between the trial and real-world patient populations. Despite rigorous efforts to match patients based on criteria similar to those in the KarMMa-1 trial, there were significant limitations. For example, discrepancies between the different sources in patient demographics and treatment history, as well as data missingness affected the analysis. While external control data provided valuable context, it was noted that it could not fully substitute for randomised controlled trial data, which remains the gold standard for assessing long-term efficacy and safety.

The presentation concluded by acknowledging that the external control study, while useful for contextualising the findings of the KarMMa-1 trial, was not the primary basis for the initial conditional marketing authorisation. The need for more comprehensive data, including randomised controlled trials, was recognized to support future full marketing authorisation. The efforts to use RWE were appreciated as a supplementary approach, but the focus remained on obtaining robust, high-quality evidence through rigorous clinical trials.

Feedback from panel discussion

- The multi-stakeholder discussion explored the nuanced role of external controls in clinical trials, particularly when incorporating RWD. It was noted that external controls can provide valuable context for single-arm trials, especially in cases of rare or high-need conditions where randomisation may not be feasible. However, their application is complex and demands careful trial design to manage various challenges. Key concerns include ensuring data comparability, dealing with uncertainties related to the timing of data (whether contemporaneous or historical), geographic representation, and the completeness of the available data. One point of emphasis was the importance of tailoring methodologies to the specific research question at hand. While external controls may be appropriate in certain situations, randomisation should be prioritised whenever possible, even in rare diseases. Innovative trial designs were also encouraged to address these complexities. The panel also stressed the need for validating external comparators by comparing data from multiple sources. Examples were cited where external controls either aligned with or diverged from trial data, underscoring the necessity for rigorous standards and transparency. Biases introduced by external controls were another major concern, with calls for thorough scrutiny, transparency, and early engagement with regulators to mitigate potential issues. Comprehensive regulatory guidance on the use of external controls would also be beneficial.
- While external controls can be useful in situations of high unmet need, they require careful planning and rigorous standards to address uncertainties and biases. Considerations such as assessing feasibility appropriately, minimising biases, and ensuring methodological rigor are essential for generating reliable RWE.

The next three years: roadmap for RWE guidance

Summary of session 3

Key messages

- The MWP is part of EMA's Committee for Medicinal Products for Human Use (CHMP) working parties and is committed to maintaining high standards of evidence. The future focus areas include external controls, Bayesian statistics, platform trials, the development of a guideline on predictive biomarker co-development, as well as the application of AI in both clinical development and pharmacovigilance.
- Their roadmap for the development of RWE guidance includes providing guidance on external controls derived from RWD and using external data to supplement control arms in clinical trials. A panel discussion further highlighted the importance of involving patients and considering their perspectives throughout the drug development process, underscoring the significance of patient-centric approaches.

Introduction to the Methodology Working Party

Summary of presentation of Kit Roes (Regulator - MWP Chair)

A comprehensive overview of the Methodology Working Party, established in 2022 to enhance the decision-making capabilities of the CHMP and the broader European Medicines regulatory network (EMRN) was provided. Set-up in response to the evolving needs of evidence generation and data integration, the methodology working party (MWP) consolidates expertise from previously separate groups—Biostatistics and Modelling & Simulation—into a unified, multidisciplinary entity. The MWP now also includes the important areas of Clinical Pharmacology, Real World Data, Artificial Intelligence & Data Science and Pharmacogenomics.This integration aims to address more effectively complex issues linked to drug development and evidence requirements.

The MWP is engaged in a range of activities including offering product-related support, producing guidance documents, and developing concept papers. It has increased its interactions with stakeholders over the past year to tackle shared challenges and foster network confidence. The MWP includes 23 diverse experts and a broader network of more than 200 additional specialists, comprising methodological assessors and academic professionals, which enhances its capacity for addressing various scientific and regulatory challenges.

Key areas of current focus include RWE, Bayesian statistics, platform trials, and the use of AI throughout the medicine product lifecycle. The party has contributed to significant initiatives such as the Data Quality Framework and is working on a new three-year rolling work plan that will be informed by stakeholder feedback. Future priorities include refining guidance on external controls, predictive biomarker co-development, and expanding its scope to include medical device interactions.

The presentation underscores the importance of designing trials with clear research questions to minimise the need for external controls post hoc, and emphasises a focus on key scientific considerations over rigid definitions of what is acceptable. Additionally, it highlights the party's

commitment to collaborating with other regulatory and research groups and leveraging Horizon Europe projects to advance methodologies in real-time. This collaborative approach aims to ensure that regulatory guidance supports innovation while maintaining high standards of evidence and effective decision-making.

MWP Roadmap for the development of RWE guidance

Summary presentation of Olaf Klungel (Regulator – MWP)

First, an overview and in-depth analysis of the existing global guidance on RWE, with guidance available from various regulatory and health authorities, including the FDA, EMA, and ICH, was shown and laid out a roadmap for future development in this area. . Notably, the FDA has issued extensive guidance related to RWE, particularly focusing on externally controlled clinical trials and pragmatic trials that utilize RWD. The EMA has also contributed significantly with its data quality framework, guidance on registry-based studies, and a reflection paper on non-interventional studies using RWD. Additionally, ICH is currently working on a guidance mainly focused on safety assessments of medicines.

Despite the substantial number of guidance provided by these organizations, several critical gaps still exist. Notably, there is a lack of specific guidance on using external control data to supplement control arms in clinical trials. While there is some guidance available on external controlled trials from the FDA and National Health Institute for Health and Care Excellence (NICE), this does not fully address the need for a comprehensive approach that integrates both clinical trial data and RWD. Furthermore, guidance on pragmatic clinical trials, which are typically conducted post-authorisation and utilise RWD is available, but may require further refinement and development.

The importance of addressing these gaps was emphasised with the need to develop more integrated guidance that would cover the use of external controls and pragmatic trials comprehensively. These future guidance should not only focus on current needs but also be adaptable to emerging methodologies and innovations in the field. This approach would ensure that the guidance remains relevant and useful as new developments and technologies emerge.

The presentation concluded with a call for a dynamic and responsive process in RWE guidance development. The necessity of ongoing stakeholder engagement to capture diverse perspectives and needs was highlighted. This will help ensure that future guidance is well-informed, practical, and aligned with the latest advancements in RWE methodologies. By addressing these gaps and maintaining a flexible approach, the development of RWE guidance can better support the evolving landscape of clinical research and evidence generation.

Feedback from panel discussion

- The multi-stakeholder discussion provided an in-depth examination of the challenges and opportunities associated with the use of RWE in healthcare. One key focus was the importance of establishing robust data quality frameworks and clear guidelines for evaluating the suitability of data sources for regulatory questions as well as for performing appropriate feasibility assessment. With the European Health Data Space (EHDS) expected to increase data availability and expand the number of parties generating RWE, there will be a stronger need to ensure data integrity and apply advanced methodologies, such as AI and large language models, for analyzing unstructured data. Approaches similar to those used in clinical trials, including staged assessments and clean-room methodologies, were advocated to enhance the reliability

of causal inferences drawn from RWE. Another perspective emphasised the critical role of academia in harnessing RWE, particularly in fields where traditional randomised controlled trials are difficult to conduct, such as paediatrics and rare diseases. Continuous updates to data sources, ethical compliance, adequate quality, population covered and duration of data collection, especially for off-label medication use, were highlighted as essential. Academic institutions must work closely with regulatory bodies to ensure that data used for evidence generation is both current and properly sourced for regulatory purposes. Upcoming review of the pharmaceutical legislation is expected to place greater responsibility on academia to provide high-quality RWD for regulatory submissions, e.g. for repurposed medicines. From a patient representative viewpoint, there was a call for more active involvement of patients and citizens in the RWE process. Patients were seen as key contributors not only in study design but also in providing experiential data and interpreting results. Mechanisms that allow citizens to have control over their data were deemed important, and retrospective analysis of existing RWD was suggested as a way to expedite research. However, there was a cautionary note about the need to balance innovation with the risks associated with rapidly implementing new technologies, particularly in the context of degenerative diseases. In the context of clinical guidelines development, the integration of RWE was acknowledged to pose challenges related to transparency and data quality. A structured, transparent approach to categorizing and interpreting RWE, including clear specifications of data sources and methodologies, was advocated. There is a need to expand existing data quality frameworks and provide practical guidance to help end-users make evidence-based decisions. A more comprehensive approach that blends traditional research methodologies with RWE was seen as essential for improving the quality and applicability of clinical guidelines.

- The panel emphasised the critical need for comprehensive data quality frameworks, greater stakeholder involvement, and a balanced approach to integrating innovation. The discussion highlighted that improving the use of RWE requires collaboration among researchers, patients, regulators, and academia to ensure that evidence generated is reliable, ethically sourced, and applicable to real-world healthcare decisions.

Summary and take-home message

The workshop was considered by all participants as successfull in advancing the discussion on the use of RWE in medicines regulation. It was emphasised that while RCTs remain the primary method for demonstrating efficacy, RWE plays a crucial role in understanding disease epidemiology, treatment effects and safety.

The RWE draft reflection paper is a step towards integrating RWD effectively into regulatory decision making. Feedback from stakeholders suggested a need for clearer definitions, a focus on analytical bias, and improved explanations of the paper’s applicability to both primary and secondary research.

While RWE methods discussed offer powerful tools, the successful use in a regulatory context depends on rigorous standards, clear methodologies and effective collaboration. Improving the use of RWE demands collaboration among researchers, patients, regulators, and academia to ensure that the evidence generated is reliable, ethically sourced, and relevant to real-world healthcare decisions.

Key takeaways included the importance of designing research protocols with a focus on impactful evidence, utilizing methods such as target trial emulation, and ensuring thorough planning to enhance RWE reliability. The European Medicines Regulation Network's commitment to advancing the use of RWE by establishing its value and enabling its use collaboratively with all stakeholders was underscored as essential for faster drug development, optimized regulatory assessments, and addressing unmet medical needs.

Appendix 1. List of speakers

Emer Cooke	EMA
Peter Arlett	EMA
Jeppe Larsen	Danish Medicines Agency
Patrice Verpillat	EMA
Tomasz Dylag	DG Research and Innovation, European Commission
Kit Roes	MWP Chair, Medicines Evaluation Board (MEB)
Mencía de Lemus Belmonte	CAT member
Xavier Kurz	ESEC RWE
Olaf Klungel	MWP member
Almath Spooner	Abbvie
Helga Gardarsdottir	Utrecht University
Bettina Ryll	Melanoma Patient Network Europe
Holger Schunemann	Humanitas University
Harald Enzmann	CHMP Chair
Daniel Morales	EMA
Xabier García de Albéniz	RTI Barcelona
Juan Jose Abellan Andres	EMA
Daniel Prieto-Alhambra	Oxford university, DARWIN Coordination Centre
Rima Izem	Novartis
Helene Nordahl	Novo Nordisk
Anthony Matthews	Karolinska Institutet
Rhea Fitzgerald	PRAC member
Carla Torre	MWP, PRAC and CHMP member
Marcia Rueckbeil	EMA
Elina Asikanius	SAWP and MWP member
Maurille Feudjo Tepie	UCB
Donna Rivera	FDA
Andrea Buzzi	EMA
Theodor Framke	EMA
Mehmet Burcu	MSD
Denis Lacombe	EORTC

Jan Cornelissen	EMA, Erasmus MC Cancer Institute
Bruno Delafont	CHMP member
Marieke Schoonen	Amgen
Viviana Giannuzzi	Fondazione per la Ricerca Farmacologica Gianni Benzi onlus
George Paliouras	Duchenne Data Foundation
Ioana Agache	EAACI and BDSG member

Appendix 2. Acronyms

AI	Artificial Intelligence
BDSG	Big Data Steering Group
CAT	Committee for Advanced Therapies
CC	Coordination Centre
CHMP	Committee for Medicinal Products for Human Use
DARWIN EU	Data Analysis and Real World Interrogation Network
EAACI	European Academy of Allergy and Clinical Immunology
EC	European Commission
ECT	Externally Controlled Trial
EHDS	European Health Data Space
EMA	European Medicines Agency
EMRN	European Medicines Regulatory Network
ESEC	European Specialised Expert Community
EU	European Union
FDA	Food and Drug Administration
HCP	Health Care Professional
HMA	Heads of Medicines Agency
ICH	International Council for Harmonisation
IHI	Innovative Health Initiative
IMI	Innovative Medicines Initiative
MWP	Methodology Working Party
NICE	National Institute for Health and Care Excellence
PRAC	Pharmacovigilance Risk Assessment Committee
PRIME	Priority Medicines
RCTs	Randomised Controlled Trials
RF	Reflection Paper
RTI	Research Triangle Institute
RWD	Real-world Data
RWE	Real-world Evidence
SAWP	Scientific Advice Working Party
TDA	Data Analytics and Methods Task Force

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Report on the joint HMA/EMA Big Data Steering Group workshop on real-world evidence (RWE) methods: Harnessing real-world data for regulatory use
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