

WHITEPAPER

Real World Evidence (RWE) for Medical Devices



Real-world evidence (RWE) refers to data regarding the use, effectiveness, and safety of medical products (such as drugs, biologics, and medical devices) that is derived from real-world sources, including electronic health records, claims data, patient registries, and other healthcare databases. Unlike data collected in controlled clinical trials, RWE is generated in routine clinical practice and reflects the diverse patient populations, clinical settings, and healthcare delivery systems encountered in real-world healthcare settings.

RWE has gained increasing attention and importance in healthcare and regulatory decision-making for several reasons:

1. Complementing Clinical Trial Data: While clinical trials provide valuable evidence for regulatory approvals, they often have limitations in terms of patient representativeness, duration, and generalizability. RWE can complement clinical trial data by providing insights into the long-term effectiveness, safety, and real-world performance of medical products across broader patient populations and clinical settings.

2. Supporting Regulatory Decisions: Regulatory agencies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), are increasingly recognizing the value of RWE in regulatory decision-making processes. RWE can support various regulatory activities, including drug and medical device approvals, labeling decisions, post-market surveillance, and regulatory policy development.

3. Post-Market Surveillance: RWE plays a crucial role in post-market surveillance by enabling continuous monitoring of the safety and effectiveness of medical products once they are on the market. By analyzing real-world data, regulators can detect potential safety signals, monitor product performance over time, and make informed decisions regarding product safety updates, labeling changes, or market withdrawals.

4. Healthcare Decision-Making: RWE is also valuable for informing healthcare decision-making by providers, payers, policymakers, and other stakeholders. It provides evidence on the comparative effectiveness, cost-effectiveness, and real-world outcomes associated with different treatment options, facilitating informed clinical decision-making, reimbursement decisions, and health policy development.

5. Patient-Centered Research: RWE can capture patient-reported outcomes, preferences, and experiences, providing insights into the real-world impact of medical products on patients' lives. This patient-centered perspective is increasingly important in healthcare research, regulatory evaluations, and healthcare delivery.

6. Challenges and Limitations: Despite its potential benefits, RWE also presents challenges and limitations, including data quality issues, biases inherent in observational data, privacy and data protection concerns, and the need for standardized methodologies and regulatory acceptance criteria. Addressing these challenges requires collaboration among stakeholders and ongoing efforts to improve data quality, transparency, and regulatory standards.

Importance of RWE

RWE is becoming increasingly important in regulatory submissions for medical devices. Traditionally, regulatory submissions have relied heavily on data from clinical trials conducted in controlled settings. However, RWE provides insights into how medical devices perform and are used in real-world clinical practice. Here are some impacts of RWE on medical device regulatory submissions:

1. Supplementing Clinical Trial Data: RWE can complement data from clinical trials by providing information on the long-term effectiveness, safety, and performance of medical devices in diverse patient populations and real-world settings. This can strengthen the overall evidence base supporting regulatory submissions.

2. Expanded Indications: RWE may support expanded indications for medical devices by demonstrating their effectiveness and safety in patient populations or clinical scenarios not fully captured in traditional clinical trials. This could lead to broader labeling and use of medical devices.

3. Post-Market Surveillance: RWE plays a crucial role in post-market surveillance by providing continuous monitoring of medical device performance and safety once they are in routine clinical use. Regulators can use this data to identify potential safety concerns, inform regulatory decisions, and require post-market studies or labeling updates.

4. Regulatory Decision Making: Regulators, such as the FDA in the United States and the EMA in Europe, increasingly consider RWE in regulatory decision-making processes. Well-designed real-world studies can provide valuable insights into the real-world performance of medical devices, influencing regulatory decisions related to approval, labeling, and post-market requirements.

5. Reduced Regulatory Burden: RWE may offer opportunities to streamline regulatory processes and reduce the burden of conducting large-scale clinical trials, particularly for certain types of medical devices or post-market studies. This can lead to faster approval times and more efficient regulatory pathways.

6. Value-based Healthcare: RWE contributes to the shift towards value-based healthcare by providing evidence of the real-world effectiveness and cost-effectiveness of medical devices in improving patient outcomes and healthcare delivery. This can influence reimbursement decisions and market access for medical devices.

7. Challenges and Considerations: Despite its benefits, leveraging RWE in regulatory submissions also poses challenges, such as ensuring data quality, patient privacy protection, standardization of methodologies, and regulatory acceptance. Addressing these challenges requires collaboration among stakeholders, including regulators, industry, healthcare providers, and patients.

Overall, the integration of RWE into regulatory submissions for medical devices represents a paradigm shift towards a more evidence-based, patient-centered approach to medical device regulation and healthcare decision-making.

Start to end regulatory submission process for medical device by using real world evidence

The use of RWE in regulatory submissions for medical devices involves several steps from the collection of data to its analysis and incorporation into the submission. Here's a generalized start-to-end process:

1. Identifying Regulatory Requirements: The first step is to understand the regulatory requirements for using real-world evidence in medical device submissions. This involves reviewing relevant guidance documents, regulations, and expectations from regulatory authorities such as the FDA in the United States or the European Medicines Agency (EMA) in the EU.

2. Defining the Research Question: Clearly define the research question or objective for which real-world evidence will be used. This could involve assessing the safety, effectiveness, or performance of the medical device in real-world clinical practice.

3. Data Source Selection: Identify suitable real-world data sources that can provide the necessary information to address the research question. Common sources of real-world data include electronic health records (EHRs), claims databases, registries, medical charts, and patient-reported outcomes.

4. Data Collection: Collect the relevant real-world data from the chosen sources. This may involve accessing existing databases or conducting new data collection efforts, such as prospective observational studies or data linkage projects.

5. Data Management and Quality Assurance: Ensure that the collected data is managed effectively and meets quality standards. This includes data cleaning, validation, and verification processes to ensure accuracy, completeness, and reliability.

6. Analysis and Interpretation: Analyze the real-world data to answer the research question or objective. This may involve statistical analysis, epidemiological methods, or other analytical techniques to assess the safety, effectiveness, or performance of the medical device in real-world clinical settings.

7. Evidence Synthesis: Synthesize the findings from the real-world evidence analysis into a coherent narrative. This involves summarizing the key results, discussing their implications, and placing them in context with existing evidence from clinical trials or other sources.

8. Regulatory Strategy Development: Develop a regulatory strategy for incorporating the real-world evidence into the medical device submission. This includes determining the appropriate regulatory pathway (e.g., premarket approval, 510(k) clearance, or post-market surveillance), preparing the submission documents, and identifying any additional data or analyses needed to support the submission.

9. Submission Preparation: Prepare the regulatory submission documents, including the real-world evidence analysis plan, study protocols, data summaries, statistical analyses, and any other supporting documentation required by regulatory authorities.

10. Regulatory Submission: Submit the regulatory application to the appropriate regulatory authority, such as the FDA or the relevant notified body in the EU. Include the real-world evidence and supporting documentation as part of the submission package.

11. Regulatory Review: The regulatory authority reviews the submission, including the real-world evidence, to assess the safety, effectiveness, and quality of the medical device. This may involve additional requests for information or clarification from the applicant.

12. Decision and Approval: Based on the review, the regulatory authority makes a decision on the regulatory application. If the submission is approved, the medical device may be granted market authorization or clearance for commercial distribution.

13. Post-Market Surveillance: Aftermarket authorization or clearance, continue to monitor the real-world performance of the medical device through post-market surveillance activities. This may involve ongoing data collection, analysis, and reporting of adverse events or other safety issues.

14. Lifecycle Management: Use real-world evidence to inform lifecycle management activities for the medical device, including label updates, post-market studies, and modifications to manufacturing processes or indications for use.

Throughout this process, it's essential to adhere to regulatory requirements, maintain data integrity and patient privacy, and communicate transparently with regulatory authorities regarding the use of real-world evidence in medical device submissions. Collaboration between medical device manufacturers, healthcare providers, regulators, and other stakeholders is critical to ensure the effective use of real-world evidence in regulatory decision-making.

How Real World Evidence Helps in Regulatory Submission Process in USA and EU

United States

In the United States, RWE is increasingly recognized as a valuable resource in the regulatory submission process for medical devices. While traditional pathways for medical device approval often rely on data from controlled clinical trials, the incorporation of RWE offers additional insights into the real-world performance, effectiveness, and safety of medical devices. Here's how RWE is being utilized in the medical device regulatory submission process in the USA:

1. Supporting Pre-market Activities: RWE can be leveraged during the pre-market phase to provide supplementary evidence alongside data from clinical trials. This can include data on device performance, patient outcomes, and safety in diverse clinical settings and patient populations. The FDA may consider RWE when assessing the benefit-risk profile of medical devices seeking market approval.

2. Expanding Indications: RWE can support efforts to expand the indications for use of medical devices by providing evidence of their effectiveness and safety in new patient populations or clinical scenarios. This can potentially lead to broader labeling and use of medical devices beyond their initial approved indications.

3. Post-market Surveillance and Studies: Once a medical device is on the market, RWE plays a crucial role in post-market surveillance and monitoring. Manufacturers are often required to conduct post-market studies or surveillance to gather real-world data on device performance, safety, and long-term outcomes. RWE obtained from these studies helps regulators and manufacturers identify and address potential safety concerns promptly.

4. Regulatory Decision Making: The FDA's Center for Devices and Radiological Health (CDRH) increasingly considers RWE in regulatory decision-making processes. Well-designed real-world studies and analyses can provide valuable insights into the real-world performance of medical devices, influencing regulatory decisions related to market approval, labeling, post-market requirements, and risk management.

5. Quality and Standards: To ensure the reliability and validity of RWE, the FDA emphasizes the importance of data quality, study design, and analytical methodologies. The FDA's framework for the use of RWE in regulatory decision-making outlines standards and requirements for generating, analyzing, and reporting real-world data to support regulatory submissions.

6. Collaboration and Guidance: The FDA collaborates with industry stakeholders, academic researchers, healthcare providers, and patient groups to develop guidance documents and frameworks for the use of RWE in regulatory submissions. These guidance documents provide recommendations and best practices for generating, analyzing, and integrating RWE into the regulatory process.

7. Continuous Learning and Improvement: The incorporation of RWE into the regulatory submission process reflects a commitment to continuous learning and improvement in medical device regulation. By leveraging real-world data, regulators and stakeholders can gain a better understanding of how medical devices perform in routine clinical practice and make more informed decisions to protect public health.

European Union

In the European Union (EU), RWE is increasingly recognized as a valuable component of the regulatory submission process for medical devices. The regulatory framework for medical devices in the EU is governed by the Medical Device Regulation (MDR) and the In Vitro Diagnostic Medical Devices Regulation (IVDR), which set out requirements for the assessment, approval, and post-market surveillance of medical devices. Here's how RWE is utilized in the medical device regulatory submission process in the EU:

1. Clinical Evaluation and Performance Assessment: The MDR and IVDR require manufacturers to conduct a clinical evaluation to assess the safety and performance of medical devices. RWE can be used as part of the clinical evaluation process to supplement data from clinical investigations and provide additional evidence on device performance, effectiveness, and safety in real-world clinical practice.

2. Post-Market Surveillance and Vigilance: Similar to other regulatory jurisdictions, the EU emphasizes the importance of post-market surveillance and vigilance to monitor the safety and performance of medical devices once they are on the market. RWE plays a crucial role in post-market surveillance by providing continuous monitoring of device performance, detecting potential safety issues, and informing regulatory decisions regarding device safety updates, recalls, or other regulatory actions.

3. Post-Market Clinical Follow-up (PMCF) Studies: The MDR and IVDR require manufacturers to conduct post-market clinical follow-up (PMCF) studies to gather additional clinical data on medical devices once they are on the market. RWE generated from PMCF studies can provide valuable insights into the long-term outcomes, real-world use, and safety profile of medical devices in routine clinical practice.

4. Health Technology Assessment (HTA) and Market Access: In addition to regulatory approval, medical device manufacturers may need to undergo health technology assessment (HTA) to demonstrate the clinical and cost-effectiveness of their devices for reimbursement and market access in EU member states. RWE plays a crucial role in HTA by providing evidence of the real-world clinical outcomes, patient outcomes, and economic impact associated with medical devices.

5. Collaboration and Guidance: The European Medicines Agency (EMA), the European Commission, and national competent authorities collaborate with stakeholders, including industry, healthcare providers, academia, and patient groups, to develop guidance and best practices for the use of RWE in regulatory submissions for medical devices. These guidance documents provide recommendations on study design, data collection, analysis, and reporting standards to ensure the reliability and validity of RWE used in regulatory submissions.

6. Continuous Improvement and Innovation: By incorporating RWE into the regulatory submission process, the EU aims to promote continuous improvement and innovation in medical device regulation. RWE allows regulators to gain insights into how medical devices perform in real-world clinical practice, identify areas for improvement, and make evidence-based regulatory decisions to protect public health and promote patient safety.

Overall, the integration of RWE into the medical device regulatory submission process in the USA represents a significant evolution in regulatory approaches, aiming to enhance the efficiency, effectiveness, and safety of medical devices throughout their lifecycle and EU reflects a commitment to evidence-based decision-making, patient-centered care, and continuous learning in medical device regulation and healthcare delivery

How Real World Evidence utilized in regulatory approval procedures for medical devices

United States

Submitting regulatory applications for medical devices that incorporate RWE in the United States typically follows a structured process outlined by the U.S. Food and Drug Administration (FDA). While the FDA has expressed interest in leveraging RWE to support regulatory decision-making, the specific procedures for submitting applications that rely on RWE may vary depending on the type of submission and the regulatory pathway chosen. Here's a general overview of the procedure for regulatory submission using RWE in medical devices in the USA:

1. Pre-submission meeting (if applicable): Before submitting a regulatory application, it may be beneficial to request a pre-submission meeting with the FDA. During this meeting, the device sponsor can discuss the proposed use of RWE, the study design, data sources, and other relevant details with FDA representatives to receive feedback and guidance.

2. RWE study design: Design a study or studies that will generate RWE to support the regulatory submission. The study design should be carefully planned to address specific regulatory questions, such as safety, effectiveness, or performance of the medical device in real-world settings. Considerations include study objectives, patient population, data sources, study endpoints, statistical methods, and ethical considerations.

3. Data collection and analysis: Collect real-world data from various sources, such as electronic health records, registries, claims databases, patient-reported outcomes, and other relevant sources. Ensure that the data collected are of high quality, reliable, and relevant to the regulatory questions being addressed. Analyze the data using appropriate statistical methods to generate valid and reliable evidence.

4. Regulatory submission preparation: Prepare the regulatory submission package, including the RWE study protocol, study reports, statistical analysis plan, and any other relevant documents. Clearly describe the study design, data sources, analysis methods, results, and conclusions in the submission to demonstrate the validity, reliability, and relevance of the RWE generated.

5. Submission of regulatory application: Submit the regulatory application to the FDA through the appropriate pathway, such as a premarket submission (e.g., 510(k), PMA) or a request for De Novo classification. Include the RWE evidence as part of the submission package to support the safety, effectiveness, or performance of the medical device.

6. FDA review: The FDA will review the regulatory submission, including the RWE evidence, to assess the safety and effectiveness of the medical device. The review process may involve interactions between the FDA and the device sponsor to address any questions, concerns, or requests for additional information related to the RWE study design, data analysis, or interpretation.

7. Decision: Based on the review of the regulatory submission and the RWE evidence, the FDA will make a regulatory decision regarding the approval, clearance, or classification of the medical device. This decision may include labeling requirements, post-market surveillance commitments, or other conditions related to the use of RWE in regulatory submissions.

European Union

Primary pathway for regulatory approval of medical devices in the EU is through conformity assessment procedures, such as CE marking under the EU Medical Device Regulation (MDR), RWE can complement traditional clinical trial data and support various aspects of regulatory submissions. Here's how RWE can be utilized in the context of regulatory approval procedures for medical devices in the EU:

1. Identifying Regulatory Requirements: Review the specific regulatory requirements outlined in the EU MDR and relevant guidance documents issued by the European Medicines Agency (EMA) and other regulatory authorities.

2. Evidence Generation Planning: Develop a strategic evidence generation plan that outlines how RWE will be collected, analyzed, and integrated into the regulatory submission. Define clear research questions, identify appropriate data sources, and plan study designs and analyses to generate robust RWE.

3. Data Source Selection: Identify suitable real-world data sources within the EU that can provide relevant information to support the safety, efficacy, or performance of the medical device. This may include electronic health records, medical registries, claims databases, patient registries, or other healthcare databases.

4. Data Collection and Management: Collect and manage the real-world data according to established protocols and data quality standards. Ensure compliance with data protection and privacy regulations, such as the General Data Protection Regulation (GDPR), and maintain the confidentiality and integrity of patient information.

5. Study Design and Analysis: Design observational studies or analyses to generate RWE that addresses specific research questions related to the medical device. Use appropriate statistical methods and epidemiological techniques to analyze the data and draw valid conclusions.

6. Risk Assessment and Benefit Evaluation: Conduct a comprehensive risk assessment and benefit evaluation based on the RWE generated. Assess the safety, effectiveness, and performance of the medical device in real-world clinical settings compared to traditional clinical trial data.

7. Regulatory Strategy Development: Develop a regulatory strategy that outlines how the RWE will be incorporated into the regulatory submission. Determine the most appropriate regulatory pathway (e.g., CE marking under MDR Annex IX or Annex XVI), prepare the submission documents, and address any regulatory considerations or challenges.

8. Submission Preparation: Prepare the regulatory submission documents, including the RWE analysis plan, study protocols, data summaries, statistical analyses, and any other supporting documentation required by the regulatory authority.

9. Regulatory Submission: Submit the regulatory application to the appropriate regulatory authority in the EU, such as a notified body or a competent authority. Include the RWE and supporting documentation as part of the submission package and clearly articulate how the RWE contributes to the overall assessment of the medical device.

10. Regulatory Review and Decision: The regulatory authority will review the submission, including the RWE, to assess the conformity of the medical device with regulatory requirements and determine whether market authorization should be granted. Be prepared to respond to any requests for additional information or clarification from the regulatory authority.

11. Post-Market Surveillance: Aftermarket authorization, continue to monitor the real-world performance of the medical device through post-market surveillance activities. Use ongoing RWE to support product lifecycle management, including label updates, post-market studies, and risk mitigation strategies.

Note: It's important to engage with regulatory authorities early in the regulatory approval process to discuss the use of RWE and ensure alignment with regulatory expectations. Collaboration between medical device manufacturers, healthcare providers, regulators, and other stakeholders is essential to successfully leverage RWE for regulatory approval in the EU.

List of countries which accept RWE in regulatory submissions

RWE is increasingly being recognized as valuable data in regulatory submissions in various countries. While the acceptance and use of RWE in regulatory processes may vary, several countries have shown openness to incorporating RWE into their decision-making processes. Here's a list of some countries that have shown acceptance of RWE in regulatory submissions:

1. United States: The U.S. Food and Drug Administration (FDA) has been at the forefront of integrating RWE into regulatory decision-making through initiatives like the Real-World Evidence Program. The FDA has accepted RWE for various purposes, including supporting labeling claims, post-market surveillance, and drug approvals.

2. European Union: The European Medicines Agency (EMA) has shown increasing interest in RWE, particularly for post-authorization monitoring of drugs and assessing effectiveness in real-world settings. The EMA has provided guidelines and frameworks for the use of RWE in regulatory submissions.

3. United Kingdom: The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK has also embraced RWE for regulatory decision-making. The MHRA has acknowledged the potential of RWE in supplementing traditional clinical trial data and has provided guidance on its use.

4. Canada: Health Canada has expressed interest in leveraging RWE to inform regulatory decisions. While the incorporation of RWE into regulatory submissions is still evolving, Health Canada has shown willingness to consider RWE for various purposes, including post-market surveillance and label expansions.

5. Japan: The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan has recognized the value of RWE in complementing traditional clinical trial data. While the use of RWE in regulatory submissions is relatively new in Japan, the PMDA has shown interest in exploring its potential applications.

6. Australia: The Therapeutic Goods Administration (TGA) in Australia has started to explore the use of RWE in regulatory decision-making. While formal guidance on RWE is still developing, the TGA has shown openness to considering RWE for various purposes, including post-market surveillance and label expansions.

7. Switzerland: Swissmedic, the Swiss Agency for Therapeutic Products, has also shown interest in incorporating RWE into regulatory decision-making processes. While the use of RWE is still evolving in Switzerland, Swissmedic has acknowledged its potential benefits and is exploring ways to integrate it into regulatory submissions.
