GetReal Institute Conference 2024: A Summary of Key Highlights

The GetReal Institute Conference 2024, held on May 14–15 in the beautiful city of Utrecht, brought together experts to discuss the theme "A Growing Convergence: RWE for Regulatory and HTA Decision-Making." Following the successful inaugural event in 2023, this year's conference focused on the latest developments in the integration of real-world evidence (RWE) into regulatory and health technology assessment (HTA) processes.

DAY 1 OPENING REMARKS

Shahid Hanif, GetReal Institute Managing Director, kicked off the conference by welcoming attendees and outlining the institute's mission to promote the adoption of RWE in regulatory and clinical decision-making. He presented the agenda, which included reflections on the past year, updates from international regulatory bodies, and discussions on the progress of RWE adoption. Hanif encouraged audience interaction and introduced the panellists for the first session.

Session 1: 'Throw Back' to Last Year – How is Regulatory and HTA Converging?

The conference opened with a Fireside Chat featuring Irene Nunes (Genmab, USA) and Per-Olof Thuresson (Roche, Switzerland), moderated by GetReal Institute. The dialogue centred on the convergence of regulatory decision-making and Health Technology Assessment (HTA), underlining the imperative for robust evidence, standardised Real-World Data (RWD) collection and analysis, and overcoming challenges in data access, privacy, and interoperability across Europe and the US. Wrapping up with a Q&A session, the necessity for collaborative efforts to tackle RWD limitations was emphasised.

Key Takeaways **—** In optimising Real-World Data (RWD) utilisation in healthcare and research, the following critical priorities were identified:

1. Standardising RWD Collection and Analysis: Promote global guidelines for consistent, high-quality data.
2. Improving Causal Reasoning in RWD: Enhance methods to better infer causality from RWD.
3. Enhancing Data Collection: Ensure source data is comprehensive, accurate, and timely.
4. Ensuring Data Transportability: Make data compatible and scalable across different contexts.

Session 2: What Does Good Look Like? Progress in Regulatory Decision-Making with RWE

Moderated by Álmath Spooner (AbbVie, Ireland), this session brought together regulatory experts to share insights and perspectives. Patrice Verpillat (EMA) discussed the agency's

forward-looking vision for Real-World Evidence (RWE) by 2025, emphasising initiatives like DARWIN EU and the upcoming ICH M14 guideline. Donna Rivera (FDA) detailed the FDA Oncology RWE Program, criteria for 'good' RWE, and new initiatives including a draft glossary for clinical and RWE research terminology. Alison Cave (MHRA) reflected on the progress since 2018, the impact of RWE during COVID-19, and ongoing challenges with data quality and building the evidence base for regulatory decisio-making. Finally, Katrien Oude Rengerink from CBG-MEB underscored the importance of transparency, methodological rigor in observational research, and the necessity for appropriate data sources.

Key Takeaways — The session highlighted the need for:

1. Leveraging existing initiatives in evidence generation: utilising existing frameworks to improve RWE reliability, while integrating insights from multiple HTA and regulatory bodies.
2. Advancing methodological rigor: the importance of transparent and rigorous observational research methods to elevate the credibility and validity of RWE findings.
3. Embracing GetRal Institute as a neutral form to facilitate open dialogue and tackle challenges surrounding Real-World Data utilisation, fostering strong collaboration and innovation within the field.

Session 3: The Big Debate – Progress Towards Adopting RWE in HTA Regulation

This lively Oxford-style debate, moderated by the GetReal Institute, addressed the motion, "This house believes we are making good progress towards adopting RWE as part of the HTA regulation."

Arguments Against the Motion: Inka Heikkinen (MSD) and Anke van Engen (IQVIA) highlighted the continued preference for randomised controlled trials and slow progress in RWE integration.

Arguments For the Motion: Iñaki Gutiérrez-Ibarluzea (BIOEF) and Juan Carlos Rejón-Parrilla (AETS) emphasised the necessity of RWE for decision.

The audience vote shifted from a near-equal split to a majority against the motion, indicating a need for further discussion on RWE integration in HTA regulation.

Key Takeaways — The session highlighted the challenges and opportunities in integrating Real-World Evidence (RWE) into Health Technology Assessment (HTA) regulation and highlighted the need for focused efforts and strategic initiatives to advance the adoption of RWE. Key insights include:

1. The pace of incorporating RWE into HTA regulation is slow, necessitating accelerated efforts and strategic initiatives.
2. There is a pressing need to advocate for the adoption of RWE in regulatory and HTA decision-making processes.
3. A persistent preference for randomised controlled trials (RCTs) over RWE in the HTA Regulation remains a significant barrier to advancing the use of RWE for HTA decision-making.
4. RWE is vital for informed healthcare decision-making to reveal unintended consequences unattainable through trials and must be continually promoted to regulatory bodies.
5. The debate highlighted that adopting RWE in the HTA Regulation remains contentious, requiring sustained dialogue, research, and policy development to address barriers and concerns.

Session 4: Deploying Methods in HTA – Experiences of HTA Bodies Using RWE Methods

Chaired by Blythe Adamson (Flatiron, USA), this session featured insights from various HTA bodies on their use of Real-World Evidence (RWE) methods. Anja Schiel (Norwegian Medical Products Agency) discussed the differing evidence requirements and the critical role of RWE in supporting internal validity. Farah Hussein (Canada's Drug Agency) emphasised how comparative effectiveness RWE addresses core HTA questions, stressing the importance of data quality and transparency. Stephen Duffield (NICE) highlighted NICE's increased use of RWE and the development of the NICE RWE Framework, which focuses on employing robust and transparent methods.

Key Takeaways **—** This session brings forward avenues for improving decision-making processes within HTA bodies, thus enhancing healthcare outcomes. Key considerations include:

1. Differing Evidence Requirements: RWE is pivotal in supporting internal validity across HTA bodies with varying evidence requirements.
2. Addressing Core HTA Questions: Comparative effectiveness is indispensable for tackling fundamental HTA inquiries, emphasising the need for high data quality and transparency in decision-making.
3. Evolving RWE Framework: NICE's expanding use of RWE and the ongoing refinement of the NICE RWE Framework underscore the importance of adopting robust and transparent methodologies.

DAY 2

Day 2 of the conference delved into the practical applications of RWE methodologies, focusing on their significance in various aspects of healthcare decision-making. Experts provided valuable insights into patient-centric outcomes, pharmacovigilance, vaccine monitoring, and methodological rigor. While the keynote session explored the potential acceleration of convergence between regulatory and HTA processes. The day concluded with a dynamic multi-stakeholder panel, discussing top priorities and actionable strategies for advancing evidence-based healthcare practices.

Session 5: Methods Deep-Dive – A Scientific Discussion on RWE Methods Being Applied

During this session, experts provided valuable insights into the scientific applications of RWE methods. Bettina Ryll (MPNE, Sweden) emphasised the pivotal role of RWE in patient-centric healthcare, drawing from personal experiences with melanoma and advocating for the inclusion of overlooked outcomes such as quality of life and long-term effects, citing examples like Bijwerkingencentrum Lareb and PRIME-ROSE. Delphine Saragoussi (Evidera, France) delineated the significance of RWE in pharmacovigilance and pharmaceutical research, stressing the importance of selecting appropriate methods tailored to study objectives for scientific rigor. Miriam Surkenboom (VAC4EU, The Netherlands) highlighted collaboration for vaccine monitoring and RWE on medicine safety in pregnancy, advocating for data accessibility and comprehensive utilisation through harmonisation to ensure data comparability and evidence generation efficiency. Manuel Gomez (UCL, UK) explored Target Trial Emulation (TTE) in comparative effectiveness research, discussing good study design principles, challenges, and methods for addressing biases, underlining the importance of clear research questions and robust analysis.

Key Takeaways **—** During this session, experts provided valuable insights into the scientific applications of RWE methods, focusing on patient-centric outcomes, pharmacovigilance, vaccine monitoring, and methodological rigor. Here are the key takeaways:

1. Optimising healthcare decision-making through RWE: Prioritising the integration of RWE methodologies to capture quality of life and long-term effects. Leveraging direct patient-reporting platforms and incorporating precision medicine strategies in real-world clinical trials.
2. Advance Pharmacovigilance and Research Standards: Acknowledging the vital role of RWE in drug safety monitoring and pharmaceutical research, while underlining the significance of method selection tailored to study objectives to maintain scientific rigor.

3. Advocating for data accessibility and harmonisation: Actively supporting initiatives and policies to enhance data accessibility and comparability to facilitate evidence generation.
4. Champion the use of Target Trial Emulation (TTE) for simulating RCTs with RWD: TTE Methodology for Comparative Effectiveness Research.

Session 6: Keynote – A Vision for The Future: What If We Accelerate the Convergence of Regulatory & HTA?

The keynote session of Session 6 delved into the potential acceleration of convergence between regulatory and HTA decision-making processes. Patrice Verpillat (EMA) emphasised the distinct evidence requirements of regulators and HTA bodies, underscoring the importance of managing uncertainty. Highlighting the DARWIN EU initiative, Verpillat showcased how RWD analyses can support decision-making, advocating for collaborative efforts and shared principles between regulatory and HTA bodies. Niklas Hedberg (TLV) echoed these sentiments, stressing the necessity for collaborative advancements in scientific methods and infrastructure development to address challenges in research validity. He urged for fair comparisons in evidence generation and cautioned against practices like data mining. Advocating for a streamlined approach, both speakers concluded on the importance of cooperative evidence generation across regulatory and HTA bodies to optimize resources and foster innovation.

Key Takeaways **—** The session delved into the intricacies of evidence assessment within regulatory and HTA frameworks, highlighting distinct priorities, collaborative opportunities, validity challenges, and the importance of fairness in evidence generation.

1. Regulators and HTA bodies have different priorities in evidence assessment, with regulators focusing on efficacy and HTA bodies on comparative effectiveness. Encouraging collaboration between regulatory and HTA bodies to share insights and resources, facilitating joint scientific consultations and alignment on RWE principles is essential.
2. Maintaining validity in research, especially balancing external and internal validity, remains a significant challenge that requires careful consideration of research design and execution, ensuring that research questions are meticulously formulated to address key uncertainties.
3. Advocate for fair comparisons in evidence generation processes, discouraging biased practices such as data mining and phishing that could distort findings and compromise reliability.

4. Efforts should be directed towards a more cooperative and streamlined approach to evidence generation across regulatory and HTA bodies to optimise resources and enhance innovation.

CLOSING DISCUSSION – REGULATORY & HTA TOWN HALL

In a dynamic multi-stakeholder panel moderated by Niklas Hedberg (TLV), insights from the two-day conference were shared, emphasising top priorities for the field. Patrice Verpillat (EMA) highlighted significant progress in HTA and regulatory collaboration, praising DARWIN EU as a game-changer. Donna Rivera (FDA) echoed the need for collaborative efforts in regulatory decision-making. Iñaki Gutiérrez-Ibarluzea (BIOEF) emphasised robust methods to reduce uncertainty in RWD use, calling for greater transparency. Elena Petelos (University of Crete/HTAi Greece) underscored the importance of the European Health Data Space (EHDS) and harmonising data standards, advocating for broader dialogues involving regulators and payers. Wim Goettsch (University of Utrecht, Netherlands) acknowledged political aspects and the need to move beyond the RWE bubble, suggesting collaboration with groups like ISPOR and HTAi. Bettina Ryll (MPNE, Sweeden) stressed increased awareness around data sources, ethical RWD use, and involving more clinicians in discussions. The session closed with an interactive discussion on breaking the RWE bubble, incentivizing clinicians, and democratising research with RWD.

Each speaker made recommendations to advance the field, fostering a collaborative and innovative approach:

1. **Enhance RWD standardisation:**
   - Promote global guidelines for the standardisation of RWD collection and analysis.
   - Address challenges related to data access, privacy, and interoperability among electronic medical records (EMRs).
   - A compilation of a repository of RWE Best practices and Guidelines to be up taken by GetReal Working Groups.

2. **Foster Collaborative Efforts:**
   - Encourage collaboration between stakeholders, including patients, regulators, sponsors, physicians, and academics, as well as professional associations, MEPs, and related EU health experts.
   - Leverage GetReal events to facilitate open dialogue and address limitations in RWD utilisation.
   - Leverage initiatives like EHDS and DARWIN EU for evidence generation and integrate insights from multiple HTA and regulatory bodies.

3. **Improve RWE Utilisation:**
   - Advocate for the adoption of RWE in regulatory and HTA decision-making.
   - Promote the use of RWE to bridge gaps in clinical trials, especially for under-represented or excluded demographic subgroups.

4. **Advance Methodological Rigor:**
   - Emphasise the importance of transparent and rigorous observational research methods.
   - Utilise frameworks such as estimand and target trial frameworks to improve the reliability of RWE.
   - Enhance methods for causal reasoning, data collection, study designs, and data transportability.

5. **Support Innovation and Research:**
   - Initiate pilot projects to explore new methodologies and address existing challenges in RWE integration.
   - Focus on key areas such as safety monitoring through collaborations like VAC4EU and IMI ConcePTION.

6. **Promote Harmonisation and Convergence:**
   - Align the efforts of regulatory and HTA bodies to avoid duplication and streamline evidence generation.
   - Advocate for harmonising data standards and methodological guidelines across different healthcare systems.

7. **Facilitate Educational and Awareness Efforts:**
   - Increase awareness of the value and ethical use of RWE, particularly regarding patient consent and data governance.
   - Involve clinicians and other healthcare professionals in discussions to provide practical insights and improve primary data collection.

8. **Future Discussions and Debates:**
   - Continue to address the practicalities of integrating RWE into HTA regulation.
   - GetReal to foster further debates and discussions to refine strategies for better RWE adoption and utilisation.

The conference concluded with a call for continued dialogue and collaboration to advance evidence generation methods and integrate RWE into decision-making processes effectively.