Novo Nordisk's Position on Engaging with Real World Data and Evidence

Building RWE at Novo Nordisk for patients living with chronic disease

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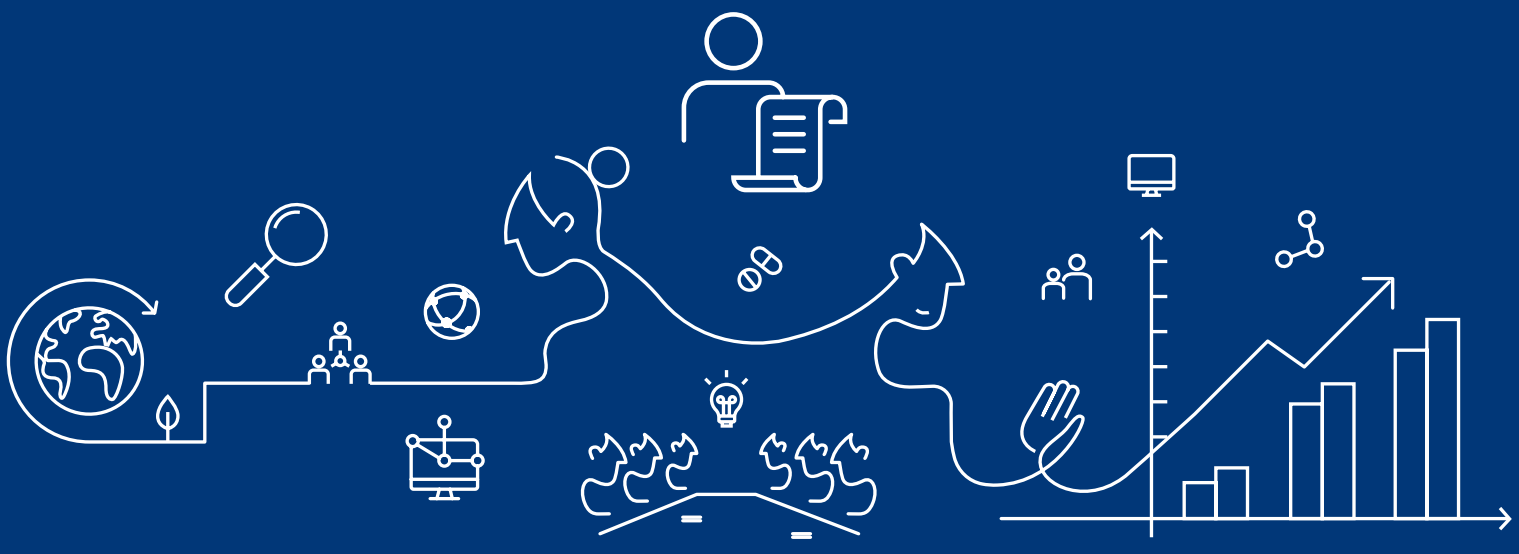
Novo Nordisk RWE forum



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Introduction

Our mission is to drive change to defeat serious chronic diseases and our work is guided by the Novo Nordisk Way.

At Novo Nordisk we have a rich history in understanding and bringing treatments to patients living with chronic and rare diseases. Our mission is to drive change to defeat serious chronic diseases and our work is guided by the Novo Nordisk Way. The Novo Nordisk Way describes the values and behaviours that guide everything we do. Key values of the Novo Nordisk Way include creating value through a patient-centred business approach, and innovation for the benefit of patients and society at large.

We have long been utilising real-world evidence (RWE) to support our mission. As we broaden our pipeline in the cardiometabolic and rare disease spaces and, inspired by the increased use and acceptance of RWE and rapid real-world data (RWD) proliferation, we want to affirm our commitment to generating evidence that makes our innovations more accessible to patients. This commitment drives positive change for a healthier world.

This paper will provide our vision on why, how, and with what intent we will be engaging in RWE. We hope such clarity serves as a lasting motivation for ourselves, as well as our partners, industry peers and stakeholders in collaborating with us. Please note that specific Novo Nordisk examples are referenced throughout the paper in the footer.

In the context of this paper, we employ the following definitions, and we acknowledge that these definitions resonate in different ways to different stakeholders;

Real-world Data (RWD): Patient-level data on health status and/or the delivery of health care, that is routinely collected outside of traditional clinical trials, from a variety of sources. RWD can include primary data, collected for a specific use case,[1] or secondary data, collected from routinely available clinical documentation.[2]

Real-world Evidence (RWE): Clinical evidence generated through the analysis of RWD. RWE can be generated through many types of study design or analysis.[3]

[1] For example: Study-specific case report forms, clinical outcome assessments
[2] For example: Medical claims data, disease registries, electronic medical record extraction
[3] For example: Pragmatic trials, observational studies

Novo Nordisk's Therapy Area-Specific RWE Generation

Our innovative cardiometabolic and rare disease portfolio requires generation and application of RWE to address challenges across therapy areas and ultimately bring value to patients.

At Novo Nordisk, we have a robust portfolio of innovative therapies, spanning major chronic cardiometabolic diseases and rare haemato-endocrinological conditions. We aim to lead in all the therapy areas in which we are present, with the ultimate aspiration to prevent and cure disease, therefore ameliorating patient lives.

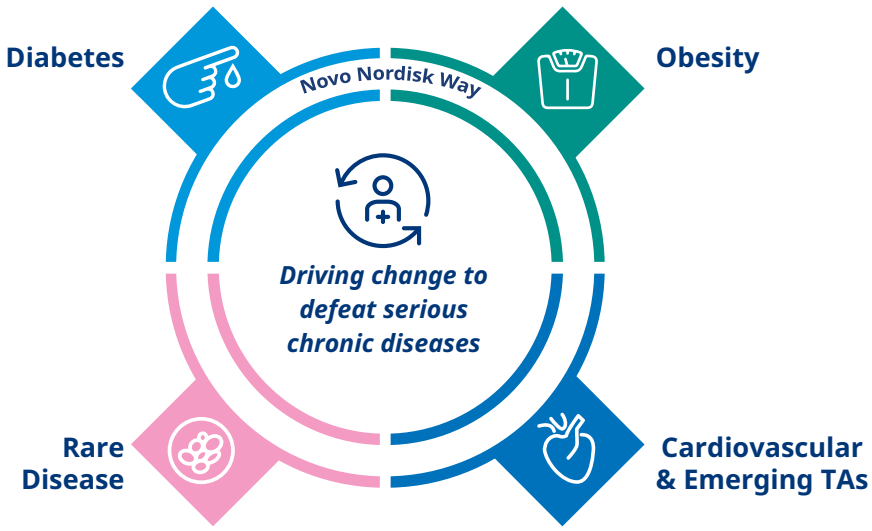
The application of RWE across our portfolio helps to fulfil this ambition.

Our innovative cardiometabolic portfolio addresses **heterogenous, often overlapping and frequently under-characterised populations**. Whilst **our rare diseases portfolio** presents novel scientific challenges, including the need to **identify and contextualise under-/mis-characterised patients**. For example, there is a compelling need for characterisation of people living with obesity by measures beyond body mass index (BMI), alongside an organisational commitment to better define the role of systemic inflammation in cardiometabolic conditions. Additionally, sickle cell diseases present a need for the development of much more granular understanding of the experience and impact of pain.

RWE plays a pivotal role in addressing challenges within these therapy areas (TAs). As such, we consider generating RWE a **key component** of our **integrated evidence plan (IEP)**, encompassing the identification of research questions and evidence needs and the resultant strategy comprised of data and evidence-generating activities to fulfil those needs. It is essential for patients, moreover society, that we increasingly **integrate RWE early on** and **throughout the product lifecycle**.

Our commitment to this approach is necessitated by our cardiometabolic portfolio, as IEPs can often support multiple TAs given the overlap in comorbidities. For example, understanding the natural history of Type 2 Diabetes can inform the risk of kidney or liver diseases. Following our principle of creating value by having a patient-centred business approach, it is highly pertinent for us to understand the patient experience holistically and to therefore **develop Real World Studies to generate RWE** in a corresponding fashion. We are adopting a **portfolio mindset** that seeks to promote synergies in RWE across treatments and TAs.

Figure 1. Novo Nordisk's Portfolio of key therapy areas



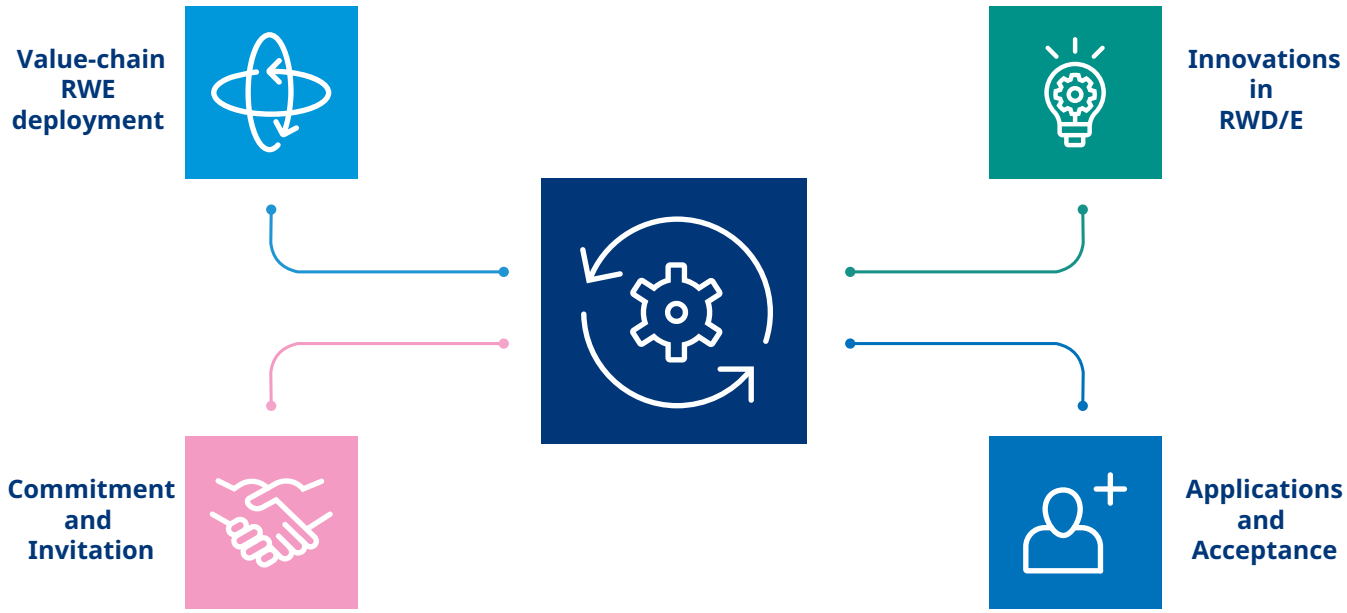
Value Chain Deployment of RWE

We take a cross-functional approach to RWE to ensure it is used to its full potential across the value chain.

Novo Nordisk strives to ensure RWE is used to its **full potential** throughout the **value chain**. Beyond cross-functional governance and collaborative forums, we are also guided by an **enterprise mindset** that emphasises a holistic and inclusive approach to evidence planning and execution throughout the product lifecycle. This approach encompasses all functions and ensures global-to-local cohesion.

Our intention is achieved through **integrated evidence planning** and **data stewardship**, with the ambition of doing so across TAs. In tandem, we **develop a consolidated view of data requirements and availability** to empower internal stakeholder decision-making across multiple functions.

Figure 2. Novo Nordisk's engagement with RWE



Our experience and knowledge in generating RWE are core pillars to the design of our IEPs and clinical discovery and development programs. Once a research question and evidence need has been defined, we decide what the most suitable evidence generating activity is to address it, e.g., primary demonstration of efficacy requires a traditional randomised clinical trial (RCT); safety and effectiveness in every day clinical practice requires RWD. The strategy and evidence-generation activity to address the need is facilitated by our cross-functional governance structure, ongoing access to and partnerships with RWD sources and study design expertise. We pilot certain RWE generating activities before fully launching them to ensure they will address the evidence need and stakeholder requirements and create value for patients.

TA-level IEPs remain the norm across industry and facilitate a more strategic and long-term view of our portfolio, enabling us to identify synergies, delivering both efficiency and the ability to meet needs more successfully. Furthermore, developing a central, common, and comprehensive repository of clinical trial data and RWD facilitates more efficient and effective data sourcing strategies and IEP execution.

At an organisational level, we have a federated approach to RWD/E which empowers teams across discovery, development, commercial and operational functions.

The Novo Nordisk RWE Corporate Strategy aims to bring innovative treatments to patients faster and to decrease unmet medical need by leveraging the full potential of RWE across the product lifecycle through four strategic priorities. These priorities are securing agility in organisational processes to simplify RWE generation efforts, embedding fit for purpose RWE in the evidence generation strategy across the full value chain, employing leading and high-quality internal capabilities and external partnerships to support RWE activities and strengthening internal & external stakeholders' understanding and appreciation of the value and impact of RWE. In order to guide RWE understanding and excellence, and facilitate enterprise-wide optimisation, RWE leaders meet regularly to anchor the Corporate RWE Strategy and its embedded initiatives across the organisation.

Our value chain approach to RWE allows all functions across the product lifecycle to support and benefit from RWE, and this effort is led by RWE hubs across discovery, development, commercial and operational functions. Contrary to a highly centralised set-up, this set-up promotes intimacy to local health systems and patients, whilst enabling RWD/E approaches befitting the diversities and varying maturities of local contexts.

Exploring Innovations in RWD & RWE

We proactively investigate the promising opportunities arising from rapid advancements in data and methodologies.

A **rapidly advancing** landscape in **data and analytical methods** provides a fertile foundation for us to pursue our RWE ambitions. In line with the Novo Nordisk Way, we are curious and innovative for the benefit of patients and society at large and are therefore committed to investing in and developing innovative solutions and advanced methodologies. This investment aims to improve organisational use of RWE to address evidence gaps and create value. We therefore maintain a forward-looking approach and actively explore opportunities to seize new possibilities.

PRAGMATIC TRIALS

Pragmatic trials allow real-world comparison of treatments within routine clinical practice, and therefore allow us to **contextualise the benefit** of our therapies beyond the setting of a traditional RCT. This is increasingly pertinent in the cardiometabolic space, as the number of treatment options increases, and comparison between these options is not practical within the scope of traditional clinical trials. We are therefore performing some of the earliest large-scale pragmatic trials in our TAs. One example of this is the ongoing randomised **P**ragmatic trial on **O**besity **S**emaglutide in **E**mplo**Y**er settings (POSEY)[4], which looks to determine the effectiveness of semaglutide 2.4 mg vs. commercially available medications for chronic weight management in participants with obesity in a multi-employer setting in the US. POSEY is run in collaboration with Loma Linda University, California, US.

LINKAGE

We are actively exploring the possibilities of linking RWD of patients enrolled in clinical trials to better contextualize their experience and outcomes. Data sources used for linkage include, but are not limited to, electronic medical records (EMR), laboratory and claims data. We believe linkage not only offers better contextualisation of the patient experience, but a more efficient and reliable way of **following patients beyond the trial setting**. Multi-source data linkage opens opportunities for greater health care data access and amplifies our ability to adopt innovative study methods and advanced analytics in our aim to generate value in an agile and simple way. As an example, RWD linkage to the extension arm of a clinical trial can allow for RWE generation at launch to inform discussions with key external stakeholders. This is particularly important in Novo Nordisk's TAs, as these are life-long conditions that can have significant impact on patient lives and the broader society, beyond the scope of a randomised clinical trial. As an example, the **SE**maglutide once-weekly randomized **PRA**gmatic Trial (SEPRA)[5] uses tokenization and linkage of study participants' trial data to their claims data, to support evaluation of clinical outcomes.

[4] A Pragmatic Clinical Study in a Multiple EmploYer Setting – Beat Obesity Together

DIGITAL

Proliferation of **digital health solutions** (DHS) has benefited many of our patients. We are investigating diverse ways to incorporate DHS in our operating norm as part of our care package, improving the patient experience without compromising on ethics or quality of delivery. For example, we have been collaborating with manufacturers of continuous glucose measurement (CGMs) and their corresponding patient support apps, easing drug titration utilising IcoDose and Dose Check.[6] We are also working to ease drug delivery with smart pens[7] and have used them to evaluate the association between treatment adherence and continuous glucose monitoring outcomes,[8] providing valuable insight into treatment injection behaviour. As we expand into new TAs, we increasingly see DHS as an integral part of care innovation and scientific exploration of, important and otherwise hard to study, endpoints.

Additionally, the swift advances in artificial intelligence and machine learning (AI/ML) present significant opportunity for rapid analytics and more sophisticated use of unstructured clinical datasets.

[5] https://www.ispor.org/docs/default-source/intl2023/ispor23zacherlepostersubmitted-pdf.pdf?sfvrsn=d624c228_0

[6] Dose Check (novonordisk.com)

[7] NovoPen® 6 and NovoPen Echo® Plus (novonordisk.com) .

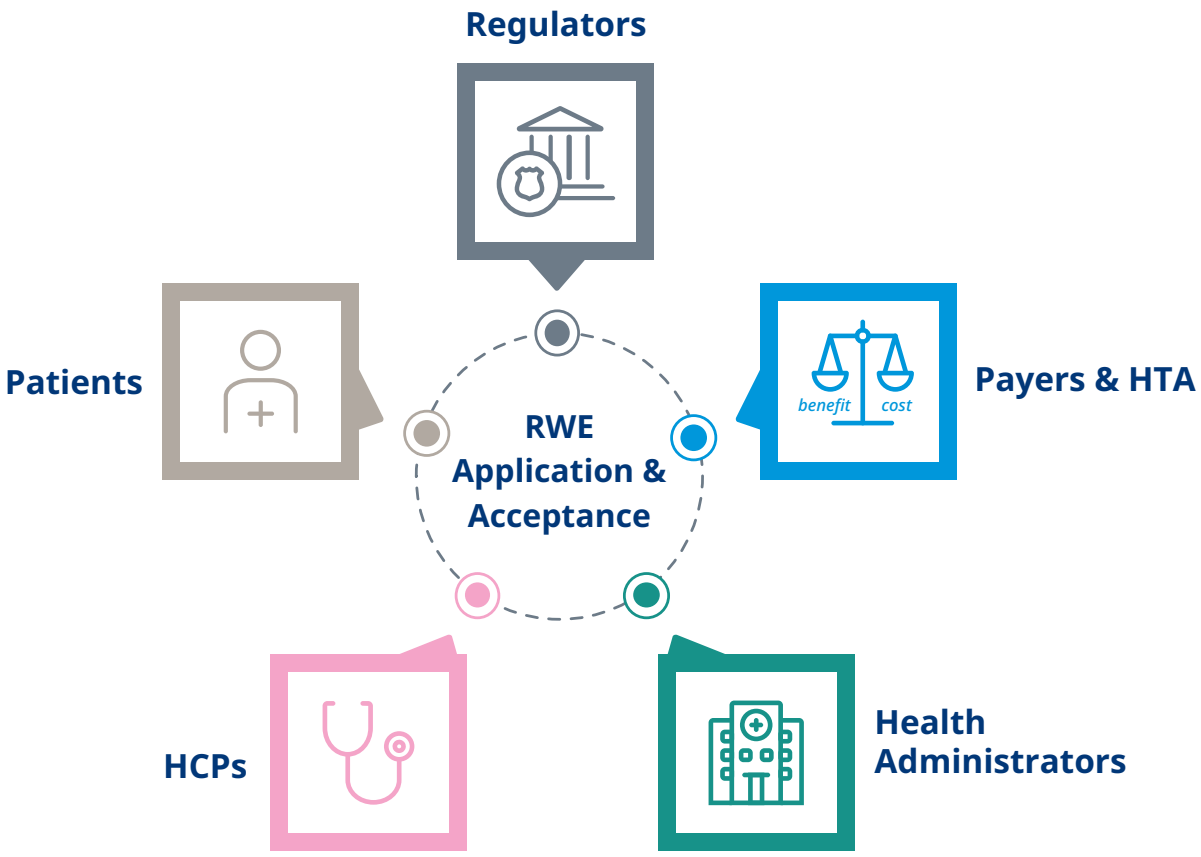
[8] Association Between Treatment Adherence and Continuous Glucose Monitoring Outcomes in People With Diabetes Using Smart Insulin Pens in a Real-World Setting - PMC (nih.gov)

RWE Application & Acceptance

RWE empowers the external environment to make decisions and take actions in our fast-evolving cardiometabolic and rare disease areas

Novo Nordisk commits to generating RWE that is **fit for purpose** and **relevant** to aid decision-making for external stakeholders, to ultimately bring innovative treatments to more patients. As such, we take a proactive, as opposed to a reactive, stance in shaping and influencing policies to ensure they reflect the realities and needs of patients living with chronic disease. We believe in the increasing potential for RWE to **inform decisions** and **empower actions** of **Regulators**, **Payers and Health Technology Assessment Bodies (HTAs), Health administrators, Healthcare professionals (HCPs)** and **Patients** as they engage with our innovations. As a global company we realise how geographic variations, e.g., maturity of RWD infrastructure, can affect the needs of our stakeholders or allow for additional value generation for patients. This is considered by our regional and local teams when executing RWE generating activities to ensure they meet our stakeholders' demands.

Figure 4. RWE External Landscape



REGULATORS

RWE is increasingly an integral element that **informs regulatory decisions**, driven by the European Medicines Agency's RWE vision to establish the value of RWE across all regulatory domains[9] and the 21st Century 21st Century Cures Act, mandating the FDA's integration of RWD into regulatory decision making.[10]

Thus, RWD derived from routinely collected health data, offer an opportunity to expedite new indications through providing **proof on patient-relevance of therapeutic benefits, and safety and effectiveness**.[11,12]

At Novo Nordisk we actively embrace these trends and the need to shape our focus, given their pertinence in therapy areas that we engage in. An example of how we have recently leveraged RWD to support Regulatory decision making is our Post Authorisation Safety Drug utilization Study to assess safe real-world utilization of Saxenda and Victoza in obesity.[13]

We believe that it is necessary to explore alternatives to traditional RCTs, to fulfil the promise of RWD in regulatory decisions. For example, modernising cardiovascular event definition, or refining the understanding of patient impact of pain and vaso-occlusive crisis in sickle cell disease, are both compelling scientific issues to resolve using real-world approaches.

PAYERS & HTA

In the context of the rising burden of chronic non-communicable diseases globally, we are keenly aware of Payers' needs to **balance optimising outcomes** for individual patients and **striking the right cost/benefit ratio** at a population level. Equally, in TAs that are witnessing incoming waves of innovations, such as Obesity and Metabolic Dysfunction-Associated Steatohepatitis (MASH), informed payer decisions must be based on comprehensive understanding of disease aetiology, epidemiology, burden and experience. RWE allows us to contextualise clinical trial results and provides an indispensable vehicle to inform Payer and HTA decisions. We are routinely carrying out Burden of Disease and Costed Patient Pathway studies across our assets and TAs, and increasingly so in new treatment paradigms such as Obesity and MASH with use of local (e.g. UK and US) data to identify populations with high clinical and economic burden. For example, a retrospective cohort study we conducted in the US allowed us to determine that obesity-related complications are a cost driver in people with obesity for at least 8 years from initial diagnosis.[14] With EU HTA, the value of RWE, including its use in indirect treatment comparisons and external control methodologies to demonstrate relative impact, is expected to increase further.

HEALTH ADMINISTRATORS

As the **global burden of chronic disease** continues to rise, healthcare resources become increasingly stretched and **patient pathways become more complex**. By utilising RWE to inform and support these necessary health system transformations and provide evidence of effectiveness of therapies, it aids **more robust patient care**. Furthermore, to help face the colossal health challenges at a population level, we have made commitments towards **primary prevention** of obesity and are actively exploring innovative and advanced approaches to early risk identification and management within our recently established Transformational Prevention Unit (TPU).

HEALTHCARE PROFESSIONALS (HCPS)

We believe that RWE better informs clinical decisions and ensure the right treatments get to the right patients, through enablement of finer definitions of **clinically meaningful patient cohorts** and validated **novel measurements** to ultimately improve patient lives sustainably and inclusively. It is also reasonable to anticipate that an increasingly broad and diverse range of HCPs will be involved in caring for conditions which our therapies will address. RWE can be used to determine gaps, address, and measure changes in practice for care pathway effectiveness. Whether using RWD to identify 'fast progressors' within MASH, or generating evidence which assesses the adoption and impact of testing for specific cardiovascular biomarkers, we remain dedicated to upgrading understanding on **care pathway effectiveness**. Where appropriate we support relevant skill, capability and workflow advancements in accordance with evidence-based recommendations.

PATIENTS

Patients living with chronic disease may endure reduced quality of life and a high burden of comorbidities, while self-treating (with over-the-counter or alternative therapies) or self-funding prescription medications can also be common. Our evidence generation activities look to help alleviate the burden of the disease on patients. The Awareness, Care & Treatment In Obesity Management – A Multi-Country Observation Among Teens (ACTION Teens) Real World Study is a strong example of this, identifying perceptions, attitudes and barriers to effective obesity care amongst adolescents living with obesity, their caregivers and HCPs. In addition, RWE offers a uniquely valuable lens into the complex and multifaceted nature of the lived experience. In response, Novo Nordisk places a strong **emphasis on patient centricity,** exploring **use of patient-reported outcomes** (PROs) and actively leveraging digital means to gather data that holistically characterises patient preference, behaviour, experience and needs. Use of PROs are represented in aforementioned examples, e.g., POSEY, SEPRA, ACTION TEENS. By analysing RWE, we can develop effective strategies to facilitate patient access to our innovations.

Furthermore, Novo Nordisk emphasises the need for diversity in RWE generation, by inclusion of more geographies and populations, including vulnerable and harder-to-reach sub-populations where there is a rising prevalence of chronic diseases. It was for this reason that we partnered with DarSalud Care and LifeDOC Research to investigate the prevalence and impact of obesity in adolescents living in Tennessee, US, a state with some of the highest rates of obesity in the US, with a focus of sub-group analysis based on social determinants of health.

[9] EMA: European Medicines Agency RWE vision by 2025

[10] FDA: 21st Century Cures Act | FDA

[11] https://www.fda.gov/science-research/science-and-research- special-topics/real-world-evidence

[12] https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.2479

[13] Investigating the potential non-authorized use of two different formulations of liraglutide in Europe: A real-world drug utilization study - PubMed (nih.gov)

[14] Real-world costs of obesity-related complications over eight years: a US retrospective cohort study in 28,500 individuals (nih.gov)

Commitment to RWE

We aim to bring treatments to patients faster and improve their experience by continuously expanding our RWE capabilities and through collaboration with the external environment.

We are keenly aware of the burden of proof that comes with the innovations that we are passionate about and see an opportunity to engage RWE in impactful ways to enable patient and health system benefits. Novo Nordisk believes that **partnering with our stakeholders** to **innovate** in, **generate** and **act on** RWE, will be critical.

To that effect, we will continue to expand our RWE capabilities and build partnerships that further leverage RWD/E, unleash the power of **data and analytics**, work to increase acceptance and use of RWE across stakeholders, shed new light on **cardiometabolic** and **rare diseases**, and inform and enable better delivery of **patient care** and **therapeutic value**.

ON DATA AND ANALYTICS

Data infrastructure development and analytics innovations are driven by a diverse host of academic, professional, and commercial organisations across the globe. We are very encouraged by the spirit of collaboration taken by many ambitious and focused groups in therapeutic areas that we work in, as well as revolutionary applications of advanced analytics and technologies such as generative AI.

ON DISEASE FRONTIERS

Scientific understanding is rapidly deepening in our TAs, both by virtue of the **research community's cumulative effort** and through enablement of **new technical possibilities**. As a pioneer in many of these disease areas, we see tremendous promise in collaborating on the cutting edge of these innovations with academic and technology innovators. We are already embarking on some of these frontiers in cardiovascular conditions with renowned centres across the world. For example, we partnered with the University of Leicester, to investigate the impact of COVID-19 lockdowns on the BMI of people living with obesity.[17]

ON EVIDENCE-BASED CARE DELIVERY[18]

As healthcare systems adapt to care for people living with life-long cardiometabolic conditions with new treatment options, robust and thoughtfully generated evidence plays a crucial role. We see for ourselves, a role to collaboratively define the needed evidence and to produce it in a way that is **relatable and actionable for all relevant stakeholders**, in particular healthcare providers, HCPs, and patients. The Diabetes Remote Intervention to Improve use of Evidence-based medications (DRIVE) Study,[19] conducted in collaboration with Mass General Brigham in the US, is a strong example of such a partnership.

We hope that our stakeholders and peers will be willing to join with us on furthering the advancement, application, and acceptability of RWE, which we believe will ultimately bring greater value to society and patients. We are humbled by the importance of this pursuit and commit to an **openness** to adapt, with the aim of staying a **principled, thoughtful**, and **valued** partner to all, to ultimately continue our mission for the past 100 years: to improve patient lives.

[15] https://classic.clinicaltrials.gov/ct2/show/NCT05013359

[16] Poster 270: https://onlinelibrary.wiley.com/doi/full/10.1002/oby.23626

[17] The impact of COVID-19 lockdowns on the body mass index of people living with obesity: A UK retrospective cohort study using the UK Clinical Practice Research Datalink - ScienceDirect

[18] Evidence-based care delivery involves integrating the best available evidence from research and real-world data into clinical decision-making and patient care. It ensures that treatments and interventions are rooted in proven effectiveness and patient outcomes, leading to improved healthcare quality, better patient experiences, and cost-effective care.

[19] Abstract 16149: Recruitment Strategies for a Remote Implementation Study in Diabetes Management - Insights Into Optimizing Enrollment | Circulation (ahajournals.org)

Conclusion

We will continue to be guided by the Novo Nordisk Way and apply the same passion, skills, and commitment as our founders to our purpose of driving change to defeat serious chronic diseases.

Despite the increase in use and acceptance of RWE globally, many opportunities remain for innovation, improvement, and a clear opportunity to shape the future of RWE. At Novo Nordisk we believe this cannot be done in siloes, and so it is crucial to build and maintain good relations with stakeholders and partners to successfully drive change for a healthier world. We will continue to be guided by the Novo Nordisk Way and apply the same passion, skills, and commitment as our founders to our purpose of driving change to defeat serious chronic diseases.

Glossary of Terms

Term	Definition
AI	Artificial Intelligence
BMI	Body Mass Index
CGM	Continuous Glucose Measurement
DHS	Digital Health Solutions
EMR	Electronic Medical Record
HCP	Healthcare Practitioners
HTA	Health Technology Assessment
IEP	Integrated Evidence Plan
MASH	Metabolic Dysfunction-Associated Steatohepatitis
ML	Machine Learning
PRO	Patient Reported Outcome
RCT	Randomised Clinical Trial
RWD	Real World Data
RWE	Real World Evidence
TA	Therapy Area

References

1. For example: Study-specific case report forms, clinical outcome assessments
2. For example: Medical claims data, disease registries, electronic medical record extraction
3. For example: Pragmatic trials, observational studies
4. A Pragmatic Clinical Study in a Multiple Employer Setting – Beat Obesity Together
5. https://www.ispor.org/docs/default-source/intl2023/ispor23zacherlepostersubmitted-pdf.pdf?sfvrsn=d624c228_0
6. Dose Check (novonordisk.com)
7. NovoPen® 6 and NovoPen Echo® Plus (novonordisk.com) .
8. Association Between Treatment Adherence and Continuous Glucose Monitoring Outcomes in People With Diabetes Using Smart Insulin Pens in a Real-World Setting - PMC (nih.gov)
9. EMA: European Medicines Agency RWE vision by 2025
10. FDA: 21st Century Cures Act | FDA
11. https://www.fda.gov/science-research/science-and-research- special-topics/real-world-evidence
12. https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.2479
13. Investigating the potential non-authorized use of two different formulations of liraglutide in Europe: A real-world drug utilization study - PubMed (nih.gov)
14. Real-world costs of obesity-related complications over eight years: a US retrospective cohort study in 28,500 individuals (nih.gov)
15. https://classic.clinicaltrials.gov/ct2/show/NCT05013359
16. Poster 270: https://onlinelibrary.wiley.com/doi/full/10.1002/oby.23626
17. The impact of COVID-19 lockdowns on the body mass index of people living with obesity: A UK retrospective cohort study using the UK Clinical Practice Research Datalink - ScienceDirect
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