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Sponsored Webinar

The Role of Real-World Evidence in Regulatory Decision Making: Current Use and Future Potential

Webinar Host:

Dr Chantal van Gils, Director of Epidemiology and Real-World Evidence for the NDA Advisory Board

NDA

About the host

Dr Chantal van Gils

Chantal is a renowned expert in real-world research, epidemiology, and health economics. She has extensive experience conducting population-specific analyses and applying quantitative methods to clinical research.

Throughout her career, she has applied her expertise to diverse clinical studies, including pragmatic trials, natural history research using registry data, and integrated analyses.

As a thought leader in her field, Chantal provides strategic and scientific guidance to pharmaceutical companies. She assists with all stages of development and regulatory activities, with specialized experience in oncology and advanced therapies. Chantal's work aims to inform decision-making through real-world evidence generation. Her work aims to improve decision-making and benefit patients worldwide.

Use of Real-World Data in Regulatory Decision Making

The use of real-world evidence is growing as drug development faces complex challenges. Regulators recognize real-world evidence's potential role when used appropriately. However, considerations around precisely how real-world evidence can support regulatory decision-making remain uncertain, especially for establishing a treatment's primary efficacy.

In a TOPRA webinar from the 5th of October, Dr Chantal van Gils, Director of Epidemiology and Real-World Evidence for the NDA Advisory Board, presented the current state of RWE scientific advancements and provided research implications of RWD and RWE in the context of regulatory decision making. Traditionally, randomized controlled trials have been considered the gold standard for demonstrating both the efficacy and safety of new medical products. Randomized trials are preferred because they help minimize bias by randomly assigning patients to treatment or control groups. This randomized design allows for a direct comparison of outcomes between groups to clearly establish if any differences are due to the treatment itself rather than other factors. However, drug development is now facing more complex issues that make large, randomized trials more difficult to conduct.

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Increasing Reliance on RWE

There has been notable growth in medicines targeting very rare or small patient populations. For these populations, randomized trials may be impractically large or simply not feasible to conduct. Additionally, as treatments target more niche indications, large randomized trials examining overall clinical outcomes are becoming harder to implement. These challenges have led to an increase in regulatory decisions being made based on data from single-arm trials or other non-randomized study designs. However, such alternative study designs inherently introduce more uncertainty when assessing a treatment's benefit-risk profile. Real-world evidence aims to play a role in helping to minimize this uncertainty if it is collected and analysed rigorously.

Another area where real-world evidence is evolving is in the development and approval of advanced therapy medicinal products, or ATMPs. This class includes gene therapies, cell therapies and tissue-engineered products. For these complex biological products, clinical trials often enrol small numbers of patients and have limited follow up periods due to the nature of the conditions treated and the novelty of these advanced therapies, despite significant uncertainties around their safety. So real-world evidence generated post-approval could play an even greater role in understanding long-term (comparative) effectiveness and safety versus standard of care for ATMPs.

Established vs. Emerging Roles for RWE

As a result of these challenges, regulatory agencies are now seeing a rise in the number of new product submissions and label extension requests based primarily on data from single-arm trials conducted without randomization as the primary source of evidence. While these types of earlier-stage studies can provide benefits like accelerated access to promising new therapies, they conversely also heighten uncertainties around determining the true size of a treatment's effect which randomization aims to control.

Post-marketing drug safety surveillance provides a clear example of an area where real-world evidence has long been established and widely accepted by regulators as the standard source of evidence. For decades now, pharmacovigilance studies examining

adverse events in real-world clinical practice settings after approval have routinely relied on large healthcare databases and other real-world data sources to efficiently monitor product safety profiles at a population level. However, the role of real-world evidence in establishing a new treatment's efficacy prior to approval remains significantly more limited and uncertain at present. Recent analyses have found that while approximately 40% of all new marketing authorization applications submitted to the European Medicines Agency considered real-world evidence in some supporting capacity, a much smaller fraction actually integrated real-world data as supportive evidence within the central clinical efficacy studies forming the basis for approval decisions.

Real-world evidence studies aimed at demonstrating efficacy typically require adjustment methods to ensure comparability between outcomes observed in treated patient cohorts versus outcomes seen in alternative treatment groups, such as patients receiving standard of care or placebo controls. Real-world evidence is increasingly being explored by sponsors as one potential way to generate this needed external comparative evidence in situations

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where randomized controlled trials are not feasible or considered unethical due to practical or patient care related constraints.

Building consensus on RWE

A variety of specific real-world data sources and methodological approaches may be employed to generate suitable external comparator cohorts. Key considerations for regulators revolve around ensuring any comparative populations are adequately comparable and that biases are minimized, for example by requiring baseline characteristics and eligibility criteria to closely match between treated and external comparator groups.

Regulators are exploring ways to incorporate real-world evidence appropriately. The FDA has issued

guidance on using RWD/RWE to support regulatory decisions and conducts an Advancing Real-World Evidence program.

Meanwhile, the EMA jointly established a task force with Heads of Medicines Agencies (HMA) to guide RWD analysis. This launched DARWIN EU, a network of EU databases complemented by expertise. EMA also published reviews of its RWD studies and highlighted the importance of external data in a recently published draft reflection paper on single-arm trials.

Both the FDA and EMA see potential for real-world evidence but are still refining frameworks and guidelines as its ability to reliably substitute for randomized trials remains an ongoing area of research.

Regulators

Regulators generally advise sponsors to engage in early scientific advice discussions on a case-by-case basis when considering the inclusion and role of real-world evidence within the overall evidence generation plan for a given product in development. The key is to propose fit-for-purpose evidentiary approaches specifically tailored to each unique situation and unmet medical need. Methodological rigor is paramount, accounting for biases, data representativeness, quality, and ability to meet various information requirements.

While randomized controlled trials undoubtedly remain the strongest standard, the changing landscape of drug development necessitating more nuanced solutions means real-world evidence will likely continue expanding its key supportive functions and, in some instances subject to robust analytical methodology, could potentially fulfil primary evidence needs as well when appropriately justified to regulators. Future success will also rely heavily on continued collaboration between sponsors and health authorities to refine evidential frameworks and build precedent, as well as standardized analytical techniques and consistent decision-making to maximize real-world data acceptance globally over the long run.

Conclusion

In summary, real-world evidence has evolved into an integral part of the drug development and regulatory review continuum. Through ongoing advancement of methodological approaches, early regulatory engagement, and collaborative learning, real-world evidence holds significant promise to help address contemporary challenges around uncertainty of evidence and access barriers, especially for ultra-rare disease populations and conditions where conventional randomized trials prove difficult or impractical. However, reliably establishing when and how real-world data alone could substitute for randomized trials as primary evidence of efficacy remains an open issue requiring ongoing clarification, precedent-setting applications, and continual strengthening of evidential frameworks going forward in order to fully enable its potential role in this key capacity.

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14. Ongoing collaborations as per joint EMA/EUnetHTA21 workplan:

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