Real-World Evidence for Neonatal Drug Development: Challenges and Opportunities

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Progress in developing safe and effective drugs to reduce morbidity and mortality in neonates has been limited by many factors, including the rare nature of many neonatal conditions, high background rates of complications, the absence of suitable animal models, poorly defined outcome measures, and the lack of a sustainable clinical trial infrastructure for this vulnerable population.[1] Over the past 3 decades, few new drugs have been approved by the U.S. Food and Drug Administration (FDA) that have significantly improved survival and outcome, particularly in neonates born preterm.

Although randomized clinical trials have been and will continue to be an essential component of drug development, real-world data (RWD) can also assist neonatal drug development by generating real-world evidence (RWE), representing another option for establishing a drug's safety and efficacy.[2] In this article, we discuss the uses of RWD/RWE for advancing neonatal drug development, challenges encountered in acquiring RWD, and strategies to enhance the acquisition of RWD.

A leader in these efforts is the Critical Path Institute (C-Path). C-Path is a nonprofit organization dedicated to accelerating the pace and reducing the costs of medical product development through innovative methodologies and collaborative approaches. Created under the aegis of FDA's Critical Path Initiative,[3] C-Path fosters public-private collaborations by linking industry, academia, regulatory agencies, and other stakeholders in areas with significant unmet medical needs to help develop essential drug development tools that streamline and accelerate the therapeutic innovation process.

C-Path's International Neonatal Consortium (INC) is a dedicated initiative that specifically brings together a global coalition of experts and stakeholders to accelerate the development of safe and effective therapies for neonates.[4-6] Based on FDA's U01 funding mechanism in 2020, a proposal titled "Exploring the use of Real-World Data to Generate Real-World Evidence in Regulatory Decision-Making", C-Path/INC received an award to develop a RWD Analytics Platform (RWDAP) to help accelerate neonatal drug development.[7] Despite encountering significant challenges, RWD from approximately 386 000 neonates worldwide have been obtained to date.

Data from over 28 distinct contributors were collected and integrated, including electronic health records (EHRs) from hospitals in the US and internationally (~198 000 patients), neonatal registries (~184 500 patients), and neonatal clinical trials conducted by the pharmaceutical industry and academia (~3500 patients). The overall goal is to use these data to support drug development, facilitate studies of a variety of neonatal diseases, and improve access to innovative therapies for neonates.

Opportunities for Using RWD/RWE

The FDA defines RWD as "data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources" and RWE as "clinical evidence about the usage and potential benefits and risks of a medical product derived from analysis of RWD, regardless of the type of study design."[2]

Although the terms RWD and RWE are sometimes used inconsistently or interchangeably, such data and evidence can promote the development and use of safe and effective medical products.[8] For example, RWD can inform clinical trial design by providing insights into the natural history of disease and corresponding treatment patterns.[9] Although this "contextual" use of RWD does not generate RWE for a drug-outcome association, it can help select appropriate outcome measures, endpoints, and comparators leading to more pragmatic and efficient trial designs. Interest is also increasing in using RWD to expand labeling indications for approved drugs or to satisfy postmarketing commitments and requirements. For years, what is now called RWD has been an invaluable resource for postmarketing surveillance by detecting rare side effects, monitoring long-term safety and efficacy, and supporting drug performance outside of clinical trials.[10,11] The potential for RWD to generate rigorous RWE for effectiveness has only recently been recognized.

RWD can also provide insights into differential treatment responses based on genetics, environmental influences, or disease specific subtypes and endotypes. Such insights can better inform personalized medicine approaches, optimize therapeutic benefits, and better align drug development with patient needs leading to improved outcomes, better quality of life (QOL), and adequate reimbursement. Finally, RWE can foster global collaborations which can drive the exchange of ideas, promote standardization, and accelerate innovation.

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Challenges of Using RWD in Neonates

Standardized data are needed to facilitate comparative analyses and decision-making, but RWD comes in many different formats and measurement units (especially when operating in different countries). This diversity includes EHRs, administrative claims data, and patient registries among other sources. Using the term "fit for use" to describe RWD sources includes issues of relevance and reliability. Relevance refers to availability of data for key study variables as well as sufficient numbers of representative patients for analysis. Reliability is often operationalized as involving accuracy, completeness, and traceability of data sources which can vary significantly. Another important consideration involves linking of neonatal data to maternal data and long-term outcomes (eg, through school age), recognizing that changes in healthcare providers/settings often occur which can lead to missing or fragmented data.

Acquiring RWD requires negotiating individual data use agreements (DUAs) and contracts while addressing de-identification and privacy concerns. In our experience, this task often took institutions a year or longer to complete. Multiple institutional review board (IRB) applications were often required, each with its own set of conditions and stipulations. This time frame discouraged some researchers from sharing RWD and many institutions were not willing to share data for any research purposes. Regulators recognize the potential of RWE, but evidentiary standards for demonstrating the safety and effectiveness of a drug are the same regardless of study design and RWD may or may not be able to produce the required evidence. In parallel, expectations are emerging and experience is being gained regarding RWD, adding to the complexity of multinational drug development efforts.

Extracting RWD and uploading it to the RWD-AP required considerable expertise and resources. A significant financial burden was associated with data extraction, cleaning, storage, and analysis and all institutions wanted to be compensated for these efforts. Integrating these data required advanced technical infrastructure and data science skills that were not always readily available. Some institutions were hesitant to share data due to proprietary concerns or fear of losing a competitive advantage, thereby limiting the availability and utility of RWD. In addition, although the NIH Data and Specimen Hub (DASH) is designed to share de-identified data from sponsored clinical trials, some data were not posted for years after trial completion and individual approvals to access each trial were needed.

Recommendations for the Use of RWD

The challenges surrounding the use of RWD are substantial but not insurmountable. Coordinated efforts among researchers, healthcare providers, regulators, industry, funders, payers, and legislators are urgently needed. For example, the quality of data can be improved by standardizing data entry, enhancing the functionality of EHR systems to capture currently unstructured data, and implementing rigorous quality control measures. Long-term follow-up can be improved by enhancing communication, interoperability, and data sharing between different providers and hospital systems, while at the same time addressing privacy concerns. Although different laws and regulations exist, global regulatory agencies can seek to converge on general approaches to the use of RWD/RWE, thereby streamlining processes and decreasing regulatory uncertainty. With regard to specific applications involving RWD, regulatory bodies can continue to engage with relevant parties to guide and support the appropriate use of RWE.

Artificial intelligence, machine learning, standardized data structures, and common data models can facilitate data aggregation and integration from various sources. Collaborations among stakeholders can promote the development of suitable infrastructure to easily export data. The use of central institutional review boards (IRBs), paired with master contracts and reliance agreements, could significantly streamline the approval process. Of note, this approach is only effective if individual sites adhere to the determinations of the central IRB.

Adequate investments in infrastructure, data science, and training of skilled personnel are necessary to generate high-quality RWD. Fostering data sharing, transparency, and collaboration are equally important. These approaches can be encouraged by policies that recognize and reward data contributors while convincing industry of the benefits (eg, faster drug development, increased public trust) of sharing data. Finally, the global nature of research and healthcare offers an opportunity for international collaborations to provide high-quality RWD and foster the exchange of best practices and innovative solutions.

Specific guidance for the use of RWD in generating RWE has been published by the Food and Drug Administration (FDA), focusing on sources of data, study design, and regulatory considerations.[11] For example, guidance on data from EHR and medical claims as well as the design and conduct of externally controlled trials is available.[12,13] Also of note, RWD/RWE will not replace traditional randomized trials and may not be appropriate in many situations.

Conclusions

The use of RWD/RWE can advance the field of neonatal drug development and carries the potential for accelerated and more efficient drug discovery, better-informed patient care, and more precise therapeutic approaches. At the same time, standards or best practices related to data quality, regulatory compliance, data integration, data acquisition, and ethical, legal, and logistical complexities should be developed.

Enhancing data quality, promoting regulatory convergence, fostering data sharing, and strengthening global collaboration are strategies that will require significant investment in a robust infrastructure, technical skills training, efficient legal and ethical procedures, and recognition of the need for data sharing. These processes will need robust funding mechanisms involving governments, industry, foundations, academic organizations, nurses, and parents that can

be facilitated by public-private partnerships similar to INC. RWE-driven drug development represents an evolution in scientific methodology as well as a renewed commitment to advancing neonatal health on a global scale. ■

Declaration of Competing Interest

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