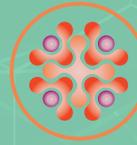




In partnership with



ARM Foundation
for Cell & Gene Medicine



WHITE PAPER:

**Enabling the Future of
Cell & Gene Therapies
through Non-Proprietary
Patient-Owned Data
Collection**



EXECUTIVE SUMMARY

There is a substantial unmet need for therapies to treat rare diseases. For as much as 95 percent of the 7,000 to 10,000 rare diseases that exist, there are no approved therapies today. But as researchers come to understand the genetic basis for many of these conditions, new approaches are rapidly advancing to treat them.

Cell and gene therapies have emerged as a new treatment paradigm, and with them has come the potential to alter the course of many rare diseases. In many cases, there is an opportunity to correct the underlying dysfunction with a one-time administration of a therapy and provide either a functional cure or a substantial improvement in health outcomes. In other cases, long term symptom relief will be the primary therapeutic objective. Some of these indications may require more than one dose to achieve continued symptom relief and scientists and companies are working on technologies that will enable the use of a repeat dose.

While developing a therapy for a rare disease can be challenging, gene and cell therapies face additional hurdles. These innovative technologies intended to address monogenic or polygenic rare diseases with potential for lifelong positive outcomes with their single or repeat administrations face more extensive regulatory requirements, as well as the need to address issues presented from payers, providers, and patients regarding the durability and long term safety of these new therapies. For example, regulatory bodies require follow-up studies of up to 15 years to understand the effects of these in vivo and ex vivo approaches to disease amelioration. Much like the innovative approaches to treat disease, data collection also needs to be innovative. The ability to collect data, develop real world evidence and disseminate and share the data has to be modernized to keep pace with the development and regulatory needs.

This paper explores the primary issues and requirements for data gathering that cell and gene therapy developers face. It also considers solutions, and the role a standardized non-proprietary data collection platform, such as RARE-X, can play in addressing these challenges. The paper finds:

- For developers of these therapies, access to natural history studies is essential to standardize endpoints and understand the heterogeneity of a genetic disease. But because the patient populations are small, the emergence of competing efforts to gather patient data can divide a patient population and silo the data. Even if the holders of the data are willing to share it, it is essential that it conform to common standards so it can be combined with other data sets.
- Though academic centers may be reluctant to share data for competitive reasons, or because they are restricted from doing so because of narrow consent agreements, and even when an institution is willing to make data available, the process may be protracted because an institutional review board may need to consider and approve any outside use of data. If it does share its data, the value of the data may be limited by a lack of rigor needed to meet the standards of regulators and drug developers, or because it uses variables, outcomes, and measures that are different than other studies.
- Companies may choose to collect data themselves, but when they do, they may be unwilling to share it with others for competitive reasons. They may also be reluctant to share data because they have invested money and resources into building a data set and don't see a benefit in giving it away to someone else.
- The challenges of long-term follow up studies involve many of the same issues as data collection for therapeutic development, but there are additional considerations. These include the need for data for HTAs and payers to evaluate the value of these new therapies or to support outcomes-based payments. This can be complicated by the fact that patients treated with a one-and-done therapy may lose regular contact with providers and may become harder to track.



It is critical for all stakeholders to recognize the shared need for data for cell and gene therapies extends across patient organizations, providers, payers, regulators, and developers. Rather than each of these stakeholders seeking to tackle the challenge on their own, experts across the ecosystem have recognized that patient organizations are best situated to gather the data needed by stakeholders and ensure that it is appropriately shared with others. The challenge, though, is that patient organizations are stymied by the cost, lack of infrastructure, and access to the expertise needed to build robust data sets that can meet the demands of regulators. New and re-imagined data collection and sharing through non-proprietary platforms can address these challenges.

RARE-X is a nonprofit that is enabling rare patient communities to gather, structure, and securely share critical data through a common platform. The organization is leveraging existing technology powered by the Broad Institute of MIT and Harvard and designing its platform to adhere to Global Alliance for Genomics and Health (GA4GH) standards to facilitate global data sharing. It is working to remove one of the greatest obstacles to progress in rare diseases by eliminating barriers for patients to gather, structure, engage, and responsibly share research-ready data with scientists, drug developers, and clinicians.

RARE-X provides infrastructure for a rare disease community to build a registry without having to create and resource it themselves. It also provides standardization tools so that datasets can be integrated where possible. And RARE-X offers operational support to ensure patient organization data are robust and meet the needs of developers, regulators, and payers.

RARE-X is not competing with alternative providers but offers a way for any data owner to collaborate with others by using its federated data platform. A federated data system is a meta-database made up of connected databases. The databases remain independent and self-contained, but they are transparently connected and can be queried together. Such a framework allows for the sharing of large datasets from around the world, which RARE-X believes will be critical to driving advances for rare disease researchers, as the value of data increases in the aggregate.

When the U.S. Food and Drug Administration approved Zolgensma in 2019, the first gene therapy to treat children less than two years of age with the most severe form of the rare genetic neuromuscular disease spinal muscular atrophy, it signaled the promise of how this new class of therapies could transform the lives of patients with the progressive and deadly rare disease. SMA type 1 is the leading cause of genetic death in infants. Left untreated, the muscles of children with the condition grow weaker over time. More than 90 percent will require the permanent use of a ventilator or die by the age of two.

Rather than each of these stakeholders seeking to tackle the challenge on their own, experts across the ecosystem have recognized that patient organizations are best situated to gather the data needed by stakeholders and ensure that it is appropriately shared with others.



Zolgensma works by replacing the defective or missing SMN1 gene that underlies this deadly condition in these infants with a functional version of the gene. It can halt progression of the disease by providing sustained expression of the SMN protein with a single, one-time treatment. The case of Zolgensma is not only a leap forward in our ability to transform rare diseases, but a reminder of the critical role patient data can play in the development of cell and gene therapies. The FDA approved Zolgensma based on a single-arm study that used available natural history data of patients with infantile onset SMA as primary evidence of the effectiveness of Zolgensma.

The data gathering will continue long after approval for Zolgensma's marketer Novartis Gene Therapies, which now must collect long-term follow-up data on patients treated with the gene therapy. Gene therapies, unlike traditional medicines, command a high one-time or installment-based payment (Zolgensma has a price tag of \$2.1 million) but are expected to provide long-term benefits. Although they may offer better value for money, and their price may be less than the cumulative cost of chronic care, the high up-front cost is difficult for today's healthcare system to absorb. And because these therapies are relatively new, there is limited experience to understand how lasting their benefits in the real-world will prove over time. Gene therapy companies need to address questions by regulators, payers, providers, and patients about the long-term safety and efficacy of these new types of therapies, understand their performance over time, and determine their true value.

"Gathering requisite data to enable long-term follow-up of patients receiving cell and gene therapies is difficult given the lack of sufficient registries and monitoring systems optimized for this requirement," said Morrie Ruffin, co-founder and board member of the ARM Foundation for Cell and Gene Medicine. "There is a need to create new tools and methods for this purpose that could be standardized to meet regulatory and health technology assessment long-term follow-up requirements that integrate real-world evidence obtained directly or remotely from patients with electronic health records and claims data."

The ARM Foundation, in partnership with RARE-X, convened experts in real world evidence strategy and operations from industry and the patient community to better understand these challenges and how they could be addressed through common registry platforms designed specifically for long-term follow up. Their ideas and recommendations are featured in this white paper.

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– *Morrie Ruffin,
Co-founder and Board
Member, ARM Foundation
for Cell & Gene Medicine*

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EMERGING THERAPIES

There is a substantial unmet need for therapies to treat rare diseases. For as much as 95 percent of the 7,000 to 10,000 rare diseases that exist, there are no approved therapies today. Many of these conditions progress over time and lead to premature death. Of the estimated 400 million people worldwide afflicted with a rare disease, half are children, and 30 percent of them will die before they reach the age of five. As researchers come to understand the genetic basis for many of these conditions, they can take new approaches to treating them. Cell and gene therapies have emerged as a new treatment paradigm, and with them a chance to alter the course of many rare diseases. In some cases, there is an opportunity to correct the underlying dysfunction with a one-time administration of a therapy.

Cell and gene therapies encompass a variety of different therapeutic approaches under the banner of regenerative medicine. While traditional small molecule drugs act on proteins involved in disease either by inhibiting or mimicking them, regenerative medicines, in essence, fix what is broken. These therapies can repair, replace, and correct the biology of a body. Gene therapy seeks to modify or introduce genes into a patient's body with the goal of preventing, modifying or alleviating debilitating symptoms, or potentially even curing disease. It can be used to either replace a mutated gene that causes disease with a functional copy, or introduce a new, correct copy of a gene into the body to fight disease. Genome editing is a means of inserting DNA to replace, remove, or modify the genome at specific locations. Cell therapies mostly rely on the use of purified cells that are infused into a patient to grow, replace, or repair damaged tissue. And tissue engineering restores or replaces damaged tissues through a combination of scaffolds, cells, and biologically active molecules.¹

Cell and gene therapies are areas of dynamic investment and therapeutic development activity. These approaches provide a means of repairing, replacing, and regenerating organs, tissues, cells, genes, and metabolic processes. There were 1,085 gene, cell and tissue-based therapeutics companies working worldwide to develop therapies and 1,220 ongoing regenerative medicine and advanced therapy clinical trials as of December 31, 2020, according to the industry trade group Alliance for Regenerative Medicine. These companies raised a combined \$19.9 billion in 2020, up from \$9.8 billion in 2019.²

The regulatory activity around cell and gene therapy has been robust. Wilson Bryan, director of the FDA's Office of Tissues and Advanced Therapies at the Center for Biologics Evaluation and Research noted during a BIO Digital conference in June 2020 that the number of investigational new drug applications—the filing to get regulatory clearance to begin human clinical studies of an experimental therapy—tripled in the last three years.³

**3X INVESTIGATIONAL
NEW DRUGS**

The number of
investigational
new cell and gene
therapy drug
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1 Regenerative Medicine, Alliance for Regenerative Medicine website, <https://alliancerm.org/technologies/>, accessed September 16, 2020

2 Lambert, Janet; 2021 Cell Gene State of the Industry Briefing; Alliance for Regenerative Medicine; <https://alliancerm.org/publication/2019-annual-report/>; accessed January 13, 2021; http://alliancerm.org/wp-content/uploads/2021/01/SOTI_2021-pdf.pdf, accessed January 20, 2021.

3 Mezher, Michael; Cell and Gene Therapies: FDA official on COVID-19 impact, Regulatory Focus, June 8, 2020; <https://www.raps.org/news-and-articles/news-articles/2020/6/cell-and-gene-therapies-fda-official-on-covid-19-i>, accessed September 16, 2020



Because underlying genetic variants drive rare diseases—as much as 80 percent by some estimates⁴—much of the work around cell and gene therapies targets rare diseases. In fact, 647 of the ongoing cell and gene therapy trials as of the end of 2019 (61 percent) were for rare disease indications, the Alliance for Regenerative Medicine reported.⁵ These therapies have the potential to address many diseases at their root cause and may, in some cases, free people with these conditions from requiring ongoing medication with a single administration of a therapy.

UNIQUE CHALLENGES IN A TOUGH DATA LANDSCAPE

Though developing any therapy for a rare disease can be challenging, cell and gene therapies face additional hurdles both in the development phase and long after they are approved. During the discovery and development phase of rare disease therapies, the small patient populations that define these conditions can limit the understanding of a disease. The clinical development pathway for cell and gene therapy is often compressed from three phases into two. The gold standard registration trial—a randomized, double-blind, placebo-controlled trial, is often not possible in cell and gene therapy. Once a cell or gene therapy is approved, regulators have imposed requirements for long-term follow-up studies of up to 15 years to understand the effects of these new therapeutic approaches.

Real-world evidence is one of the tools that can help address the challenges in both shaping the development path of an experimental therapy and also in providing insights into the safety and durability of these emerging therapies once they are approved. Real-world evidence can provide critical insight needed to design clinical trials. Understanding how a disease manifests itself, the way it progresses, and how measures of biomarkers of a given disease fluctuate and change over time is critical if a developer of a therapy hopes to provide proof that an experimental therapy is delivering meaningful benefit to a patient.

With the signing of the 21st Century Cures Act at the end of 2016, Congress gave the FDA a mandate to consider how it could incorporate real-world evidence into the regulatory review process to accelerate the development of life-saving medicines so that people who needed them could get them faster. Real-world evidence comes in many forms. The FDA defines it in sweeping terms as “data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials.”⁶ Real-world evidence is derived from real-world data, which in today’s connected world can come from a diverse range of sources as information technology has enabled the collection and analysis of unstructured data. Real-world data includes electronic health records, medical claims and billing data, data from patient registries, as well as patient-generated data from the use of mobile devices.⁷ As the ability to harness real-world data becomes easier through advances in information technology, it promises to help address a data gap in rare disease cell and gene development that can slow or limit patient access to transformative therapies.

4 Field, Marilyn J., et al.; Rare Diseases and Orphan Products: Accelerating Research and Development, Institute of Medicine, page 52, 2010 https://www.ncbi.nlm.nih.gov/books/NBK56189/pdf/Bookshelf_NBK56189.pdf, accessed September 16, 2020

5 Rare Disease & Regenerative Medicine 2019, Alliance for Regenerative Medicine, <https://alliancerm.org/indication-data/rare-disease-regenerative-medicine-2019/>, accessed September 16, 2020

6 Framework for FDA’s Real-World Evidence Program, U.S. Food and Drug Administration, December 2018, <https://www.fda.gov/media/120060/download>, accessed September 14, 2020.

7 ibid



Nevertheless, the availability of real-world data within most rare diseases remains inadequate. In part, that's because for most rare diseases, no one has bothered to gather the data at all. For developers of cell and gene therapies, the challenge of gathering the data they need is time consuming and expensive, but essential.

"If we don't have a good understanding of the natural history of a disease, it makes it much more difficult to standardize endpoints, especially in rare diseases where even in a single gene disorder you look at significant patient variation in progression of the disease and potential response to treatment," said Paul Howard, director of public policy for Amicus Therapeutics. "That makes the entire field very challenging because it makes it harder to have a study that has statistically valid results, even in a small population, that's going to convince regulators that you have a strong efficacy signal."

Amicus Therapeutics is pursuing gene therapies for lysosomal storage disorders including Fabry disease and Pompe disease, rare metabolic disorders that are relatively well understood and characterized, but still have substantial evidence-generation needs. They are also pursuing gene therapies for various forms of Batten disease, an ultra-rare lysosomal storage disorder where data are not readily available.

"This is a significant barrier that we all face. Even if there's multiple patient disease organizations trying to create registries, there's subdividing of the patient population potentially further," he said. "And if data formats are not standardized, then you face a real challenge trying to scale the data in a way that's going to be credible with regulators."

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— Paul Howard, Director of Public Policy, Amicus Therapeutics

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Academic centers may run natural history studies of rare diseases but access to these data sets can be problematic for therapeutic developers. While some institutions may be reluctant to share the research with other academic institutions over concerns of being first to publish, they may be willing to work with biopharmaceutical companies. They often face restrictions, however, because of how participants in any given study consented for their data to be used. If an institution is willing to make data available, an institutional review board may need to review and sign off on any outside use of the data, which can be a protracted process.

And even if the institution is willing to make the data available, they may do so only in the aggregate by providing an analysis of the data rather than patient-level data, which would be more useful. In all cases, there can still be overriding limitations because of the quality of the data, which may not be viewed by regulators as adhering to standards high enough to be used for decision making about the safety and efficacy of a therapy. Even when academic researchers are willing to make the data they collect available, there can be a disconnect between the data they have and what therapeutic developers need.



“For each rare disease there are limited resources for research and often a paucity of good data sets that one could use for drug development in these rare diseases. Many times, academic investigators have done a small study, but the study may not be fit for purpose,” said Petra Kaufman, senior vice president of clinical development for Novartis Gene Therapies’ analytics and translational medicine. “Maybe it doesn’t have the outcomes that you need for drug development because they were not designed for drug development necessarily, but maybe for an academic understanding of the course of the disease and potential outcome measures.”

Those problems can be further complicated by the fact that investigators at different universities or in different countries may track different variables, different outcome measures, different biomarkers, or collect data in different ways. In the absence of a ready source of real-world data for industry, therapeutic developers are often left with few alternatives to developing their own data sets. The problem with this is that once created, companies are often reticent to share their data with others. This can be a problem because once academic partners and patients have worked to provide data, they don’t want to repeat the exercise when the next entity comes along and needs to create a new data set for themselves.

Companies that have gathered data may be unwilling to share it with others for what they view as competitive reasons. They may also be reluctant to share data as a matter of principle. They may take the attitude that they have invested money and resources into building a data set and don’t see a reason why they should give it away to someone else.

Even when available data does exist and the owners of the data are willing to share it, therapeutic developers may feel driven to create their own data sets because what is available may not provide adequate detail, may have not asked questions the developer needs to answer, or may fall short of the standards that regulators require.

In the case of Novartis Gene Therapies’ gene therapy Zolgensma, there were several studies of SMA that had been done in Europe and the United States, but they proved to be of limited value because they were retrospective studies. The SMA Foundation convinced what was then Zolgensma’s developer AveXis to conduct a prospective natural history study, which turned out to be critical for establishing outcomes and measures for patients with the condition. The National Institutes of Health funded an additional biomarker and natural history study for infantile SMA led by researchers at the Ohio State University Wexner Medical Center. The studies showed infants with SMA would decline from their first visit forward. More than 90 percent of the children died by the age of 20 months. It gave the company data robust enough to use as a comparator arm for its clinical trial that led to an approval of Zolgensma.

“Clinical trials in this population require an understanding of disease progression and identification of meaningful biomarkers to hasten therapeutic development and predict outcomes,” said Stephen Kolb, director of the Ohio State ALS/Motor Neuron Disease Translational Research Program at Ohio State’s Neurological Institute, when the study was published in the *Annals of Neurology* at the start of 2018. “This study has generated definitive controlled data on the natural history of infantile-onset SMA. With the advent of effective disease-modifying therapies, it’s likely not ethical or feasible to perform future clinical trials that have a placebo arm in which sick children don’t receive available treatment. Thus, our data sets are critical for future investigation of improved therapies.”⁸

8 NeuroNext Biomarker Study Explores Natural History Of Infantile-Onset SMA, press release, Wexner Medical Center, The Ohio State University, January 8, 2018, <https://wexnermedical.osu.edu/mediaroom/pressreleaselisting/neuronext-biomarker-study-explores-natural-history-of-infantile-onset-sma>, accessed 10/28/20



The expense of these studies, the limited patient populations, and the need to get data fit for drug development, makes it essential to get different stakeholders to cooperate, according to Kaufmann. “The lesson is that everybody has to work together. If a rare disease community is looking to advance towards treatments, there’s a lot they can do to get ready and to set the stage for that,” she said. “If they do it in a collaborative way, then they can ensure that the data sets that they generate are useful as a basis for drug development.”

THE LONG HAUL

The challenges of long-term follow up studies involve many of the same issues as data collection for therapeutic development, but there are additional considerations. The high price tag for gene therapies is expected to make novel payment arrangements, such as outcomes-based payments or annuity-based payments, the norm. But doing so will add to the burden on gene therapy developers, who will not only need to gather data to satisfy regulatory demands for proof of the long-term safety and durability of these therapies, but also to address payer concerns about value.

“How do you get that long-term follow-up information that’s going to be needed not only to satisfy FDA, but to potentially get the kind of outcomes-based arrangement you want with a payer?” said Amicus’ Howard. “There’s a real strong market incentive to develop that platform to answer that need. It’s still a couple of years away for us, but that means we need to be setting it up now.”

There is a growing shift away from industry-owned and operated registries, the vehicle companies often use to fulfill post-marketing regulatory commitments. Instead, regulators, clinicians, patient groups, and other stakeholders in the rare disease community are increasingly pushing for registries to be owned and operated by the affected disease community. This is a welcome shift, yet most rare disease communities aspiring to establish longitudinal disease registries are struggling. They tend to operate with limited resources and funding. Though industry can apply substantial resources to help a registry succeed, rare disease communities often cannot. The successful execution of a registry, particularly one that can fulfill regulatory requirements, requires a level of investment and scale of operation that often isn’t possible for a rare disease community.

For cell and gene therapy, long-term follow-up efforts are complicated by the fact that for patients treated with a therapy with curative intent the patient may become difficult to follow. If the therapy is successful, the patient may no longer see a specialist, and over a period as long as 15 years, may change insurers and doctors. It will be critical to develop methods to follow a patient that are not too burdensome so as to compromise their willingness to participate. These methods should also not rely on regular contact with a specific physician as that may prove to be unreliable.

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The lesson is that everybody has to work together. If a rare disease community is looking to advance towards treatments, there’s a lot they can do to get ready and to set the stage for that. If they do it in a collaborative way, then they can ensure that the data sets that they generate are useful as a basis for drug development.

– Petra Kaufman, SVP,
Clinical Development,
Analytics & Translational
Medicine, Novartis Gene
Therapies

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“How do you engage patients and clinicians to make sure that we can learn over the long-term, how they feel, function, and survive? It is so critical because it’s a new modality. We must figure out how to follow patients so we can know what happens to them after receiving gene therapy,” said Novartis Gene Therapies’ Kaufmann. “But it has to be patient-centered. And it has to be patient-friendly, especially now with COVID, but that’s a great opportunity for disruptive innovation.”

One such form of potential disruptive innovation is the use of data tokenization. In essence, data tokenization would be a means for aggregators of diverse types of health data to protect the identity and privacy of patients while linking their data throughout the healthcare continuum, such as claims records and electronic health records. A consenting participant in a prospective research study can allow someone to generate a token that links a researcher to their various data for a study.

Other technological solutions may ease the burden on patients for long-term follow-up studies by allowing them to respond to surveys or enable regular check-ins through the use of web-based surveys and telehealth visits to avoid requiring patients to travel for a site visit. Craig Lipset, founder of Clinical Innovation Partners and an adjunct assistant professor in the department of health informatics at Rutgers University, cautions, however, that companies will need to design such tools with an expectation that technology will change over time.

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These models will need to be built with an expectation of evolution. There is nobody that can launch an app today in the year 2020 and say with a straight face that the patient will be using this app until the year 2030. That’s hard though for researchers.

— *Craig Lipset, Founder of Clinical Innovation Partners,
Adjunct Assistant Professor, Department of Health Informatics,
Rutgers University*

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“These models will need to be built with an expectation of evolution. There is nobody that can launch an app today in the year 2020 and say with a straight face that the patient will be using this app until the year 2030,” he said. “That’s hard though for researchers. They don’t make that type of upgrade of our tools for patients. They like things to be very consistent from day zero until last visit, but in this environment for that type of duration of follow-up, we’re not going to have that luxury.”

Lipset, though, thinks cell and gene therapy development would be foolish to think they will be able to rely on direct patient input and engagement for all long-term follow-up data they will want to capture. “It would be very dangerous for anyone in the cell and gene therapy space to assume that they will have long-term stickiness and connectivity with everybody in their studies that they would otherwise need,” he said. “Using different types of real-world data approaches can have at least an assurance and insurance that the information will be there and that what happened to the patient will not be an unknown.”



A SHARED NEED

The need for long-term follow-up data for cell and gene therapies extends across patient organizations, providers, payers, regulators, and developers. Rather than each of these stakeholders seeking to tackle the challenge of gathering long-term data alone, we believe that patient organizations are best situated to gather the data needed by stakeholders and ensure that it is appropriately shared with others. Patient organizations are motivated to act in the best interest of patients and see to it that data are shared with anyone they believe is working to advance diagnosis, treatments, and cures for their condition.

The challenge for patient organizations, though, has been the cost, lack of infrastructure, and access to the expertise needed to build robust data sets that can meet the demands of regulators. To leverage the full potential of their data, they have come to realize they also need to be standardized so they can be used in conjunction with other data sets involving the same condition or a different disease that may be related because of an underlying gene, shared symptoms, treatment with the same therapeutic agents, or other linkages.

The solution to both front-end data-gathering and long-term follow-up of cell and gene therapy lies with enabling patients and disease communities to operate data collection efforts that meet the expectations of regulators, and are structured and governed so that patients can support the right data being shared at the right time. The problem is that patient communities often lack the technical sophistication necessary for creating a data collection platform. Turning to outside vendors can be expensive. Further, partnering with organizations that offer to do this at no cost can leave them without control over their data or unable to move it to another platform if they choose to do so.

THE RARE-X SOLUTION

RARE-X is a nonprofit that is enabling rare patient communities to gather, structure, and securely share critical data through a common platform. The organization is leveraging existing technology powered by the Broad Institute of MIT and Harvard and designing its platform to adhere to Global Alliance for Genomics and Health (GA4GH) standards to facilitate global data sharing. It brings patient organizations' data collection capabilities in a way that is meaningful without creating an unwelcome burden on them. And it uses shared data environments with proper governance and flexible consent that makes it accessible to researchers and drug developers.

The organization is working to remove one of the greatest obstacles to progress in the area of rare diseases by eliminating barriers for patients to gather, structure, engage, and responsibly share research-ready data with scientists, drug developers, and clinicians. The RARE-X collaborative data platform provides a means for patient organizations to easily share patient registries, natural history studies, genomic information, electronic health records, and other data with researchers, clinicians, and drug developers. RARE-X provides technology and services to these groups free of charge to enable stakeholders in the rare disease world to gather, harmonize, and share data. Its model levels the playing field for patient communities and researchers, who otherwise might not have the resources needed to assemble, access, and analyze the needed data for pivotal research, by removing financial barriers that have limited the ability to harness comprehensive data sets to the largest and best endowed organizations.



One way to address the shared need for data is to eliminate the data silos that currently exist throughout the rare disease ecosystem. RARE-X is not competing with alternative providers but offers a way for any data owner to collaborate with others by using its federated data platform. A federated data system is a meta-database made up of connected databases. The databases remain independent and self-contained, but they are transparently connected and can be queried together. Such a framework allows for the sharing of large datasets from around the world, which RARE-X believes will be critical to driving advances as value of data increases in the aggregate.

For patient communities, RARE-X supports their efforts to collect data, structure it, adhere to rigorous standards, and share it responsibly. Equally important, the organization ensures data that is developed with proper quality checks is validated and adheres to good clinical practice standards. For clinicians, RARE-X provides the access to data needed to accelerate diagnosis and better track health outcomes. And for researchers and therapeutic developers, RARE-X's federated data platform gives them access to the data they need to identify, develop, and track the impact of breakthrough treatments and cures.

ADVANCING CELL AND GENE THERAPIES

RARE-X understands the needs of cell and gene therapy developers. It is building a technology platform that supports the rare disease ecosystem through the entire life cycle of a therapy including development and long-term outcomes tracking. It is doing so with direct input from industry partners and regulators to ensure collaborators gather the data required and that the data adhere to regulatory standards. The ARM Foundation for Cell and Gene Medicine is serving as valuable partner for RARE-X in convening the relevant stakeholders to inform and support this effort. As a non-profit, RARE-X is motivated by doing what is in the best interests of



A Patient Organization-Led Collaboration Points a Way Forward

The World Federation of Hemophilia has led a multi-stakeholder collaboration to create a gene therapy registry to provide long-term outcomes data of hemophilia patients treated with gene therapy, as the first gene therapies for hemophilia A and hemophilia B are advancing toward marketing approval.

Hemophilia is a genetic bleeding disorder that is caused by low levels of a protein known as a clotting factor needed to stop bleeding. People with the condition can experience spontaneous and potentially life-threatening bleeding from modest injuries. The condition can cause painful bleeding into joints and joint damage over time. Today, the standard of care is the use of replacement factor therapy, which requires regular injections of expensive therapies.

Gene therapies have the potential to free people with the condition from a reliance on factor replacement therapy and correct the mutation underlying the disease to allow their bodies to produce adequate amounts of the clotting factor they lack. But these therapies will likely be approved with limited experience in people with the disease and many questions about the long-term safety and efficacy of these therapies will be left unanswered. Patient groups, gene therapy developers, regulators, physicians, and payers all have questions that will require long-term follow up of patients to answer.

“You can see how easy it will be to get multiple, diluted registries because everybody has their own need. It is about understanding that the only way we can all meet our obligations and support will be by doing it together,” said Ian Winburn, global medical lead, hemophilia, endocrine, and inborn errors of metabolism, rare disease for Pfizer and a member of the World Federation of Hemophilia Gene Therapy Registry Steering Committee. “That is where leadership is required. It requires a group, or a collection of groups, to put their head above the parapet and to take leadership and ownership of that.”

The World Federation for Hemophilia joined with the International Society of Thrombosis and Hemostasis Scientific and Standardization Committee, the European Haemophilia Consortium, the U.S. National Hemophilia Foundation, the American Thrombosis and Hemostasis Network, as well as gene therapy developers and regulatory liaisons to develop a gene therapy registry to gauge the long-term safety and efficacy of these treatments in people with the condition.

patients and helping them get the answers and therapies they need.

The organization is initiating a series of demonstration projects in partnership with rare disease communities, biopharmaceutical companies, academic medical centers and other partners. The pilot programs will apply technology proven in other large-scale public health and genomic data-sharing initiatives to support the global needs of those developing treatments and caring for rare disease patients. By enabling rare patient communities to more easily gather, structure, and share critical data securely through a common platform in collaboration with researchers, drug developers, and clinicians anywhere in the world, RARE-X will accelerate diagnosis, disease understanding, and development of future treatments and cures across more than 9,500 rare diseases.

Cell and gene therapy developers need access to more data and higher quality data to transform development and commercialization of these new therapies. RARE-X understands that the road to accelerating disease diagnosis, drug development, and driving down costs will take a new approach. That is why like-minded individuals and organizations are coming together to support the development of RARE-X.

If you are interested in becoming involved in one of our pilot projects, contact us today at rare-x.org/connect.



“A collaborative global strategy is required to ensure a large enough patient pool to allow robust evaluation and detection of low incident events that may otherwise go undetected,” the collaborators wrote in the November 2020 issue of the *Journal of Thrombosis and Haemostasis*. “If events are captured in disparate registries or databases, we will regrettably not benefit from the power of combined data.”⁹

While the authors said gene therapy has the potential to provide a functional cure, many unknowns exist about the long-term safety and efficacy of these therapies. This includes concerns about whether liver damage or cancer could develop years after treatment and unknowns about whether the benefits of a treatment will continue to be as robust years after treatment and the production of a needed factor will remain stable and adequate to prevent bleeding episodes. The best way to determine that is to track patients over many years.

The gene therapy registry will seek to include data on all patients with hemophilia who are treated with a gene therapy. The World Federation of Hemophilia will also leverage existing gene therapy registries and repositories.

In a separate commentary published in the journal *Haemophilia* in July 2020, participants in the World Federation of Hemophilia Gene Therapy Registry write that because of the gaps in evidence, collaboration is essential to answering questions that need to be addressed.

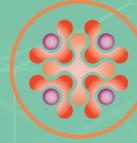
“This data collection/surveillance effort should be a shared responsibility. Healthcare providers and patients will need to work together to collect standardized data on patients who receive gene therapy, ensuring that their experiences are captured in a registry, over their entire lifetime,” they write. “Such longer-term data will assist regulators and manufacturers who are also closely monitoring signals of potential safety events and may provide assistance to payers regarding the efficacy and potential safety milestones needed to inform their reimbursement strategies.”¹⁰

9 Konkle et al., Core Data Set on Safety, Efficacy, and Durability of Hemophilia Gene Therapy for a Global Registry: Communication from the SSC of the ISTH; *Journal of Thrombosis and Haemostasis*, November 2020, <https://doi.org/10.1111/jth.15023>, accessed December 10, 2020.

10 Konkle et al, World Federation of Hemophilia Gene Therapy Registry, July 2020, <https://doi.org/10.1111/hae.14015>, accessed December 10, 2020



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