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Precision medicines for neurodegenerative disorders: optimizing clinical development.

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Precision medicine, a new paradigm of individualized treatment, is revolutionizing healthcare. This innovative approach utilizes lifestyle and environmental factors, molecular, cellular and image profiling, as well as genomic information to enable treatment and management of disease that is specialized and unique to a given patient.

Momentum for the implementation of precision medicine in clinical practice is increasing. The price of exome sequencing and wholegenome sequencing continues to fall while the catalog of disease-associated copy number variants or deleterious sequence variants—produced from genome-wide association studies, array comparative genomic hybridization and next-generation sequencing (including exome sequencing and whole-genome sequencing)—is rapidly growing.

Leveraging access to numerous biomarkers and diagnostics, oncology has been the front-runner in the successful implementation of precision medicine approaches. Similar progress in neurology and other therapeutic areas has also been witnessed with recent advances in the discovery and development of multimodal diagnostic biomarkers. As of 2022, seven advanced therapies have been approved for neurodegenerative disease.

While these advances offer a promising outlook for patients who have few or no treatment alternatives, cell and gene therapy development continues to face many challenges inherent with studying neurodegenerative disorders. From reviewing therapeutic approaches to applying a gene therapy in a neurodegenerative disorder, this article shares key considerations for addressing the specific complexities of these diseases and optimizing clinical development to support patient-centric trials.

Understanding the challenges of neurodegenerative diseases

Each neurodegenerative disease has a different pathophysiology, which can be identified by elements that are common across more than one disease, such as inflammation, cell death, impaired/failure of axonal regeneration, demyelination, and/or structural and functional neuronal deficits.

Current treatment strategies target a small subset of the population and focus on symptomatic relief only, without altering disease progression. Although rapid progress in the understanding of the molecular and genetic pathogenesis of neurodegenerative diseases has led to the development of new therapeutic approaches in an attempt to arrest or delay neurodegenerative processes, many challenges still face the field, such as:

- **Common underlying causes and unique mechanisms of toxicity**[1,3]
  Certain pathologic features of neurodegenerative disease may be common to more than one disorder and can include abnormal accumulation of proteins, aggregation of proteins, misfolded proteins, RNA toxicity and translational products from repeat expansion within genes.
- **Timely diagnosis of neurodegenerative diseases**
  With overlapping symptoms, it is difficult to make a differential diagnosis in the early stages of a neurodegenerative disorder. By the time symptoms are evidenced, significant damage may be present as pathological alterations typically begin long before symptoms are present. Furthermore, there is a lack of predictive preclinical models that can accurately translate favorable preclinical outcomes to the clinic.
- **Potential timing considerations for treatment administration**
  Knowing that a disease progresses over time before symptoms manifest, researchers must consider the timing and the administration of a treatment. Different cell populations may be affected along the timeline, and evidence suggests that neurons may be in an atrophic state for some time before actually dying; therefore, it may be desirable to target different cell populations at different stages of a disease.
- **Studying symptomatic patients in clinical trials**
  While genetic testing may help identify individuals when they're asymptomatic and at risk, the nature of the risk cannot be precisely characterized, and testing cannot predict clinical successes when treating identified individuals. Genetic testing in rare diseases with a monogenetic etiology has a more precise diagnostic utility, but many neurodegenerative diseases often have multiple genes involved in the pathophysiology of the disease. Here, genetic testing can be less precise, particularly when applied to asymptomatic individuals, which also can make the development of targeted therapies more challenging. Testing can also have major psychological and financial impacts on an individual and their family, should the test be positive.

Complexities in the application of precision medicines: Friedreich's ataxia

Consider the example of Friedreich's ataxia (FA), a rare neurodegenerative disease characterized by defective production of frataxin, a protein vital for nerve and muscle health. Patients typically present with difficulty walking but can also exhibit vision, hearing and speech problems; they may also develop cardiac abnormalities, muscle weakness, poor coordination and a loss of vibratory sense in the lower extremities. About half of all patients with FA will develop some form of carbohydrate intolerance, with a third typically developing diabetes, indicating the broader systemic reach of the disease. FA typically presents from around age 10 to 15, with most patients being symptomatic by age 20; however, the age of diagnosis can range from 2 to 50 years of age.

The pathogenesis of FA is complex, as frataxin messenger RNAs are mostly expressed in tissues with a high metabolic rate; as a result, only certain neurons are susceptible to frataxin deficiency. The dentate nucleus is affected early in the disease but tends to progress at a steadier pace over time, while the corticospinal tract degenerates over time and contributes to problems observed in the later stages of the disease. For example, the spinal cord exhibits diminished white matter as an early feature in young, ambulatory patients, but this symptomatology often progresses quite significantly over a few years from diagnosis. The proprioceptive system will also show significant early developmental hypoplasia but progresses minimally from its early point.

The choice of the treatment target for patients living with FA depends on a patient's age, desired goal and practical considerations. Addressing the proprioceptive system after early childhood treatment is not ideal. However, with the dentate nucleus, treatment is likely to be most effective early in the course of the disease, when it is functionally affected, but still shows limited atrophy. As the corticospinal tract degenerates over time, contributing to disease progression throughout its late stages, treatment may be able to affect these issues even in the later stages of the disease.

Examining therapeutic approaches for addressing neurodegenerative disease mechanisms

Considering the complexity of neurodegenerative disorders like FA, there are many implications for developing a therapeutic. Drug development sponsors must consider which systems are affected, the time at which they are affected during the course of the disease and whether to treat systemically versus target the central nervous system (or both simultaneously). If the targeted system is responsive to therapy, drug developers must also determine how they deliver the therapy to the targeted tissue.

Therapeutic approaches with RNA

RNA therapeutic approaches offer several opportunities to address multiple disease mechanisms that have been implicated in neurodegeneration through gene regulation.

Table 1: RNA therapeutic approaches[2,3]

Platform	Overview	Limitations
miRNA – microRNAs	• 2,000 miRNAs have been identified in humans • They are known to regulate several important cellular processes and thought to regulate about 30% of genes in humans • miRNAs can act as signaling molecules for intercellular communication • miRNA-mediated silencing is an attractive therapeutic modality in neurodegenerative diseases with aberrant protein production	• miRNAs may cause toxicity related to (passenger strand) off-target toxicity • Active mature miRNAs are thought not to re-enter the nucleus, an important limitation that may lower efficacy in the cell nucleus
siRNA – small or short interfering RNAs	• siRNAs have been more widely tested in clinical trials for treatment of different types of diseases • DNA constructs encoding therapeutic RNAi following delivery by lentiviral vectors have been clinically tested	• Naked siRNA cannot passively diffuse through cellular membranes; it has low transfection efficiency, poor tissue penetration and nonspecific immune stimulation[2] • Multiple delivery pathways, both viral and nonviral, have been developed to bypass these problems
ASOs – antisense oligonucleotides	• ASOs are short, synthetic, single-stranded nucleic acids of about 20-25 bases long that bind cellular RNA and reduce, restore or modify protein expression via several distinct mechanisms • ASOs classically bind to complementary mRNA through Watson-Crick base-pairing, endonuclease-mediated transcriptional knockdown • ASOs can knock down gene expression by sterically blocking splicing factors and altering pre-mRNA splicing or by preventing ribosome recruitment to block mRNA translation	• ASOs are degraded by endo- and exonucleases and re-administration is required; they are especially problematic in central nervous system disorders requiring invasive delivery methods • Pharmacological profiles of ASOs can be enhanced via chemical modifications; efforts are underway to improve delivery/crossing of the blood-brain barrier and improve target engagement

Across these RNA therapeutics, the common limitations include the risk of off-target toxicities, the ability to be easily degraded by ribonuclease or other enzymes, along with a poor ability to pass through cell membranes as well to cross the blood-brain barrier. These limitations, in turn, have required the development of various delivery pathways, including both viral and nonviral means, as well as chemical modifications in various backbone structures in the case of antisense oligonucleotides.

In the area of neuroscience, there are currently dozens of RNA-based therapeutics in development, in areas such as Duchenne muscular dystrophy (DMD), amyotrophic lateral sclerosis (ALS) and Huntington's disease, along with a several treatments targeting myotonic dystrophy and Angelman syndrome.

Gene editing approaches

Most of the more common gene editing methods have evolved out of naturally occurring systems. These include zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs) and clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 9 (CRISPR-Cas9).

Table 2: Gene editing approaches[4]

Platform	Overview	Size	Limitations
ZFNs	• ZFNs can generate gene point mutations, deletions, insertions, inversions, duplications and translocations in a complex genome[4] • The small size of ZFNs allows multiple delivery systems to be utilized	• Small (2.1 kb)	• The design process is complex, time-consuming and labor-intensive; specialized expertise is required • It is difficult to predict off-target cytotoxic effects • Some nucleotide sequences do not have a corresponding ZFN
TALENs	• TALENs allow for specific editing with few off target effects • TALENs generate double-strand breaks at specific loci; these mutations are transmitted through the germ line • TALENs are easier to design than ZFNs; there are fewer constraints on site selection	• Large (5.7 kb)	• The size of TALENs affects the efficiency of the delivery • 5' base of a TALEN target site must be thymine; the binding efficiency is impacted by chromatin accessibility
CRISPR-Cas9	• CRISPR-Cas9 does not require a custom design of novel proteins for each DNA target site • By changing the 20-base pair protospacer of the guide RNA, CRISPR-Cas9 can be easily adapted to target any genomic sequence • The design of constructs is relatively easy and cost-effective; CRISPR-Cas9 has a significant advantage over other approaches	• Medium (4.5 kb)	• It is challenging to deliver via viral vectors due to the size of the Cas9 protein (~3.2-4.2 kb); they have a higher level of off-target effects • Continuous expression of Cas9 proteins at high concentrations has been linked to toxicity • The binding efficiency is impacted by chromatin accessibility
MegaTAL	• MegaTAL is the fusion of a TAL effector with a meganuclease • MegaTAL is suitable for a variety of delivery platforms	• Small (2.0 kb)	• Reengineering for new specificities is challenging • Some mismatches are tolerated • MegaTAL can have off-target effects
ARCUS	• ARCUS offers high edit control; all types of edits are possible, and ARCUS deactivates after editing • There are low off-target effects; ARCUS requires productive binding before editing • Off-target cuts are easy to detect	• Very small (0.93 kb)	• ARCUS is expensive and requires a highly complex process to design

Using any of these nucleases in *ex vivo* treatment of cells is much easier than delivering the nucleases to the tissues *in vivo*. However, like many of the advanced therapeutic technologies touched upon in this article, the mode of delivery to the target cell remains a critical challenge. Furthermore, all of these gene editing technologies have the potential for off-target effects resulting in unwanted induction of DNA mutations or deletions and impairment of gene function.

Therapeutic approaches with viral vectors

Traditional viral vector systems utilize the inherent ability of a virus to bind to a host cell and introduce genetic materials. They have been used in recent precision medicine clinical trials[5] and serve as an effective form of gene delivery as the virus structure prevents degradation of genetic material along its journey to the target cells. The main drawbacks include immunogenicity and cytotoxicity as well as the challenge to manufacture cost-effectively at a commercial scale.

Table 3: Viral vector approaches[6,7]

	Overview	Limitations
Retrovirus (includes oncoretroviruses, lentiviruses and spumavirus)	• Genetic material is in the form of RNA • Reverse transcriptase is employed to produce DNA, which is then incorporated into the host genome by an integrase enzyme • New transgene integrated into host genome; integration is generally not specific within the human genome	• There is the potential for disruption of critical host genes; the activation of proto-oncogenes can lead to risk for malignancies
Adenovirus (AV)	• Human AVs are ubiquitous, and most people have been infected with one or more serotypes; they have significant preexisting immunity[6] • AVs are strongly immunogenic	• The majority of gene therapy trials (mostly cancer) have been conducted with AV; they can be replication-defective or replication-competent, producing a significant preexisting immunity, which is a barrier to administration of the therapeutic
Adeno-associated viruses (AAVs)	• AAVs have been used in 250-300 clinical trials to date[7] • They are small (20 nm), replication-defective, nonenveloped viruses; they have a linear single-stranded DNA genome of approximately 4.8 kb • AAVs have the advantage of producing a relatively mild immune response and not being associated with causing human disease • AAVs can infect both dividing and quiescent cells • AAVs persist in an extrachromosomal state without integrating into the genome of the host cell; native virus integration of virally carried genes into the host genome does occur	• The carrying capacity of the vector is relatively limited; large genes are not suitable in AAV • Humoral immunity from infection with the wild-type AAV is relatively common • The use of AAVs may result in the genetic material not being passed along to the next generation of cells, potentially producing a problem for the durability and long-term expression of the therapeutic gene • Many regions of the central nervous system are difficult to access with viral vectors

Optimizing clinical operations for a neurodegenerative disease therapy

As of April 2022, 92 advanced therapies comprising 19 gene, 17 RNA and 56 non-genetically modified cell therapies were approved for global use.[8] Of these, one gene therapy for spinal muscular atrophy (SMA) and six RNA-based therapies for DMD, SMA and fatigue syndrome have been approved for neurologic indications.

With more than 3,500 therapies in various stages of development, the current pipeline of cell, gene and RNA therapeutics is strong. Within this pipeline, development for neurological diseases comprises 227 gene therapies. Twenty-seven of these are in the clinical stage development; many of those are targeting Huntington's disease and the muscular dystrophies. There are also 95 cell therapies targeting areas such as stroke, Parkinson's disease (PD), Alzheimer's disease (AD), spinal cord injury and ALS, and 123 RNA-based therapeutics targeting DMD, ALS, Huntington's disease, spinocerebellar ataxia, Angelman syndrome and frontotemporal dementia.

The pipeline of potentially life-changing treatments is promising, but developing sophisticated therapeutics requires special considerations spanning patient identification and long-term monitoring to codevelopment of biomarkers, assays and companion diagnostics.

Neurodegenerative diseases are grouped based on pathophysiologic similarities and characteristics of progressive decline of motor and cognitive functions. However, clinical symptomatology and disease progression varies significantly, which dictates a tailored approach to patient management within these diseases along with further disease-specific refinement incorporating individualized tactics and algorithms for phenotypes within an indication.

Thinking holistically about a biomarker strategy

The genetics of neurodegenerative diseases have led to significant advances in the understanding of disease pathogenesis and biomarkers. For example, for PD, a mutation identified in α-synuclein (SNCA or α-syn) associated with a large Italian family (the Contursi kindred) led to the identification of SNCA as the major protein component of Lewy bodies in the substantia nigra and cortex, lesions that are pathognomonic for PD.[9,10] Environmental toxins such as rotenone, which are known to induce PD, cause SNCA to form oligomers. SNCA oligomers are believed to be pathogenic in PD, and SNCA is a robust target for therapeutic intervention. Later discoveries in mutations relevant to PD pathological processes accelerated, targeting further investigation of their role and search for new therapeutics. There are now 24 known PARK genes, including an additional SNCA mutation (A30P; PARK4).

While monogenetic cases of PD account for fewer than 5% of all cases, genetic risk factors account for up to a third of cases.[11] A large genome-wide association study meta-analysis identified 90 risk signals for PD that account for an assessment of risk factors listed in the PDGene database.[12] These genetic risk factors provide important clues regarding disease mechanisms, as well as inform therapeutic targets and biomarkers, enabling researchers to focus more precisely on specific mechanisms associated with disease-relevant genes. For this reason, clinical trials may focus on specific monogenic PD subjects, such as PD with GBA mutation.

Evaluating patient-centric applications of biomarkers

When embarking on a drug development program in neurodegenerative diseases, sponsors must begin with the end goals in mind and think holistically about their biomarker strategy. At the start of the development process, the importance of various assays must be assessed to determine if they will add value and provide information that enables more informed treatment decisions, setting the stage for possible commercialization that may include companion or complementary diagnostics.

In many clinical trials, assays can serve a key role in a program if they help identify the right patients and specific stages of their disease. Sponsors must determine how biomarkers will be used, for example, as a screening biomarker to identify a specific subpopulation for a substudy and/or as an endpoint in a clinical trial.

Ideally, the use of a biomarker can track disease progression and correlate predictably in response to a therapeutic intervention, which would reduce a study's duration and number of patients needed. It is imperative that all sampling in a study should be critically assessed and focused on obtaining what is "absolutely necessary" rather than "nice to have." Sponsors should evaluate several factors before trial initiation, such as:

1 Considering the invasiveness of sample collection

Sponsors must evaluate the advantages and disadvantages of collecting blood, collecting cerebrospinal fluid (CSF) and/or performing a biopsy.

- Spinal taps for CSF collection and biopsy are costly, may produce adverse events and pose additional risks for patient recruitment and retention. For example, in recent discussions between Fortrea and more than 300 PD investigators, the presence of a spinal tap as a study procedure was suggested to reduce recruitment rates up to 80%.
- Skin biopsy remains to be controversial in its utility for PD trials. While it is not associated with high costs or adverse events, it can be painful for patients; combined with CSF, skin biopsy poses a bigger challenge to recruitment.
- Blood collection is less invasive, less likely to produce an adverse event and less costly than CSF or tissue collection, but the frequency and overall volume of blood collection required during the study may also have an impact on burden imposed upon the patient. Beyond the cost and invasiveness, blood sampling should be assessed for the level of information provided versus biopsy specimens or CSF; exosomal α-syn in blood shows diagnostic sensitivity and specificity comparable to CSF α-syn.

2 Determining the value of incorporating biomarkers

The selection of biomarkers must be based on the product's mechanism of action. For example, with therapeutic monoclonal antibodies, measurement can examine antibody-bound α-syn versus free α-syn levels in the CSF and peripheral tissues, or with therapies that aim to reduce α-syn transcription via antisense mechanisms, the direct assessment of α-syn transcripts or protein levels can be performed.

Sponsors must also recognize that biomarker utilization in healthcare is quite low. While this does not necessarily reflect inherent limitations of biomarkers, identifying biomarkers that could be used to support clinical trials in neurological diseases is not part of the standard of care. Early patient identification for trial prescreening can be limited, leading to a longer screening and higher costs of the study.

3 Examining the role of genetic testing

Development of precision medicines typically focuses on monogenic patient phenotypes, like PD with *GBA* or AD with homozygous APOE4, which requires additional steps in patient enrollment. As the genetic testing for these indications are not part of standards of care and not routinely performed as part of disease management, databases of potentially qualified patients do not exist. Multiple stakeholders should closely collaborate to implement comprehensive genetic screening of patients.

Sponsors can contract with vendors that have access to patient registries and relationships with neurological disease organizations. While this can be expensive, this targeted approach will allow for prescreening of patients as part of their genetic counseling and invitations to participate in a trial. Along with looking at specific groups known to carry certain mutations or geographical areas where a neurodegenerative disease is more prevalent, these data-driven strategies can help enrich the screening process.

4 Considering data stratification to better define the product target profile

Proactive stratification of data for differentiating treatment effects on particular patient phenotypes, for example, homozygous APOE4 in early Phase I trials, could help better define the product target profile.

Incorporating imaging biomarkers

Recently, the development of various molecular brain imaging techniques has enabled pathological changes in the brain to be inferred without autopsy. While some diagnostic criteria for neurodegenerative disease are described neuroimaging findings as only characteristic findings, not as biomarkers, a few groups have identified several molecular imaging techniques as biomarkers in diagnostic criteria of certain neurodegenerative diseases.

- The National Institute on Aging lists magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), positron emission tomography (PET) and amyloid imaging in its diagnostic guidelines for AD
- The Dementia with Lewy Bodies (DLB) Consortium's clinical diagnostic criteria for DLB describe MRI, dopamine transporter (DaT) imaging and 123I-metaiodobenzylguanidine myocardial scintigraphy as potential biomarkers
- The Progressive Supranuclear Palsy Study Group defines MRI, SPECT/PET, DaT imaging and tau imaging as biomarkers

When incorporating imaging assessment into study planning, there are several practical factors sponsors should consider:

- **Patient selection:** Sponsors must evaluate the effectiveness of an imaging modality as diagnostic to select the right patient and treatment effect.
- **The use of radioactive tracers:** It is important to understand that the use of radioactive tracers, such as DaT-SPECT, can vary by county, state and site.
- **Imaging variability:** Methods can be employed to reduce imaging variability, such as the selection of one or two tracers for a global study. This process may require providing tracers to sites, which involves complex planning and orchestrated logistics, including delivery of tracers, preparation and patient scheduling. These extra steps can increase burden on sites, have financial implications and may impact study enrollment if patients have to reschedule.
- **The availability of newer imaging techniques:** Advanced, newer imaging techniques may not be available globally, which can impact site selection. In early-phase trials, testing and evaluating newer techniques for an investigative product-targeted area of therapeutic effect allows evaluation of a technique's utility and potential risk/benefit rationale for use in bigger studies.

- **The overall treatment duration:** For highly selective, early-phase monogenic trials with shorter duration, priority should be given to diagnostic modality rather than efficacy imaging biomarkers, which require much longer treatment duration, for example:
  - Free-water imaging may require measuring the increase of free water in PD over the course of four years[13]
  - Volumetric MRI examining brain atrophy (using a PD network atrophy pattern) is higher in individuals with PD versus healthy controls and also correlates with disease severity (progression of motor, cognitive and global outcomes) after a 4.5-year follow-up[14]
  - DaT-SPECT can differentiate PD as a supporting diagnostic tool; significant longitudinal change is observed in DaT binding in all striatal regions, with the greatest change in DaT binding at year 1[15]

Understanding the unique safety, regulatory and logistical considerations for cell and gene therapies

Just as biomarkers that track disease progression and correlate predictably in response to a therapeutic intervention could greatly support future clinical trials, tracking biomarkers of neuroinflammation can be important for understanding the impact immune reactions can have on treatment safety and efficacy.

Safety concerns are common for most gene and allogeneic cell therapy products, like immuno-inflammation (antibody and T-cell responses) as well as those unique to the therapeutic modality. An in-depth understanding of cell or gene therapy is needed to develop comprehensive safety monitoring plans prior to trial initiation, as these plans impact not only patients and their families but also personnel at institutions where these therapies are administered. They also impact people in the broader community where these patients and institutions reside.

Managing immunoreactions

A key area of focus is managing an immunoreaction and the potential risks associated with it. Treatment with immunosuppressive medications, such as corticosteroids and tacrolimus, raises the question of concomitant infection as well as other adverse effects associated with the use of these agents. The risks of immunosuppression in low- and middle-income countries, where endemicity of infections and vaccine coverage differ, are not well characterized. In addition to an increased risk of infection, prolonged corticosteroid doses are associated with a potential for infection, tuberculosis reactivation, strongyloides-related hyperinfection and increased susceptibility to fungal diseases.

Recognizing safety considerations for virus-based delivery systems

Viral shedding is a concern common to virus-based delivery systems and requires various and repeated sampling, all of which should be handled as if potentially infectious; the samples should be collected from patients over days to months following dosing to monitor shedding.

While testing is typically stopped after two to three consecutive negative tests, the U.S. Food and Drug Administration (FDA) has occasionally asked for testing up to six months post-administration. Another standard for all genetic products is handling requirements that treat the material as infectious and/or toxic, as well as potentially a contaminant to the broader environment, which is known as “gene pollution.”

Examples of unique safety considerations for viral products include target organ toxicity such as hepatotoxicity or dorsal root ganglion toxicity seen with AAV vectors; off-target effects, particularly mutagenesis, associated with integrating vectors and gene editing modalities; over-expression of transgene products (both systemically and locally within tissues and organs); and inappropriate cellular migration and/or differentiation of cell therapies.

Planning for long-term follow-up (LTFU)

Cell and gene therapies require lengthy follow-up due to their unique safety risks. Cell or gene therapies can produce permanent or very long-lasting changes, which puts subjects at risk for undesirable or unknown outcomes that present as delayed adverse events. LTFU studies aim to continue the evaluation and assessment of patients past the immediate follow-up period after dosing and are important in the monitoring and understanding of long-term product safety. AAV gene therapies typically carry a regulatory requirement for five years LTFU post-dose, and this is extended to 15 years for any therapy that employs gene editing or utilizes an integrating vector. Therefore, a well-planned LTFU program must comprehensively assess the risks associated with the product's mechanism of action, the modality of delivery, dosing levels, co-medication regimens required as part of administration of the therapeutic, as well as disease comorbidities of the target patient population along with the baseline health status of a treated individual.

Preclinical and clinical experience with the product or similar products may be considered relevant in the assessment of the risk for delayed adverse events. For example, experience with gene therapy products in the same vector type, administered by a similar route, or given for the same clinical indication may contribute helpful information. However, for novel products, such information may not be available or applicable, or it may be limited, in which case data from well-designed preclinical studies should be used in assessing the risk of delayed adverse events.

In 2020, the FDA published the final version of "Long Term Follow-Up After Administration of Human Gene Therapy Products" with detailed guidance for the industry regarding proper evaluation of safety risks and LTFU planning, including designs and duration of such investigations. Planning for the LTFU study should start at the same time as planning for the active study, and it is important to evaluate the most efficient pathway for the one LTFU study or basket design for the program of the planned investigation with the asset.

Incorporating patient-centric practices through decentralized clinical trial strategies

Running a precision medicine trial is similar to running a rare disease trial, as the patients are just as valuable, which highlights the importance of maintaining a high level of patient engagement through the trial. Focused strategies are required to make these types of studies more efficient while keeping the burden for patients as low as possible and also fulfilling all stakeholders' needs. Starting with consent for the interventional study, families will need to understand the importance of the patient staying in the LTFU study. Keeping the patient and family engaged until the end of the observation period of these LTFUs is a challenge. Sponsors should consider that patients may have to travel long distances to reach the study site; incorporating travel assistance or decentralized trial support can help ease the burden. The patient's caregivers should also be considered as they are often the ones coordinating the patient's travel and staying on site with them during and after treatment, which represents a significant investment of their time and effort. While caregivers may not be defined in the design of the study, their critical role should not be overlooked. All efforts should be made to reduce the patient and family burden, allowing flexibility with schedules and on-site versus remote visits based on the patient preference.

Innovations in decentralizing trials, including reducing the number of sites in these unique long-term studies, can play an essential role throughout these efforts. For example, intuitive decentralized trial solutions can streamline data collection and aggregation from various sources, enable patients to connect remotely with services, reduce study burden and enhance support and engagement. Introducing these solutions into the study program as the patient progresses away from the acute post-treatment environment and into the long-term monitoring phase can be highly beneficial.

Navigating regulatory requirements

Regulatory submission may require extensive, country-dependent supporting documentation, potential involvement of multiple additional committees and longer approval timelines.

- In the US, in addition to the general requirements—which include FDA clearance (30 days), central IRB and local institutional review board (IRB) reviews—gene therapy-related requirements apply. An Institutional Biosafety Committee (IBC) will review the study at each site; timelines and requirements are dependent on the site or the central IBC, if acceptable by the sites. The National Institutes of Health (NIH) Recombinant DNA Advisory Committee review and submission process is no longer required per the Federal Register Notice. This new change is directed toward eliminating duplicative reporting to the NIH and FDA.

  Sites registered with the NIH Office of Science Policy, either experienced in gene-based therapy or mRNA engineered vaccines or preregistered in advance of starting an engagement in such trials, saves sponsors weeks or more in the startup activities. The central IBC, with the gained experience and expertise in a space of such trials and expertise in the registration process with the NIH, became the partner of choice for regulatory activities in this challenging space of clinical research.
- In Europe, investigational medicinal products (IMPs) containing a genetically modified organism (GMO) are governed by country regulations and may require additional third-body approval steps for the use and release of the GMO. The standard approval timelines under the Clinical Trial Regulation No 536/2014 (EU CTR) are 60 to 106 days. For advanced therapy IMPs, the review timelines may be extended for an additional 50 days if additional expert review is required. Beyond the standard review of a clinical trial application (CTA) under CTR No 536/2014, a biosafety review for the GMO must be performed. The relevant environmental authority evaluates the clinical trial in accordance with Directive 2009/41/EC and Directive 2001/18/EC, which cover the contained use of GMOs and deliberate release of GMOs into the environment for an experimental setting, including the export and import, respectively.

  Some EU member states consider clinical trials with GMO medicines as deliberate release according to Directive 2001/18/EC (e.g., Spain). Other member states consider them as contained use according to Directive 2009/41/EC or assess them on a case-by-case basis (e.g., France, UK). The core technical dossier of the GMO and environmental assessment are required for obtaining the GMO approval beyond the other standard CTA documentation.
- There are also differences on how the product modality is perceived and treated by local agencies; therefore, a thorough review of regional guidance is required, and if a sponsor is facing any ambiguity, consulting with an agency may be necessary.

Handling logistical challenges

In addition to cold chain requirements standard for medicinal products, there are specific requirements with cell and gene therapy products that make this process more challenging. Cell therapy products are unique in that they consist of viable, typically human, cells that are autologous or allogeneic. Hence, the cold chain for a cell therapy product must be capable of maintaining a living product in a viable state throughout storage and distribution all the way to administration to the patient.

Cells are highly labile, remaining viable only within narrow ranges of time and temperature. Cells also require oxygen and nutrients when metabolically active. Therefore, cell therapy products require either just-in-time delivery to patients or cryogenic storage temperatures to preserve the cells in a metabolically inactive state as well as shipment in a cryogenic frozen state at ultra-low temperatures (-110°C).

Gene therapy products consist of nucleic acids packaged in a variety of different forms: viral vectors, inorganic complexes or naked DNA/RNA. As these products are inherently more stable than cells, their storage and distribution can typically leverage approaches taken for conventional pharmaceuticals and biologicals.[16] However, the majority of gene therapy products are shipped as frozen and require strict cold chain management similarly to cell therapy.

Due to the labile nature of cell therapy products and the time sensitivity in handing cells, it is important to establish clear and practical guidance for clinical sites to ensure correct product handling, including thawing, the maximum allowed time for administration and any additional preparation needed. Autologous products also require additional chain of identity custody ensuring administration of the product, as intended, to the right patient. Therefore, an integrated platform is essential for complete visibility and cohesive scheduling to connect manufacturing, the cell collection center, the administration site and transportation.

Ongoing work to make a difference for patients

As more is understood about the causes and pathophysiology of neurodegenerative diseases, better preclinical models have helped better predict clinical success, while high-efficiency genome editing tools, particularly CRISPR-Cas9, have made it possible to generate targeted mutations in these models.

Biomarker research will continue to determine how to best provide earlier detection of the neurodegenerative diseases to identify presymptomatic patients and better predict clinical outcomes. However, even if a genetic therapy can be delivered prior to the onset of neurodegeneration, many barriers remain in effectively targeting tissues *in vivo* as well as fine-tuning the expression of these genes to avoid unwanted effects.

Research continues to make great strides in precision medicine and confront these challenges, using both novel tools to modify genetics and lessons learned from past and current clinical trials. These will ultimately make a difference across a wider range of neurodegenerative and neuromuscular diseases and help address unmet medical needs for patients.

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