WORLDWIDE CLINICAL TRIALS

WHITE PAPER

DEVELOPING GENE-BASED THERAPEUTICS

Strategic considerations for regulatory, operational, and commercial success

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As of July 2020, more than 1,000 INDs have been opened in the US for gene therapy products, with 134 INDs opened in the first 7 months of 2020 alone.[1] Researchers estimate that 30 to 60 gene therapy products will be launched for clinical usage by 2030.[1, 2] However, the regulatory, operational, and commercial forces that impact gene therapy development continue to evolve dramatically – not just in the US but throughout the world. For advanced therapy medicinal products (ATMPs) in general and gene therapies in particular, regulatory, operational, and commercial considerations vary from region to region, and even from country to country within a region, depending on the nature of the interventional product. There may be incomplete international harmonization of regulatory requirements – in part because requirements may remain unsettled and elusive at local and regional levels. There also may be inconsistent standards of care against which to compare the effect of an innovative therapy in terms of healthcare utilization and patient outcomes.

This variability can present both significant challenges and significant opportunities where the design and conduct of clinical trials is concerned. An understanding of regulatory and operational demands at the national, regional, and local levels, coupled with an ability to design and manage innovative studies, is crucial to success when the regulatory and operational context is in flux. The same is true where commercialization of the therapy is concerned, as the path to commercialization of a gene therapy or other ATMP can be more uncertain than that of a non-ATMP therapeutic. Developing a database supporting the value proposition of a potentially transformative therapy must occur in parallel with clinical development. By partnering with stakeholders that can operationalize an understanding of how all these factors interact – from early in the strategic planning process and throughout the implementation of the clinical development program – a sponsor can more effectively navigate these shifting regulatory, operational, and commercial streams.

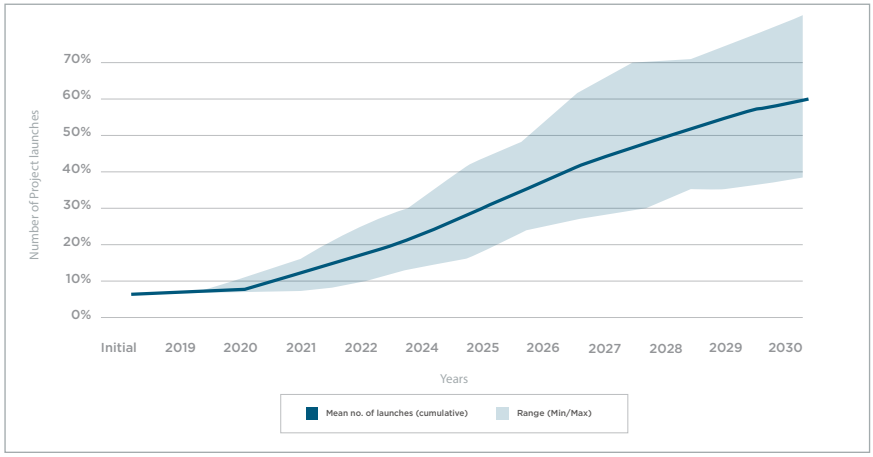

Figure 1: Projected Gene Therapy Launches through 2030[2]

UNDERSTANDING AND ENGAGING REGULATORS AT ALL LEVELS

The nature of regulatory bodies differs between the US and Europe, and insight into the dynamics of different groups within each agency is crucial. Depending on the nature of the indication and the attributes of the test product in development, a sponsor will interact with different regulatory divisions of the US Food and Drug Administration (FDA), and it is important to appreciate the ways in which the tone and tenor of an engagement can differ from division to division. The FDA offers guidance in the area of gene therapy,[3] but guidance is less mandated than in Europe, potentially introducing a level of uncertainty into the development process.

In contrast, regulatory bodies in Europe have subject matter experts in specific indications, but they are not isolated within separate divisions of the European Medicines Agency (EMA) in the way that they are in the FDA. Arguably, this has led to a more holistic approach to regulation and engagement in the EU, even though local committees in different regions

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of Europe have a great deal of input and oversight when it comes to conducting clinical trials.

The When and the How of Regulatory Engagement

So when and how best to engage with regulators? A gene therapy may qualify for an expedited pathway if it can be shown to meet an unmet need or have better efficacy and safety than an existing therapy. If a sponsor chooses to pursue an expedited pathway designation, it is advisable to engage with regulators early in the development process. Sponsors seeking engagement with the FDA might arrange a CATT or an INTERACT meeting, for example. A CATT meeting can take place even before a developer has a product. It is intended to promote a dialogue between staff in the FDA's Center for Biologics Evaluation and Research (CBER) and prospective innovators/developers of advanced manufacturing technologies. According to the CATT website, "inquiries or meeting requests submitted to the CATT should focus on novel technologies that can have a significant impact on product development, manufacturing process and control strategies, and may also have regulatory implications. This includes manufacturing and analytical methods for those products or classes of products for which the center has limited experience with the manufacturing or development process."[4]

An INTERACT meeting, by contrast, is for an innovator that already has a product in development but is akin to a pre-pre-IND meeting. INTERACT generally consists of "one informal and non-binding consultation and is intended for innovative investigational products that introduce unique challenges due to the unknown safety profiles resulting from the use of complex manufacturing technologies, development of innovative devices, or cutting-edge testing methodologies."[5] This may be particularly advantageous for gene therapy products, given the complexities of the manufacturing process and uncertainties regarding efficacy and safety data to be obtained from preclinical paradigms as part of an IND-enabling process.

Early engagement can help a sponsor plan whether to seek FastTrack designation or, later, breakthrough designation or another expedited pathway designation, for example based upon a surrogate end point.

Expedited pathway designations also exist in Europe, but they are typically sought later in the development journey than they are in the US. That is not to say that regulatory engagement necessarily commences later. In the EU, a sponsor can approach an agency at the national level or the EMA itself. In the UK, a sponsor can take advantage of the National Scientific Advice procedure offered through the Medicines and Healthcare products Regulatory Agency (MHRA). Like engagements with the FDA, but unlike engagements with the EMA, the National Scientific Advice procedure offered through the UK's MHRA is free and attests to the degree to which regulators want to encourage sponsors to engage. As for the timing of an engagement with the MHRA? The Innovation Office's website is quite clear: "It's never too early to talk to us about your innovation."[6]

Such engagements not only present an opportunity for regulators to gain early insight into the work of sponsors but also allow sponsors to ask questions and gain insights into the concerns and thinking of regulators. On this point, it is important to understand that while it is necessary for regulatory agencies to play a gatekeeping role designed to ensure the safety of novel products, they are also very much interested in acting as unofficial partners, helping to guide developers toward a successful launch. Topics of considerable regulatory interest in gene therapy include the discussion of preclinical models to evaluate off-target effects, the utility of natural history studies, and innovative biostatistical concepts that can inform an eventual interventional program. Also of interest are opportunities to leverage preclinical and manufacturing data from one application to another

and the continuous reassessment of clinical data for new opportunities to ascertain safety and efficacy.[1]

Large pharmaceutical firms may have established departments whose sole function is to interact with different regulators, but a smaller innovator may not. For those firms that do not have resources dedicated to regulatory engagement, it will be strategically advantageous to partner early on with preclinical, clinical, and regulatory experts that can bring their experience to these interactions. A highly dynamic team composed of these consultants will be familiar with expectations of regulators in many geographies and can provide a sponsor with deeper insights into the issues and concerns of different regulators (at all levels). While an innovator may find seemingly detailed regulatory information on the web, guidance relating to gene therapy products is evolving and may not necessarily mirror local and regional conventions. Partnerships can bring the deeper insight gained from a history interacting with regulators and from sideline conversations whose subtleties never make it onto the web.

INNOVATIVE TRIAL DESIGNS

Regulatory, operational, and commercialization evolution demands uncommon creativity when it comes to gene therapy trial design. Unlike trials involving IP that are administered every few hours, days, or weeks, a single administration of a gene therapy may be wholly transformative for the patient. Multiple applications may not be required if a persistent and enduring beneficial effect can be demonstrated – particularly if the observed effect is both objectively ascertained and clinically significant. The effectiveness of Zolgensma in treating children with spinal muscular atrophy (SMA) with confirmed biallelic mutations in the survival motor neuron 1 (SMNI) gene stands as a clear example.

That single-administration distinction can affect the economics of manufacturing to scale (as shall be seen later) as well as the design of a clinical trial. When gene therapy is directed toward an orphan indication, it is prudent to use antecedent research with observational studies to further clarify the natural history of a disease and disease burden as well as the surveillance methodology for post-trial follow-up to confirm acceptable long-term safety. An innovative suite of trial designs thus becomes an enabling substrate for program development, including designs that accommodate an individual patient's prior disease trajectory, delayed treatment (e.g., "delayed start designs"), and the potential to transition control groups to the active therapeutic substance on an accelerated timetable based upon evolving clinical efficacy and safety data (including confirmation of a surrogate end point in select indications).[7] Among 12 designs for rare diseases, six are noteworthy when it comes to gene therapy trials: parallel, delayed start, randomized placebo phase, "pre- versus post-" designs, stepped wedge design, and adaptive randomization (e.g., where uninformative dosage levels or regimen is discontinued within study). Only a fraction of possibilities have been used to date.

However, a framework for clinical development exists within regulatory guidance.[8] Staggered enrollment of patients based upon disease phenotype or patient age with conservative dose escalation is uniformly cited. Noted are product-specific adverse events, such as inflammatory responses to vectors or mechanical injury due to the procedure for introducing gene therapy (e.g., intrathecally) and immunological responses to vectors, the transgene product, or modified autologous cells. Decision nodes also influence the choice of design and are based upon reversibility of outcome, rapidity of response, and the amount of time on control treatment.

The need for long-term follow-up for gene therapy trials can add an additional operational demand, depending on the nature of the vector involved. A longer-term observational research study, on the

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other hand, also allows a sponsor to determine the persistency of an effect demonstrated in a controlled trial, the potential impact of gene therapy on healthcare utilization, and the longer-term safety context in which these observations are observed.

If a gene therapy targets a rare disease, particularly ultra-orphan indications, this poses further challenges to trial design. Populations are limited and they often are geographically dispersed. Patient segmentation inherent within gene-based therapeutics limits the number of patients available during clinical development. This impacts the sample available for evaluation during clinical development and, considering the number of patients that might potentially be treated in any given year, it potentially impacts the viability of the manufacturing process for the gene therapy product.

All clinical development strategies under this remit generally attempt to minimize the total sample of patients required on both active and control while maximizing the proportion of patients treated with the investigational agent. Due to the difficulty of implementing double-blind or placebo-controlled studies, historical data transformed into an "external control" can provide an important reference for clinical and biostatistical contrasts, although important details in that transformation remain unsettled.[9] Bayesian statistical methods may also provide powerful tools for determining whether captured clinical data suggests that a boundary indicating product efficacy has been crossed.

While many different trial designs may be appropriate to a gene therapy project, a variety of common designs – such as crossover and Latin Square designs (in which every patient receives every treatment), "n of one" studies or alternating designs (which imply a time series design) – are not appropriate for a gene therapy–based clinical development plan. An understanding of how the nuances of trial design affect the need for pre-randomization observational data as well as downstream outcomes is critical to the long-term success of any gene therapy project.

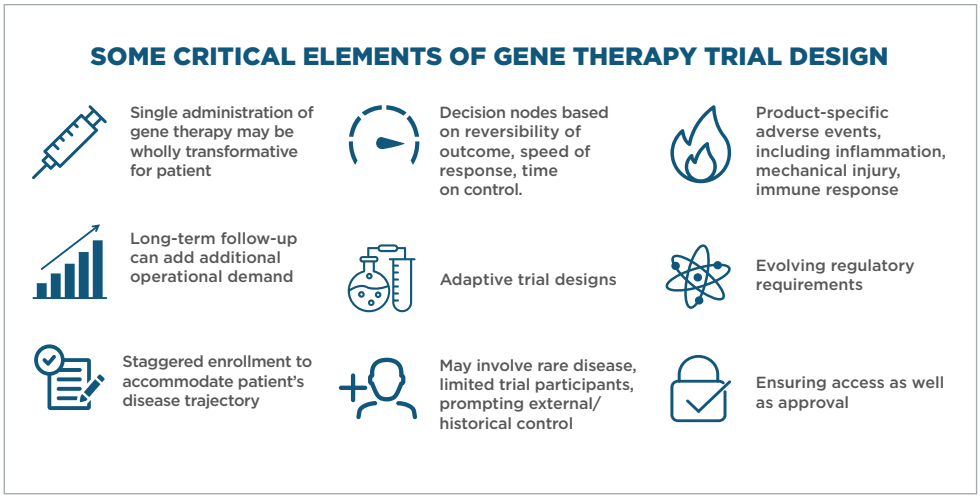

Figure 2: Critical elements of gene therapy trial design

MONITORING CONVENTIONS

Monitoring conventions differ in the world of gene therapy, too, and those differences demand careful attention from the earliest stages of setting up a trial.

Site Monitoring and Logistics Management Considerations

Confirming that biosafety controls are in place for gene therapy products is essential for trial operations. This would include controls for receiving, storing, securing, and handling genetically modified materials. A site's assertions

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of compliance with biosafety controls are important to procure but they must be validated by the CRO prior to the commencement of a study. Gene therapy trials require a more rigorous process for reviewing biosafety of each site, and that involves both more pre-study effort on the part of the sponsor and CRO staff as well as more active pre-study engagement with prospective sites.

Nor is it only a question of biosafety monitoring controls at the site level; there are also biosafety monitoring questions to consider related to the transportation of the genetic/vector materials to (and potentially from) each site. Are there specific containment or refrigeration controls that need to be maintained, monitored, and documented? Is the viability or potency of shipped materials time-sensitive? These questions apply not only to the length of time that materials are in transit but also to the timing of delivery with respect to administration. If the therapy is designed to be delivered in multiple doses, it will be important to ensure that subsequent doses are safely delivered to patients at the requisite times for subsequent dosing. These questions all demand a level of monitoring and logistics management expertise where time-sensitive materials are involved – as well as a site training component to ensure that site personnel thoroughly understand how to handle and prepare the therapeutic agent. All this has to be factored into overall trial design and scheduling.

Participant Screening and Monitoring Considerations

As part of both a site selection and candidate pre-screening process, steps must be taken to ensure a site is not situated in a region where there is a high incidence of immunity to a candidate vector, such as a targeted adeno-associated virus (AAV), and that individuals selected do not themselves have a pre-existing immunity to a specific vector.[10] This requires that conventional feasibility assessments be augmented by a consideration of existing immunogenicity. Methods of detecting pre-existing AAV immunity include cell-based in vitro or in vivo transduction inhibition assays and ELISA-based detection of total anti-capsid antibodies, which may also detect neutralizing antibodies.[10] Transduction inhibition assays, in vitro and in vivo, screen for both neutralizing antibodies as well as other factors that modulate AAV transduction efficiency.[11, 12]

When considering which assay to employ in patient screening, it is important to understand the benefits and limitations of each and how that relates to the clinical outcome. This information is generally provided by individuals within scientific services, and it has a direct impact on the operational solution that a CRO may advance. For example, although the in vivo transduction inhibition assay can screen for both neutralizing antibodies and additional inhibition factors, the in vitro transduction inhibition assay and total anti-capsid antibody assay have the advantage of being scalable, easier to standardize, and amenable to analytical validation. Additionally, achieving early clinical proof-of-concept can be maximized by identifying individuals without pre-existing immunity by using both a cell-based in vitro transduction inhibition assay and total anti-capsid antibody assay.

Different vectors will require different biosafety procedures, so it is critical that the CRO understand the nature of the vectors involved in the program. There may be question of viral shedding and whether it is a factor that must be considered in trial design. There may be a risk of exposure through the environment due to viral shedding - to researchers, caregivers, and family members - so accommodations must be considered in the event that that is a plausible factor impacting surveillance. It may be pertinent to collect samples of various bodily fluids such as blood, urine, semen, oral and nasal swabs, as well as stool.[13] These samples should be collected at different time points after gene-based therapy administration, which may include weekly visits until two consecutive visits without detected viral shedding.[13, 14]

It is also critical that partners employed by the sponsor understand and be able to monitor the technologies involved in the modification of the gene. The story of the shortened life of Jesse Gilsinger remains a sobering case study in what can happen if a full understanding of the interaction of both the modified genetic material and the delivery vector itself are not fully investigated and understood before human trials occur.[15]

The Evolution of Monitoring Conventions and Expectations

When the therapeutic agent is incorporated into the gene, the agent alters the gene – and an altered gene may lead to an altered response to other events in ostensibly unrelated areas. This can affect both long-term monitoring and the extent of the detail captured during long-term data collection. The use of targeted AAVs, for example, are traditionally considered to have low potential for integration into the host genome because of the specificity of their targets. For that reason, AAV vectors may be exempted from a standard 15-year follow-up requirement.[16] However, herpesvirus-, gammaretrovirus-, and lentivirus-based vectors are not exempt, which influences both the design and monitoring aspects of a trial.

But these exemptions and qualifications may not themselves be forever fixed. The researcher who co-led the safety study in which Jesse Gilsinger died went on to develop seminal work advancing an understanding of the nature of AAVs.[15] In 2018, he published a paper clarifying possible toxicities associated with AAVs and dosing, which has focused new attention on the use of AAVs with a more informed design and operational footprint for this important aspect of therapy.[17]

The evolving state of the art and the deeper understanding the various aspects of gene-related therapies create changes that ripple quickly through the landscapes of regulations, operations, and commercialization. The results can be surprising, and not always in encouraging ways. In August 2020, the FDA denied an application for approval of a hemophilia A gene therapy based on safety updates from an ongoing Phase 3 study and instead requested a longer-term follow-up data processing study from all study participants.[18]

Large pharmaceutical companies may have the resources to weather these unanticipated monitoring demands or follow trial participants for many years. after the conclusion of a trial, but companies with more limited resources may not. It becomes critical to determine, at the earliest stages of a trial, how monitoring will commence, how it will be efficiently applied, and whether (or how) it needs to be continued over what could be many years.

Data Requirements in Longer-Term Monitoring

With regard to long-term monitoring, there are also open questions about what data needs to be collected over time and how it will be captured, reported, analyzed, and secured (particularly as security ensures personal data privacy, which is subject to different regulations around the world). As noted in the FDA's Human Gene Therapy for Rare Diseases Guidance for Industry, "considerable information can be gained by collecting clinical measurements repeatedly over time. Such a longitudinal profile allows the assessments of effect, largely based on within patient changes, that otherwise could not be studied."[19] If the alteration of one gene affects a physiological process seemingly unrelated to the intended target, the connection between the therapy and the ostensibly unrelated process may not be obvious without ongoing analysis of large amounts of data. This makes it incumbent on the sponsor and the organization doing the data collection and analysis to plan the type of analysis that will be conducted over the course of potentially many years.

On this latter point, it is also important to consider, at an early date, how best to engage trial participants that may need to travel great distances to participate

in the trial. Participants may be onsite for only a short period while the gene therapy is being administered, but they may then travel to homes that are hundreds of miles away. Frequent in-clinic monitoring may not be feasible after administration. Depending on the nature of the therapy and the condition it is meant to address, a variety of monitoring options might be viable – from home visits to telehealth to active monitoring via wearable devices – and these alternatives must be weighed and incorporated into the trial during the design phase (particularly as certain monitoring options will require additional human resources, training, and equipment).

FORMULARY PLACEMENT AND REIMBURSEMENT MECHANISMS

The history of gene therapy development is one complicated by successful registrations with commercial failures. The first gene therapy approved in Europe (Glybera) was at once a clinical success and a commercial failure. The condition it successfully addressed was so rare – and the cost of treatment was so high – that insurers could not justify the million-dollar price tag per patient attached to the therapy. Nor could the product be manufactured cost-effectively when it would never be manufactured at a large scale. Few (if any) of the people afflicted with the condition could afford to pay out of pocket for the treatment.[20]

Adoption and Access, Not Just Regulatory Approval

Ultimately, getting a therapy approved by regulators is not the only challenge that developers face. The greater challenge is to ensure that the therapy is accessible. This raises strategic questions for developers that are best addressed early on in the clinical development stratagem. How can a developer recoup R&D investment and map a plan for long-term profitability when payers may be reluctant to cover the cost of a therapy – unless the intervention dramatically and objectively impacts the lives of those receiving the therapy in an enduring manner? Matters of approval, adoption, and patient access loom large here, and the absence of long-term clinical durability data amplifies the uncertainties and risks that complicate payer coverage and reimbursement determinations.

For payers, considerations involve questions about the long-term safety (and long-term efficacy) of gene therapy as well as a question about the likelihood of recouping costs: Why agree to pay millions for a therapy when the individual benefitting from the treatment (or the family supporting the patient) may change insurance plans within the next three years?[21] In that scenario, the patient's departure will dramatically decrease the likelihood that the payer's fully burdened outlay for the therapy will ever be recaptured, even if clinical benefit is fully sustained. Thus, innovative approaches to collect data assessing the impact of gene therapy on a system of care should be developed during the clinical development process for review at the time of product approval in order to inform formulary placement and reimbursement decisions. Gathering additional information following approval in a "real-world" setting provides a complementary initiative.

Consider Luxturna, a gene therapy designed to treat an inherited disorder that causes blindness, which carries a price tag of $850,000. It faced constraints from payers controlling access after its 2018 FDA approval.[22] Some of the proposed plans were highly complex; at the same time, they reflected considerable innovation, illustrating the benefits of early partnership with a diverse spectrum of organizations and individuals who specialize in translating observed clinical benefit into commercial solutions that can benefit all affected patients. The constellation of potential approaches for gene therapy products will vary depending on the nature of the indication and the procedures required for administration, but examples might include a "step edit" therapy for a more common condition

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that has alternative therapies; the need for prior authorization before a product could be administered and reimbursed; the utilization of a specific gene therapy network for product access; capping fees through a stop-loss program (one specifically for gene therapies that would cover that employers cost above a particular threshold); as well as various combinations of out-of-pocket expense requirements for individual patients.[17] In the case of Luxturna, BlueCross BlueShield guidelines provided an initial authorization period of one month, with no renewal criteria, allowing one lifetime injection per eye.[23]

Uncommon Approaches to Commercialization

A variety of uncommon approaches to commercialization – ranging from annuity-based payments and outcome-based payments to outcome-based rebates, and other mechanisms – provide potential paths forward. The approaches differ in their implementation, but they strive to enable affordability by spreading risk between the payer and the developer. In the annuity-based payment approach, a payer agrees to pay a fixed price in installments over time. In the outcomes-based payments approach, the payer pays a portion of the price up front and the balance after use – but only if the therapy delivers specific defined objectives. An outcome-based rebate variant has payers paying the full cost up front but receiving rebates from the developer if specific outcomes are not achieved. In the outcomes-based annuity approach, the payer pays a fixed price in installments over time, but only as long as the therapy delivers the specified outcomes.[24] The aforementioned reimbursement approaches illustrate the importance of planning for longitudinal cohort studies or registries subsequent to product approval — not only for the purpose of acquiring safety information (as may be mandated by regulatory guidance) but also for the acquisition of efficacy data that may speak to the persistency of the effect, the clinical meaningfulness of the effect, and the impact of therapy on other sources of healthcare utilization for a given condition.

The challenges associated with gene therapy commercialization are best addressed from the earliest stages of development and should be multifaceted in execution. For example, early planning might lead to a specific publication strategy targeting the diverse interests of payers as well as physicians. Other strategies initiated during clinical development might exploit access to integrated delivery networks for study conduct, where every patient/care provider transaction can be recorded to assess the overall changes in burden of care and healthcare utilization that results from the introduction of a novel therapy. Similarly, protocol design may accommodate through a "piggybacking" procedure the addition of economic measures as well as clinical measures as an integral part of the trial. It is important to consider these issues from the earliest days of development – even pre-IND – because key components of a successful commercialization plan may depend on safety and efficacy data captured along the path to approval. In a post-approval setting, that data may be far more difficult to deduce.

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SUMMARY

From the standpoint of regulations, trial design, monitoring, and commercialization, the world of gene therapy development exists in an ongoing state of flux. Regulatory agencies may have diverse procedures and offer different ways for engaging with developers, yet without any assurance of international harmonization. The FDA's INTERACT program in the US and the MHRA's Innovation Office in the UK encourage developers to interact with regulators from an early date and provide "lampposts" that highlight an efficient and informed development pathway. By taking advantage of early engagement opportunities, an innovator company may be able to navigate the development landscape far more effectively and expeditiously. Such engagement is most impactful when it begins at the earliest stages of development and continues in a strategic manner throughout the development journey.

The evolving nature of the regulatory engagement as well as the evolving nature of the technologies involved in gene therapy development require uncommon thinking when it comes to trial design itself. Trial designs that may be perfectly appropriate to non-ATMP development are not always appropriate to gene therapy development efforts, particularly if small population of patients are the intended recipients of boutique (bespoke) products.

From the standpoint of monitoring, gene therapies can introduce distinct complexities that can evolve over time, consistent with the safety profile that will be confirmed during development. There may be biosafety concerns relating to the logistics of transporting and handling IP; there may be short- and long-term personnel training and data acquisition considerations.

It is important for a sponsor and its partners to understand the types of sites needed for a gene therapy trial and to be able to work closely with those sites – potentially for many years. This places even greater emphasis on the need for staff continuity — at the care centers as well as on the partner team — over the duration of the entire program. Indeed, because of the novelty of gene therapies and the potential need to monitor patients for as long as 15 years in some circumstances, it is important to cultivate sites with staff that is generally consistent and that do not incur heavy turnover and are willing to engage in trials involving new technologies and new monitoring protocols. Similarly, it is important for a sponsor and its partners to plan how best to engage trial participants that may need to travel great distances to participate in the trial, how best to monitor their progress over time, and how to partner with patient advocacy and other indication-specific organizations during what could be a very long data acquisition processes.

In all, a successful gene therapy clinical development program requires all involved to have an appreciation of the underlying science and disease pathophysiology and to be adaptable, innovative, and predictable in areas relating to operational performance. There are no other therapeutic areas or technologies in which the importance of strategic – not just transactional – partnerships are as crucial to success.

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