Xtalks WHITE PAPER

THE INTERSECTION OF RARE DISEASE AND ADVANCED THERAPIES

What it Means for Clinical Development

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INTRODUCTION

Eighty percent of rare diseases are known to be of genetic origin,[1] making rare diseases an obvious target for advanced therapies (gene therapy, somatic-cell therapy and tissue-engineered products). However, these complex medicines present challenges over and above the well-documented hurdles of rare-disease research. This white paper explores hard-won lessons learned and best practices in providing safe and life-changing advanced therapies for people with rare diseases as the field evolves.

Rare diseases, by definition, affect small numbers of patients individually but taken together are a living reality for approximately 350 million people worldwide, more than double the numbers for cancer and AIDS.[2] The current inventory of rare diseases tops 7,000, but a recent *Nature Review* article argued that this list could exceed 10,000 as our understanding grows of clinically significant mutations.[3] There is no treatment for 95 percent of rare diseases,[4] representing a significant unmet need. Although the number of scientific publications about rare diseases continues to increase, with an average of five new diseases described each week in the medical literature, knowledge remains lacking.[5] Fewer than 1,000 rare diseases benefit from even minimal scientific knowledge.[5]

Despite their low prevalence, rare diseases are invariably devastating to affected people and their families; most are chronic and many are life-threatening.[1] Eighty percent are known to be of genetic origin,[1] making rare conditions an obvious target for gene therapy and other advanced therapeutics, such as reprogrammed-cell therapy. However, the path to advanced therapeutics for rare diseases has been far from smooth since the pioneering and troubled gene-therapy trials of the mid-1990s.[6] As well as the hurdles of rare-disease development in general, developers face the unique realities of working with complex gene-altering products (see Table 2).

Even with these added scientific and operational complexities, nine advanced therapies for rare diseases were approved in the E.U. and seven in the U.S. by the end of the 2018 reporting period (Fig. 1)[2] and 587 advanced-therapy rare-disease trials were coming up fast behind them (Fig. 2)[7]. Such hard-won successes are yielding valuable lessons in how to develop safe and effective advanced therapies that are radically altering the future for people with rare diseases.

> *"These trials are inspiring and – if this is the right word – intimate. The community is so small and the number of patients in the world is so tiny, that there's a sense of unity for everybody involved: they're exciting for the science behind them and the potential benefits for these patients and the sites are enthused to participate."*
>
> — Nicholas Vanneman, Clinical Trial Manager, Medpace

STAKEHOLDER INTEREST IN ADVANCED THERAPIES

Advanced therapies are therapeutic modalities that involve gene therapy, human cell and tissue products ('cell therapy') or tissue engineering. All these modalities are being tested in rare diseases (Table 1). [2,7,8,9] Advanced therapies make up a small proportion of available rare-disease drugs, which are dominated by small-molecule and protein-based therapies (see Fig.1), but are generating disproportional interest among stakeholders. By the beginning of 2019, there were over 300 companies active in developing regenerative medicines for rare diseases fueled by over $9.8 billion in global financing.[7] Unlike small molecules and proteins, gene therapy can cross the blood-brain barrier, a huge unmet need in rare diseases, many of which have neurological manifestations. More significantly, they have the potential to offer a one-time, curative treatment for some of the most devastating diseases.

GENE THERAPIES

There have been more than 2,000 gene-therapy clinical trials; of these, 65 percent are in cancers.[10] Gene therapy aims to replace a mutated gene, inhibit transcription of a mutated gene that is functioning incorrectly, or introduce a gene that can help fight the disease. Gene therapy is delivered through a viral vector (transduction) or non-viral vectors (transfection) such as plasmids, liposomes or particle-mediated gene transfer.

In the case of *in vivo* gene therapy the transgene is packaged into a virus and then injected. By contrast, in *ex vivo* gene therapy, bone-marrow stem cells are removed from the patient, undergo viral transduction in a lab, are cultured, harvested and then reintroduced into the patient. Although *ex vivo* gene therapy is a type of cell therapy (see opposite) it is often discussed with gene therapy.[2,9]

Viral vectors are the most successful gene-therapy platform in rare diseases. Historically, adeno-associated virus (AAV) has been one of, if not the most, prevalent viral vector used in gene therapy.[2,6] For example, Zolgensma® (onasemnogene abeparvovec-xioi), an AAV serotype 9 (AAV9) vector containing a transgene encoding a functional copy of the SMN gene, has transformed motor-neuron function in patients with spinal muscular atrophy (SMA; see Case Study, page 12).[11] In another neurologic disorder, Huntington's disease, the AAV vector encodes an RNA to harness RNA-interference mechanisms that inhibit expression of the pathogenic gene.[2]

Three AAV-based gene therapies have reached the market so far, all for rare diseases. The first, in 2012, was Glybera® (alipogene tiparvovec) approved in the E.U. for reverse lipoprotein lipase deficiency (LPLD). It was later withdrawn by manufacturer Uniqure as commercially non-viable due to the small number of patients with LPLD.[12] In 2017, Luxturna® (voretigene neparvovec-rzyl) was approved in the U.S. and the E.U. for RPE65 mutation-associated inherited retinal dystrophy.[10] Zolgensma joined this exclusive list in 2019.[11]

Strimvelis®, a retroviral vector technology, showed efficacy and safety in adenosine deaminase deficiency associated severe combined immunodeficiency (ADA-SCID)[14] and in 2016 became the first *ex vivo* gene therapy approved for a rare disease.

Lentiviral vector platforms appear promising in hematological diseases such as beta-thalassemia and Wiskott-Aldrich syndrome, as well as neurological disorders such as cerebral adrenoleukodystropy.[2,15]

CELL THERAPIES

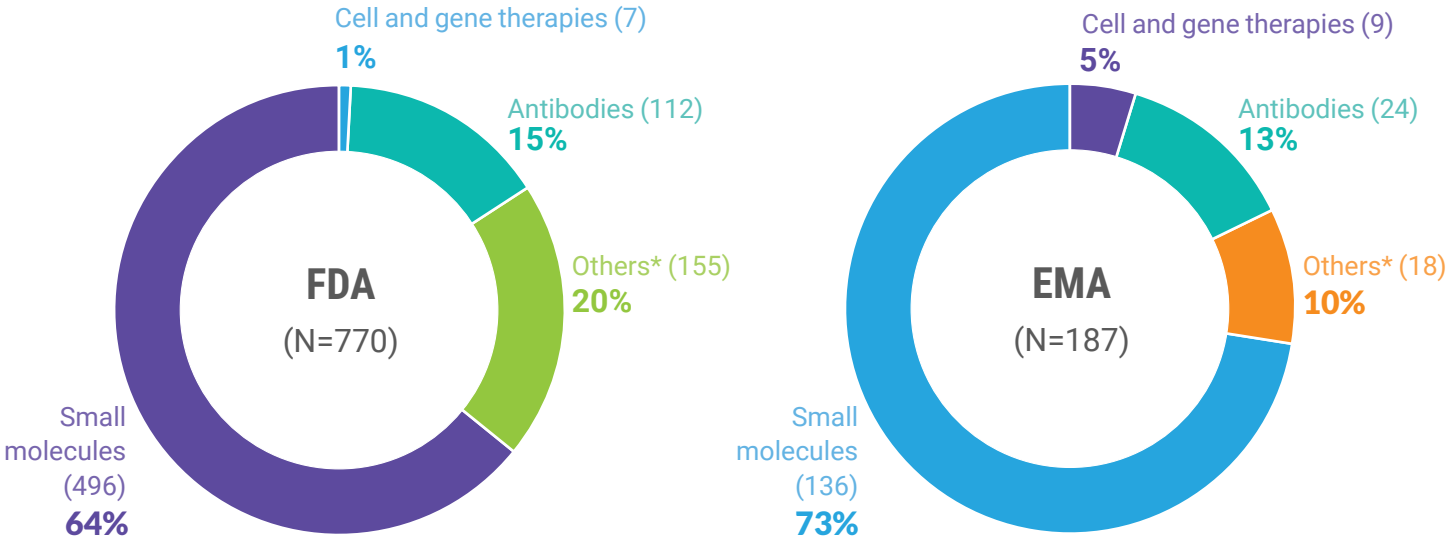
Cell therapies contain cells or tissues whose biology, physical function or structure have, in the words of the European Medicines Agency (EMA), "been subject to substantial manipulation" then reintroduced into patients.[16] Cell therapies can be classified as either autologous (from the patient) or allogeneic (from a human donor or 'off-the-shelf').[2,17] Target cells include T cells, dendritic cells, hematopoietic stem and progenitor cells (HSPCs), mesenchymal stromal cells, CD34-selected cells, induced pluripotent stem cells (iPSCs) and embryonic stem cells, among others. iPSCs are of particular interest because they can be reprogrammed into a wide variety of cell types for many diseases.

CAR T cells were the pioneers in cell-therapy development.[2] Two CAR T cell therapies were approved in the U.S. in 2017 and in the E.U. in 2018, both in rare cancers: Kymriah® (tisagenlecleucel) for acute lymphoblastic leukemia and Yescarta® (axicabtagene ciloleucel) for large B-cell lymphoma.[8,2] In June, 2019, the EMA granted conditional approval to Zynteglo®, a CD34+ -based cell therapy and the first treatment for beta thalassemia.[1,18]

TISSUE ENGINEERING

Tissue engineering attempts to cure disease or damage by creating functional human tissue from lab-manipulated cells held in a scaffold, matrix or other substrate.[16] Tissue engineering lags behind the other advanced therapies in rare diseases, with four trials underway at the end of 2018, versus 583 studies ongoing in gene and cell therapy (Table 1).[7] Approaches include incorporating reprogrammed cells onto tissue scaffolds for placement in the appropriate tissue such as the eye.[2]

Fig. 1: Number of Approved Therapies for Rare Diseases



*Others = protein-replacement therapies, enzymes, cytokines, blood, hormones/growth factors and vaccines. FDA and EMA may classify rare-disease modalities differently. Data from: Tambuyzer *et al*. *Nature Reviews Drug Discovery* 2020.[2] Percentages do not total 100 in EMA chart due to rounding.

Data to end of 2018.

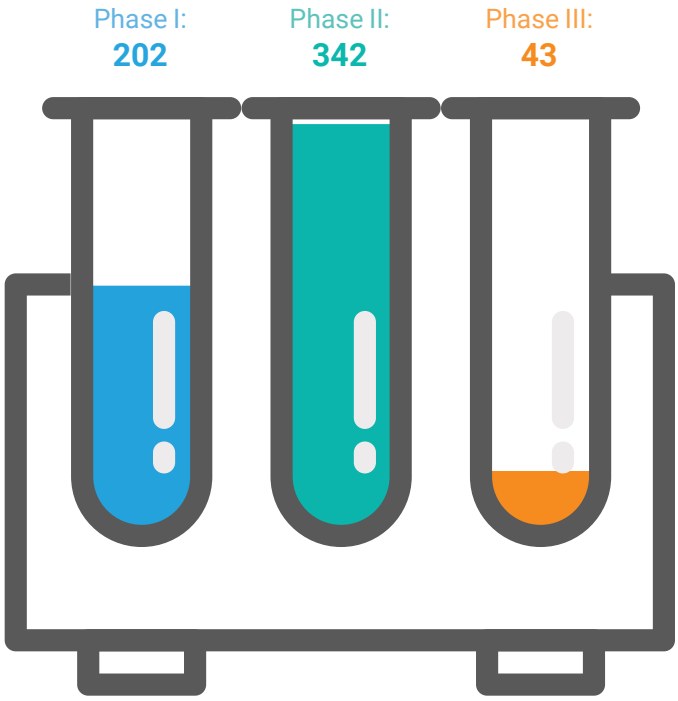


Fig. 2: Clinical Trials of Advanced Therapies for Rare Diseases

Total:
587

Data to end of 2018.
Data from: Alliance for Regenerative Medicine.[7]

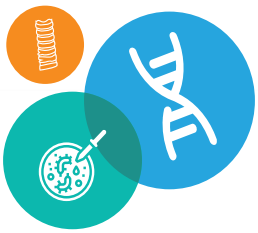


Table 1: Clinical Trials Involving Each Technology

Gene therapy	Cell therapy**	Tissue engineering
Phase I: 61	Phase I: 141	Phase I: 0
Phase II: 141	Phase II: 199	Phase II: 2
Phase III: 22	Phase III: 19	Phase III: 2

**Includes gene-modified cell therapy. Data from Alliance for Regenerative Medicine.[7] Data to end of 2018.

ADDED CHALLENGES OF CLINICAL DEVELOPMENT OF ADVANCED THERAPIES FOR RARE DISEASES

Developers of advanced therapies are faced with the well-documented hurdles of rare-disease research and must navigate the scientific, clinical, regulatory and operational complexities specific to advanced-therapy studies. Many of the high-level concerns overlap (see Table 2): sparse disease knowledge; lack of surrogate markers and validated clinical endpoints; study-power limitations due to small patient numbers and lack of a placebo or other conventional comparator; patient heterogeneity, frailty or cognitive disability; few specialists and specialized sites; and complex regulatory environments, as examples.

The intimidating complexities of rare-disease research are so well documented that a body of literature has arisen using existing trials to highlight successes and translatable solutions. For example, Rebecca Crow of Newcastle University, UK, and colleagues across Europe and the U.S., published a checklist for clinical trials in rare disease in the peer-reviewed journal *Trials* in 2018 based on their study in Duchenne muscular dystrophy, FOR-DMD.[19] Martina Schuessler-Lenz and co-authors at the European Medicines Agency took the unprecedented step of publishing a commentary in *Clinical Pharmacology & Therapeutics* in 2020 on lessons from the approval of Zynteglo (discussed on page 13).[18]

In the case of advanced-therapy research, the challenges multiply further. A 2018 review article from the FDA authors Lapteva *et al*[8] and a 2020 FDA guidance document[20] focus specifically on obstacles for advanced-therapy research in rare diseases. Both papers highlight the hurdles from the ground up, starting with a lack of understanding of the natural history (which may be completely derailed by the therapy itself, as shown in the Case Study, page 12); establishing manufacturing and quality standards in a brand-new, unpredictable biological product; assessing safety without access to healthy subjects; optimizing *in vivo* vector bio-distribution and transgene expression in the absence of good animal models; and predicting immunogenenicity and tumorigenicity, with "the general recognition that, for many regenerative medicine therapy products, their safe and effective delivery to the target tissue is as important as their therapeutic effect."[8]

Operationally, advanced-therapy studies require more planning, specialized resources and skills and coordination than for other trial programs. For example, sponsors and clinical research organizations (CROs) may need to plan for a single study visit in a center that can meet the product storage and transfer requirements, carry out invasive procedures such as intra-cardiac or intra-cranial delivery, accommodate a patient in the hospital for several weeks and then monitor (and retain) the patient for several years. If the patient is a child or cognitively impaired, further logistical, ethical, safety and humane considerations affect advanced-therapy program planning.

Table 2: Challenges of Rare-Disease Clinical Development with Advanced Therapies[2,8,10,20–22]

Challenges of Rare-Disease Research				
Limited knowledge of disease etiology and pathophysiology	Justification of indication and population	No or limited preclinical models	Limited number of experienced clinical investigators	Few patients and geographical dispersion
Small portion of treatment-naïve patients	Patient heterogeneity	Study-power limitations	Dose-finding and dose-optimization difficulties	Standard of care may not be established
Surrogate indicators (biomarkers) may not exist	Clinical endpoints may be ill-defined or lack clinician consensus	Meaningful treatment benefit may be ill defined	Late diagnosis	Disease severity: patients may be frail, pediatric, cognitively impaired
Lack of proximity to treatment center	Recruitment and retention of patients due to patient-related challenges	Anxieties around initiating first- in-human trial	Traditionally, drugs are investigated in adults before testing on children	

Added Challenges with Advanced Therapies

Trial related

- Complex trial design
- Control group difficult or impossible: natural-history studies almost always required
- Non-validated endpoints because therapy changes natural history
- Even smaller sample sizes than other rare-disease studies
- Genotype/phenotype heterogeneity
- Prior immunization worries
- Invasive, complex administration
- Lack of site experience
- Long follow up (years): patient retention problematic, children may withdraw consent when they become adults
- Heterogeneous regulatory requirements and national procedures at country level

Product related

- Sub-optimal animal models
- Transduction potency
- Vector-related failures
- Detailed understanding required of *in vivo* fate of cell/vector
- Fewer manufacturing runs, smaller samples, harder to establish critical process parameters (CPP) to ensure critical quality attributes (CQAs)
- CQAs more variable
- CQAs need to be established before approaching regulators
- Difficult GMP implementation
- Impurity, identity test, characterization, potency assay
- Complex manufacturing process
- Potential for immunogenicity and tumorogenicity, elevated transaminases
- Shedding studies: GMO aspects to consider
- Uncertain reimbursement

SETTING UP FOR SUCCESS IN ADVANCED-THERAPY TRIALS FOR RARE DISEASES

COMMITMENT TO COLLABORATION

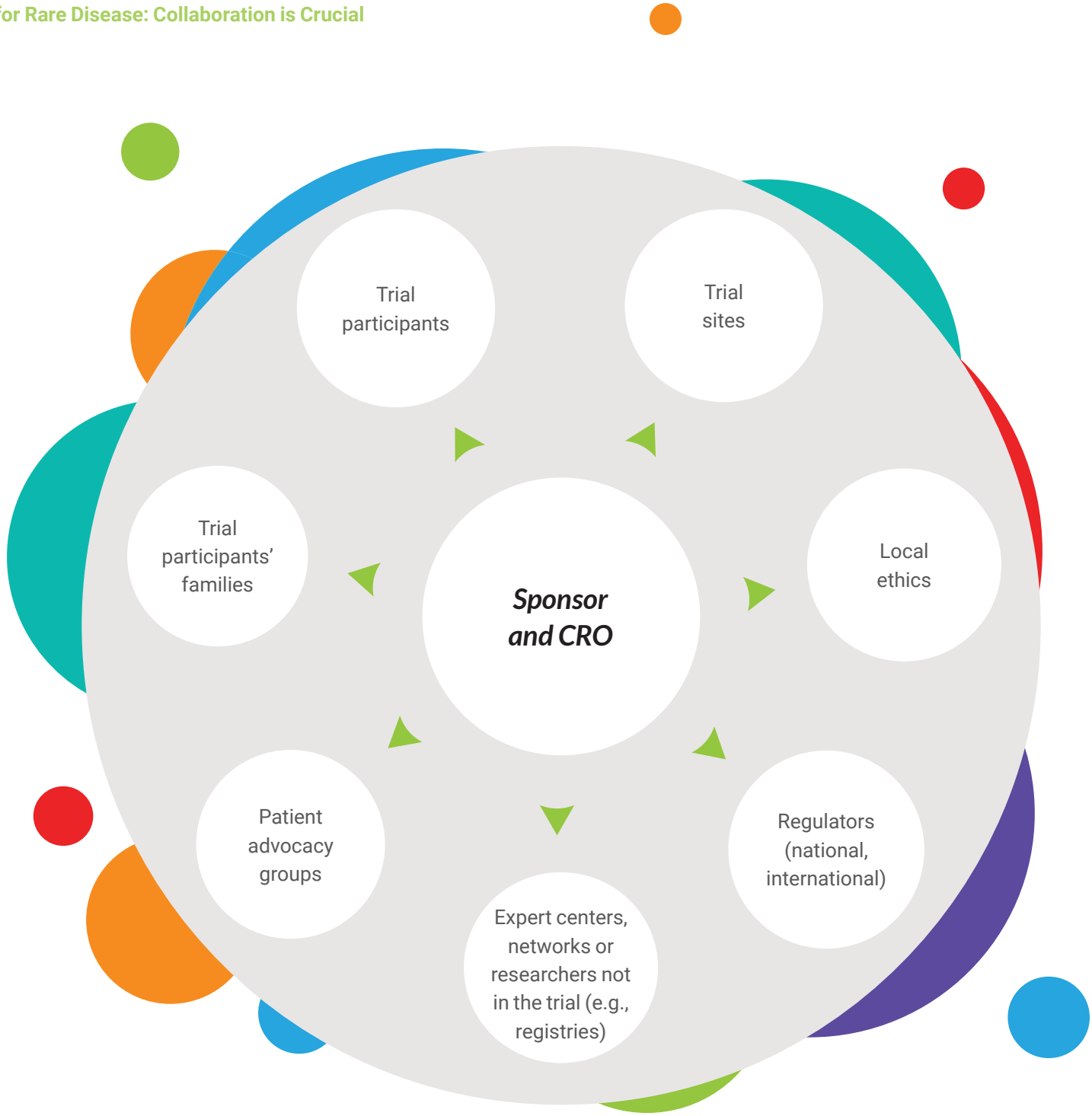
All clinical trials rely on collaboration but nowhere is this more true than in advanced-therapy studies in rare diseases where patient numbers and experts are at a premium. Figure 3 illustrates this interconnectedness. "In many conditions the natural history of the disease is relatively unknown. Because we need to learn we need to cooperate," said Terence Eagleton, MD, Vice-President of the Medical Department, Medpace. Thus, the collaborative mindset needs to start with patients and their families, who should be viewed as *de facto* experts in their diseases. Tauna Batiste, Executive Director, Batten Disease Support and Research Association (BDSRA), commenting on patient-advocacy conferences said, "[They] invigorate and motivate those investigators, those clinicians: they get to see the patient's real world firsthand and they take that energy back with them." As discussed further on page 12 that patient-centered mindset should carry forward into every aspect of the trial, from endpoint design to the final report.

Scientific collaboration is essential between sites and the sponsor, and a CRO with a cross-functional team of medical doctors and advanced nurse practioners is an asset here. Said Dr. Eagleton of CRO Medpace, "We embed ourselves in the trials as an active participant in the project team. This is essential in these complex studies." Crow *et al* blamed their recruitment, endpoint and delivery challenges in the FOR-DMD trial on the lack of CRO involvement.[19] Non-study experts such as registries and research networks, both national and international, can also provide natural history data, guide study design and provide insight on study endpoints and the technology itself.[22,23]

Collaboration should also happen at the most basic operational level, said Michelle Petersen, MS, Senior Director of Clinical Trial Management at Medpace: "We go to the sites asking, 'Where are the gaps in your ability to conduct this trial and how can we help you close them? Are you missing a liquid-nitrogen storage freezer?' We dig into all of the details that could derail the study if not properly planned for." Training, too, should adapt seamlessly to the learning needs of the site. For example, in a recent webinar[24] Meredith James, Master Physiotherapist, ATOM International, presented the company's outcome-measure training that uses video monitoring of clinical evaluations to continually update site skills and reduce inter-site variability.

Finally, working with regulators and health technology assessment bodies closely – and early – can make the difference between success and failure in advanced-therapy development, patient access and commercialization.[1,18] The pivotal relationship with the regulators in these complex studies is discussed further on page 13.

Fig 3: Advanced-therapy Development for Rare Disease: Collaboration is Crucial



RELEVANT AND SIMPLE ENDPOINTS

Nowhere does collaboration pay off more than in the design of endpoints of advanced-therapy trials. In many rare diseases – especially where there is no current treatment – validated trial endpoints do not exist, nor even a well-documented natural history (so endpoints may become irrelevant as the disease progresses). Moreover, biomarkers used routinely in the clinic may not be acceptable to regulators as trial endpoints.[25] Therefore, the developers should proactively seek regulators' advice on qualified biomarkers, particularly when novel biomarkers and methodologies for drug development are used.

Patient advocates are increasingly asked for input on study endpoints to ensure that the endpoints are clinically relevant – that the benefit makes a difference to patients' lives.[26,33] This is especially important for endpoints that could change as the disease progresses. This trend is boosted by regulators now requiring and issuing guidance on patient-focused drug development, especially in high-cost treatments.[8,20,21,33]

Patient involvement in endpoint design can be unfamiliar to clinical investigators, but it's central to success, said Ann Woolfrey, MD, Senior Medical Director at Medpace. Dr. Woolfrey explained using the example of sickle-cell disease: "If you just focused on how the product improves the hemoglobin biomarker, does that really make a difference in the patient's life? You have to really think through what the most important endpoint is, not just what your drug can do."

There's still a long way to go before all developers accept patient representatives as research partners, Tauna Batiste of the BDSRA said in a recent webinar:[27] "They think of advocacy groups as only helping with recruitment, spreading the word." Dr. Woolfrey agreed that patient input "could be leveraged in more cases."

A further advantage of patient-led endpoints is that they encourage patient compliance, since they track benefits most important to families and participants against the perceived risk of gene therapy. For example, a study of one-time gene-replacement therapy in SMA analyzed speech because, although it was not a formal motor milestone, it was needed for "crucial early social interactions," according to the scientific language of the study authors.[28] Little imagination is needed to appreciate that a child who could speak would be a key endpoint for families. By the end of the study, 92 percent of the children were communicating with their caregivers.[28]

In medically frail patients, endpoint practicality is also a factor. Dr. Woolfrey commented: "Patient input is critical because something could be scientifically interesting but is not feasible for patients to do."

Whatever endpoints are chosen, best practice suggests that they should be focused, simple and approvable by regulatory agencies. For example, despite the scientific complexity of Zolgensma (see Case Study), one of the primary endpoints in the registration study was a simple yes/no answer: could the baby sit unsupported for 30 seconds or more? "While we all want to learn more about the rare disease, the goal is a successful completion and registration of a new product to treat these patients," said Michael Oldham, MD, MPH, Medical Director, Medpace. "Sometimes you can get that accomplished with a simple endpoint."

INTEGRATE PATIENTS INTO ALL TRIAL FUNCTIONS

As crucial as it is, patient advice on endpoints should be just one part of patient-advocacy involvement. Regulators – and current best practices – encourage a patient-centered stance on every aspect of operational, clinical and regulatory functions of advanced-therapy development.[8] The Office of Tissues and Advanced Therapies of the FDA actively supports "systematic inclusion of patient experiences and preferences" in advanced-therapy studies and offers a Patient Representative Program for participation in FDA decision making.[8,29] The FDA and the EMA take their own advice, according to a recent *Nature* review, making extensive use of patient-advocacy networks such as the National Organization for Rare Disorders (NORD) in the U.S. and the European Organisation for Rare Disorders (EURORDIS) in the E.U. to stay informed on specific rare disorders.[2]

Patient organizations also play a crucial role as third-party, credible sources of information to patients interested in trials and can act as conduits for recruitment and, occasionally, trouble-shooters if miscommunications arise over trial-participants' needs, said Tauna Batiste of the BDSRA in a recent webinar.[27] At the operational level, patient-centered planning includes designing study visits to minimize patient burden; getting creative with digital technology for enrollment, monitoring and retention to minimize site visits; and giving advice on communicating appropriately at all stages, especially study close.[27]

Patient groups can also provide educational opportunities for physicians and reimbursement support once the product is approved[26] (see also Case Study).

CASE STUDY: 'THE BOY'[11,30]

Spinal muscular atrophy (SMA) is a devastating genetic neuromuscular disease of infants that leads to progressive muscle weakness and paralysis and, in its most severe form, death or permanent ventilation for most babies by age two. At fault is a defective SMN1 gene, which encodes a motor-neuron survival protein called SMN. SMA is the leading cause of infant genetic death in the US. On May 24, 2019, the FDA approved Zolgensma, an AAV-vector-based gene therapy for SMA. The one-time intravenous infusion provides a functional copy of the SMN gene. The FDA approval rested on data from 36 patients in the Phase-III STRI1VE trial and Phase-I dose-finding START trial. After Zolgensma, some children could sit up, stand, walk and talk – motor milestones unheard of in the natural history of the disease. One of the children became known as 'The Boy', a poster child for the drug's benefits during FDA consults. "The whole indication was turned upside down," said Michelle Petersen of Medpace. "We've seen patients who were never supposed to sit up preparing for preschool instead of dead at age one. The impact of a single patient story has been helpful to the regulators in determining the risk-benefit of therapies."

PARTNER WITH REGULATORS EARLY

A key lesson learned during rare-disease development, and advanced-therapy programs in particular, is that engaging early in productive discussions with regulators and payers is crucial for navigating the complex waters of advanced-therapy development and ensuring successful commercialization and patient access.

Several jurisdictions provide formal mechanisms for developers to interact early with regulators, not only on the regulatory framework but also to get regulators' opinions on the available data and key factors such as the value and limitations of proposed animal models and manufacturing expectations. Such timely feedback acts as an incentive for companies to take on the risks of drug development in this fi eld. In the U.S., the INTERACT (Initial Targeted Engagement for Regulatory Advice on Center for Biologics and Evaluation Research Products) program provides such consultation before the pre-IND meeting.[31] The Committee for Advanced Therapies (CAT) provides a similar service to SME (micro, small or medium-sized enterprise) developers in the E.U., providing evaluation of quality (CMC), non-clinical and scientifi c packages at any stage of development or certifi cation.[32]

Advanced therapies employ cutting-edge technologies, so the onus is on the developer to demonstrate the company's expertise with the product and work closely with the regulatory authorities to ensure alignment on the development strategy. While the regulators will not make concessions on patient safety, they will provide considerable input on the design of potential studies, manufacturing process and quality controls and allow for flexiblity on the approach so long as the proposal is scientifically justified.

There are several accelerated regulatory mechanisms to speed up advanced therapy development such as Breakthrough Therapy and Fast Track designations and the E.U.'s PRIority Medicines (PRIME) scheme (see Table 3).

Under PRIME, the MAA (marketing authorization application) review of Zynteglo took just 150 days and, in March 2020, was enshrined as a published case study on the fast-track approval of a rare-disease drug.[1,18] The authors credited early, frequent "iterative engagement" with the EMA throughout the development program for its success; in particular, the gene-therapy's developer benefited from pre-discussion of complex issues that could have delayed the marketing- authorization application.[18]

Orphan drug legislation, enacted in the U.S. in 1983 and the E.U. in 1999, also offers developers accelerated regulatory pathways, as well as a host of other development advantages such as extended market exclusivity and fee reductions (Table 3).

Specific to advanced therapies in the U.S. is the Regenerative Medicine Advanced Therapy Designation, which, in addition to benefits common to all fast-track provisions, provides support on the lengthy post-approval monitoring requirements for these trials.

Table 3: Regulatory Provisions and Accelerated Mechanisms for Advanced-therapy Developers in the U.S. and E.U.

Name	Benefit to sponsors
U.S.[33,34,35]	
Orphan designation (Disease prevalence <200,000 or 7.5 in 10,000 or >200,000 with no prospect of a profit)	Market exclusivity 7 years, tax credits, expedited regulatory pathways as below, user-fee waivers.
Breakthrough Therapy designation	Intensive guidance on efficient development, expedited reviews, rolling review.
Regenerative Medicine Advanced Therapy designation	All Breakthrough Therapy features plus accelerated approval and support to satisfy post-approval requirements.
Fast Track designation	Expedited development and reviews, rolling review.
Accelerated approval	Approval based on surrogate endpoint or intermediate clinical endpoint expected to predict benefit.
Priority review	6 months vs 10 months for marketing review.
E.U.[5,33,35]	
Orphan designation (Disease prevalence <5 in 10,000 or >5 in 10,000 with no prospect of a profit)	Market exclusivity 10 years, additional 2 years for the pediatric indication; mandatory centralized procedure; various fee reductions; free scientific advice with EMA; EMA and HTA (health-technology assessment) parallel consultations; access to conditional marketing authorization; accelerated approval; PRIME (see below).
PRIME scheme	Dedicated contact point at EMA, early and proactive support, scientific advice, assistance with trial design, accelerated assessment of MAA.
Accelerated assessment of MAA	Reduced review time of MAA from 210 days to less than 150 days.
Conditional marketing authorisation (CMA)	Early marketing authorization based on initial data demonstrating positive risk-benefit for products that can address high unmet medical needs in the interest of public health. The holder is required to meet certain obligations.

PLAN FOR SITE VARIABILITY AND LONG FOLLOW UP

Specific to advanced-therapy trials are three key operational challenges: patient frailty, site-specific capabilities and long-term monitoring for safety related to immunogenicity and tumorigenicity.

As discussed on page 11, patients in these studies are medically vulnerable. They are often babies and children. Long-distance travelling and long hospital stays – required for all advanced-therapy trials – are difficult for families or caregivers. Once at the site, standard medical procedures might cause trauma. For example, in fibrodysplasia ossificans progressiva (FOP) a simple blood-pressure cuff can cause heterotopic ossification (bone formation outside of the skeleton). Patient advocates can be helpful in both anticipating and solving many of these operational challenges.

As excitement over gene therapy grows, an increasing number of sites are developing the expertise to handle advanced therapies through academic recruitment, peer-to-peer training, or dry-runs of procedures before the trial starts. However, trial sites that do not feel confident to handle advanced therapies, despite these approaches, can be included through a centralized dosing approach. In this scenario, experienced sites dose the product and the less-experienced sites handle all other aspects of the trial.[10]

In advanced-therapy trials, it may be necessary to accommodate site-specific standard operating procedures (SOPs) for some medically complex procedures, such as lumbar puncture. Dr. Oldham of Medpace said: "You often have to walk a balance between which procedures must be followed absolutely in a protocol-specified way and what you can allow to be done per institutional standard practices."

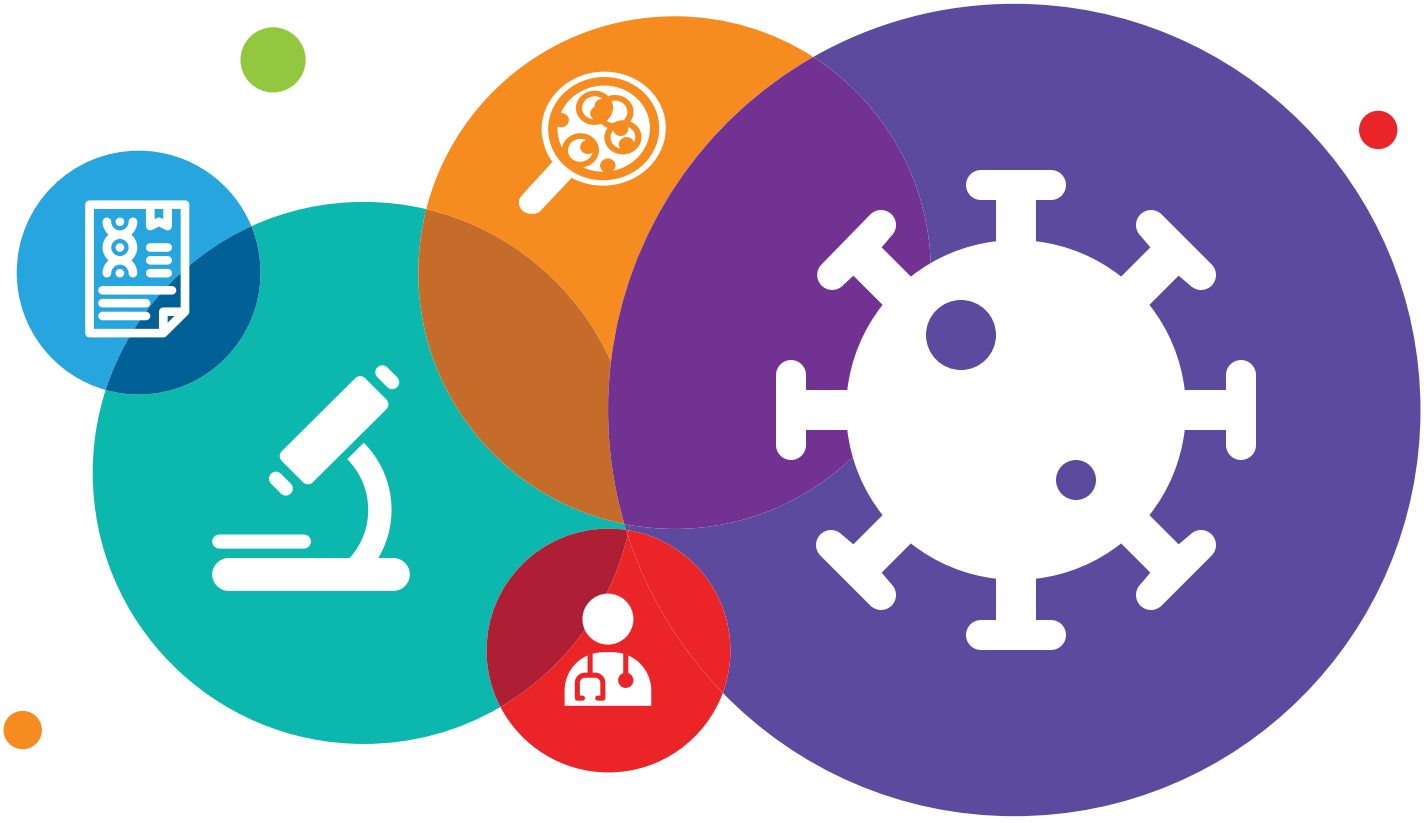
Safety issues due to immunogenicity arise from the patient's immune response to the biological product, which should be anticipated at the product design stage but cannot be predicted per patient. Immune reactions can range from local administration-site reactions to serious systemic inflammatory responses such as cytokine-release syndrome.[8] Appropriate on-site clinical monitoring, management of immunogenicity, having an ICU bed on standby and adequate follow-up should be planned in detail in all advanced-therapy studies.

The risk of tumorigenicity arises with any gene-altering product by triggering unexpected cellular differentiation and proliferation. Some viral vectors, for example, have the potential to integrate at inappropriate locations and activate oncogenes.[8] Again, the risk of tumorigenicity should be minimized at the product design stage, characterized prior to clinical investigation through well-designed non-clinical assessments and then assessed through continual monitoring integrated into the clinical trial program.

ADJUST FOR COVID-19

The coronavirus-disease 2019 (COVID-19) pandemic has required all drug developers to revisit their plans. Assuming that the trial still goes ahead, the main logistical challenge is site access and IP management: "We can't ship gene therapy to patients' homes," said Dr. Eagleton. He and his colleagues at Medpace have been assisting trial sponsors to reprioritize what is most important. For example, the frequency of certain lab tests may be reduced or home health nurses may be utilized for sample collection. Home monitoring and telemedicine can replace site visits in some cases, in consultation with regulators. Michelle Petersen said, "It's figuring out what we can do remotely to both protect the endpoints and the patient's safety." Many commentators have said that COVID-19 accommodations may, in effect, provide proof-of-concept for patient-supported digital platforms in advanced-therapy trials. Already some rare-disease trials have integrated technologies co-designed with patient advocates such as wearables, smartphone applications and connected home devices linked to online platforms that analyze data in real time and reduce person-to-person contact.[2]

Whatever adjustments are made due to COVID-19, added to the already complex nature of advanced therapies, it is more essential than ever to work closely with regulatory agencies to ensure that trials pivot successfully to protect patients and trial integrity and meet regulatory expectations.



CONCLUSIONS

The clinical development of advanced therapies for rare diseases is one of the most complex and ambitious endeavors undertaken by industry. However, developers can draw upon ever-expanding experience – both successes and failures – to glean lessons learned and best practices in pre-clinical design, trial operations, regulatory pathways and medical science. Ultimately, the development of advanced therapies for rare diseases holds the promise of making available remarkable therapies that will change the future for rare-disease patients everywhere.

PROFESSIONAL RESOURCES

Xtalks Webinar. *How Advanced Therapies are Changing the Landscape of Rare Disease.* https://xtalks.com/webinars/how-advanced-therapies-are-changing-the-landscape-of-rare-disease/

Xtalks Webinar. *Rare Disease Clinical Development: Strategies for Ensuring Endpoint Integrity.* https://xtalks.com/webinars/part-3-rare-disease-clinical-development-strategies-for-ensuring-endpoint-integrity/

Xtalks Webinar. *Rare Disease Clinical Research: Spotlight on the Patient and Caregiver.* https://xtalks.com/webinars/part-1-rare-disease-clinical-research-spotlight-on-the-patient-and-caregiver/

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Publishing enquiries:
John Hughes 416 977 6555 x 228;
jhughes@honeycombworldwide.com

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