Fulfilling the Promise

Strategies for cell and gene therapies

With Heart

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For patients worldwide,

a thriving pipeline of cell and gene therapies (CGT) promises to make life-changing treatments more accessible. For biopharmaceutical companies, the heterogeneity of these therapies presents unprecedented technical, logistical, and strategic challenges. Companies must navigate largely uncharted waters with only a few CGT approvals to date.

Parexel has a legacy of helping companies navigate complex product development. Our consulting group includes former regulators and health technology assessment (HTA) professionals alongside industry luminaries—experts who have been there—relentlessly identifying solutions to overcome the most challenging regulatory and market access hurdles since the start of the CGT era. In this eBook, we review our perspectives on four of the most significant challenges:

- Avoiding regulatory and chemistry manufacturing and control (CMC) pitfalls
- Understanding patient needs
- Communicating about clinical trials
- Establishing value for market access

We hope you find it helpful on your journey.

Paul Bridges, Ph.D.
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Expert insights

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3 ways to avoid CMC and regulatory pitfalls

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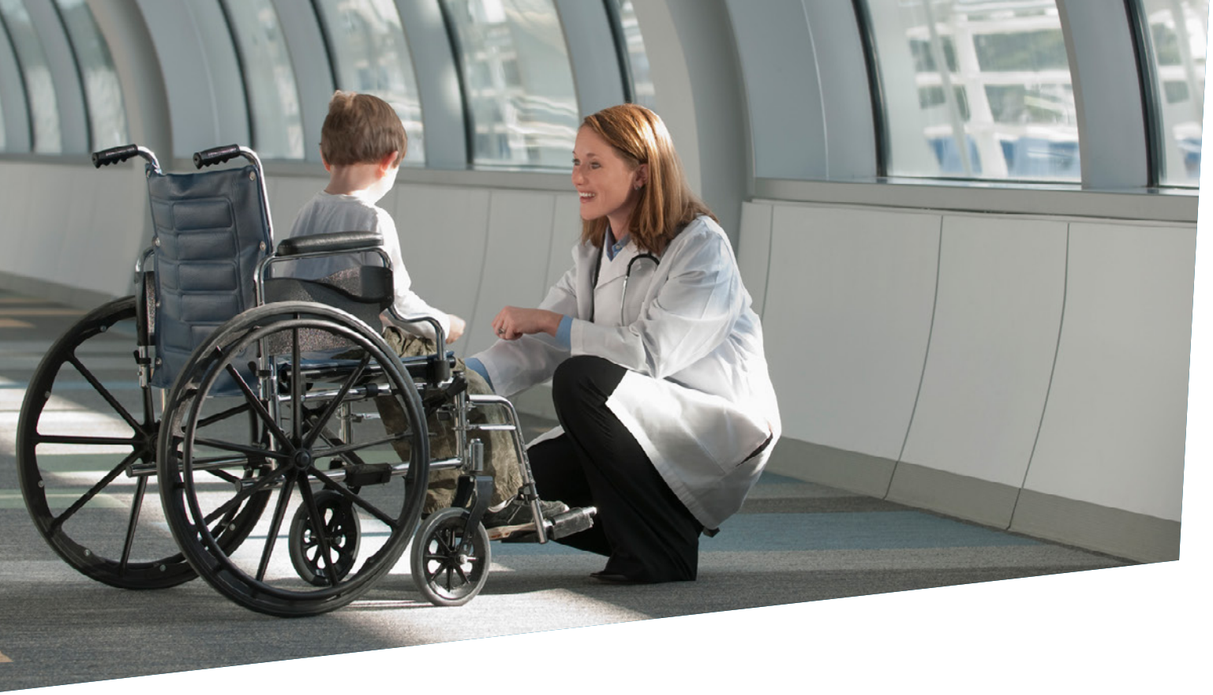
The technical and logistical challenges of developing cell and gene therapies (CGTs) can be daunting. For example, products for rare diseases can demonstrate dramatic clinical efficacy in a small number of patients, leading to regulatory approval so rapidly that it precedes planning. Regulatory requirements vary from country to country. Manufacturing processes are complex and often present scale-up challenges that have not been confronted before. Rare disease patients can be challenging to locate and are typically scattered around the globe. And CGT products have not been studied long enough in patients to precisely characterize their long-term safety and efficacy.



Former FDA officials Mo Heidaran and Steve Winitsky bring a combined 20 years' experience from the agency's Center for Biologics Evaluation and Research (CBER). Both have served as Acting Branch Chiefs in CBER's Office of Tissues and Advanced Therapies (OTAT) where they supervised reviews of CGT files. During his tenure at OTAT, Mo served as a Division of Cell and Gene Therapy (DCGT) representative to several FDA- and CBER-wide working groups and outside organizations such as United States Pharmacopeia (USP). Steve served as the primary clinical reviewer for approximately 90% of the cardiovascular files regulated by OTAT and was involved in working groups that were responsible for drafting and finalizing FDA and CBER Guidances and implementing the Prescription Drug User Fee Act (PDUFA) and 21st Century Cures initiatives. They now provide Parexel clients with strategic chemistry manufacturing and control (CMC), technical, and regulatory support during every stage of CGT product development.

The dazzling heterogeneity of these therapies, from gene-editing technologies to tissue engineering to pure cell-based treatments to gene-modified cellular products (see Table 1), adds another layer of complexity. There are no well-established development pathways: Each class of CGT products (some of them overlapping) faces a fast-evolving regulatory landscape and a unique set of manufacturing challenges.

Think comprehensively, start early

Craft comprehensive strategies early in development to reduce CMC's and regulatory risks. Here are three risk mitigation practices:

1 Understand the evidence requirements in every locality

The regulatory requirements for CGT products are complex and differ from country to country—even different countries within the EU have diverse regulatory considerations. Both the U.S. and European regulatory and CMC frameworks are more advanced than those in other parts of the world, which often don't provide detailed guidance for CGT sponsors or harmonize their requirements with other regions. Because of these differences, simultaneously complying with different regulatory processes for CGT trials conducted in multiple countries is a massive undertaking.

Companies can't necessarily focus solely on the U.S. because the patients for these products, particularly those who have rare diseases, must be recruited and enrolled worldwide, in places like Australia, Canada, and the Middle East. To initiate trials in multiple countries, companies must understand the regulatory process and the precise nature of evidence required by regional Health Authorities (HAs).

Standards of clinical evidence also differ between countries. It is essential to know which comparators, endpoints, and clinical outcomes each HA considers meaningful and interpretable. Which preclinical models are accepted, and how much in vitro and animal testing is required? How many trials are necessary to establish efficacy? How do different HAs view the use of adaptive trial designs, synthetic control arms, real-world

Table 1. A sampling of cell therapies, gene therapies, and tissue-engineered products approved in Europe and the United States

Product	Drug Class	Starting Material	Modification & Delivery	Indication
Strimvelis	Gene Therapy—Ex vivo	Patient's own CD34+ (bone marrow) cells	Transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence—administered intravenously	Severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID)
Luxturna	Gene Therapy—In vivo	Recombinant adeno-associated virus (rAAV) vector	Modified to deliver a functional copy of the normal human RPE65 gene—administered via subretinal injection	Biallelic RPE65 mutation-associated retinal dystrophy
Zolgensma	Gene Therapy—In vivo	rAAV vector serotype 9	Modified to contain a transgene encoding the human survival motor neuron (SMN) protein—administered intravenously	Children under two with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene
Provenge	Somatic cell therapy product—autologous	Patient's own peripheral blood mononuclear cells	Activated ex vivo with PAP-GM-CSF (sipuleucel-T)—administered intravenously	Asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer
Kymriah	Chimeric antigen receptor (CAR) T-cell therapy—autologous	Patient's own lymphocytes (white blood cells)	Genetically modified with a lentiviral vector encoding a CAR that recognizes the CD19 protein on CD19-positive B lineage tumor cells—administered intravenously	Children or young adults (up to 25 years of age) with refractory or relapsed acute lymphoblastic leukemia
Holoclar	Tissue-engineered product—autologous	Human corneal epithelial cells containing stem cells	Expanded ex vivo—transplanted without suture	Moderate to severe limbal stem cell deficiency due to physical or chemical ocular burns

PAP=prostatic acid phosphatase; GM-CSF=granulocyte-macrophage colony-stimulating factor

evidence, and statistical methods for handling loss to follow-up?

The impact of these issues is often magnified for CGTs intended to treat rare diseases. It's optimal to use a historical control in trials where a concurrent control arm is considered unethical or when patients refuse to risk randomization to a placebo. But sponsors need to know that, for example, the FDA has one of the most uncompromising stances on historical comparator arms of any HA in the world.

2 Don't let clinical and regulatory progress outpace manufacturing

A CGT product may demonstrate safety and efficacy in clinical trials before scale-up processes are validated. Manufacturing CGTs is complex. For example, it takes many steps and 3-4 weeks to produce autologous CAR-T cells for injection into a patient—it's the equivalent of manufacturing a new product for each individual.

Scrambling to scale up or scale out production according to current good manufacturing practices (CGMP) is complicated. But it's even harder to change manufacturing processes, from the clinical trial product to the commercial product, at a late stage of development. HAs require rigorous demonstration of product comparability, especially if data from patients who received an early-phase product and those who received the commercial product are combined.

The solution is to embed manufacturing considerations into the development program so that process validation, manufacturing consistency, and CGMP compliance become a priority much earlier in the product lifecycle. CMC experts need to be at the table from day one to address product quality, process consistency, in-process controls, and batch release procedures.

Even for products developed by large companies, manufacturing can become a significant pain point post-approval. Smaller companies, or those that start their development program in an academic setting, should prepare early to manufacture the product reproducibly and systematically assess quality. This can be accomplished by achieving phase-based compliance. For example, small biotech companies should work on developing biologically relevant potency assays—as well as qualifying and validating them—from day one. This work will help

"For CGTs, there is often an incomplete understanding of critical quality attributes and critical process parameters, making comparability extraordinarily complex and problematic."

define the critical quality attributes (CQAs) and critical process parameters (CPPs) early in the product development cycle, which is particularly important for products granted an expedited regulatory mechanism (such as breakthrough therapy designation).

Manufacturing changes are inevitable over a product's development lifecycle and need to be managed proactively. For CGTs, there is often an incomplete understanding of CQAs and CPPs, making comparability extraordinarily complex and problematic.

3 Create a strategic global regulatory roadmap

A comprehensive global regulatory strategy for CGTs is critical to a successful product launch: Should the first marketing application be submitted in the U.S.? In Australia? In China?

Most companies will want their CGTs approved worldwide and understand that the FDA or European Medicines Agency (EMA) approval may expedite approval from other HAs. The U.S. regulatory path is well defined and not as complicated as in some other countries with less mature processes. Smaller HAs may rely on prior FDA (or EMA) approval as evidence that a reputable agency has already vetted the data. But that doesn't work in reverse. For example, the FDA examines data independently and applies what it considers absolute approval standards—it does not rely on other countries' approval as a reference.

Despite a relatively immature CGT regulatory framework, China is surging as a CGT development hotbed, in CAR-T cell therapies in particular. Other Asia-Pacific countries are close behind. As a result, many international companies are starting trials in China to submit a marketing application to the National Medical Products Administration (NMPA) in China first. As of June 2020, there were 357 registered CAR T-cell trials in China.

For some companies, adding external expertise and resources from contract research organizations with a global footprint can be an essential part of a risk mitigation strategy.

Make an unprecedented commitment to strategic planning

CGTs are potentially life-transforming therapies that can be rapidly developed, and so often qualify for expedited approval, and generally have excellent prospects for commercial success. To develop them successfully, particularly on a global scale, sponsors must make an unprecedented commitment to strategic regulatory and CMC planning—from the earliest phases of development—to ensure phase-based readiness for meeting HA expectations.

Expert spotlight

Mohammad (Mo) Heidaran, Ph.D.
Vice President, Regulatory Consulting
Parexel International

Mo is a recognized expert in the development of cell and gene therapies with more than nine years of experience at the FDA's Center for Biologics Evaluation and Research (CBER), including almost seven years in the Office of Tissues and Advanced Therapies (OTAT), as a CMC Reviewer, then Team Lead and Acting CMC Branch Chief. Before OTAT, Mo also worked in the Office of Compliance and Biological Quality. He has 15 years of biotech experience in research, product, and intellectual property development, and nine years of laboratory training at the National Cancer Institute. In his current role, Mo provides clients with strategic CMC technical and regulatory support. He is a member of several internationally recognized organizations, including the USP Bio-5 Advanced Therapies Expert committee and International Society of Cell & Gene Therapy North America Legal and Regulatory Affairs.

Steve Winitsky, M.D.
Vice President, Regulatory Consulting
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Steve brings more than 11 years of FDA experience as a Medical Officer, Team Leader, and Acting Branch Chief in the OTAT in CBER. He gained extensive experience with review and supervision of files for cell and gene therapies—INTERACTs (previously known in OTAT/ Office of Cellular, Tissue and Gene Therapies (OCTGT) as pre- pre Investigational New Drugs (INDs), preINDs, INDs, and biologics license applications (BLAs); device files—510(k)s, investigational device exemption (IDEs), premarket approvals (PMAs); and combination biologic and device files. In his current role, Steve provides strategic clinical and regulatory support to clients for all stages of development for cell and gene therapies.

How to better prepare patients for a cell or gene therapy trial

An interview with CAR T-cell therapy patient and patient advocate Doug Olson

A decade ago, Doug Olson was facing a grim prognosis. When first diagnosed with chronic lymphocytic leukemia (CLL) in 1996, he was treated with "watchful waiting." But as his CLL progressed, he went through two rounds of chemotherapy and, after experiencing thirteen years in remission, he'd become resistant.

By spring 2010, CLL had invaded 50% of his bone marrow and a bone marrow transplant—a treatment that works for many patients but can have serious side effects—looked like his only option. At that point, his physician, Dr. David Porter at the University of Pennsylvania, told him he might qualify for a clinical trial that was testing an experimental new treatment called chimeric antigen receptor (CAR) T-cell therapy. After joining that trial as Patient #2, Olson achieved a complete remission and is cancer-free to this day. He now volunteers for the Leukemia & Lymphoma Society's (LLS) peer-to-peer support program and First Connection, which allows patients and their loved ones to speak with someone who has been diagnosed with a form of blood cancer. Parexel spoke with him about how healthcare providers and trial sponsors can better communicate with patients about CGTs.

Q: Do you think patients are well informed about CGTs?

Doug: I regularly speak to cancer patients who are newly diagnosed or have relapsed and are considering CAR T-cell therapy. I've found it's a mixed bag as to what they come away with after speaking with their doctor. I think the medical community can do a better job of communicating.

First, medical personnel need to start by understanding that they are dealing with a scared human being—they have cancer that is unresponsive to standard treatment and are running out of options. Empathy is the primary context for a discussion of regulator-approved therapies or clinical trials.

Second, while many patients are well educated and have researched their condition extensively, others know very little about it and are not comfortable with scientific concepts and terms. When investigators explain a CGT to a patient, they need to understand the person who they are speaking to and target their message for them: What is their education level? How sophisticated is their knowledge of their disease? Do they have a family support group? Do they understand how clinical trials work?

> Patients want to know they will be cared for throughout the trial. They need to understand that participating in clinical research has meaning; no matter the outcome, the trial will generate knowledge that could help others with the same condition.

A patient who is afraid and has run out of treatment options needs to understand that enrolling in a clinical trial does not make you a guinea pig or a mouse in a cage.

Q: Are the potential benefits and risks of CGT clinical trials communicated well?

A: There are strict rules around informed consent that dictate how risks are communicated to patients and their families. But beyond that, healthcare providers need to educate and provide context to patients. The initial discussion with a healthcare provider is critical to how the patient views participating in a clinical trial.

I know physician-investigators don't want to give patients false hope, but patients need hope. I don't mean that someone should promise a cure. But I believe that patients want to know they will be cared for throughout the trial. They need to understand that participating in clinical research has meaning; no matter the outcome, the trial will generate knowledge that could help others with the same condition.

Physicians give patients a long list of all the things that could go wrong. But it would help patients understand the likelihood of adverse side effects to weigh the risk against the possible benefit of the new treatment.

For me, participating in a clinical trial was empowering. I did not have to sit back and wait for cancer to beat me; I could try to beat it first.

Q: What do you think might improve how physicians talk with patients about trials?

A: My physician was a very kind, honest, and caring individual. He was always upfront when there was bad news but never removed hope. If every physician were like him, I suspect patients would enter more freely into clinical trials.

But that is unrealistic: Someone could be an excellent physician with limited communication skills that might improve with a little training. If we could change the game of how principal investigators communicate about clinical trials through education, we could recruit and retain more patients in trials. Some of the skills needed to talk with a cancer patient are closer to those of a social worker—and perhaps bringing a trained individual into the discussion could help.

A patient who is afraid and has run out of treatment options needs to understand that enrolling in a clinical trial does not make them a guinea pig or a mouse in a cage. They will be taken care of during the trial, and if the treatment does not work for them, there may be other trials they can participate in—the science is moving fast.

Patients have one thing top of mind: I have cancer, and I don't want it.

Expert spotlight

Doug Olson, Ph.D.

Cancer survivor and CAR T-cell patient

Doug Olson received his bachelor's degree in Chemistry from Maryville College and his Ph.D. in Medicinal Chemistry from Purdue University. Most of Doug's career has been spent in the Medical Device and In Vitro Diagnostics industry. Doug served as President of DPC's Instrument Systems Division and corporate Chief Scientific Officer prior to its sale to Siemens Health Care. Doug is the holder of eight U.S. patents and author of a number of publications. Doug is a cancer survivor and patient number two in the initial CART 19 clinical trial. He is a former member of the Board of Directors of the Eastern PA chapter of LLS and is on the Board of Directors of BÜHLMANN Laboratories and BÜHLMANN Diagnostics Corp and currently serves as Chief Executive Officer of BÜHLMANN Diagnostics Corp.

Differentiating your cell or gene therapy trial with a staged communications strategy

Nichola Gokool, Senior Director, Medical Communications, *Parexel International*
Jakki James, Director, Patient Communications, *Parexel International*

Jakki James and Nichola Gokool have worked in the trenches of medical communications for decades. They are passionate about empowering patients with understandable, transparent clinical trial information, and driving innovation in communications with physicians and sites. They focus on engaging all the clinical trial participants at the right time, through the right channels, and with the right information. They've helped Parexel clients successfully recruit and retain patients, principal investigators, and sites for many complex cell and gene therapy trials.

"New treatments generate scientific buzz, but they can also create fear and confusion. That's why CGT trials demand clear, concise, and coordinated communications."

Clinical trials of cell and gene therapies (CGTs) pose enormous technical challenges. For example, chimeric antigen receptor (CAR) T-cell therapies involve harvesting T cells from a patient, transporting the extracted cells to a manufacturing site, genetically engineering them with a disarmed virus, expanding and cryopreserving them, and then transporting, thawing, and infusing them back into the patient.

They also present unprecedented communications challenges: How do trial sponsors convey the right information about these novel, complex treatments to patients, their families, physician investigators, sites, and the broader medical community?

New treatments generate scientific buzz, but they can also create fear and confusion. That's why CGT trials demand clear, concise, and coordinated communications. A holistic strategy that precisely targets, educates, and engages stakeholders is as critical to a CGT trial's success as logistical and technical excellence.

Take it one step at a time

A sound communications strategy starts at the protocol development and optimization stage and continues until the data analysis is complete and results are published. Here are four critical inflection points and how to handle them:

1. First contact

In a complex and competitive clinical trial landscape, sponsors need to articulate critical points to principal investigators (PIs) in the smallest possible package of materials:

- What is novel about the treatment's mechanism of action?
- What is the clinical rationale (unmet need) for the study?
- What does this product candidate bring to the table versus competitors?
- Are there any outstanding safety questions or issues?

There are multiple communication channels to choose from: printed materials versus online portals versus videos versus podcasts versus smartphone apps. Which medium will work best to describe a new study to different audiences?

For physicians

Do not send PIs 200 slides and 15 peer-reviewed journal articles about a new CGT study. They do not have time to review that. The most effective way to convince PIs to participate in a new trial is to let them review the material presented by their peers in the medical community. Delivered in either video, digital, or printed format, this type of peer-to-peer engagement provides credibility and validation.

Proactively addressing safety concerns is critical because PIs and site staff are pivotal to recruiting patients. If they have questions that go unanswered, they may not encourage patients to participate. Finally, most physicians can use a dialogue tool or script to talk with patients and parents about trials and address questions proactively and positively.

For patients

Be clear and concise, and don't patronize. Simplification is not always appropriate. In some circumstances, you can conduct a relatively sophisticated conversation around the science. For example, a large proportion of CAR T-cell trials enroll oncology patients whose disease has progressed despite multiple rounds of treatment. Acknowledging what's happened and addressing concerns is essential. Meanwhile, gene therapy trials often enroll pediatric patients. Decisions are made by family members, many of whom have researched the genetic condition extensively and are actively participating in patient advocacy groups (PAGs). Remember to:

- Know your audience. Use imagery, tone, and culturally appropriate language that resonates with the relevant disease community.
- Speak directly to the patient and family. Apply a gentle, informal voice and use personal pronouns.
- Use plain language. Structured and well-organized materials enhance—rather than obscure—understanding of CGTs.
- Add visual detail and nuance. Consider methods such as icons and graphics to help define and depict unfamiliar terms when warranted.
- Use appropriate delivery formats. Provide a combination of text and engaging visual representation of the CGT and how it works.

2. Informed consent

The current informed consent (IC) process often requires patients to read through incomprehensible technical documents. Providing information in layperson language is essential to ensure full comprehension so that the patients and their families can make fully informed decisions about their involvement and options in a CGT trial.

You can supplement a traditional IC document with engaging, interactive formats to help guide the discussion. CGT studies in rare pediatric diseases require materials appropriate for children or parents unfamiliar with medical terminology. For example, we created a “Super Cell” character for one recent CGT study to explain the treatment’s mechanism of action. We have also created characters to walk children and parents through the study design, explaining what will happen at clinic visits and the procedures involved.

Family-friendly IC materials can help patients and parents overcome any initial reluctance and hesitation around clinical trial participation. When study coordinators used a video during the IC process, trials achieved 55% higher randomization rates and 30% higher patient screening rates.

3. Progress engagement

Internal Parexel data shows that trials using patient education and engagement tactics achieve higher recruitment and retention versus those that don't. Trials that employ user-friendly engagement tactics to explain the study had:

26%
Higher patient screening rates

6x
Lower dropout rates

3x
More high enrolling sites

77%
Higher randomization rates

For investigators and site staff, clinical trials are not just about logistics, study operations, and protocol adherence. Appropriately focused communications can help site staff understand the scientific landscape and the value their role can bring, especially if updates on recent publications are shared. For patients, trials are primarily about dealing with their disease and any issues arising from the treatment. It's too easy to forget that trial participants can benefit from hearing news about the "bigger picture": How is the study progressing? What data can be shared?

To remedy that, build agreed touchpoints into the trial's plan and program and publish study progress bulletins quarterly. When information is delivered consistently throughout the lifecycle of the study, it nurtures enthusiasm and engagement. If investigators, site staff, patients, and families know they are part of a broader community (give them the actual numbers, such as "we have enrolled 139 patients to date"), retention and compliance improve.

If a trial sponsor provides regular, detailed data about how a study is progressing, PIs and site staff can better answer patients' questions, which builds confidence. Timing is essential: PIs need to answer questions when asked, so inform them proactively. In rare disease trials, PAGs are often involved in educating and recruiting patients, and sponsors should update them about a trial's progress.

> "When study coordinators used a video during the informed consent process, trials achieved 55% higher randomization rates and 30% higher patient screening rates."

4. Study closeout

A recent survey[1] of 3,654 clinical trial participants showed the majority (85%) said it was "somewhat" or "very" important to them to receive a summary of the study results yet

61% said they never received a results report or an update after their study ended

1/4 said they never received any updates during the trial

22% received a thank-you card for participating

Effective follow-up communications are not a "soft," nice-to-have element of clinical trials; they are a must-have for patients. Sponsors have an obligation—especially to patients who made a risky decision to participate in a CGT trial—to close out a study properly.

At Parexel, we are committed to two crucial end-of-study activities:

Thank-you notes

When a Parexel study completes, we send thank-you messages to patients and sites. We include the promise, "We appreciate your time, and we hope to follow up with you once we have compiled the data from this study." This practice is a simple but often forgotten tool.

Study results

Regardless of the outcome, sponsors must provide a high-level summary of study results in plain language to patients. A printed infographic that is not too text-heavy, or a video, can work well.

CGT trials demand communications excellence

Sites and PIs are overwhelmed by the growing number of CGT trials seeking their participation. Sponsors increasingly understand that an excellent communications strategy is a differentiator for recruiting and retaining patients and PIs.

[1] Center for Information and Study on Clinical Research Participation (2020). 2019 Report on Participation Experiences. Perceptions & Insights Study: Public and Patient Perceptions of Clinical Research. [online] Boston: CISCRP. Available at: https://www.ciscrp.org/wp-content/uploads/2019/12/Participation-Experiences-04DEC-1.pdf [Accessed 15 December 2020].

Expert spotlight

Jakki James
Director, Patient Communications
Parexel International

Jakki has 15 years' experience managing global patient and site clinical trial communications. She has worked to drive the adoption of patient- and site-centric innovation activities, including Parexel's Patient Advisory Councils and Patient Community initiatives. She oversees the development of compliant, patient-centered communications for global clinical trials. Jakki holds a BA (Hons) in English and Higher Diploma in Business. She has co-authored medical communications articles and publications, including an award-winning poster for International Society for Medical Publication Professionals (ISMPP).

Nichola Gokool
Senior Director, Medical Communications
Parexel International

Nichola has a deep understanding of the medical communications market with over 13 years' experience in the healthcare/pharmaceutical industry. She is passionate about driving innovation within patient, physician, and site communication activities. She supported the formation of Parexel's Patient Advisory Council. Nichola holds a BSc (Hons) in Nutrition and Dietetics and regularly publishes at medical communication conferences.

Communicating value to providers and payers

Emma Medin, M.D., MSc, Vice President, Pricing & Market Access, *Parexel International*
Jamie Kistler, Ph.D., Director, Medical Communications, *Parexel International*

As market access and medical communications strategy experts, Drs. Emma Medin and Jamie Kistler help companies communicate the value of cell and gene therapies (CGTs) to providers and payers. The complexity and novelty of CGTs—including proprietary manufacturing processes—require a comprehensive communication strategy to win healthcare providers' trust. Meanwhile, the one-time, front-loaded costs of these treatments have necessitated new payment models to win payer approval and be affordable. Medin and Kistler offer some best practices for telling a resonant value story.

Understand the patient's journey so you know where to add value

Kistler: Consult thought leaders from the start of development to get a clear picture of the disease and unmet needs. Input from national and cross-regional advisory boards with experts and community-level healthcare providers (HCPs) can precisely reveal what the journey looks like for patients and caregivers and where there may be gaps in HCP understanding. These insights inform how biopharmaceutical companies communicate about a novel CGT product from day one. Setting the scene for a new treatment—especially a transformative one—should happen long before the product launches. For example, there may be multiple treatments already available to patients; ensuring that there is a straightforward value narrative for a novel CGT product—one that resonates with payers and regulators as well as HCPs and patients—is critical. There may be important differences (beyond cost) that will affect how patients and providers choose between them. Sponsors can disseminate information on the patient journey and how a novel CGT addresses unmet needs through many different channels, including direct discussions between field medical teams and the HCPs treating patients, educational symposia programs, and peer-reviewed publications. But mapping out the who, what, why, how, and when early on in planning is critical for success:

- Who are the external audiences that need the information?
- What specific information does each audience need?
- Why do they need that information?
- How should that information be disseminated to each audience to ensure adequate reach and understanding?
- When is the appropriate time to disseminate the information?

Generate the evidence that payers want to see

Medin: In markets with value-based pricing and health technology assessment (HTA) agencies, comparative effectiveness data is essential; how does your treatment perform versus current clinical practice versus a placebo? Also, payers want to know how a product works in real life, outside the rarefied setting of a clinical trial. Does it work for the average person? Regulatory agencies often approve drugs for rare diseases on a set of evidence that payers will consider insufficient. If you have not gathered the evidence that HTA agencies are looking for, you will come up short in their assessments. Mitigate this risk with an evidence-generation plan. The one-time upfront costs of CGTs require new payment models, such as outcomes-based models, which need to be negotiated with payer agencies and prepared for from an evidence generation standpoint.

Tell an informed, evidence-based medical value story

Kistler: One of the most critical elements of a CGT communication strategy is an informed, evidence-based, and integrated scientific and value narrative about the product and disease state developed with input from a cross-functional team and, in some cases, external experts. For CGTs, this includes how you will communicate about early preclinical data, proprietary manufacturing data, and clinical data that is sometimes unique compared with standard pharmaceutical products, for example, cellular pharmacokinetic data and health economics and outcomes data as they become available. You have to establish why the new product is needed, why it's safe, how it can be viably scaled up, and how effective it is. The communication strategy is a lot like a score for an orchestra—except it must be conducted over several years as the product progresses. Consider all the different instrument sections and audiences. To gain HCPs' and other key audiences' trust, tell a consistent and integrated scientific and value story in all external communications (such as press releases, websites, educational symposia, disease awareness campaigns, publications, and congress activities).

"The communication strategy is a lot like a score for an orchestra—except it must be conducted over several years as the product progresses."

Jamie Kistler, Ph.D.

Seize early opportunities for scientific advice

Medin: Invest in early scientific advice meetings. You can have a joint meeting with the European Network for Health Technology Assessment (EUnetHTA) and the EMA in the European Union. You can also apply for country-specific consultation meetings. For example, the U.K.'s National Institute for Health and Care Excellence (NICE), one of the most prestigious HTA agencies, is one of the HTA agencies you can submit to the earliest. Sponsors can submit data for review a full three months before their expected review by the Committee for Medicinal Products for Human Use (CHMP). Some sponsors are reluctant to seek advice like this because they are afraid they will receive advice they won't want to follow. Scientific advice is non-binding, but you should always consider it. These consultations are critical for sponsors to develop evidence-generation plans that can satisfy both regulators and payers and understand what can become hurdles for a successful launch.

Be clear-eyed about clinical and commercial viability

Kistler: Even if you are a small biotech company whose strategy is to license or sell the CGT in your pipeline, you need a solid value story told consistently and well. Companies increasingly realize that charging astronomical prices for these exciting new therapies may not be a viable business plan, even with vast unmet needs. Developers, both small and large, need to articulate the value—or expected value—of their product and how it will be commercially viable. What is the competition in this therapeutic area? How robust is the efficacy data? What price point can win reimbursement? It takes strong integration between the scientific, clinical, and market access teams to answer these questions well.

Engage with payers' challenges from day one

Medin: For a product administered once with a lifelong effect, such as gene therapy, you need to address the payer landscape very early in development. These products can create difficult issues on the payer side. Based on results to date, it is doubtful that you can launch a product without a managed-entry agreement. There are several payment models under development, such as annuity payment models, pay-for-performance models, risk pooling models, and licensing. But only a handful of gene therapies have gained market access as of yet. The reimbursement landscape is fluid now, and temporary solutions such as separate budgets for innovative treatments are in some markets. However, payment models will probably evolve to a standard.

How to build a compelling value story

- Establish value with consistent communication at every stage of development.
- Understand that an effective publication strategy for a CGT starts with preclinical data, includes clinical and manufacturing data, and continues with health economics data after launch.
- Give HTA agencies the data they want.
- Seize the opportunity offered by early scientific advice meetings, don't fear them.
- Realize that exciting science is not enough. A successful CGT product must meet safety and efficacy standards, fill an unmet need, and be commercially viable.

Expert spotlight

Emma Medin, M.D., MSc
Vice President, Pricing & Market Access
Parexel International

Emma has more than 12 years' experience working in market access and health economics and outcomes research (HEOR), supporting small, large, and emerging pharma clients with their Phase III clinical trial programs; global market access and evidence generation strategies; and reimbursement dossiers and HEOR tool adaptations for Europe and beyond. Emma has worked on HTA agency strategies, health economic models, comparative effectiveness analyses, and real-world evidence strategies that leverage secondary data assets for gene therapies, somatic cell therapies, and tissue-engineered products.

Jamie Kistler, Ph.D.
Director, Customer Strategy, Medical Communications
Parexel International

Jamie has nearly 20 years of combined academic, clinical, and medical communications experience. She has a depth of expertise in oncology, hematology, and rare disease. She has direct experience in developing and implementing medical communication strategies for both gene and CAR T-cell therapies.

Parexel regulatory and access consulting

With Heart

Relentlessly identifying every opportunity to help you start making a difference faster.

Our 1,000+ consulting team includes ~100 former regulators and HTA assessors, alongside industry luminaries who know what it takes to get your drug from the lab to the world. With unrivaled real-world experience and a collective resume unlike any other team in the industry, our elite group can help you identify and navigate the requirements of regulators, providers, payers, and patients holistically, and early. So you can get your innovation from the lab to the people who need it most, faster—with heart.

Parexel supports the development of innovative new medicines to improve the health of patients. We provide services to help life science and biopharmaceutical clients everywhere transform scientific discoveries into new treatments. From clinical trials to regulatory and consulting services to commercial and market access, our therapeutic, technical and functional ability is underpinned by a deep conviction in what we do. Parexel was named “Best Contract Research Organization” in December 2020 by an independent panel for Informa Pharma Intelligence.

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