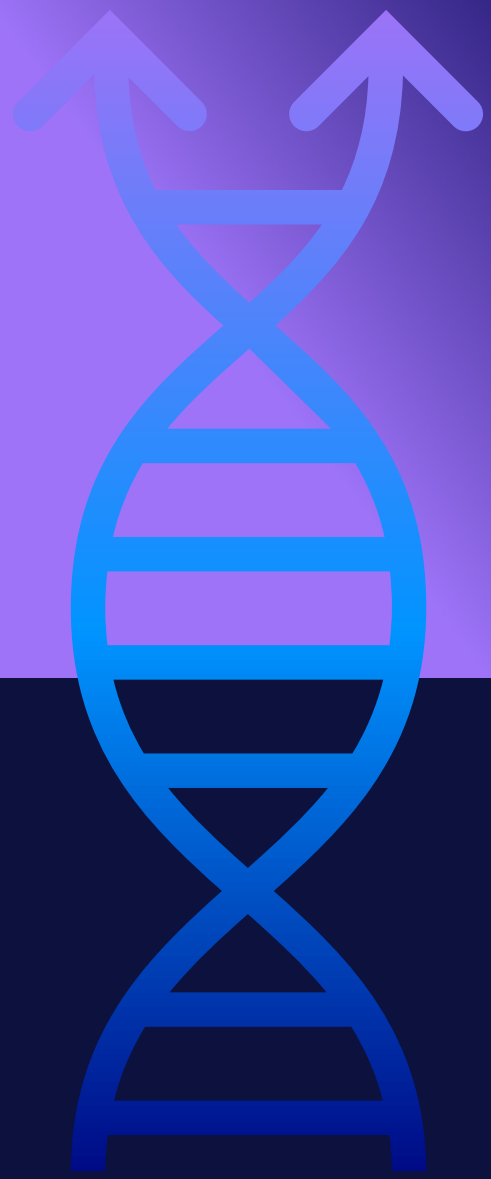
Enhancing the delivery of gene therapies through specific care models: examining centers of excellence (COEs)



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Centers of Excellence (COEs) as a care model example

What are COEs, and what is their role in facilitating gene therapy access?

Gene therapies are increasingly coming to the market, a trend that is expected to continue in the coming years. As of Q4 2023, more than 2,000 products were in the pipeline, with ~300 products in phase II trials and above[1]. To ensure these novel therapies can be effectively integrated and administered in clinical practice, sufficient preparation and processes are required.

Gene therapies are highly specialized technologies with a complex care pathway that requires a multi-disciplinary care team, expertise, and technical capabilities. Given this complexity, gene therapies require care models that can effectively coordinate administration and care. These models can take different forms, one of which is centers of excellence (COEs). COEs are specialized clinical centers within healthcare institutions that provide comprehensive and multi-disciplinary care to patients with complex conditions[2].

COEs can be gene therapy-specific or disease-specific. To date, most gene therapies have targeted rare diseases, which require specific knowledge and expertise. For some rare diseases, COEs supporting diagnosis, care, treatment, and research have been established[3]. Some of these disease-specific COEs are able to support gene therapy administration. In other cases, centers may develop expertise in gene therapy that is not limited to any specific disease area.

While COEs are not the only option and the optimal model of care for gene therapy will depend highly on the existing governance and infrastructure of a given country, they are one key model that has been acknowledged as needing further development. Regardless of whether a COE is disease-specific or gene therapy-specific, further developments can help ensure they have the capabilities for determining gene therapy eligibility, administering treatment, and facilitating appropriate follow-up care. They can also provide practical insights that may be transferable to other models of care.

In this context, roundtable participants discussed areas of focus, along with opportunities and best practices for different domains related to COEs:

- Improving COE designation and qualification
- Enhancing the care delivery model for gene therapy
- Optimizing workforce management and training for members of the multi-disciplinary team (MDT)

Improving COE designation and qualification

Gene therapies are currently administered at sites with specific capabilities, i.e., those that have the infrastructure and expertise required for diagnosis and treatment. Because gene therapies often target small patient populations spread across various locations, sites with these capabilities may not be available everywhere[4]. COEs enable centralized coordination of care for patients with complex conditions within a wide geographical area[2]. These centers, therefore, play a crucial role in the effective delivery of gene therapies, highlighting the importance of strategically selecting, assessing, certifying and qualifying them.

Certification processes for COEs to be able to deliver gene therapies vary across geographies. In Europe, designation, which includes the selection, assessment, and certification of a center to be labeled as a COE, is usually performed by national authorities[4]. In the United States (US), there is no regulatory oversight for COE designation, and private health insurers, scientific societies, and hospitals can define their criteria[5].

Manufacturers are often involved in the qualification of the designated COEs for their specific therapy. Qualification takes place after a center is certified and may take several months to complete. This process includes activities such as on-site assessment, introductory meetings, and site readiness training[4].

Although national authorities can be largely responsible for COE designation and manufacturers often play a role in qualification, exact roles and responsibilities can differ across countries and are not always completely clear. This lack of clarity can lead to misalignment and redundancy in designation and qualification processes[4]. For example, while authorities or other institutions may designate centers, manufacturers may still need to establish contracts with these centers, in which the specific requirements and criteria necessary to administer their therapies are outlined. Qualification processes may also require hospitals to implement workflows and processes for each treatment, which may not be sustainable in the long term as more become available[6].

The predicted increase and uptake of gene therapies further highlight the need to standardize processes to ensure consistent quality administration and optimal patient outcomes. As more therapies become available, there will be a need for COEs to integrate them into their treatment pathway routinely.

Roundtable participants, therefore, noted the importance of developing clear, specific and transparent criteria for the designation and qualification of COEs, as well as the need to standardize processes to better integrate gene therapies into clinical practice.

Several promising opportunities to enhance the designation and qualification of COEs were discussed, drawing on examples from established best practices.

First, clear criteria for COE designation and qualification can better distinguish stakeholder roles and responsibilities and minimize delays between therapy availability and site readiness.

Making criteria transparent can also promote patient centricity. Clarity on COE standards (e.g., gene therapy experience, service quality, and treatment outcomes) can enable patients and families to compare different centers, make informed decisions about their care and build confidence in the quality of care they can expect to receive[4,7].

Best practices

In Germany, specific thresholds to demonstrate the experience and expertise of centers are set as standard. Patient organizations play a crucial role in setting these thresholds, as they are regularly involved in developing guidelines establishing quality and technical standards for COEs[4].

The establishment of criteria for COE designation and qualification should be based on expert opinion and feedback from all relevant stakeholders, including manufacturers and regulators, as well as healthcare professionals (HCPs) and patients, to maintain focus on optimal patient care. The involvement of manufacturers and regulators can be particularly relevant when specific COE requirements (pre or post-gene therapy administration) are outlined in the product label. HCPs, on the other hand, can provide practical insights on what constitutes high-quality care and effective patient management. Similarly, patients can bring valuable perspectives from their experience of access to specialized services. Clear processes for COE designation and qualification will also reduce inconsistencies in the provision of care and facilitate the exchange of expertise across different centers.

The April 2024 Framework for assessing, funding, and implementing high-cost specialized therapies highlights the Medical Services Advisory Committee's (MSAC) role in not only recommending products for use, but also advising on the number of sites, treatment settings, and hospital selection criteria based on safety and quality. After MSAC's recommendation, jurisdictions may designate specific sites for administering the therapies[8].

In Germany, the Federal Joint Committee (G-BA) released quality criteria for hemophilia gene therapy dosing centers, which were inspired by guidelines from the European Association for Haemophilia and Allied Disorders (EAHAD)[9,10]. EAHAD is a multi-disciplinary association of healthcare professionals dedicated to the care of individuals with hemophilia and other bleeding disorders.Their guidelines help ensure that treatment centers maintain high standards for patient care.

Parent Project Muscular Dystrophy

The Certified Duchenne Care Center Program (CDCC), developed by Parent Project Muscular Dystrophy (PPMD), allowed the creation of a network of certified Duchenne Muscular Dystrophy (DMD) centers in the United States with the goal of promoting patient access to optimal care and services and reducing care discrepancies[11].

The CDCC Certification Committee, which includes clinicians, parents, non-active industry, and PPMD, reviews site applications and visit summaries, and makes suggestions/recommendations regarding certification[11]. The program ensures that COEs comply with established treatment guidelines set and updated by the Centers for Disease Control (CDC) in collaboration with PPMD[8]. As of 2022, PPMD's CDCC Program supports care for more than 4,600 people living with Duchenne and Becker muscular dystrophy at 36 Certified Duchenne Care Centers in 22 States and the District of Columbia[12].

In 2008, the European Neuroendocrine and Tumor Society (ENETS) set up a certification program, resulting in the accreditation of 67 COEs[13]. The principal goals of this program are to:

- *Increase competence and expertise of the multi-disciplinary team*
- *Increase adherence to ENETS guidelines, focusing on patient-oriented care*
- *Increase participation in clinical trials*
- *Establish a systematic approach for a collaborative and continuous improvement of the participating centers*
- *In order to qualify for the certification, centers must have a clear organizational structure where the responsibilities of the centers and affiliated treatment partners need to be formalized[14]*

Another promising opportunity to improve transparency and clarity in COE designation and qualification is stakeholder collaboration, which can support the development of guidelines for gene therapy provision and standard operating procedures (SOPs).

Minimizing clinical care variability across institutions through standardized guidelines is crucial for ensuring consistent quality and safety measures for all patients receiving gene therapy[4].

Achieving this requires multi-stakeholder collaboration. Industry, scientific societies, and COEs can work together to define the elements needed for safe and high-quality gene therapy provision. In particular, collaboration between scientific societies can facilitate the establishment of overarching scientific principles for safe and high-quality patient access.

Collaboration between pharmaceutical companies and hospitals can help translate these principles into practical guidelines, ensuring widespread and efficient patient access. Comprehensive guidance from industry is especially crucial, considering the diverse types of gene therapy, each with distinct storage and administration requirements.

Moreover, close collaboration among centers can support sharing knowledge and best practices, both with each other and with prospective centers. This exchange of experience and expertise can help continually improve care standards and better ensure that new and existing centers can benefit from collective learning.

In terms of SOPs, development can be accelerated by leveraging existing templates tailored to specific treatments or procedures (e.g., bone marrow transplants), ensuring an efficient use of resources[6].

Best practices

The Australian Health Genomics Policy Framework provides comprehensive national guidelines, regulations, and standards that support high-quality and safe use of genomics in healthcare. It is a collaborative and coordinated approach between all levels of the government and multiple stakeholders[15].

In Germany, there are clear quality guidelines for cell and gene therapy (CGT) provision[4]:

- *Scientific societies develop criteria for minimum quality standards encompassing the structure, process, and outcome of CGT care provision*
- *The Federal Joint Committee (G-BA) collaborates with the Paul Ehrlich Institute to set specific quality requirements for the use of CGTs based on the developed criteria*
- *The G-BA outlines precise regulations for implementing the quality guidelines, and the G-BA's Pharmaceuticals Sub-Committee oversees the process and provides feedback on quality assurance measures*

Enhancing the care delivery model of gene therapy

Different care models can support the administration of gene therapies, depending on the characteristics of the healthcare system.

In the field of hemophilia, for example, the European Association for Haemophilia and Allied Disorders (EAHAD) and the European Haemophilia Consortium (EHC) have called for first-generation gene therapies to be introduced by hub and spoke models[17].

While hub and spoke models will not necessarily be the norm across all diseases and not all countries may fully apply such models, they are an important and prominent aspect of gene therapy delivery.

The hub and spoke model offers a unique approach for treating the small numbers of geographically dispersed, gene therapy-eligible patients by concentrating specialized care at a central hub while delivering basic services through local spokes[18]. In this context, the hub serves as a specialized medical center with focused gene therapy expertise and advanced infrastructure[19]. The spokes, on the other hand, provide initial diagnosis and basic care to patients, permitting the majority of healthcare needs to be addressed locally[20].

While promising, the hub and spoke model also presents challenges that must be addressed to facilitate effective gene therapy provision[21].

Firstly, implementing the hub and spoke model for gene therapy administration may require adaptions. For example, the model may need to be adjusted depending on the healthcare system context and type of gene therapy (e.g., in-vivo or ex-vivo).

Secondly, implementing the hub and spoke model may require significant upfront financial investment to acquire specialized equipment, trained personnel, and sustainable long-term funding mechanisms to ensure the viability of hubs.

Thirdly, the inherent nature of gene therapies, with their potentially one-time administration followed by extended follow-up, complicates traditional models of care and hospital funding. Additionally, fragmented budgets and diverse funding models across regions and countries can create disparities in resource allocation, potentially leading to unequal service provision between hubs. For example, in Italy, decision-making on the designation of CGT treatment centers is a regional competency, and funding is allocated by regional authorities[4].

Several promising opportunities to facilitate the implementation of the hub and spoke model for gene therapy delivery were discussed, drawing on examples from established best practices.

Clear guidance and protocols outlining the roles and responsibilities of hubs and spokes are essential to ensure high-quality patient care along the gene therapy care continuum. A well-defined hub and spoke model requires centralized strategic planning that involves multiple stakeholders, including patients, healthcare providers, and payers, to develop a uniform set of criteria that will underpin equitable and efficient access to gene therapy[10].

As a general rule, the role of *hubs* should include all aspects related to gene therapy delivery pre and post-infusion[20]. Hubs should also maintain tight control of critical aspects (e.g., quality control measures, safety to avoid cross-contamination, storage) to ensure high-quality and safe patient access to gene therapies[19].

Similarly, the responsibilities of *spokes* should be clearly defined to ensure timely referrals and follow-up monitoring of patients after gene therapy is administered. Structured protocols for the follow-up period are needed to support the assessment of treatment outcomes and possible side effects[10].

Spokes could also provide counseling about treatment options and expectations around gene therapy and support hubs with national and international data collection[19].

Standardized protocols *across the hub and spoke network* are essential to facilitate coordination between hubs and spokes, ensuring consistent and timely access to specialized care and an efficient utilization of resources. Prioritizing the development of these protocols between hubs and spokes is essential when using this model in order to achieve efficiency and maintain high standards of care throughout the network. At the same time, it is essential that, in practice, the definition of objectives for hubs and spokes can be adapted to meet the needs of the local context, as the organization of the healthcare system can significantly influence how the hub and spoke model is implemented[21]. For example, it was highlighted in the roundtables that in some contexts, the spoke could be responsible for gene therapy administration, such as when the spoke has gene therapy experience or when patient travel to the hub is very difficult.

Best practices

EAHAD

EAHAD and EHC proposed a flexible/modifiable hub and spoke model with the aim of making hemophilia centers better qualified to deliver gene therapy[19]. This recognizes that the model may need to be modifiable depending on the country or regions within the same countries. Therefore, two different scenarios for the application of the hub and spoke model are envisioned.

- *Scenario 1: the hub has gene therapy experience, and the spoke minimal experience*
- *Scenario 2: the hub acts as a dosing center and is experienced in gene therapy delivery; the spoke is a management center with gene therapy experience*

This model has clear guidance on the responsibilities of hub and spoke centers around:

1. *Counseling about treatment options and discussing expectations*
2. *Patient selection*
3. *Laboratory monitoring and diagnostic testing for the gene therapy program*
4. *Education and training of HCPs and the multi-disciplinary team*
5. *Preparation of the gene therapy product and dosing*
6. *Short-term and long-term follow-up of patients post-treatment*

In Italy, gene therapies are reimbursed regionally, and the application of the hub and spoke model may be limited. Consequently, in some instances, adaptations have been made where both hubs and spokes are involved in administering gene therapy.

For example, in the Emilia Romagna Region, a hub and spoke model with one prescribing center has been adopted for (chimeric antigen receptor) CAR T-cell therapies. In contrast, in other regions (e.g., Campania and Lazio), multiple prescribing centers have been identified[22].

In the United Arab Emirates (UAE), a single gene therapy hub is structured to provide treatment and follow-up after administration. However, as patients may also come from abroad and may not travel back to the UAE for follow-up visits, an alternative solution was implemented: the clinics in the patient's country of origin conduct the appropriate follow-up activities under the direction of the hub.

Guidelines published in Germany and Italy recommend that a pre-infusion agreement detailing educational activities and checklists (e.g., for patient screening) should be established between hub and spoke centers[23].

Besides context, the type of gene therapy is another factor that should be considered when implementing the hub and spoke model, as it may also influence the provision of care. For example, ex-vivo gene therapies are highly complex, and in this context, hubs are needed to ensure safe and efficacious administration[24]. In contrast, in-vivo gene therapies are less technically demanding and could potentially be administered by smaller "spoke" centers, especially as they become a more common part of the treatment pathway.

Finally, patient preferences should be accounted for in the choice of the care coordination model. Involving patients and patient organizations in the design and implementation of the hub and spoke model may better ensure that it addresses their specific needs, taking into account their journey from diagnosis to care[10]. For example, patients often express their preference for follow-up and monitoring to be close to their home, as it decreases travel time. In some cases, the hub and spoke may not be applicable as patients may prefer to receive local specialized care[25]. In cases where the hub and spoke model is implemented, the provision of logistic support via a patient assistance program may facilitate patients' travel between hubs and spokes, improving patient experience, ensuring adherence to treatment protocols, and supporting ongoing data collection activities.

Optimizing workforce management and training for members of the multi-disciplinary team (MDT)

With more gene therapies potentially becoming available in the coming years, it is crucial to ensure that the healthcare workforce can sustain their uptake. Notably, roundtable participants highlighted that limited availability of resources at the healthcare system level and insufficient workforce training may impact gene therapy provision in various ways.

Firstly, capacity to provide gene therapy at the healthcare system level may be limited by insufficient workforce and infrastructure. In Europe, there is an estimated shortage of one million healthcare workers[26] and similar trends are seen in the United States[27]. Furthermore, investment in healthcare is now declining following an increased budget allocation during the COVID-19 pandemic[28].

Secondly, gene therapy administration and follow-up require complex care offered by a multi-disciplinary team (MDT)[29,30,31]. The MDT is responsible for patient selection and management and includes different specialties to ensure appropriate care before and after gene therapy administration[30]. Hence, it is essential that the MDT receives sufficient training and education so that information is consistent across team members and appropriately conveyed to patients[22]. However, surveys of physicians involved in the care of people with hemophilia worldwide[33] and hospital pharmacists[34] in Europe show that there is

> **Several promising opportunities that can address challenges around workforce management and training for the multi-disciplinary team have been discussed during the roundtable.**

For members of the MDT, accessible, comprehensive training is important across all aspects of gene therapy administration pre- and post-infusion. This includes education around eligibility assessment, treatment planning and delivery, follow-up monitoring, and ongoing patient care[33].

International tools and guidelines from professional associations and supra-national bodies should foster consistent educational standards across different regions to streamline training efforts. Industry can also contribute to MDT education to properly prepare them for new therapies coming down the pipeline. In particular, they can develop product-agnostic guidelines alongside established professional associations to accelerate educational efforts. Industry can also build a competency framework for clinicians focusing on the entire gene therapy care continuum (from gene therapy treatment decision to follow-up) to ensure HCPs have homogeneous skills.

Best practices

ADVANCED PHARMACY AUSTRALIA

Advanced Pharmacy Australia (formally known as the Society of Hospital Pharmacists of Australia (SHPA)) is a national professional organization that supports pharmacists working in hospitals and other healthcare settings to meet medication and related service needs. The organization provides training on gene therapy and recently offered a webinar, which included a definition of the pharmacist's role in gene therapy provision[35].

In August 2024, they published the Pharmacy Forecast Australia, highlighting the growing role of pharmacists in managing the operational and clinical aspects of advanced therapeutics[36]

Another promising opportunity discussed during the roundtable is the integration of easily accessible education on gene therapies earlier in medical training. Integration of gene therapy education in medical training fosters a well-equipped healthcare workforce, leading to enhanced patient outcomes, improved patient access, and stronger public trust and acceptance.

Basic gene therapy training should be incorporated into the core curriculum of medical and healthcare professional schools to ensure that all HCPs, regardless of their chosen specialty, possess a foundational understanding of gene therapy. This broader awareness strengthens the healthcare ecosystem and empowers professionals to identify potential gene therapy candidates, discuss treatment options with patients, and collaborate effectively within MDTs.

In the United Kingdom (UK), the Cell and Gene Therapy Catapult and Advanced Therapy Treatment Center (ATTC) network have implemented multi-disciplinary educational activities. In particular, they worked with the University of Manchester on the development of a master's program focused on challenges around CGT development and clinical delivery[16,37].

Gene therapy education should also extend beyond initial training and become an ongoing process. Implementing easily accessible platforms and formats, such as digital modules, practical simulations, and industry-led workshops, empower HCPs to continuously update their knowledge and stay ahead of rapid advancements in this dynamic field.

Muscular Dystrophy Association (MDA) offers a series of educational programs to clinicians and specialists who manage and treat individuals with neuromuscular diseases, including continuing medical education (CME)-certified grand round webinars, peer-to-peer educational slide decks, and case studies[38].

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Finally, training nurses under physician oversight for specific aspects of gene therapy provision can expand the skilled workforce and empower them to participate effectively, maximizing patient support and optimizing treatment delivery.

Comprehensive educational efforts will thus ensure the MDT members are well-equipped to manage gene therapy delivery and meet the evolving needs of patients as more therapies become available.

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