

NEW DIGS

FoCUS

Financing and Reimbursement
of Cures in the US

RESEARCH BRIEF

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Role of Centers of Excellence (COE) Networks in the Delivery of Curative Cellular Therapies in Oncology.

COE networks currently play an important role in the delivery of care for specialized service lines, including but not limited to solid organ transplantation (SOT), hematopoietic cell transplantation (HCT) and other specialty care programs. FoCUS initiated an exploration of COE networks as a potential component of financial solutions to curative therapies including emerging cellular therapies. Here we

outline the rationale for COE networks and the potential advantages and limitations for their use in the context of cellular immunotherapies for cancer.

The recent approvals (and upcoming considerations for similar therapies) by the Food and Drug Administration (FDA) for chimeric antigen receptor T (CAR-T) cells

KEY TAKEAWAYS

Immune effector therapies including CAR-T therapies for cancer are an emerging class of highly effective, yet complex and potentially toxic treatments for an enlarging group of diseases.

Expertise required to successfully deliver CAR-T therapies overlaps with the current spectrum of autologous and allogeneic HCT, with parallels including the need for cellular collection, cellular handling and processing expertise and a clinical multidisciplinary team experienced in managing cellular therapy and its complications.

Developing frameworks for immune effector cell COE are likely to be based on elements common to existing HCT specialty networks, and will likely include criteria including volume thresholds, quality standards and FACT or similar accreditation and a requirement for transparent reporting of outcomes data that are likely to be risk adjusted. Existing frameworks like those developed by the CIBMTR, NMDP and implemented in the Federally supported SCTOD are in development for immune effector cell networks.

Already, manufacturers have developed *de facto* COE that have influenced patient access to cellular therapy in the clinical trials phase, with the goal of achieving consistent practice and low complication rates. These networks will expand over time, while patient access will be determined by both payer-defined and manufacturer qualifications for administration of therapies, in addition to potential restrictions imposed by the FDA and governmental payers, including the Center for Medicare and Medicaid Services.

Ideally, COE networks will help to ensure a consistent quality of patient care and encourage improving clinical outcomes, while creating incentives for pharmaco-economically sound care with disincentives for waste. Challenges will include implementation of consistent but minimally burdensome reporting and quality standards, and broad access to patients regardless of geography, clinical need and socioeconomic background.

heralds a new wave of emerging curative cellular therapies for cancer; in these cases, for the treatment of acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL). Here a cellular product – T lymphocytes in this case – is harvested from a patient, manipulated via gene therapy and expanded in the lab to many times the original harvested number therefore enabling the cellular product to recognize and destroy cancer cells. This production activity occurs remotely, typically in the facilities of a commercial manufacturer, and the modified cell product is returned to the site of care. Subsequently, chemotherapy to reduce the number of native t-cells is administered prior to the reinfusion of the engineered cell product. This infusion may, depending on the patient and the specific product, be infused in the ambulatory or inpatient setting. Therapies developed to date have resulted in remarkable survival rates for patients with cancers failing traditional therapies; however, risks and costs for these transformative treatments are also unprecedented.

While a subset of patients may have few complications, others will have severe and potentially fatal complications including cytokine release syndrome (CRS), an inflammatory syndrome often requiring intensive care management, and neurotoxicity that may lead to severe but typically temporary complications leading to an inability to speak or even to coma-like states. Unfortunately, there are no reliable approaches accurately identifying patients at low vs. high risk for these complications, which result in significant variations in length of stay (LOS) and the overall costs of therapy. In this respect, allogeneic HCT outcomes also vary significantly from patient to patient, resulting in variable clinical outcomes including relapse rates and non-relapse mortality risks, LOS and costs. For both HCT and CAR-T therapies, highly specialized care is needed, and is felt to improve outcomes and lower risks of serious complications evolving to the life-threatening stage.

Payer-based COE networks: There are over 150 centers in the United States performing allogeneic HCT (i.e., HCT using a donor, who may be a family member or a registry-derived volunteer unrelated donor) and an even greater number of centers where autologous HCT (i.e., using stem cells harvested from the patient, as with CAR-T cells). Many large payers have developed HCT COE plan language restricting or encouraging referrals to a subset of these HCT centers. Typical criteria for inclusion in a plan or network COE program typically include volume as representative of an experienced clinical team, a requirement for accreditation, and achievement of quality standards which may include risk-adjusted rates of survival (either absolute or relative to peer institutions providing similar services). Additional criteria may include geographical distribution (to increase patient access and/or limit travel which may be costly and which can impair caregiver access and familial support).

Finally, there is usually a commitment to contracted care rates that promote an incentive on value-based care. It is likely that existing frameworks for, and lessons learned from, COE networks may inform the creation of novel financial contracting approaches, such as milestone-based contracts. FoCUS stakeholders felt such approaches may better address unique aspects of cellular immunotherapy than prevalent fee-for-service or capitation models that generally provide a fixed single payment for post-HCT care (i.e., without specific milestones).

Manufacturer-based “COE-like” cellular therapy networks:

The pivotal trials performed to date by individual manufacturers of CAR-T products typically utilized a relatively small (e.g., <30) group of cellular therapy centers. As with payer-defined criteria, manufacturers identified institutions that were skilled in clinical care of cellular therapy patients and also in clinical research for the disease (ALL or NHL to date) targeted in initial trials. Because manufacturers desired to keep complication rates low for both ethical reasons and to yield superior survival outcomes needed for approval, most centers included were already those in traditional allogeneic HCT COE networks. With approval, manufacturers have an incentive to increase the number of sites where therapies are available, while ensuring that complication rates remain low, particularly as outcomes data are being closely compared across sites and competing products.

Unique aspects of COE selection criteria and other issues relevant to immune effector cell therapies for cancer are:

Volume: Rather than using minimal volumes as an entry hurdle for determining COE status, payers may develop measures of total experience with novel therapies and participation in clinical trials as surrogates for volume. As the number of available therapies increases, experienced centers are likely to develop platforms that improve outcome across diseases and unique cell therapy types.

Potential conflicts between manufacturer and payer networks: Initially, payers will likely have to accept *de facto* COEs created by manufacturers of cell therapy products and established in the process of pivotal trials leading to approvals. However, because payer and manufacturer standards and goals in COE creation may at times differ (e.g., with respect to emphasis on value vs. scientific expertise) patient access may be impaired as they will need to seek overlap between the requirements of their payers and their clinical and geographic needs. With increases in the numbers of patients treated, payers may appropriately exert pressure on manufacturers to include centers that fit their geographic or value-based needs, although all parties have an inherent interest in maintaining quality standards and outcomes. Earlier-stage therapies may continue to be provided through a more limited network of experienced clinical trial sites, while more mature and lower-risk therapies may be

more likely to find their way to community providers with broader geographic access.

Outcomes: For HCT, governmental regulations require transparency and standardized reporting of risk-adjusted survival outcomes, accomplished via the Stem Cell Therapeutic Outcomes Database (SCTOD), facilitated by the Center for International Blood and Marrow Transplant Registry (CIBMTR) and the National Marrow Donor Program (NMDP). Specialty societies including the American Society for Blood and Marrow Transplantation and informed payers are looking beyond simple outcomes such as mortality at defined post-treatment periods to include metrics of timely evaluation and treatment, and other factors including quality of life. These may come to play a more important role with respect to high cost durable therapies.

Quality standards and accreditation: New metrics are likely to be developed specific to the intended use of the products. In the setting of HCT, the Foundation for Accreditation of Cellular Therapies (FACT) has led the development of quality standards and accreditation practices that are often required for COE inclusion but can be adapted to the needs and resources of individual centers. Payers are likely to require similar standards recently developed by FACT for immune effector cell therapies including CAR-T. The CIBMTR is collaborating with FACT and specialty societies including the ASBMT to develop platforms for assessment, reporting, and risk adjustment that can encourage and reflect quality practices.

Product costs in immune effector therapies relative to HCT: Unlike organ acquisition costs in solid organ transplant, and stem cell acquisition costs in autologous and allogeneic HCT, the product cost for current CAR-T therapies is high, often many times higher than the typical costs for the clinical care services alone, even in patients without serious adverse effects. This results in a much higher ratio of product costs to other care costs: in contrast to autologous and allogeneic HCT, the engineered product is often the primary driver of total cost, lessening the ability to create incentives for center efficiency that help to maintain cost containment.

Novel contracting issues: As mentioned above, traditional payer models of contracting have used COE status to drive volume to network centers through benefit design and other measures. As was the case for transplant in the eighties and nineties, lack of experience drives caution on both payer and provider side with potential loss of access to some populations. Understanding the payer perspective and current challenges in delivering affordable healthcare coverage while ensuring access to medical innovation is critical to the sustainability of research in addition to the development of new cures. To address this, novel methods of contracting will likely emerge to include strengthening of performance-based contracting, variable pricing base on patient factors, and others. Bundled payment approaches may strengthen, and shared risk elements may become more prevalent. Examination of cost effectiveness and efficiencies of the

new therapies will require greater importance, with payers increasingly paying attention to cost-offset analyses and quality of life measures. Estimation of pharmacoeconomic benefit (e.g., quality adjusted life year saved, QALYS) may become an important metric in making early coverage decisions.

Payer-provider relationships: These therapies have the potential to drive new forms of relationships where the payer insists on more integration of the COE with the plan's provider network for better coordination of care in return for some changes in reimbursement.

ABOUT FOCUS

The MIT NEWDIGS consortium FoCUS Project (Financing and Reimbursement of Cures in the US) seeks to collaboratively address the need for new, innovative financing and reimbursement models for durable and potentially curable therapies that ensure patient access and sustainability for all stakeholders. Our mission is to deliver an understanding of financial challenges created by these therapies leading to system-wide, implementable precision financing models. This multi-stakeholder effort gathers developers, providers, regulators, patient advocacy groups, payers from all segments of the US healthcare system, and academics working in healthcare policy, financing, and reimbursement.

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