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Managing High-Cost, Technology-Dependent Therapies: Systems for Cellular, Gene, and Advanced Biologics—A Narrative Review

Abdullah Abdulaziz Ibrahim Alghamdi [(1)] , Andualrhman Hamad Jaafari [(2)] , Bander Salem Jaber Almalki [(3)] , Abdulrhnan Saad Aldawsari [(4)] , Noor Mohammed Omar Usman [(5)] , Ashwag Ibrahim Majrashi [(6)] , Yahya Galib M. Qadhy [(7)] , Ahmed Mohammed Abu Zibnah [(6)] , Tirad Rakid Mushih Alruweaili [(8)] , Rana Ibrahim Al Musabbihi [(9)] , Sulaf Matir Sultan Alharbi [(10)] , Saeed Saad Mobark [(11)]

(1) King Abdullah Medical Complex, Ministry of Health, Saudi Arabia,
(2) First Health Cluster – Ministry of Health, Saudi Arabia,
(3) Jazan Health Cluster – Bani Malik Sector, Aldayer, Ministry of Health, Saudi Arabia,
(4) Al-Iman General Hospital – Riyadh, Ministry of Health, Saudi Arabia,
(5) azan Health – Western Sector – Khedira Health Centre, Ministry of Health, Saudi Arabia,
(6) King Salman Hospital – Riyadh, Ministry of Health, Saudi Arabia,
(7) Bish General Hospital – Jazan, Ministry of Health, Saudi Arabia,
(8) Suwair General Hospital, Ministry of Health, Saudi Arabia,
(9) Imam Abdulrahman Al-Faisal Hospital, Riyadh, Ministry of Health, Saudi Arabia,
(10) Ministry of Health Branch – Riyadh Region,, Saudi Arabia,
(11) Al-Nuaimah Primary Health Care Center, Wadi Al-Dawasir, Ministry of Health, Saudi Arabia

Abstract

Background: The advent of advanced therapy medicinal products (ATMPs), including chimeric antigen receptor T-cell (CAR-T) therapies, in vivo gene therapies, and complex biologics, represents a paradigm shift in treating cancer, genetic disorders, and autoimmune diseases. These "living drugs" and sophisticated molecules present unprecedented challenges, requiring a complete re-engineering of traditional healthcare delivery pathways. **Aim:** This narrative review synthesizes evidence from 2010-2024 on the integrated, multidisciplinary systems required to safely, effectively, and sustainably manage the clinical and operational lifecycle of high-cost, technology-dependent therapies. **Methods:** A comprehensive search of PubMed, Scopus, Web of Science, and health policy databases was conducted for peer-reviewed literature and gray literature (white papers, health system reports) addressing the operational, financial, and clinical coordination of advanced therapies. **Results:** The review identifies five critical, interdependent system pillars: (1) a robust pre-treatment patient and product pathway spanning biomarker screening, cell collection, and manufacturing; (2) a specialized pharmacy and logistics infrastructure for storage, handling, and chain of custody; (3) protocolized clinical delivery and toxicity management anchored by specialized nursing; (4) complex financial navigation and reimbursement models; and (5) coordinated scheduling and data management. Failures in any pillar risk patient harm, therapeutic failure, and catastrophic financial loss. **Conclusion:** The successful delivery of ATMPs necessitates the creation of dedicated, cross-functional "Advanced Therapy Centers of Excellence." Sustainability demands the development of standardized operational frameworks, novel value-based payment contracts, and continued interdisciplinary research to optimize these complex care ecosystems.

Keywords: advanced therapy medicinal products (ATMPs), CAR-T cell therapy, health systems delivery, multidisciplinary care, value-based healthcare

Introduction

The biomedical revolution of the 21st century has moved from the laboratory into the clinic, bringing forth a new class of treatments that are fundamentally different from conventional pharmaceuticals (Casciano et al., 2023). Chimeric antigen receptor T-cell (CAR-T) therapies, in vivo and ex vivo gene therapies, bispecific T-cell engagers, and other advanced biologics are redefining possibilities in oncology, hematology, and rare genetic diseases (June et al., 2018). These advanced therapy medicinal products (ATMPs) are often characterized as "living drugs" or highly complex biologics, possessing unique attributes: they are frequently patient-specific (autologous), have a complex and lengthy manufacturing process, require specialized handling

*Corresponding author e-mail: Trithalon2024@gmail.com (Ahmad Abdulrahman Al Mohaimeed).
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and logistics (e.g., cryopreservation at -180°C), and can induce severe and novel toxicities like cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) (Neelapu et al., 2018; Sterner & Sterner, 2021). With price tags ranging from $300,000 to over $3 million per dose, they also represent a seismic financial challenge for health systems, payers, and society (Dever & Porteus, 2017; Faraci et al., 2022).

This convergence of scientific promise with immense logistical, clinical, and economic complexity creates a critical delivery challenge. A therapy cannot save lives if the system cannot reliably deliver it (Selim et al., 2021). Traditional, siloed hospital workflows are ill-equipped to manage the orchestration required. The journey of a single CAR-T patient involves precise coordination between an outpatient clinic, an apheresis unit, a commercial or academic manufacturing facility (often thousands of miles away), a specialized pharmacy, an inpatient unit with intensive care capabilities, and multiple administrative departments handling prior authorization and reimbursement (Taylor et al., 2019; Ragoonanan et al., 2022). A single break in this "cold chain," a misstep in timing, or a delay in toxicity management can render a multi-million-dollar treatment ineffective or fatal.

This narrative review synthesizes the evolving evidence (2010-2024) on the integrated, multidisciplinary systems essential for the safe and effective delivery of high-cost, technology-dependent therapies. Moving beyond clinical efficacy trials, we analyze the requisite operational infrastructure through the lens of key support specialties: Pharmacy, Medical Laboratory, Biomedical Engineering/Equipment, Nursing, Hospital Administration, and Coordination/Medical Secretarial functions. The central thesis is that the therapeutic promise of ATMPs is contingent upon the creation of a robust, patient-centered, and resilient *delivery ecosystem*. This review will delineate the components of this ecosystem, evaluate evidence for best practices in coordination, highlight persistent challenges in financial sustainability, and propose frameworks for health systems aspiring to deliver these transformative yet demanding therapies.

Patient Qualification, Cell Collection, and the Manufacturing Bridge

The patient journey begins long before infusion, with a multi-step process that tests the resilience of institutional coordination (Table 1).

Biomarker Qualification and Apheresis

The initial role of the laboratory is paramount. For CAR-T therapies, robust flow cytometry or immunohistochemistry assays are needed to confirm the expression of the target antigen (e.g., CD19) on tumor cells, a prerequisite for treatment (Li et al., 2022). For gene therapies, genetic testing must confirm the specific mutation. Once qualified, patients undergo leukapheresis (Awasthi et al., 2023). The apheresis team, a specialized subset of the lab or nursing, must collect a sufficient yield of mononuclear cells, a process that can be challenging in heavily pre-treated, cytopenic patients (Bishop et al., 2019). The product is then shipped under strict chain-of-custody and temperature conditions to a manufacturing facility. The lab's role extends to "release testing" upon the product's return, performing sterility, viability, potency, and identity assays before the product is cleared for infusion (Tyagarajan et al., 2020; Yao & Matosevic, 2021).

The Logistics of "Vein-to-Vein" Time

This phase is a logistical labyrinth managed by program coordinators (often advanced practice providers or dedicated medical secretaries) and administrators. They secure prior authorization from insurers, a process fraught with complexity given the therapies' novelty and cost (Jagannath et al., 2023). They coordinate the precise scheduling between apheresis, manufacturing facility timelines (which can be 3-5 weeks), lymphodepleting chemotherapy, and the infusion date. Any delay can compromise patient fitness for treatment. This "vein-to-vein" time is a critical quality metric, and its management requires sophisticated project management and real-time communication systems (Shah et al., 2023). Figure 1 illustrates the end-to-end "vein-to-vein" pathway for autologous advanced therapy medicinal products (ATMPs), such as CAR-T cell therapies.

Table 1: The Multidisciplinary "Vein-to-Vein" Pathway for Autologous Cell Therapy

Phase	Key Activities	Primary Disciplines Involved	Critical Success Factors & Risks
1. Qualification & Consent	Disease staging, biomarker testing, financial clearance, comprehensive patient education.	Oncology/Hematology, Medical Lab, Administration (Financial Navigator), Nursing.	Accurate biomarker result; patient understanding of risks/costs; secured funding.
2. Collection & Shipment	Leukapheresis, product packaging, coordination with courier, chain-of-custody documentation.	Apheresis Nursing/Lab, Biomed (apheresis machine), Coordinator, Pharmacy (shipping materials).	Adequate cell yield; integrity of shipping container/temperature; flawless documentation.

3. Manufacturing & Waiting	Cell engineering at external facility; monitoring of manufacturing progress; patient health maintenance.	Coordinator, Admin (contract management with manufacturer), Treating Physician.	Manufacturing success; managing patient disease progression during wait.
4. Product Receipt & Release	Receipt of cryopreserved product, storage in vapor-phase liquid nitrogen, lab-based release testing.	Pharmacy (Receipt/Storage), Medical Lab (QC testing), Biomed (Freezer monitoring).	Unbroken cold chain; timely release test results; secure product identity.
5. Pre-Infusion Preparation	Lymphodepleting chemotherapy, final patient fitness assessment, scheduling of infusion suite.	Nursing, Pharmacy (chemotherapy), Physician, Coordinator.	Patient free of active infection; correct timing of lymphodepletion.

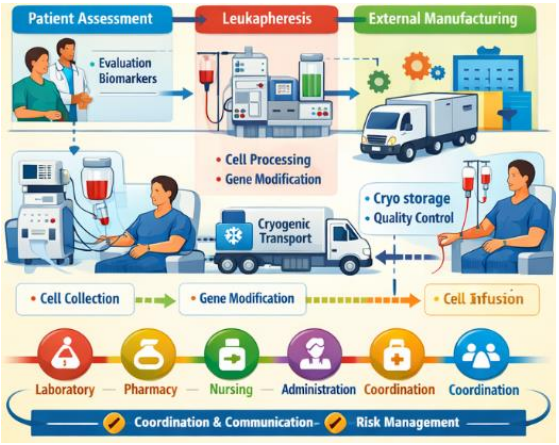

Figure 1. Integrated "Vein-to-Vein" Pathway for Advanced Therapy Medicinal Products

The Hub of Specialized Handling: Pharmacy and Biomedical Equipment Infrastructure

Upon arrival, the physical product becomes the responsibility of a highly specialized pharmacy service.

The Custodian of the "Living Drug"

The pharmacy department must establish and maintain a controlled storage ecosystem, typically involving vapor-phase liquid nitrogen freezers capable of maintaining temperatures below -150°C (Shah et al., 2020). Standard pharmacy refrigerators are insufficient. Pharmacists are responsible for the chain-of-custody, verifying patient-specific identifiers at every handoff. On infusion day, they oversee the meticulous thawing process—often using precision water baths—and reconstitution, if required (Qayed et al., 2022). They must coordinate the timed delivery of the product to the bedside, as viability decreases rapidly post-thaw. This requires a seamless handoff protocol between pharmacy, the coordinator, and the infusion nurse (Nezvalova-Henriksen et al., 2023).

Ensuring Infrastructure Reliability

The role of biomedical engineering is to ensure the absolute reliability of the specialized equipment underpinning this process. This includes not only the liquid nitrogen freezers but also continuous temperature monitoring systems with remote alarms to prevent catastrophic storage failures (Piemonti et al., 2023). They also maintain the apheresis machines, precision thawing devices, and the vital sign monitoring equipment critical for post-infusion care. Preventive maintenance and immediate response capabilities are non-negotiable, as equipment failure can result in the loss of an irreplaceable, life-saving product (Gentile et al., 2020).

The Nursing-Led Infusion and Toxicity Management

The infusion is not a routine event but a high-stakes procedure requiring expert nursing care within a setting prepared for rapid escalation.

Protocolized Infusion and Frontline Toxicity Surveillance

Nurses trained in advanced therapy protocols administer the infusion, closely monitoring for acute reactions. Their most critical role begins post-infusion as the primary surveillants for CRS and ICANS (Steinbach et al., 2023). They employ standardized assessment tools like the American Society for Transplantation and Cellular Therapy (ASTCT) CRS grading system to monitor fever, hypotension, and hypoxia, and tools like the Immune Effector Cell Encephalopathy (ICE) score to assess for neurotoxicity (Lee et al., 2019). Their vigilant assessments trigger protocolized interventions, often involving the administration of tocilizumab (an IL-6 receptor antagonist) and corticosteroids. This nursing role demands advanced critical thinking and seamless communication with the intensivist and pharmacy teams (Cunningham et al., 2021).

Enabling a Safe Clinical Environment

Hospital administration must resource and credential a dedicated clinical space, which may be an inpatient unit with ready access to intensive care or a specialized outpatient infusion center with immediate escalation pathways. They are responsible for ensuring staff are adequately trained and that institutional policies support the unique requirements of these therapies, including the management of novel toxicities (Mahadeo et al., 2019).

Financial Navigation, Reimbursement, and Value Assessment

The astronomical cost of these therapies threatens their accessibility and institutional viability, demanding innovative administrative and financial strategies (Table 2).

Navigating a Complex Financial Ecosystem

Financial navigators and administrators work to secure patient-specific funding through a patchwork of commercial insurance, Medicare, Medicaid, and manufacturer patient assistance programs (Dusetzina et al., 2019). Given the high upfront cost, hospitals often face severe cash flow challenges, especially under diagnosis-related group (DRG) payments that may not fully cover the therapy's price. This has led to the exploration of alternative payment models, such as outcomes-based agreements (OBAs), where reimbursement is partially tied to patient response at a predefined timepoint (e.g., 6-month remission) (Bach & Pearson, 2015; Neumann et al., 2021). Negotiating and managing these contracts requires sophisticated data collection on patient outcomes.

Data Management and the Role of the Coordinator/Medical Secretary

The medical secretary or clinical coordinator is the central nervous system of the entire pathway. They manage the intricate, multi-departmental calendar; serve as the primary point of contact for the patient, manufacturer, and internal teams; and ensure all documentation—clinical, logistical, and financial—is complete and accurate (Fujiwara et al., 2022). Their role in maintaining data integrity is crucial for clinical follow-up, regulatory reporting (to agencies like the FDA's REMS programs), and for providing the outcomes data necessary for value-based contracts. Figure 2 presents the five interdependent pillars required for the sustainable delivery of high-cost, technology-dependent therapies: (1) clinical–operational integration, (2) technical and infrastructure resilience, (3) financial and reimbursement architecture, (4) safety and quality governance, and (5) data management and coordination.

Table 2: Pillars of a Sustainable Advanced Therapy Delivery Ecosystem

Pillar	Core Components	Key Performance Indicators (KPIs)	Threats to Sustainability
Clinical & Operational Integration	Multidisciplinary team with defined roles; standardized protocols (SOPs) for all steps; dedicated coordinator.	Vein-to-vein time; manufacturing success rate; protocol deviation rate.	Siloed departments; lack of clear governance; staff burnout/turnover.
Technical & Infrastructure Resilience	GMP-compliant pharmacy storage; validated, monitored equipment; redundant systems for power/data.	Freezer temperature excursions; equipment downtime; product viability at infusion.	Capital cost of infrastructure; lack of biomedical engineering support; single points of failure.
Financial & Reimbursement Architecture	Expert financial navigation; diversified payer mix; exploration of OBAs and bundled payments.	Rate of denied authorizations; days in accounts receivable; success of OBA reconciliations.	Inadequate DRG payments; payer coverage restrictions; administrative burden of OBAs.
Safety & Quality Governance	Prospective toxicity management protocols; integrated EHR tools for monitoring; robust AE reporting.	Incidence of severe (Grade 3+) CRS/ICANS; time to intervention; 100-day treatment-related mortality.	Inadequate staff training; failure to recognize early toxicity; communication breakdowns.
Data Management & Coordination	Centralized tracking system (e.g., database); coordinator-led scheduling; outcomes registry.	Data completeness for key milestones; patient satisfaction scores; follow-up data capture for OBAs.	Reliance on manual tracking; poor EHR integration; lack of analytics capacity.

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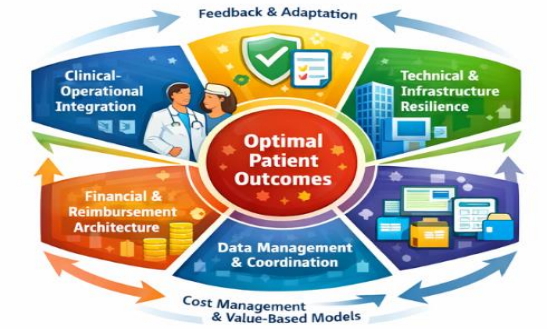

Figure 2. Five-Pillar Ecosystem Enabling Sustainable Delivery of High-Cost Advanced Therapies

Building the Advanced Therapy Center of Excellence

The evidence compels a singular conclusion: delivering advanced therapies requires a deliberately constructed, system-wide program, not an ad-hoc addition to existing services. The most successful models are organized as Advanced Therapy Centers of Excellence, characterized by formal governance, dedicated resources, and an ingrained culture of interdisciplinary collaboration (Dulan et al., 2020; Kelkar et al., 2023). These centers view the patient pathway as a single, integrated process, breaking down traditional departmental barriers.

Future progress depends on several key developments. First, operational research must move beyond descriptive case studies to produce standardized frameworks and benchmarks for vein-to-vein time, toxicity management efficiency, and cost-of-delivery (Jørgensen & Kefalas, 2021). Second, the financial model must evolve. Policymakers, payers, and manufacturers must collaborate on sustainable payment solutions that balance innovation with affordability, such as annuity-based payments or broader adoption of conditionally staged payments linked to long-term outcomes (Bishai et al., 2013). Third, health information technology must catch up. EHRs need specialized modules to track cell therapy products from collection to infusion, automate toxicity screening alerts, and capture structured data for outcomes reporting (Shah et al., 2020). Finally, education and training for all involved disciplines—from the apheresis technician to the financial counselor—must be standardized and certified to ensure a competent workforce (Ravindranath et al., 2022).

Conclusion

Cellular, gene, and advanced biologic therapies offer hope for conditions once deemed untreatable. Yet, their complexity renders them vulnerable to the frailties of fragmented healthcare systems. This review underscores that their clinical success is inextricably linked to operational excellence, financial innovation, and multidisciplinary synergy. The challenge for health systems is no longer merely one of clinical adoption, but of systemic adaptation. It demands investment not just in drugs, but in the less-visible infrastructure of coordination, cold chains, data systems, and trained personnel. By constructing resilient, patient-centered, and financially intelligent delivery ecosystems, we can ensure that the revolutionary promise of this new therapeutic frontier is fully realized for the patients who need it most. The era of the "living drug" has dawned; now, we must build the living system capable of sustaining it.

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*Corresponding author e-mail: Trithalon2024@gmail.com (Ahmad Abdulrahman Al Mohaimeed).
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