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REVIEW ARTICLE

Pharmacovigilance in Cell and Gene Therapy: Evolving Challenges in Risk Management and Long-Term Follow-Up

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Abstract

Cell and gene therapies, including CAR T-cells, CRISPR-based genome editing, and next-generation viral and non-viral delivery platforms, are transforming treatment paradigms across cancer, rare genetic disorders, immune dysregulation, and neurodegenerative disease. These therapies offer curative potential but also present safety challenges owing to prolonged biological activity, systemic immune engagement, and lasting genomic alterations. This review examines the range of related toxicities, including immune complications, genotoxicity, and organ-specific effects, with attention to atypical presentations, gaps in clinical trial safety capture, and disparities in global long-term follow-up infrastructure. Central to our analysis is a risk-adaptive, digitally enabled pharmacovigilance model that incorporates real-world data, artificial intelligence-based signal detection, and seamless pediatric-to-adult follow-up to proactively protect patients while supporting innovation. Integrated safety dashboards, pediatric transition roadmaps, and predictive monitoring tools are proposed as practical solutions to improve coordination among sponsors, regulators, and clinical sites. We also outline best practices for aligning risk evaluation and mitigation strategies with risk management plans and examine how wearable biosensors, electronic patient-reported outcomes, and multi-omics biomarkers contribute to near real-time safety surveillance. Ethical priorities such as informed consent, data privacy, and equitable access are addressed throughout. By positioning pharmacovigilance as a proactive and predictive foundation within the therapeutic landscape, this review offers a forward-looking blueprint to advance innovation while ensuring long-term patient safety.

1 Introduction

Cell and gene therapies (CGTs) have emerged as transformative modalities in modern medicine, offering the potential to cure a wide range of genetic and malignant disorders. Unlike traditional pharmaceutical treatments that primarily address symptoms, CGTs target the root causes of disease by modifying or correcting genetic defects at the cellular level. This precision approach enables durability and, in many cases, curative outcomes for conditions previously deemed refractory to conventional therapies.

Over the past decade, the development and regulatory approval of cell and gene-based therapies have rapidly advanced. On 8 December 2023, the US Food and Drug

Key Points

Cell and gene therapies are transforming treatment for cancer, rare genetic disorders, immune diseases, and neurological conditions, but they present unique and sometimes long-lasting safety challenges.

Modern pharmacovigilance frameworks that integrate real-world data, artificial intelligence, and structured long-term follow-up can detect and mitigate safety risks earlier, improving patient protection while meeting evolving expectations of global regulatory authorities.

Coordinated solutions such as integrated safety dashboards, wearable monitoring devices, pediatric-to-adult care transition plans, and ethically grounded approaches can align clinicians, researchers, regulators, and policymakers to safeguard patients while enabling innovation.

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Administration (FDA) approved two landmark therapies for sickle cell disease (SCD) in patients aged 12 years and older: exagamglogene autotemcel (Casgevy) and lovotibeglogene autotemcel (Lyfgenia). Casgevy, developed using CRISPR/Cas9 genome-editing, modifies the BCL11A erythroid enhancer in autologous hematopoietic stem cells (HSCs) to increase fetal hemoglobin, thereby reducing sickling of red blood cells. In contrast, Lyfgenia utilizes a lentiviral vector to insert a modified β-globin gene (βA-T87Q), promoting production of an anti-sickling hemoglobin variant. These approvals mark the first gene-editing and lentiviral-based therapies for SCD [1–3]. More recently, on 2 August 2024, the FDA granted accelerated approval to afamitresgene autoleucel (Tecelra), a genetically engineered T-cell receptor (TCR) therapy targeting the MAGE-A4 antigen. Tecelra is indicated for HLA-A*02-positive adults with unresectable or metastatic synovial sarcoma whose tumors express MAGE-A4, and represents the first FDA-approved TCR-based gene therapy for a solid tumor [4].

Chimeric antigen receptor (CAR) T-cell therapies have ushered in a new era in oncology, transforming the landscape of cell-based cancer treatment. Approved agents targeting CD19 and BCMA have demonstrated high response rates and durable remissions in hematologic malignancies such as B-cell acute lymphoblastic leukemia, diffuse large B-cell lymphoma, and multiple myeloma [5, 6]. The pharmacovigilance strategies developed for CAR T-cell products have guided safety monitoring practices across the CGT field [7]. As a result, insights from CAR T-cell therapy continue to shape the design, risk mitigation, and long-term follow-up strategies of emerging CGT platforms [8].

Furthermore, gene therapies such as delandistrogene moxeparvovec (Elevidys) for Duchenne muscular dystrophy (DMD), atidarsagene autotemcel (Lenmeldy) for metachromatic leukodystrophy, and eladocagene exuparvovec (Upstaza) for aromatic L-amino acid decarboxylase (AADC) deficiency further demonstrate the breadth of CGT applications across neuromuscular and neurodevelopmental disorders [9–11].

Despite their transformative potential, CGTs introduce safety challenges that differ significantly from those associated with traditional small- or large-molecule drugs. These complexities stem from the biological sophistication of CGTs, their prolonged persistence in the body, and their capacity to trigger both immune and genomic disruptions. The immunogenic profile of these therapies represents a double-edged sword: while immune activation is essential for therapeutic efficacy, it also underlies serious toxicities, including immune-mediated events such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Advances in understanding the pathophysiology of these complications, particularly the roles of cytokines such as interleukin (IL)-6 and interferon (IFN)-γ, have supported earlier intervention and more refined safety strategies [12, 13]. Still, the risk landscape remains dynamic and highly product-specific, with the potential for these conditions to escalate into life-threatening systemic inflammation and neurotoxicity without prompt recognition and intervention.

The safety profile is further complicated by delayed toxicities. Persistent expression of gene-modified cells or vectors can lead to long-term consequences, including secondary malignancies. Documented cases of T-cell leukemia developing months or even years after treatment emphasize the critical need for extended post-treatment surveillance [14, 15]. In addition, certain delivery routes, such as intrathecal administration for central nervous system targeting, introduce procedural risks that require rigorous management and specialized oversight [16, 17].

Gene-editing platforms such as CRISPR-Cas9, while engineered for precision, may introduce off-target modifications, large deletions, or chromosomal rearrangements that disrupt normal gene function. Immune responses to bacterial Cas9 proteins can lead to hypersensitivity, systemic inflammation, or even anaphylaxis in rare cases [18, 19]. Similarly, delivery systems such as adeno-associated viruses (AAVs) and lipid nanoparticles (LNPs) introduce hepatotoxicity, thrombocytopenia, and complement activation. The use of integrating viral vectors, particularly retroviruses, carries the risk of insertional mutagenesis, which has been implicated in leukemia cases observed during early X-linked severe combined immunodeficiency (X-SCID) trials. [20]. These considerations elevate the critical role of pharmacovigilance (PVG) across the CGT lifecycle. A robust PVG system ensures early detection, assessment, and mitigation of adverse events (AEs), supporting both patient safety and regulatory compliance. Continuous monitoring is essential to identify short- and long-term risks, particularly in therapies with sustained biological activity.

Risk management plans (RMPs) are essential for reducing adverse outcomes. Tailored to a product's mechanism of action and risk profile, they must be regularly updated to reflect new safety data. Real-world evidence (RWE) from post-marketing surveillance (PMS) adds valuable insight beyond clinical trials by capturing safety outcomes in diverse patient populations [21, 22]. Timely AE reporting and signal detection are central components of PVG in CGTs. These processes enable prompt safety actions and promote transparency among regulators, healthcare providers, manufacturers, and patients—helping to maintain public trust [23, 24].

As cell and gene-based therapies evolve to incorporate advanced genome editing technologies, PVG must move

beyond static post-market reporting toward adaptive, predictive safety frameworks. Leveraging artificial intelligence (AI)-driven analytics on structured real-world data (RWD), strengthening data capture infrastructures across clinical development and post-approval settings, and fostering proactive collaboration among regulators, healthcare providers (HCPs), manufacturers, and patients will be essential for early signal detection and sustained oversight of CGT safety [25, 26].

With the continued evolution of CGTs, it is now widely acknowledged that pharmacovigilance (PVG) should be embedded early in development, beginning at research and manufacturing, rather than being limited to post-marketing oversight. Emerging strategies emphasize the integration of predictive safety modeling—including multi-omics profiling, AI-driven simulations, and early manufacturing quality surveillance—prior to first-in-human exposure. Variability in vector potency, gene editing efficiency, and cellular phenotypes during the chemistry, manufacturing, and controls (CMC) process can introduce unanticipated safety risks, underscoring the need for early and continuous collaboration between PVG and CMC teams. Adaptive platform trials and real-time incorporation of RWE are increasingly utilized to dynamically refine safety strategies during clinical development. Notably, our group recently published comprehensive reviews exploring gene therapy and immune modulation in oncology and beyond, with particular emphasis on emerging strategies, expanding clinical applications, and evolving long-term safety considerations [27, 28]. Embedding pharmacovigilance as a proactive, cross-functional discipline throughout the CGT product lifecycle can enhance early signal detection, optimize long-term follow-up planning, and ultimately improve patient outcomes across diverse populations.

Drawing on the authors' collective experience as a contract research organization (CRO) with integrated medical, safety, and regulatory functions, this review provides pragmatic insights into the evolving PVG landscape. CROs operate at the nexus of diverse stakeholders, offering a unique advantage across therapeutic modalities, geographic regions, and regulatory environments. This broad exposure enhances their ability to detect emerging safety trends that may be obscured in siloed settings. A resilient and forward-looking PVG infrastructure will be critical to unlocking the full therapeutic potential of CGTs while safeguarding patient well-being. This review highlights several distinctive advances, including a CRO-based framework for real-time, AI-enhanced pharmacokinetic/pharmacodynamic (PK/PD) and safety-monitoring dashboards; a comprehensive pediatric transition-of-care roadmap aligning developmental milestones with long-term follow-up (LTFU); and a comparative evaluation of global LTFU frameworks extending beyond the USA and EU, alongside broader insights into predictive analytics, registry integration, and ethical considerations shaping the future of PVG in CGTs.

2 Acute and Delayed Toxicities in Cell and Gene Therapies

CGTs are transforming disease management across oncology, rare disorders, and immune dysregulation. Yet their complex biology gives rise to safety profiles that diverge from traditional therapies—not only in severity and timing but in atypical presentations that challenge conventional diagnostic frameworks. This section re-examines acute and delayed toxicities in CGTs, with emphasis on evolving patterns, diagnostic nuance, and real-world monitoring strategies. CRS and ICANS are among the most common acute toxicities associated with CAR T-cell therapies. CRS typically manifests within the first few days following infusion, most commonly within 1–7 days—and results from supra-physiological immune activation and a massive surge in pro-inflammatory cytokines, including IL-6, IFN-γ, tumor necrosis factor (TNF)-α, and IL-1β. CRS typically presents with fever, hypotension, hypoxia, and signs of organ dysfunction. According to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus guidelines, CRS severity is no longer graded by the presence of fever alone, but rather by the most severe clinical manifestations—specifically, the degree of hypotension and hypoxia. This shift enables a more objective and consistent assessment of CRS severity across clinical trials and real-world settings [13]. Diagnostic evaluation includes serial measurements of pro-inflammatory cytokines (e.g., IL-6, IFN-γ, TNF-α, IL-1β, soluble IL-2 receptor) alongside coagulation studies (fibrinogen, prothrombin time [PT], and partial thromboplastin time [PTT]) to capture both inflammatory and consumptive coagulopathy components. Management is tailored to CRS severity. Tocilizumab, with or without corticosteroids, is typically initiated for grade $\geq$ 2 CRS per current treatment algorithms [29]. In more severe cases (grades 3–4), intensive care measures such as vasopressor support, mechanical ventilation, and renal replacement therapy may be required [29]. Current investigations aim to integrate early cytokine signatures and clinical biomarkers into predictive models—such as the multi-cytokine panel identified by Teachey et al. [30], which associated elevated IL-6, IFN-γ, IL-10, and G-CSF with severe CRS, and the classification-tree algorithm developed by Hay et al. [31], which uses early fever and serum MCP-1 levels to anticipate grade $\geq$ 4 CRS, enabling preemptive interventions and refined risk stratification. Atypical presentations of CRS following CAR T-cell or gene therapies are increasingly recognized. In some cases, patients develop hypotension and organ dysfunction consistent with CRS but remain afebrile, complicating the

diagnosis since fever is typically the earliest clinical sign [32]. Moreover, CRS onset may be delayed beyond the usual 1–7 days post-infusion, with cases reported up to 2–3 weeks after therapy [33]. These atypical courses can resemble other hyperinflammatory conditions, particularly bacterial sepsis and hemophagocytic lymphohistiocytosis (HLH), owing to overlapping features such as shock, cytopenias, and systemic inflammation [34]. To distinguish CRS from these entities, HCPs may consider biomarkers. Procalcitonin (PCT), for instance, tends to be markedly elevated in bacterial sepsis compared with sterile CRS [35]. In contrast, extraordinarily high ferritin levels (often > 10,000 µg/L) combined with coagulopathy, particularly hypofibrinogenemia, are more indicative of HLH or macrophage activation syndrome (MAS) than isolated CRS [36]. However, given potential biomarker overlaps, interpretation must be contextualized within the full clinical picture to ensure accurate diagnosis and appropriate management [37, 38].

ICANS can occur independently of, concurrently with, or following CRS, most often emerging 3–10 days after infusion. Clinically, it spans a spectrum from mild confusion and aphasia to seizures and, in rare cases, cerebral edema. Grading relies on the ASTCT consensus framework, which uses the immune effector cell-associated encephalopathy (ICE) score—assessing orientation, naming, command following, writing, and attention—supplemented by level of consciousness, seizure activity, motor findings, and neuroimaging or electroencephalogram (EEG) evidence of cerebral edema [13]. These objective criteria, embraced by both SITC and ASTCT, ensure uniform severity assessment across trials and inform monitoring frequency and intervention thresholds [39]. From a pathophysiological perspective, endothelial activation and blood–brain barrier (BBB) disruption appear to underlie severe neurotoxicity following CAR T-cell therapy, emphasizing the importance of early recognition and tailored supportive care strategies such as corticosteroids and anticonvulsants, while investigational therapies continue to target the underlying neuroinflammatory cascade [40].

In pediatric CAR T- cell recipients, the Cornell Assessment of Pediatric Delirium is used alongside the ICE score to accommodate developmental differences in baseline neurologic function [41]. High-dose corticosteroids remain the cornerstone of ICANS management—tocilizumab shows limited benefit for neurotoxicity—and are initiated promptly upon grade ≥ 2 events [42]. Supportive measures include seizure prophylaxis or treatment with antiepileptic agents and aggressive control of elevated intracranial pressure in severe cases [33]. Emerging biomarkers such as serum neurofilament light chain (NfL) and S100B are under investigation for early risk stratification: elevated pre-infusion NfL correlates with subsequent moderate-to-severe ICANS [43], while rising S100B levels may reflect BBB disruption [44, 45]. Reports of central nervous system (CNS) relapse in pediatric acute lymphoblastic leukemia (ALL) patients treated with blinatumomab, an agent with minimal CNS penetration, highlight the importance of vigilant neurologic monitoring and tailored prophylactic strategies in CGT recipients [46, 47].

ICANS is a potentially serious neurological complication of cell therapies, characterized by symptoms such as confusion, aphasia, tremors, seizures, and, in severe cases, cerebral edema. Although ICANS typically presents within the first week of post-infusion, often in conjunction with CRS, peer-reviewed reports have documented several atypical patterns. For example, delayed onset beyond 10 d, and even as late as 3 to 4 weeks after therapy, has been observed [48, 49], though such cases occur in only about 10% of patients [49]. Moreover, while ICANS usually follows or accompanies CRS, neurotoxicity can also develop in its absence, with patients exhibiting minimal CRS symptoms or even severe ICANS after only a transient fever [49, 50]. In addition, although most cases involve diffuse encephalopathy with confusion and global cognitive impairment, some patients present with isolated focal neurologic deficits, such as deep focal motor weakness or visual disturbances, as the primary manifestation [50]. Furthermore, emerging reports describe unusual variants, including parkinsonian movement disorders and acute myelopathy leading to paralysis, often occurring after initial recovery from typical ICANS or CRS [51]. Moreover, pediatric and adult patients display broadly similar incidence and timing, with pediatric cases reported in roughly 25–40% (with approximately 10–15% being severe) [52], comparable to adult rates [53]; however, younger age may be a risk factor for severe neurotoxicity, and children may require modified assessment tools.

Overall, these atypical presentations of CRS and ICANS highlight the need for vigilant, prolonged monitoring to detect delayed, CRS-independent, or focal neurotoxic effects across all age groups. High-dose corticosteroids are the backbone of therapy for grade ≥ 3 CRS and ICANS, but their prolonged use increases the risk of profound immunosuppression, opportunistic infections, and may impair CAR T-cell persistence and anti-tumor efficacy [54, 55]. In clinical practice, balancing this risk with toxicity control requires vigilant immune monitoring, including quantification of CAR T-cell counts and cytokine profiles after steroid administration to ensure sustained therapeutic activity [56]. Despite the availability of ASTCT consensus-based management algorithms [13], a subset of patients develops refractory CRS and ICANS that require intensive care unit (ICU) level support.

RWD show that CRS occurs in up to 90% of CD19 CAR T-cell recipients, with 10–30% experiencing grade ≥ 3 severity, while ICANS occurs in 30–70% of cases, including 15–40% that are classified as severe [57]. These critically ill

patients often face additional complications such as tumor lysis syndrome, immune effector cell–associated HLH-like syndromes, cardiovascular events, severe infections, acute kidney injury, and multi-organ dysfunction. This highlights the need for proactive risk stratification and biomarker-guided monitoring, including early tracking of IL-2, IL-6, IL-10, and IFN-γ, to facilitate timely interventions and improve clinical outcomes.

Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) is a rare but life-threatening complication that can occur after immune effector cell (IEC) therapies such as CAR T-cells or bispecific T-cell engagers. Clinically, IEC-HS resembles secondary HLH, but its pathogenesis is driven by sustained IEC activation rather than inherited cytotoxic defects or infection [58]. It most often arises during the resolution phase of CRS, when engineered T cells continue to proliferate and secrete inflammatory cytokines [58]. Patients typically present with persistent fevers and a rapid rise in ferritin levels, often exceeding 10,000 ng/mL. They may also have severe cytopenias affecting at least one blood cell lineage, liver injury indicated by elevated transaminases, and signs of coagulopathy such as low fibrinogen and high D-dimer levels. In some cases, evidence of macrophage activation, such as hemophagocytosis seen on bone marrow biopsy, may also be observed [58]. Diagnostic recommendations blend elements of the ASTCT consensus CRS grading scale with modified HLH-2004 criteria, emphasizing exclusion of alternative causes (e.g., severe infection with herpes simplex virus [HSV], cytomegalovirus [CMV], Epstein–Barr virus [EBV], and human herpesvirus 6 [HHV-6] disease progression) [59]. Key laboratory triggers include hyperferritinemia, elevated soluble IL-2 receptor (sCD25), and high levels of IFN-γ and IL-18, although real-time cytokine assays remain investigational. First-line treatment involves high-dose corticosteroids. If the condition does not respond to steroids or progresses rapidly, cytokine-directed therapies are used. These include anakinra, which blocks the IL-1 receptor, and emapalumab, a monoclonal antibody that targets IFN-γ [60]. Ongoing studies are evaluating predictive biomarkers—such as CXCL9, IL-18, and sCD163—to enable earlier diagnosis and risk stratification, with the goal of initiating preemptive therapy and improving survival [61, 62].

Immune effector cell-associated hematotoxicity (ICAHT) is a distinct toxicity category characterized by delayed or persistent cytopenias, including neutropenia, anemia, and thrombocytopenia, which occur or continue beyond 30 days after CAR T-cell infusion, in the absence of disease relapse or conditioning-related marrow suppression [63, 64]. Late ICAHT predisposes patients to severe infections, transfusion dependence, and bleeding events, contributing substantially to nonrelapse morbidity and mortality [64]. ICAHT involves bone marrow injury from lymphodepleting chemotherapy, cytokine-mediated suppression of hematopoiesis, particularly by IL-6 and IFN-γ, and immune-driven destruction of hematopoietic progenitor cells [64]. Diagnosis requires exclusion of alternative etiologies, including disease progression, viral reactivations such as CMV and EBV, or emerging myelodysplastic changes, typically through bone marrow biopsy and targeted infectious workup [63]. Management is mainly supportive and includes red blood cell and platelet transfusions, the use of growth factors such as G-CSF or thrombopoietin receptor agonists to stimulate blood cell production, and antimicrobial prophylaxis to reduce the risk of infection. In refractory cases, infusion of previously harvested autologous HSCs has restored multilineage counts in small series [65]. Risk stratification using scores such as CAR HEMATOTOX, which incorporates baseline cytopenias and inflammatory markers, helps identify high-risk patients undergoing CAR T-cell therapy and guide early interventions [64]. Ongoing research is focused on validating biomarkers (e.g., CXCL9, soluble IL-2 receptor) for early risk prediction and refining management algorithms to improve outcomes in ICAHT [62, 66].

One key approach to reduce risk and improve access in CAR T-cell therapy targets the lengthy, patient-specific manufacturing process. Autologous CAR T-cell production can take several weeks and may fail in patients with rapidly progressing disease. To overcome these limitations, allogeneic or "off the shelf" CAR T-cell therapies, engineered from healthy donor T cells and edited to eliminate T-cell receptors and HLA molecules, are advancing through late-stage clinical trials and show promising efficacy and safety profiles. These universal platforms aim to provide scalable, immediately available treatments while reducing the risk of graft-versus-host disease [12, 67]. Parallel efforts employ precise genome-editing platforms (CRISPR/Cas9, TALENs) to knock out endogenous T-cell receptors and HLA molecules, creating universal donor cells that retain specific antitumor activity while minimizing alloreactivity [68]. Concurrently, detailed studies of CRS pathophysiology highlighting IL-6 and IFN-γ as central mediators have refined intervention timing and broadened therapeutic options [69]. Early administration of tocilizumab (anti-IL-6R) at lower CRS grades now prevents progression to severe toxicity without compromising efficacy [70]. Moreover, preclinical and case-based evidence supports targeting IFN-γ in refractory CRS or CAR T-associated HLH–like syndromes: emapalumab (anti-IFN-γ) has successfully abrogated life-threatening hyperinflammation in patients unresponsive to tocilizumab and steroids [71]. Together, scalable "off-the-shelf" manufacturing and mechanism-guided cytokine blockade represent a shift toward more rapid, predictable, and safer CGT delivery models, potentially shortening treatment timelines and further mitigating acute toxicities [72].

Gene editing and gene transfer approaches introduce unique early safety concerns that differ from those seen with immune effector cell therapies. CRISPR-Cas9-based editing, in particular, can cause unintended DNA damage, including off-target double-strand breaks and large on-target genomic rearrangements, such as deletions, inversions, and translocations, as demonstrated in both preclinical models and human cells [73, 74]. Because Cas9 and related nucleases are derived from bacteria, both innate and adaptive immune responses may be triggered; studies have identified preexisting T- and B-cell immunity against Cas9 proteins, and rare cases of severe hypersensitivity, including anaphylaxis, have been reported [75]. Recombinant AAV vectors, while generally well tolerated, are associated with transient hepatocellular injury. Clinical trials have documented dose-dependent transaminase elevations, occasionally progressing to acute liver failure, typically managed with corticosteroids or other immunosuppressants [76]. In addition, systemic AAV administration can activate both classical and alternative complement pathways, resulting in thrombotic microangiopathy, consumptive thrombocytopenia, and coagulopathy; complement inhibitors such as eculizumab have shown potential in mitigating these adverse effects [77].

3 Long-Term Safety and Risk Management in Cell and Gene Therapies

Building on the management of acute events, long-term safety surveillance in CGTs has evolved to address a complex spectrum of delayed toxicities. With improved patient survival and extended follow-up, HCPs are increasingly focused on persistent hematologic abnormalities, secondary malignancies, cardiovascular complications, and immune-mediated sequelae that emerge weeks to years after treatment.

Persistent cytopenias remain among the most common delayed effects following CAR T-cell therapy, with prolonged neutropenia, anemia, and thrombocytopenia reported beyond 6 months in a substantial subset of patients. These hematologic deficits may contribute to an increased susceptibility to infection-related complications, which frequently co-occur in the post-treatment period [78, 79]. These prolonged cytopenias not only increase bleeding risk and transfusion dependence but also require careful diagnostic workup, including bone marrow biopsy, multiparameter flow cytometry, and cytogenetic analysis, to distinguish treatment-related marrow suppression or immune-mediated hematotoxicity from disease relapse or evolving myelodysplasia [79–81]. As a results of cytopenias, infections affect 20–60% of CAR T-cell recipients. Early infections (occurring within days 0–30) are predominantly bacterial, driven by profound neutropenia and mucosal barrier injury, whereas later phases shift toward viral reactivations, such as CMV, EBV, and HHV-6 (a neurotropic virus associated with encephalitis), as well as opportunistic fungi or encapsulated bacteria due to sustained B-cell aplasia and hypogammaglobulinemia [82–84]. Proactive supportive measures, including G-CSF for neutropenia, red cell and platelet transfusions, intravenous immunoglobulin (IVIG) for hypogammaglobulinemia, and tailored antimicrobial prophylaxis, are critical to reducing infection-related non-relapse mortality, which accounts for over half of all post-CAR T deaths [83–86].

The risk of secondary malignancies remains a concern in cell and gene therapies, particularly with approaches that use integrating vectors [87]. Early gene therapy trials revealed the potential for insertional oncogenesis leading to leukemia. Although modern CAR T-cell strategies now use self-inactivating lentiviral vectors to mitigate this risk, delayed malignancies, including rare T-cell neoplasms, have still been documented [87]. The SCID-X1 trials serve as a cautionary example, where several pediatric patients developed T-cell leukemia following treatment with retroviral vectors due to integration near proto-oncogenes such as *LMO2*, *CCND2*, and *BMI1*, underscoring the genotoxic risks associated with integrating vector platforms [88]. As a result, regulatory agencies now mandate follow-up periods of up to 15 years for high-risk vector systems [89].

To reduce these risks, alternative strategies under investigation include non-viral delivery systems, such as Sleeping Beauty and PiggyBac, which use transposons to insert genetic material, as well as genome editing tools such as CRISPR-Cas9. While these methods offer promising advantages, they also carry risks of off-target effects and genomic instability that must be carefully managed [90, 91]. Genome editing tools can inadvertently disrupt tumor suppressor genes such as *TP53*, and preclinical studies have shown that p53 loss may be selected during CRISPR-Cas9 editing, potentially predisposing cells to secondary clonal outgrowth [92].

Given the risks associated with CAR T-cell and gene therapies, long-term safety surveillance is essential to maintain a favorable benefit–risk profile and preserve the curative potential of these advanced treatments [88, 93]. Recent preclinical and clinical findings suggest that insertional mutagenesis is not confined to retroviral systems. Reports from the FDA and academic groups have linked PiggyBac vector insertions near *PBX2*, as well as leukapheresis samples containing *TET2* or *JAK3* mutations, with clonal expansion and post-treatment leukemogenesis [94]. These findings emphasize the need to incorporate baseline leukapheresis genomic profiling, vector integration site mapping, and clonal tracking using cell-free DNA or single-cell RNA sequencing into pharmacovigilance frameworks for cell and gene therapies.

Cardiovascular toxicity has emerged as a critical long-term safety concern across multiple CGT platforms, including CAR T-cell therapies, AAV-based gene therapies, and CRISPR-mediated interventions [95]. Unlike the acute cardiac events linked with cytokine surges during the initial treatment phase, delayed cardiovascular toxicity is characterized by a broader range of manifestations. Studies have shown that around 10% of patients undergoing CAR T-cell therapy may develop new heart problems, such as cardiomyopathy or heart failure, especially if they experience severe CRS. Similarly, significant heart rhythm disturbances have been observed in patients with severe CRS [96–98]. The underlying mechanisms involve interleukin-6-driven myocardial depression reminiscent of septic cardiomyopathy, persistent systemic inflammation, immune cell infiltration into myocardial tissue, and endothelial dysfunction that leads to microvascular injury [96, 99]. In addition, AAV-based gene therapies have been linked to immune-mediated myocarditis, exemplified by a fatal case reported in DMD, as well as thrombotic microangiopathy related to complement activation and endothelial injury [96]. Similar concerns are emerging for other gene-editing platforms. Although clinical data for CRISPR-based therapies remain limited, immunogenic reactions observed in early studies raise the possibility of analogous cardiovascular risks [97, 100].

Given these potential complications, a rigorous cardiovascular surveillance strategy is indispensable throughout the treatment continuum. Pretreatment evaluations should include a detailed cardiac history, baseline electrocardiograms (ECG), echocardiography, and biomarker assessment (e.g., troponin, B-type natriuretic peptide [BNP]), especially for patients with preexisting cardiac conditions [101]. During and after therapy, serial monitoring with cardiac enzymes and imaging (such as echocardiography or cardiac magnetic resonance imaging [MRI] at 6–12-month intervals and annually thereafter) is recommended to detect early signs of systolic dysfunction, such as a $> 10\%$ decline in left ventricular ejection fraction (LVEF). When dysfunction is identified, timely initiation of cardioprotective interventions (e.g., ACE inhibitors or beta-blockers) and management guided by a multidisciplinary team are key to mitigating these delayed cardiovascular events [101].

Delayed immune dysregulation following immunotherapy and CGTs can manifest as autoimmune toxicities, most commonly presenting as immune thrombocytopenia (ITP) or autoimmune hemolytic anemia (AIHA), typically emerging 4–16 weeks after CAR T-cell infusion. Patients often present with isolated thrombocytopenia or signs of hemolysis—such as a positive direct antiglobulin test, elevated LDH, and low haptoglobin. First-line management generally includes high-dose corticosteroids and IVIG, while rituximab is considered for steroid-refractory cases [102]. Endocrine complications, including thyroiditis, primary adrenal insufficiency, and hypophysitis, occur in approximately 5–10% of CAR T-cell therapy recipients and often emerge months after treatment [103]. Thyroiditis typically follows a biphasic pattern, beginning with transient thyrotoxicosis and progressing to hypothyroidism. In contrast, adrenal and pituitary dysfunction may require lifelong hormone replacement therapy [104]. Because autoimmune and immune-mediated events can develop even without signs of acute toxicity, careful long-term monitoring is essential. Recommended surveillance includes regular blood tests, such as complete blood counts with differentials every 1–3 months, along with peripheral smears and tests for antibodies against red cells and platelets. Endocrine monitoring should include thyroid function tests (TSH and free T4), morning cortisol and ACTH levels, and, if abnormalities are found, a full evaluation of the pituitary and its target glands every 3–6 months for at least 1 year after therapy [86, 105].

In addition to hematologic and endocrine sequelae, delayed immune dysregulation following CGTs can also manifest with neurologic complications. Delayed immune-mediated neurologic complications include Guillain–Barré Syndrome (GBS), have been reported following CGTs, particularly CAR T-cell treatments. Unlike early neurotoxicity such as ICANS, these events typically arise weeks after infusion and are driven by aberrant immune responses targeting the peripheral nervous system [106]. GBS is characterized by progressive, symmetrical muscle weakness, areflexia, and, in severe cases, respiratory compromise. Diagnosis involves clinical evaluation, cerebrospinal fluid analysis, electromyography (EMG), and nerve conduction studies. Immunomodulatory therapies, primarily IVIG or plasmapheresis, are the mainstays of treatment. Recognizing these complications as immune-mediated rather than purely neurologic highlights the need for interdisciplinary management and LTFU in CGT recipients.

In addition to organ-specific toxicities, survivors of CGT often experience chronic fatigue, functional decline, and reduced quality of life, highlighting the need for comprehensive survivorship care plans. These should encompass physical rehabilitation, psychosocial support, and long-term monitoring of cognitive and neurodevelopmental outcomes, particularly in pediatric patients exposed to high systemic inflammation or corticosteroids. Emerging priorities also include vocational reintegration and reproductive health, as endocrinopathies such as premature gonadal failure have been observed following lymphodepleting therapies [86]. Incorporating these broader metrics into LTFU programs is essential to fully capture the impact of CGTs on patients' lives.

Table 1 provides a consolidated summary of acute and delayed adverse events of special interest (AESIs) associated with CGTs, including CAR T-cell therapies, AAV-based vectors, and CRISPR-based genome editing. The table

outlines the spectrum of toxicities across different platforms, categorizing them by onset timing (acute versus delayed), diagnostic criteria, relevant biomarkers, and current management strategies. Events range from well-characterized syndromes such as CRS and ICANS, to delayed complications such as ICAHT, GBS, secondary malignancies, and cardiovascular injury. Additional gene-editing-related risks, including off-target effects, immune responses to Cas proteins, and theoretical concerns over germline editing, are also addressed. This integrated format enables rapid comparison across toxicities and provides a practical reference for HCPs and PVG professionals involved in long-term safety monitoring of CGT recipients.

The ICH S12 guideline, adopted in 2023, codifies biodistribution and off-target analyses as essential components of nonclinical safety assessments, including evaluations of CNS, gonadal, and germline compartments prior to Investigational New Drug (IND) submission [107]. Patients should also undergo organ-specific surveillance, including cardiac imaging, liver function tests, and endocrine panels, to detect early toxicity before clinical symptoms appear [54]. Routine cancer screenings such as dermatologic exams, colonoscopy, and mammography should be incorporated to support early detection of secondary malignancies [87]. In parallel, immune system monitoring using quantitative immunoglobulins, cytokine profiling, and lymphocyte subset analyses can help identify delayed immunologic sequelae [108]. Embedding these strategies into post-marketing safety protocols, LTFU clinics, and survivorship programs shifts surveillance from passive observation to a proactive, risk-adapted, and multidisciplinary safety model [109]. Using multidisciplinary teams facilitates structured monitoring, enables early identification of delayed complications, and allows for timely, targeted interventions. A dynamic, risk-adapted approach that integrates rigorous surveillance with patient-centered care is essential for achieving and sustaining long-term clinical benefit.

4 Real-World Data and Registries in Pharmacovigilance of Cell and Gene Therapy

Real world data (RWD) has become an essential pillar of post-marketing safety for CGTs, offering insights into safety profiles across broader, more heterogeneous populations

Table 1 Adverse events of special interest in cell and gene therapy

AESI /Toxicity	CGT Modality	Description	Onset	Diagnosis /Grading System	Diagnostic Tools /Biomarkers	Management
CRS	CAR-T, CGTs	Systemic inflammatory response with fever, hypotension	Acute (1–7 days)	ASTCT 2019 Grading; Clinical criteria	IL-6, IFN-γ, TNF-α, IL-1β, sIL-2R; Ferritin; Coagulation studies	Tocilizumab, Corticosteroids, Supportive care
ICANS	CAR-T	Neurotoxicity with encephalopathy, seizures	Acute (3–10 days)	ASTCT 2019 ICE score	ICE score, EEG, Neuroimaging, CSF if infection suspected	Corticosteroids, Seizure management
IEC-HS	CAR-T	Systemic hyperinflammation resembling HLH	Acute or Delayed	ASTCT/EMA Guidelines	Ferritin, IL-1, IFN-γ, sIL-2R; Exclude infections	Immunosuppressants, Corticosteroids, Supportive care
ICAHT	CAR-T	Prolonged cytopenias post-cell therapy	Delayed (weeks)	EMA Guidelines	CBC, Bone marrow biopsy, Clonal tracking	Growth factors, Stem cell boost, Supportive care, HSCT
GBS	CAR-T	Acute inflammatory demyelinating polyneuropathy	Delayed (weeks to months)	Clinical criteria; Neurological exam; EMG	CSF protein elevation, EMG	IVIG, Plasmapheresis
Cardiac Toxicity	CAR-T, AAV	Arrhythmias, myocarditis, heart failure	Acute or Delayed (weeks to years)	ESC Guidelines; Clinical assessment	Cardiac biomarkers, ECG, Echocardiography, Cardiac MRI	Supportive care, Heart failure management, Cardiology referral
Secondary Malignancies	CAR-T, CRISPR, AAV	T-cell malignancies from insertional mutagenesis; p53 disruption	Delayed (months to years)	EMA / FDA RMPs / REMS; Clonal tracking	Integration site analysis, NGS, Biopsy	Oncology referral
Off-Target Editing	CRISPR	Genotoxicity, Insertional Mutagenesis, Tumorigenesis	Delayed (months to years)	Molecular assays; NGS	Off-target detection platforms, Clonal monitoring	Long-term surveillance, Oncology referral
Immune Response to Cas Proteins	CRISPR	Hypersensitivity, Anaphylaxis, Inflammation	Acute (hours to days)	Immunological assays; Cytokine panels	IgE/IgG testing for Cas proteins, Cytokine panels	Corticosteroids, Antihistamines, Anaphylaxis management
Delivery-Related Toxicity	AAV, LNP, CRISPR	Hepatotoxicity, Thrombocytopenia, Complement Activation	Acute or Delayed (days to weeks)	Clinical criteria; Liver function tests	LFTs, Platelet count, Complement activation assays	Corticosteroids, Supportive care, Complement inhibitors
p53 Pathway Disruption	CRISPR	Secondary malignancies due to p53 inactivation	Delayed (months to years)	Molecular profiling; Tumor suppressor screening	p53 sequencing, Clonal tracking, Integration analysis	Long-term oncology surveillance, Oncology referral
Germline Editing (Theoretical)	CRISPR	Heritable genetic alterations	Theoretical/ Unknown	Ethical review boards; Germline surveillance	Germline sequencing, Reproductive monitoring	Regulatory prohibition, Ethical oversight

AAV Adeno-Associated Virus, *AESI* Adverse Event of Special Interest, *ASTCT* American Society for Transplantation and Cellular Therapy, *CART* Chimeric Antigen Receptor T cell, *CBC* Complete Blood Count, *CGT* Cell and Gene Therapy, *CMV* Cytomegalovirus, *CRISPR* Clustered Regularly Interspaced Short Palindromic Repeats, *CRS* Cytokine Release Syndrome, *CSF* Cerebrospinal Fluid, *ECG* Electrocardiogram, *EEG* Electroencephalogram, *EMA* European Medicines Agency, *EMG* Electromyography, *ESC* European Society of Cardiology, *EBV* Epstein–Barr Virus, *GBS* Guillain–Barré Syndrome, *HLH* Hemophagocytic Lymphohistiocytosis, *HSCT* Hematopoietic Stem Cell Transplantation, *ICANS* Immune Effector Cell-Associated Neurotoxicity Syndrome, *ICAHT* Immune Cell-Associated Cytopenias of Hematologic Toxicity, *ICE* Immune Effector Cell-Associated Encephalopathy, *IFN* Interferon, *IL* Interleukin, *IVIG* Intravenous Immunoglobulin, *LFTs* Liver Function Tests, *LNP* Lipid Nanoparticles, *MRI* Magnetic Resonance Imaging, *NGS* Next-Generation Sequencing, *REMS* Risk Evaluation and Mitigation Strategy, *RMP* Risk Management Plan, *sIL-2R* Soluble Interleukin-2 Receptor, *TNF* Tumor Necrosis Factor

than those enrolled in controlled trials. Sourced from electronic health records (EHRs), administrative claims, patient registries, and spontaneous reporting systems, RWD complement trial-based findings and are particularly valuable in rare diseases, pediatric populations, and emerging clinical scenarios not fully captured in pre-approval studies [110–114]. Importantly, RWD generated from long-term follow-up (LTFU) programs not only improve clinical decision-making but also inform regulatory guidance and evolve post-marketing safety expectations. Early patient counseling further reinforces the importance of sustained vigilance as a cornerstone of therapeutic success [90, 91, 115].

RWD analyses suggest that the incidence and characteristics of acute toxicities such as CRS and ICANS among CAR T-cell recipients are generally in line with those observed in pivotal clinical trials, although notable variability persists across patient populations and treatment contexts [116]. This partial concordance reinforces the relevance of clinical trial findings and lends support to the early adoption of mitigation strategies. At the same time, RWE has highlighted atypical toxicity presentations that are infrequently captured in controlled trial environments such as afebrile CRS or toxicities, with delayed onset occurring beyond the standard 1–7-days post-infusion window [112, 116, 117]. Such events have been reported more frequently in patients with autoimmune comorbidities, advanced disease, or non-oncology CGT indications.

Beyond disease- or product-specific registries, regulatory agencies are now piloting distributed networks that link electronic health records, claims databases, and existing registries for near real-time safety monitoring. The European Medicines Agency's (EMA) Data Analysis and Real-World Interrogation Network (DARWIN EU) is a federated network that provides access to standardized real-world data across Europe. Similarly, the FDA's Sentinel Initiative is a US-based distributed system that monitors the safety of medical products and currently includes data on over 100 million lives [118–120]. Despite these advancements, several critical areas remain underdeveloped. These include limited pediatric representation, the absence of standardized biomarker integration, and the investigational status of genomic surveillance tools. Pediatric populations are often underrepresented, as many networks capture adult care and lack dedicated pediatric data streams [121]. The use of biomarkers such as cytokine panels and pharmacodynamic markers has not yet been standardized across studies, limiting the consistency of CGT-specific toxicity detection [122]. Similarly, genomic surveillance tools such as integration site tracking and clonal expansion monitoring remain investigational and are not routinely included in outputs from Sentinel or DARWIN EU [122]. As these platforms mature, expanding pediatric data sources, standardizing biomarker workflows, and embedding genomic analysis will be critical steps toward a truly adaptive CGT ecosystem.

Despite the emergence of sophisticated pharmacovigilance tools, including biomarker panels, real-time safety dashboards, and artificial intelligence (AI)-enhanced RWD analytics, their applicability differs substantially between clinical development and post-marketing use. Most of these tools are best suited to LTFU studies, where centralized oversight, structured assessments, and predefined visit schedules ensure comprehensive safety capture. In contrast, patients treated with approved CGTs outside of trials are typically monitored through risk evaluation and mitigation strategy (REMS) programs, which vary widely in data quality, frequency, and regulatory enforcement. REMS programs may require prescriber certification and patient enrollment into registries, but systematic AE reporting is not always mandated unless specifically included under elements to assure safe use (ETASU) [123]. As a result, many real-world patients receiving CGTs via commercial channels are subject to passive, registry-based surveillance without proactive follow-up. Providers often fail to report delayed toxicities such as secondary malignancies or persistent cytopenias unless specifically prompted, and patients may be lost to follow-up owing to care transitions or disengagement. Moreover, the small sample sizes used in pivotal trials, often fewer than 200 patients for accelerated approvals, further highlight the importance of REMS-based PVG in detecting long-term safety signals. However, this model remains largely reactive unless REMS registries are integrated with structured data sources such as electronic health records (EHRs), laboratory systems, or pharmacy claims [124]. Without this integration, delayed complications such as insertional oncogenesis, autoimmune syndromes, or atypical neurotoxicity may go undetected, particularly in pediatric or medically complex populations.

While RWD sources offer considerable promise, they continue to face critical limitations that must be addressed to fully support CGT safety surveillance. Spontaneous reporting systems, for instance, capture only a small fraction of actual adverse events; one review estimated that, on average, 94% of events go unreported (interquartile range [IQR]: 82–98%), delaying signal detection and limiting the ability to accurately assess event incidence [125]. Fragmented health IT architectures, incompatible EHR platforms, and heterogeneous data standards across regions further impede real-time integration and cross-database surveillance efforts [126]. Many EHR datasets remain siloed within single institutions, and registry participation is often voluntary, resulting in uneven coverage and incomplete longitudinal follow-up [127]. In addition, conventional RWD repositories frequently lack the detailed molecular or genomic annotations, robust causality assessments, and longitudinal biomarker measurements

necessary for comprehensive CGT safety evaluation [128]. Recognizing these unmet needs, regulatory agencies and sponsors are advancing efforts to better link clinical registries with biomarker platforms and deploy AI-driven analytics. Early pilots demonstrate that integrating structured RWD with immunophenotyping registries can enhance signal specificity, while machine learning (ML) algorithms applied to claims and EHR data enable automated risk stratification and dynamic longitudinal monitoring [26]. These developments reflect a critical shift: from passively collecting disparate data streams toward building an integrated, predictive safety infrastructure for CGT.

To address these challenges, regulatory agencies and sponsors should prioritize seamless transitions from protocol-based LTFU to real-world REMS surveillance at the time of approval. This includes establishing interoperable registries that persist beyond study closure, automating EHR-based data pulls, and reinforcing provider engagement through payer incentives or post-market evidence development frameworks [129]. A modular, federated data architecture that bridges LTFU and REMS environments can enhance signal continuity and reduce long-term safety gaps in CGTs. Ultimately, the strength of post-marketing safety oversight, particularly for CGTs approved with limited trial populations, will depend on aligning REMS design with modern pharmacovigilance tools and enabling cross-sector data interoperability. Proactive measures to reinforce this alignment will be essential as CGTs expand into earlier-stage, rarer, and more heterogeneous disease settings. Comparative analyses from the FDA Adverse Event Reporting System (FAERS) and WHO's VigiBase continue to reveal product-specific safety signals, underscoring the need for individualized PVG strategies [130]. For example, FAERS reviews have identified differential rates of severe pulmonary events and fatal outcomes among CAR T-cell products, highlighting the importance of product-specific stratification [112]. Furthermore, real-world pediatric cohorts, which are frequently underrepresented in clinical trials, exhibit higher rates of grade ≥ 3 CRS. This underscores the need for pediatric-specific risk models and dedicated safety monitoring frameworks [116].

Specialized CGT registries such as the Center for International Blood and Marrow Transplant Research (CIBMTR) and the European Society for Blood and Marrow Transplantation (EBMT) provide structured LTFU data across adult and pediatric cohorts, often extending beyond 15 years [131]. Complementing these registry initiatives, pharmacovigilance and regulatory teams continuously synthesize information from publicly available data streams to enhance early signal detection and regulatory compliance. Sources include FDA MedWatch alerts, EMA safety communications, WHO drug bulletins, and ClinicalTrials.gov safety updates. Tools such as FAERS and EudraVigilance are queried using Standardised MedDRA Queries (SMQs) or product-specific Preferred Terms, while machine-driven aggregation platforms and Regulatory Really Simple Syndication (RSS) feeds compile emerging safety communications and labeling changes [132]. Transcripts from advisory committees, such as the FDA's Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC), also provide critical safety insights. By integrating these diverse sources into real-time dashboards and AI-enhanced workflows, pharmacovigilance systems increasingly support proactive, product-specific safety oversight across the CGT lifecycle [133]. These collective efforts enable pharmacovigilance teams to monitor delayed toxicities, including therapy-related malignancies, and strengthen long-term safety surveillance across indications [111, 116, 117, 131]. Pediatric-focused networks, such as the Joint Accreditation Committee of ISCT and EBMT (JACIE) Pediatric Accreditation Program and EBMT's pediatric initiatives, further strengthen data granularity for younger patients and developmental endpoints [119, 134].

Table 2 highlights the evolving landscape of LTFU infrastructure for CGTs, with a focus on the growing strategic value of specialized registries. Each registry serves a distinct yet complementary function in capturing RWD critical for regulatory compliance, signal detection, and adaptive safety planning. CIBMTR and EBMT stand out as foundational platforms, offering ≥ 15 years of monitoring aligned with FDA and EMA mandates, respectively. Their dual focus on survival, toxicity, and relapses, especially in both adult and pediatric CAR T-cell populations play an indispensable role in long-term PVG strategies. In contrast, DARWIN EU and FDA Sentinel bring agility to post-market oversight through real-time evidence generation from EHRs, claims, and registries. These systems enable early signal detection and regulatory learning, though their pediatric coverage remains limited. Strategically, sponsors should view registry selection not as a static compliance requirement, but as a dynamic tool to optimize safety signal interpretation, support label expansion, and align with diverse global regulatory expectations. Leveraging this ecosystem allows for smarter trial extensions, data-driven RMP evolution, and a more resilient CGT safety architecture.

As the field continues to evolve, the strategic integration of RWD with predictive algorithms, enriched genomic annotation, and global registry networks will be essential for delivering a smarter, more adaptive pharmacovigilance ecosystem across the CGT product lifecycle [116, 117]. Equally important is the upstream integration of pharmacovigilance principles into manufacturing and early development, where predictive modeling and CMC surveillance can preemptively address safety risks before clinical exposure.

Table 2 Global registries supporting long term follow-up in cell and gene therapy

Registry	Region	Focus	Data Collected	Monitoring Scope/Duration	Pediatric Coverage
CIBMTR	USA/Global	Hematopoietic, CAR-T therapies	Outcomes, survival, toxicity, relapse data	≥15 years (FDA LTFU requirement)	Yes (Pediatric and Adult)
EBMT	Europe/Global	Cellular therapy, hematopoietic transplantation, CAR-T	CAR-T surveillance, survival, relapse, toxicity	≥15 years (EMA guidance)	Yes (Pediatric subgroups analyzed)
DARWIN EU	Europe	Advanced therapies, real-world evidence (RWE)	Regulatory evidence, EHR data, claims data	Ongoing, duration varies by study	Limited (Primarily Adult)
FDA Sentinel	USA	Drug safety, RWE, post-market surveillance	Claims, EHRs, registries, patient outcomes	Continuous, varies by product	Limited (Primarily Adult)

CART chimeric antigen receptor T cell, *CIBMTR* Center for International Blood and Marrow Transplant Research, *DARWIN EU* Data Analysis and Real-World Interrogation Network-European Union, *EBMT* European Society for Blood and Marrow Transplantation, *EMA* European Medicines Agency, *EHR* electronic health record, *FDA* US Food and Drug Administration, *LTFU* long-term follow-up, *RWE* real-world evidence

5 Regulatory Divergence and Global Execution of Long-Term Follow-Up in Cell and Gene Therapies

Ensuring long-term safety in CGTs demands more than regulatory planning—it requires the operationalization of complex, jurisdiction-specific follow-up systems across a rapidly evolving therapeutic landscape. Table 3 illustrates the global regulatory requirements for LTFU and post-marketing surveillance (PMS) in approved CGTs as of December 2024. It summarizes region-specific regulatory frameworks across major jurisdictions, including the USA, European Union, Japan, South Korea, China, Canada, and Australia. It outlines differences in regulatory authority guidance, LTFU duration (typically 5–15 years), PMS obligations, including REMS, risk management plans (RMPs), and periodic safety update reports (PSURs), along with unique features such as active surveillance mandates, registry requirements, and conditional approvals. Reflecting these divergences, recent market analyses reveal considerable heterogeneity in the maturity of CGT approval pipelines and underscore the dynamic, evolving nature of global risk management strategies [135].

Global regulatory authorities have adopted diverse approaches to LTFU and PMS in CGTs, reflecting regional priorities and evolving safety concerns. In the USA, the FDA mandates a 15-year LTFU program for integrating vector products, consisting of 5 years of active safety monitoring followed by 10 years of passive surveillance, often embedded within REMS [136]. However, enforcing a fixed surveillance duration, particularly the 10-year passive phase, poses practical challenges. Patient attrition, data fragmentation, and variability in real-world reporting practices can lead to incomplete safety datasets, thereby limiting the reliability of long-term safety conclusions. To mitigate these limitations, long-term safety frameworks for CGTs must embed robust traceability as a core element. In the context of personalized or autologous therapies, capturing essential identifiers such as batch number, product lot, manufacturing site, and date of administration is critical. These data points enable precise linkage between an intervention and any emerging adverse event, even years after treatment. By supporting root-cause analyses and regulatory accountability, traceability strengthens the integrity of long-term pharmacovigilance, especially when data collection becomes fragmented or patient follow-up is inconsistent.

These programs may incorporate patient registries, genotoxicity assays, and black box warnings for therapies deemed high-risk. In the European Union, under the EMA's Advanced Therapy Medicinal Product (ATMP) framework, LTFU requirements are determined on a case-by-case basis, supported by risk-based monitoring plans and opportunities for scientific advice to refine study duration, data collection, and risk minimization measures [136]. Reflecting growing regulatory recognition of long-term oncogenic risks, the EMA issued updated guidance in 2024 requiring secondary malignancy warnings in the labeling of all authorized CAR T-cell therapies [137]. In Japan, post-marketing all-case surveillance (PACS) remains compulsory for every approved CGT, mandating the collection of comprehensive safety and efficacy data from all treated patients, including registry enrollment and re-examination periods to monitor long-term outcomes [138, 139]. South Korea's Ministry of Food and Drug Safety (MFDS) similarly links all-case surveillance and mandatory registry participation to reimbursement

Table 3 Global oversight of CGT safety: comparative frameworks for post-marketing surveillance and long-term follow-up

Region/Country	Regulatory Authority	Framework & Scope	LTFU Duration	PMS/LTFU Requirements	Market Stats (as of December 2024)	Unique Regulatory Features
United States (US)	US FDA	REMS; Guidance on LTFU for gene therapies using integrating vectors or genome editing	15 years (5 active + 10 passive)	REMS with ETASU; patient registries; genotoxicity testing; annual safety reports	27 CGTPs approved; 22% REMS; 37% Black Box	Extensive REMS; mandatory assessments; RMAT designation
European Union (EU)	European Medicines Agency (EMA)	ATMP regulation; RMP; Guidelines for GTMPs, SCTMPs, TETs	Case-by-case; typically, 5–15 years	RMP at authorization; annual safety reports; risk minimization for integrating vectors	26 CGTPs approved; 88% under monitoring; 38% conditional	Comprehensive GVP; additional monitoring label; scientific advice (CAT)
Japan	PMDA	Guidelines on Gene Therapy and Regenerative Medicine; Focus on integrating vectors	15 years (shorter for non-integrating)	Mandatory protocols; registry participation; safety data submission	19 CGTPs approved; 79% all-case surveillance	All-case surveillance; early risk detection
South Korea	MFDS	General PMS with PSUR and re-evaluation; Risk-based evolving framework	Typically, 15 years; 5–10 for non-integrating	PSURs; re-evaluation required; limited PMS data	17 CGTPs approved; PSUR, re-eval required	Risk-focused re-exam; limited PMS data
China	NMPA	Technical Guidelines for viral vectors/gene editing; evolving PMS regulation	15 years (case-dependent)	LTFU and safety monitoring; RWD reporting; risk assessment reports	7 CGTPs approved; PMS framework evolving	Risk-based PMS under development; low real-world data
India	CDSCO (Now part of NRA)	Draft Guidelines for Gene Therapy Product Development (ICMR-DBT, 2019); draft CGT-specific CDSCO guidance announced in 2024	15 years (typically for integrating vectors)	LTFU plans expected at submission; post-approval safety updates; PVG aligned with Schedule Y	Not specified	Evolving framework; accelerated pathway under Rule 101 for CGTs approved in other major markets
Canada	Health Canada	Guidance for viral vector-based gene therapies; Emphasis on LTFU protocols	15 years for integrating; 5–10 for others	LTFU study protocols; active surveillance encouraged; post-market reporting	Not specified	Active surveillance emphasis
Australia	TGA	Australian Guidelines for ATMPs including CGTs (integrating and non-integrating)	Typically, 15 years; risk-based for non-integrating	RMP, post-approval monitoring, and LTFU data submission	Not specified	Structured LTFU aligned with ATMP risk

ATMP advanced therapy medicinal product, *CAT* Committee for Advanced Therapies, *CDSCO* Central Drugs Standard Control Organization, *CGTP* cell and gene therapy product, *DBT* Department of Biotechnology, *DCGI* Drugs Controller General of India, *EMA* European Medicines Agency, *ETASU* elements to assure safe use, *EU* European Union, *GVP* good pharmacovigilance practices, *GTMP* gene therapy medicinal product, *ICMR* Indian Council of Medical Research, *LTFU* long-term follow-up, *MFDS* Ministry of Food and Drug Safety, *NMPA* National Medical Products Administration, *NRA* National Regulatory Authority, *PMDA* Pharmaceuticals and Medical Devices Agency, *PMS* post-marketing surveillance, *PSUR* periodic safety update report, *RMP* risk management plan, *RMAT* regenerative medicine advanced therapy, *RWD* real-world data, *SCTMP* somatic cell therapy medicinal product, *TET* tissue engineered therapy, *TGA* Therapeutic Goods Administration, *US FDA* United States Food and Drug Administration

eligibility, ensuring comprehensive data capture across the treated population [137]. In China, the National Medical Products Administration (NMPA) has issued draft and finalized guidelines requiring at least 5 years of active safety monitoring and an additional 10 years of passive surveillance for gene therapies, with particular emphasis on secondary malignancy risk, germline transmission, and integration site analysis [140, 141]. India's Central Drugs Standard Control Organization (CDSCO) regulates biologics, including CGTs. While a formal CGT framework is evolving, milestones include the 2019 ICMR-DBT gene therapy guidelines, and a CGT-specific draft guidance announced in 2024. Rule 101 of the New Drugs and Clinical Trials Rules, 2019, enables accelerated approval for CGTs approved in other major markets [142]. Canada and Australia have adopted more risk-adaptive post-marketing frameworks, anchored in structured RMPs, that tailor follow-up duration and safety obligations to each product's integration profile and clinical indication [136]. Despite ICH-led efforts to harmonize LTFU requirements, real-world implementation remains hampered by patient attrition, due to relocation or disengagement, and logistical challenges in sustaining long-term data completeness.

While regulatory frameworks have increasingly formalized LTFU expectations across regions, ensuring sustained patient engagement and continuous data capture remains a major operational hurdle. Periodic re-consent requirements, mandated by ethics committees and by data privacy laws such as the European Union's General Data Protection Regulation (GDPR) and the US Health Insurance Portability and Accountability Act (HIPAA), add significant operational complexity to extended LTFU programs, making it challenging to retain patients and maintain continuous data beyond the active follow-up period. A recent review endorsed by the International Society for Pharmaceutical Engineering (ISPE), a global

organization dedicated to advancing pharmaceutical engineering and regulatory science, highlighted the need for harmonized RWD infrastructures to support global LTFU efforts, particularly for capturing vector latency, integration site analyses, and transgene-related immunotoxicity in post-approval settings [141]. While progress toward harmonized RWD infrastructure is critical, early real-world experience with CGTs is already uncovering complex safety profiles that existing frameworks were not designed to accommodate. Despite the existence of core registries (CIBMTR, EBMT) and safety databases (e.g., FAERS), fragmented EHR ecosystems and inconsistent reporting standards across jurisdictions continue to hamper real-time PVG and signal detection [143]. Early real-world cohorts have begun to reveal safety signals that diverge from controlled trial observations, such as delayed or atypical CRS presentations in frail, pediatric, or autoimmune patient populations treated with CAR T-cell therapies outside traditional oncology indications [144]. These observations demonstrate the urgent need to update toxicity grading frameworks and deploy adaptive clinical algorithms that accommodate the full heterogeneity of CGT recipients, in order to improve early detection of atypical toxicities, guide individualized interventions, and ultimately safeguard patient outcomes across broader real-world populations [13].

As the field moves toward broader global integration of CGT programs, the execution of LTFU must shift from a static obligation to a dynamic, intelligence-driven framework. Achieving this requires more than regulatory alignment; it calls for purpose-built infrastructure, sustained patient engagement, and a willingness to adopt RWE generated outside traditional trial silos [145]. This review positions LTFU not simply as a safety requirement, but as a critical enabler of trust, equity, and global scalability. By reimagining LTFU as a strategic pillar of CGT development, sponsors and regulators can forge a future in which innovation and sustained vigilance advance in tandem.

6 Case Studies from Recent Clinical Trials and Post-Marketing Surveillance in Cell and Gene Therapy

With increasing use of CGTs in real-world settings, observational data from registries and post-marketing programs are helping reveal long-term safety concerns, emphasizing the importance of robust PVG frameworks. Several case studies and reports provide valuable insight into both their clinical impact and safety challenges. One notable example is tisagenlecleucel (Kymriah®), used in children and young adults with relapsed or refractory ALL. A key phase 2 trial showed an 81% overall remission rate and longer event-free survival compared with historical data, though most patients developed CRS, highlighting the need for early detection and treatment [13, 146]. In adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), axicabtagene ciloleucel (Yescarta®) and lisocabtagene maraleucel (Breyanzi®) produced durable remissions [147, 148]. Monitoring methods such as axial imaging and minimal residual disease (MRD) tracking have helped assess treatment response and guide follow-up [149].

For multiple myeloma, B-cell maturation antigen (BCMA)-targeting CAR T-cell therapies, such as idecabtagene vicleucel, have shown durable responses with a 26% stringent complete response rate and median progression-free survival exceeding 12 months in heavily pretreated patients previously exposed to multiple drug classes [150, 151]. Phase 2 trials have reported stringent complete responses in many patients undergoing CAR T-cell therapy. However, registry data indicate a range of side effects, such as neurotoxicity and prolonged cytopenias. These findings underscore the association between disease severity, overall health status, and the likelihood of adverse effects [151].

Beyond oncology, gene therapy approaches for inherited diseases have also revealed important post-marketing safety lessons. One of the most impactful advances has been with spinal muscular atrophy (SMA). Onasemnogene abeparvovec (Zolgensma®), which uses an adeno-associated virus 9 (AAV9) to deliver a working SMN1 gene, has helped infants achieve developmental milestones that are not possible with standard care [152, 153]. While clinical outcomes have been encouraging, some patients undergoing CAR T-cell therapy have experienced elevated liver enzymes and rare instances of thrombotic microangiopathy (TMA). These AEs underscore the importance of vigilant liver function monitoring and the judicious use of corticosteroids to manage immune-mediated toxicities [154, 155]. Severe acute liver injury has also been reported, particularly in those with preexisting hepatic dysfunction or systemic inflammation [156, 157]. Thrombotic microangiopathy (TMA) has emerged as a rare but serious post-infusion complication—typically occurring within days to weeks—and is characterized by hemolytic anemia, thrombocytopenia, and acute kidney injury. Reports of TMA have contributed to updated FDA product labeling and refined PVG guidance, underscoring the critical role of post-marketing case data in shaping risk management strategies [158]. Furthermore, both preclinical and clinical findings have raised concerns about dorsal root ganglia toxicity and sensory neuron pathology following high-dose administration of adeno-associated virus serotype 9 (AAV9), particularly in juvenile animal models. [154]. Although the clinical significance in humans

remains under investigation, ongoing surveillance includes neurophysiological assessments to detect subclinical neuropathy. These observations have prompted the use of corticosteroids as standard prophylaxis and the implementation of comprehensive liver function and renal monitoring protocols as part of post-treatment follow-up [159]. Collectively, these evolving insights underscore the importance of tailored risk mitigation strategies for AAV9-based therapies and demonstrate how rigorous PMS continues to shape the safety profile of gene therapy products.

For beta-thalassemia, gene therapy using lentiviral vectors to introduce a functional β-globin gene has helped many patients become transfusion-independent [160]. Published studies show sustained engraftment of gene-modified stem cells and a generally acceptable safety profile, though the theoretical risk of insertional mutagenesis remains [161]. Furthermore, in SCD, CRISPR-Cas9 gene editing of HSCs has led to early improvements in anemia, pain episodes, and quality of life [162]. These edits target the *BCL11A* enhancer to boost fetal hemoglobin levels. So far, off-target edits appear minimal, but LTFU is needed to assess the durability and safety of these changes [162].

Recent LTFU data from gene therapy trials in hemophilia and DMD have shown both encouraging therapeutic outcomes and important areas of uncertainty. In hemophilia B, treatment with etranacogene dezaparvovec (Hemgenix®) has led to sustained factor IX expression and significant reductions in bleeding events over 3 years [163, 164]. However, data beyond this period remain limited, highlighting the need for continued observation to assess durability and long-term safety. In hemophilia A, early gene therapy trials initially demonstrated promising increases in factor VIII levels, but several studies have since reported a gradual decline in expression over time [164]. This decline raises ongoing concerns about how long the therapeutic effect can last. Similarly, in DMD, systemic AAV-based gene therapies that deliver micro-dystrophin, such as delandistrogene moxeparvovec (Elevidys®), have shown early signs of improved muscle function and reduced pathology [164]. Yet, the absence of extended follow-up data makes it difficult to assess how durable these benefits are and whether repeated dosing might be necessary. These concerns are particularly important given the potential for immune responses and vector-related toxicities. Altogether, these findings emphasize the promise of gene therapies in genetic diseases while also underscoring the importance of sustained monitoring to ensure long-term efficacy and safety.

Taken together, these case studies demonstrate how longitudinal data from trials and real-world settings are essential to refining risk mitigation protocols and enhancing PVG frameworks tailored to the complexities of CGTs.

7 Pediatric Pharmacovigilance and Long-Term Safety in Cell and Gene Therapy

Pediatric recipients of CGTs require tailored LTFU strategies that account for their ongoing physiological development. Beyond monitoring for delayed toxicities, LTFU in this population must also evaluate growth, neurocognitive development, and other age-specific outcomes to ensure comprehensive safety and efficacy assessments. Therapies administered early in life may exert unanticipated long-term effects on endocrine function, musculoskeletal development, neurocognitive outcomes, and fertility, underscoring the need for extended monitoring across critical stages of maturation. This is supported by longitudinal findings in pediatric oncology, where even reduced-intensity regimens—such as in KMT2A-rearranged infant ALL—have resulted in multisystem late effects despite apparent early remission [46, 165]. Thus, pediatric LTFU protocols include regular evaluations of physical growth parameters, developmental milestones, and neurocognitive status to ensure children continue to thrive post-therapy. For example, pediatric patients who receive CAR T-cells or gene therapy for congenital disorders should undergo periodic neurodevelopmental assessments and endocrine reviews (thyroid function, pubertal development, etc.), since cases of growth delay and hypothyroidism have been noted after intensive treatments [165–167].

Another challenge is that pediatric patients will transition through different care settings over the follow-up period. A child treated at age 5 years will likely be under adult care by the end of a 15-year LTFU [165, 168]. Ensuring a seamless transition from pediatric to adult healthcare services is essential for the continuity of LTFU in CGT recipients. This process requires close coordination between pediatric care teams and adult specialists, including the timely transfer of comprehensive medical records and individualized LTFU plans. Multidisciplinary collaboration is often necessary, as pediatricians, endocrinologists, neurologists, cardiologists, and mental health professionals may all play a role in monitoring long-term health outcomes across physical, cognitive, and psychosocial domains. Equally important is providing psychosocial support to pediatric patients and their families. The uncertainty of long-term outcomes can be anxiety-provoking; dedicated counseling and support groups help families navigate educational, social, and emotional challenges during the follow-up years [167].

Given the under-representation of children in CGT trials, real-world data and registries are critical to strengthening pediatric long-term follow-up and uncovering rare or delayed safety risks. Centralized registries are pivotal for pediatric CGT safety monitoring. Several global registries now focus on pediatric CGT outcomes; the CIBMTR

Pediatric Working Committee's 3-year update from the ELIANA trial reported stable event-free survival alongside new endocrine and growth late effects in 10–15% of children, highlighting the registry's role in uncovering delayed toxicities [169]. The EBMT Registry has now enrolled over 10,000 CAR T-treated patients worldwide, including a substantial pediatric cohort, enabling pooled analyses of late hematologic, immunologic, and secondary malignancy risks in children [170]. International pediatric PVG networks and data-sharing initiatives are increasingly pivotal in monitoring long-term outcomes of CGTs. By aggregating global pediatric data, these collaborative efforts facilitate the detection of delayed or rare AEs, thereby enhancing the safety profiles of emerging therapies across various indications. Notable examples include the FDA's Pediatric Cluster, which fosters regulatory collaboration among agencies, and the conect4children (c4c) consortium, which develops methodological considerations for pediatric PVG throughout the medicinal product lifecycle [171]. In addition, initiatives such as the International Precision Child Health Partnership (IPCHiP) are pioneering federated data networks to enable secure, cross-border analysis of pediatric genomic and clinical data [172].

Pediatric-focused CGT safety monitoring is anchored by major registries and accreditation programs, including the CIBMTR, EBMT, and the JACIE Pediatric Accreditation Program. These platforms stratify safety data by age group, require a minimum of 15 years of follow-up, and increasingly track key developmental metrics such as growth, immune reconstitution, and neurocognitive outcomes. Annual reporting with pediatric-specific parameters is emphasized by accrediting bodies to ensure regulatory compliance and uphold long-term quality standards. In addition to these major registries, several complementary pediatric-focused initiatives enhance the long-term safety landscape in CGTs. The National Childhood Cancer Registry (NCCR), developed by the US National Cancer Institute, aggregates population-based data from across the country to monitor incidence, survival, and outcomes among children, adolescents, and young adults with cancer [173]. While not specific to CGT, its expansive coverage and integration into the Childhood Cancer Data Initiative make it a valuable tool for understanding late effects in pediatric oncology. The SJCARES Registry, led by St. Jude Children's Research Hospital, is designed to support pediatric cancer data collection globally, particularly in low- and middle-income settings where LTFU infrastructure may be limited [174]. Meanwhile, disease-specific efforts such as the North American Pediatric Aplastic Anemia Consortium (NAPAAC) contribute granular safety data on rare hematologic disorders that increasingly intersect with gene therapy trials [175]. These platforms offer developmentally sensitive surveillance frameworks and help improve the underrepresentation of pediatric populations across the CGT landscape. Together, these initiatives enable harmonized, real-world data collection across centers, strengthening long-term safety learning for the pediatric CGT population.

8 Digital Integration and Predictive Algorithms Tailored for Cell and Gene Therapy Safety Monitoring

Long-term safety oversight in CGTs demands a paradigm shift from conventional PVG models. Unlike traditional therapies, CGTs engage directly with the genome, immune system, and developmental pathways, creating risks that may emerge years after treatment and often resist early detection. Meeting these challenges requires a next-generation safety ecosystem: one that integrates digital health innovations, predictive algorithms, and biologically informed risk modeling, specifically calibrated for the unique complexities of CGTs [176].

Rather than passively extracting general RWD, next-generation frameworks should rely on cross-functional PVG review teams that actively synthesize structured data (e.g., EHRs, lab results), unstructured content (clinical notes, social media), and biological signals (e.g., vector integration, transcriptomics) into one cohesive decision layer. These platforms enable real-time updates to digital safety profiles, allowing early detection of clonal expansion or high-risk phenotypes and prompting personalized follow-up. To address these gaps, future PVG in CGTs should adopt open-source tools and share code repositories to support faster peer review and implementation. Furthermore, next-generation PVG platforms should also adopt common data models, such as the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM), to enhance interoperability and enable consistent signal detection across platforms. Incorporating explainable AI methods such as SHapley Additive exPlanations (SHAP) and Local Interpretable Model-Agnostic Explanations (LIME), which clarify how AI models generate predictions, will strengthen regulatory transparency. Furthermore, integrating real-world pilot studies within LTFU protocols can help evaluate the performance and clinical relevance of these models in practice [26].

AI and machine learning (ML) approaches must be specifically tailored to the biological complexity of CGTs. Designing these algorithms requires the ability to detect clonal hematopoiesis in patients receiving integration-based therapies, identify CRISPR-associated off-target edits and indel patterns, monitor immune recovery after CAR T-cells or AAV administration, and distinguish overlapping syndromes, such as differentiating ICANS from stroke or CRS from HLH, particularly in pediatric populations where

clinical signs may be subtle or atypical [33]. Natural language processing (NLP) algorithms trained on CGT-specific adverse event ontologies can extract nuanced toxicity narratives from unstructured clinical notes, identifying early indicators of neurocognitive decline or autoimmune manifestations [177].

To fully realize the potential of PVG in CGTs, digital platforms must move beyond passive data collection and become intelligent systems capable of biologically informed risk prediction. AI models, from interpretable methods such as ElasticNet regression and decision trees to more advanced deep learning architectures such as Transformers and U-Net, are being trained on biomarkers relevant to CGTs, including IL-6, IFN-γ, ferritin, and vector integration profiles [178]. These models are beginning to demonstrate clinical utility in real-world settings. For instance, predictive algorithms using U-Net and Transformer architectures have anticipated CRS onset up to 72 h in advance, with area under the curve (AUC) scores exceeding 0.88 [179]. This marks a shift toward proactive safety surveillance, where biologically grounded algorithms inform early intervention and individualized follow-up—transforming PVG from reactive reporting to predictive prevention [179–181].

In broader support of this transformation, a recent scoping review evaluated over 50 ML models for PVG, revealing advanced techniques such as Extreme Gradient Boosting (XGBoost), Long Short-Term Memory (LSTM) networks, and Transformer-based models consistently outperformed logistic regression in both signal sensitivity and temporal forecasting [26, 182]. However, few of these studies validated their findings in clinical settings, and less than 10% made their source code publicly available or aligned with the Foundations for Trustworthy Use of AI in Medical Imaging (FUTURE-AI) principles, raising important concerns regarding reproducibility and regulatory reliability [26]. These limitations reflect ongoing concerns raised by the Council for International Organizations of Medical Sciences (CIOMS) Working Group XIV, which continues to advocate for ethical AI design, bias mitigation, and algorithmic transparency in post-marketing safety systems [183]. Importantly, symbolic AI tools such as knowledge graphs and neurosymbolic models present promising strategies to integrate heterogeneous safety datasets while preserving mechanistic interpretability, particularly in tracking complex toxicities such as ICANS, IEC-HS, and insertional oncogenesis [87].

In parallel with predictive modeling, back-end analytics are advancing to support CGT-specific safety surveillance. AI and ML are being applied to large-scale RWD to detect rare or delayed complications, such as neurotoxicity or cardiotoxicity, earlier than traditional methods. Natural language processing (NLP) is increasingly used to identify AEs from unstructured clinical notes, while tools such as integration site analysis and clonal tracking offer molecular-level insights into potential long-term risks. These technologies collectively enhance LTFU by enabling both early detection and biologically grounded signal interpretation [179–181]. Furthermore, with AI-enabled back-end analytics, patient-facing technologies are also advancing the CGT safety landscape. CGT-calibrated wearable biosensors, which track heart rate variability (HRV), skin temperature, and physical activity, have shown the ability to detect early signs of CRS a median of 7 h before clinical recognition in early trials [184]. When integrated with electronic patient-reported outcome (ePRO) dashboards and real-time cytokine panels, these sensor streams enable automated tiered alerts and escalation pathways. In pediatric populations, the use of gamified wearables designed to pair growth tracking with adherence rewards further enhances engagement and longitudinal monitoring [185]. Together, these technologies contribute to a proactive pharmacovigilance system that is continuous, biologically informed, and responsive to patient-level changes.

As wearable and app-based technologies become increasingly integrated into CGT safety monitoring, global regulatory variability poses a significant challenge. A digital tool classified as a medical device in one jurisdiction may not receive the same designation or oversight in another, resulting in inconsistencies in how safety data are collected, validated, and interpreted. These discrepancies are particularly relevant in multinational CGT trials, especially those involving pediatric populations, where data protection regulations are more stringent and consent frameworks differ by age and region. Addressing this regulatory fragmentation is essential to ensure secure, interoperable digital platforms that support compliant and meaningful long-term pharmacovigilance.

Digital biosensing tools, including wearables and app-based symptom capture, continue to gain traction in real-world settings. A recent prospective pilot using continuous temperature and HRV monitoring in relapsed multiple myeloma patients receiving CART therapy demonstrated a 103-min lead time in CRS detection compared with standard-of-care vitals [186]. Similarly, the TEL-HEMATO study revealed sustained adherence to passive wearable metrics in 70% of patients undergoing CART or hematopoietic stem cell transplantation, while also noting reduced engagement with manual symptoms and significant clinician burden in interpreting alert volumes [187]. These findings suggest that although passive biosensor integration is feasible, it requires staffing infrastructure and centralized analytics support, especially when deployed in decentralized or outpatient CGT administration models. By fusing such sensor platforms with AI engines, PVG in CGTs shifts from

retrospective reporting to predictive, personalized oversight [188]. To ensure interoperability, ePROs should be synced with both registry-level data and EHRs, enabling real-time safety dashboards that integrate patient-reported fatigue, sensor data, and biomarker alerts into one actionable platform [188]. Such dashboards would allow CGT sponsors to trigger risk-tiered follow-up protocols (e.g., auto-scheduling cardiac MRI or endocrine consultants), supported by AI-predicted event probabilities [189]. The next step is to couple those data streams with mechanistic biomarkers, both validated and exploratory, to sharpen risk stratification and support companion diagnostics. A practical example is the rule-based algorithm now in pilot use: IL-6 and HRV are ingested continuously; if IL-6 > 100 pg/mL and HRV drops ≥ 20% over any rolling 4-h window, the platform triggers an automated safety alert and schedules a nurse-led tele-consult, otherwise monitoring proceeds passively [190, 191]. This closed-loop logic enables pre-emptive action against severe AEs such as CRS or ICANS while preserving clinician bandwidth [192].

Figure 1 presents an integrated, risk-adaptive pharmacovigilance framework tailored for CGTs, spanning from preclinical development through post-marketing surveillance. In the preclinical phase, predictive safety efforts focus on anticipating acute immune-related risks—such as cytokine release syndrome and organ toxicity—using in vitro and in vivo models that evaluate inflammatory markers, off-target genomic effects, and tissue-specific toxicity. During clinical development, real-time safety dashboards, immune monitoring, and predictive algorithms support early detection of emerging toxicities such as neurotoxicity, hematologic suppression, and insertional mutagenesis. The post-marketing phase emphasizes structured LTFU, integration of real-world data, AI-enhanced signal detection, and pediatric transition planning to maintain safety oversight across the lifespan. Together, these elements establish a dynamic and proactive safety ecosystem that aligns regulatory obligations with biologically informed risk management across the CGT product lifecycle.

Table 4 summarizes key biomarkers currently applied in CGT safety, their therapeutic relevance, and validation status across clinical trials and regulatory frameworks. These molecular readouts are increasingly paired with next-generation AI and ML models to support dynamic risk profiling throughout the LTFU period. For example, CAR T-cell persistence markers (e.g., vector copy number) are monitored for insertional oncogenesis risk and immune activity, while cytokine panels (such as IL-6 and IFN-γ) support early detection of CRS and neurotoxicity. TP53 mutation screening, currently exploratory in CGTs, may soon guide eligibility and follow-up intensity in gene-editing protocols owing to its link with malignancy risk. Likewise, pre-existing neutralizing antibodies to AAV vectors are now routinely assessed prior to enrollment in gene therapy trials to mitigate the risk of hypersensitivity or treatment failure. When interpreted alongside AI-detected clinical trends, these biomarkers can inform more personalized safety interventions, redefining how pharmacovigilance in cell and gene therapy is operationalized [193].

Global harmonization and regulatory approval of these tools remain a hurdle. A CGT-specific digital oversight framework, co-developed by regulators, technologists,

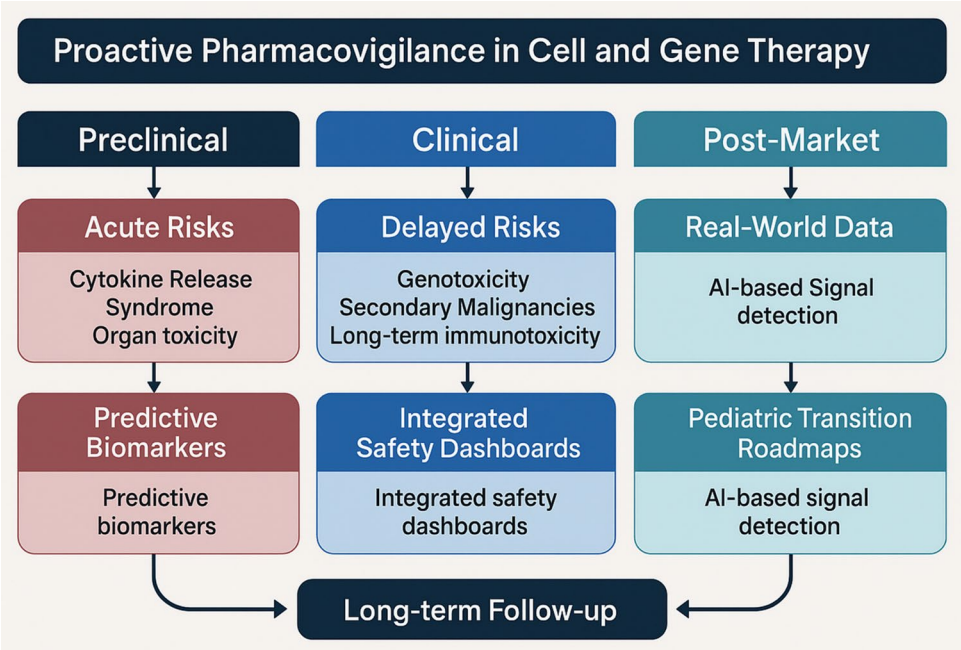

Fig. 1 Proactive pharmacovigilance in cell and gene therapy: a lifecycle approach

Table 4 Pharmacogenomic biomarkers and companion diagnostics for safety monitoring in cell and gene therapies

Biomarker	Associated CGT Application	Role in Safety Monitoring	Companion Diagnostic (if applicable)	Current Validation Status
HLA Genotype (e.g., HLA-B*57:01)	Gene Therapy (AAV vectors)	Screening for risk of immune-mediated adverse reactions (e.g., hypersensitivity)	HLA typing assays	Validated in clinical use for drug hypersensitivity; exploratory in CGT
CAR-T Cell Persistence Markers (e.g., transgene copies, vector integration sites)	CAR-T Cell Therapies (CD19, BCMA targets)	Monitoring of long-term persistence and potential for insertional oncogenesis	qPCR-based vector copy number assays	Validated in trials and post-marketing surveillance (CIBMTR registries)
Cytokine Panels (e.g., IL-6, IFN-γ, TNF-α)	CAR-T Cell Therapies	Early detection of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS)	Multiplex immunoassay panels (e.g., Luminex, ELISA)	Validated in clinical trials; integrated into standard CRS monitoring protocols
TP53 Mutation Status	Gene Editing Therapies (CRISPR-Cas9)	Risk stratification for secondary malignancies due to potential off-target effects	Next-Generation Sequencing (NGS) panels	Exploratory in CGT; validated in oncology
Pre-existing Neutralizing Antibodies to AAV Vectors	AAV-Based Gene Therapies (Hemophilia, SMA)	Patient selection and exclusion based on risk of vector neutralization and reduced efficacy	Serological assays for NAbs (ELISA, luciferase-based assays)	Validated in clinical trials and required in regulatory submissions (FDA/EMA)

AAV adeno-associated virus, *BCMA* B-cell maturation antigen, *CART* chimeric antigen receptor T cell, *CGT* cell and gene therapy, *CIBMTR* Center for International Blood and Marrow Transplant Research, *CRS* cytokine release syndrome, *ELISA* enzyme-linked immunosorbent assay, *EMA* European Medicines Agency, *FDA* US Food and Drug Administration, *ICANS* immune effector cell-associated neurotoxicity syndrome, *IFN-γ* interferon gamma, *IL-6* interleukin-6, *Nabs* neutralizing antibodies, *NGS* next-generation sequencing, *qPCR* quantitative polymerase chain reaction, *SMA* spinal muscular atrophy, *TNF-α* tumor necrosis factor alpha

and advocacy groups, is urgently needed to validate digital biomarkers, establish real-world calibration norms, and define thresholds for intervention [194]. The complexity of CGTs necessitates a collaborative approach among regulatory agencies, academic researchers, biopharmaceutical developers, and patient advocacy groups. Such multi-stakeholder partnerships are essential for developing consensus guidelines, standardizing biomarker validation criteria, and advancing the integration of pharmacogenomics into PVG frameworks [195]. As these strategies evolve, predictive PVG will play a central role in the proactive management of CGT risks. Looking ahead, the next generation of PVG in CGTs therapy will rely not on data volume alone but on the intelligent integration of multiscale information, pairing AI-enabled platforms with clinical expertise and biological insight. This co-pilot model can transform LTFU from a logistical requirement into a precision-guided, predictive component of CGT safety. Rather than replacing human judgment, AI tools will propose dynamic risk scores and early warning signals, while expert PVG teams retain final adjudication. By combining federated data architecture, tailored algorithms, and real-time clinical inputs, this collaborative paradigm will shift pharmacovigilance from reactive surveillance to anticipatory risk management.

9 Ethical and Legal Foundations of Pharmacovigilance in Cell and Gene Therapies

As CGTs redefine therapeutic possibilities for genetic and malignant diseases, the accompanying PVG frameworks must be not only scientifically rigorous but also ethically and legally robust. These therapies often require prolonged safety monitoring, including genomic analyses, organ function surveillance, and data linkage across registries—raising complex questions about informed consent, data privacy, and patient autonomy.

The duration and scope of LTFU in CGTs, which often extend 15 years or more, demand a nuanced and transparent informed consent process. Patients must be fully aware not only of the potential therapeutic risks and benefits but also of the longitudinal commitment required for post-treatment safety surveillance. This includes genetic testing, periodic biopsies or imaging, and possible recontact over time. Because CGTs carry evolving risk profiles, particularly for first-in-class products and pediatric populations, it is essential that patients and caregivers are clearly informed that new safety concerns may arise long after initial treatment [196]. In vulnerable populations, such as pediatric patients, ethical challenges are amplified. Consent becomes an ongoing

process—initially obtained from legal guardians but eventually transitioning to the child as they reach the age of assent or legal adulthood. Ensuring continued engagement and autonomy throughout this transition necessitates tailored communication strategies and ethical oversight [197].

Given the genomic complexity of CGTs and the breadth of data captured, PVG systems often involve high-dimensional datasets that contain deeply personal information. Laws such as the GDPR in Europe and the HIPAA in the USA establish strict rules for data security, consent, and transparency [198]. While these regulations are essential for protecting patient rights, they also pose challenges for international data sharing, especially in global registries and multi-country post-marketing studies.

Because CGTs engage complex biological systems and carry evolving risk profiles, particularly in first-in-class and pediatric settings, informed consent must extend beyond initial treatment to encompass the potential for delayed safety concerns [199]. Transparent communication is essential to ensure that patients and caregivers understand the long-term nature of safety monitoring, including the possibility that new risks may emerge years after therapy. In pediatric populations, this ethical obligation is amplified, requiring re-consent processes as patients mature, and careful transitions to preserve autonomy and sustained engagement over extended follow-up periods [200].

Maintaining public trust is fundamental to the sustainability of CGTs, particularly considering past controversies in gene therapy. Ethical lapses or inadequate communication—especially around long-term risks—can undermine public confidence and compromise enrollment in future trials [196]. Transparent engagement with patients, communities, and advocacy groups is therefore essential. Initiatives such as patient advisory boards and ethics consultation panels can guide the design of LTFU protocols and ensure cultural sensitivity, especially in rare disease or pediatric populations [201].

AE reporting in CGTs, particularly in the context of rare diseases and autologous products, raises important and emerging ethical considerations. In such cases, traditional models of anonymous spontaneous reporting may be insufficient, as patient identity can often be inferred owing to the personalized nature of manufacturing or the rarity of the condition. This challenges long-standing privacy norms and introduces new regulatory implications. Explicit patient consent may be required for the submission of safety data, especially when contributing to global registries or real-world surveillance platforms. As such, a shift toward transparent, patient-centered pharmacovigilance, grounded in informed and potentially dynamic consent, will be essential to ethically support AE reporting in the evolving CGT landscape.

To advance real-world safety monitoring on a global scale, interoperable and secure data infrastructures must be foundational to CGT development. These systems should incorporate role-based access controls, encryption standards, dynamic consent models, and audit trails that safeguard patient privacy while preserving research utility. Dynamic consent, which allows participants to modify their consent preferences over time, offers a promising pathway to balance evolving privacy needs with the long-term data requirements essential for predictive pharmacovigilance [202].

Robust ethical oversight must also be embedded throughout the entire CGT lifecycle. Multidisciplinary committees composed of ethicists, healthcare providers, data scientists, and patient advocates should be engaged from early development through post-marketing follow-up. Treating ethical governance as a core operational element, rather than a secondary consideration, ensures that patient rights, transparency, and trust are preserved as CGTs move from innovation into global clinical practice. Strengthening of both data integrity and ethical accountability will be critical to meeting the demands of a rapidly expanding, interconnected therapeutic landscape.

10 Building a Predictive and Strategic Pharmacovigilance Model for the Global Cell and Gene Therapy Landscape

CGTs have redefined therapeutic possibilities across oncology, rare genetic diseases, and beyond. However, their biological complexity, prolonged activity, and evolving risk profiles require a predictive, multidimensional PVG strategy that can respond dynamically to both known and emerging safety challenges.

The acute toxicity landscape of CGTs, including life-threatening complications such as CRS and ICANS, demands structured, multidisciplinary care supported by simulation-based education, consensus grading systems [e.g., the American Society for Transplantation and Cellular Therapy (ASTCT)] and real-time decision support tools [203–205]. Embedding these protocols into standardized ICU escalation pathways has improved both the speed and consistency of acute toxicity management across diverse healthcare environments.

Beyond the acute setting, LTFU platforms such as CIBMTR and EBMT have become essential for capturing real-world safety outcomes, particularly in detecting delayed effects and supporting reimbursement modeling. Harmonization initiatives, including ICH guidance, seek to unify global data standards, while mobile health technologies such as ePROs and telehealth are increasingly leveraged to improve access and continuity of care, particularly in low- and middle-income countries (LMICs) [162, 206].

Advanced analytics, including ML, NLP, and causal AI platforms, are reshaping PVG workflows by enabling earlier

signal detection, dynamic patient stratification, and adaptive monitoring strategies [163]. Investments in explainable AI methods, real-world model validation, and algorithm transparency are critical to ensure regulatory trust and actionable insights. Incorporating explainable models such as SHAP and LIME helps clarify model predictions, supporting regulatory acceptance.

Given the risks of insertional oncogenesis and off-target gene editing, molecular surveillance must be systematically embedded within LTFU protocols. Techniques such as integration site mapping, clonal evolution tracking, and high-sensitivity CRISPR off-target assays (e.g., crispr2vec, ddPCR) enable early detection of genomic instability and support long-term patient safety monitoring [207]. These molecular insights must be coupled with real-time digital surveillance to provide a comprehensive safety net.

Historical analyses of Adverse Events Reporting System (FAERS) data highlight those biologic agents and products subject to REMS account for a disproportionately high number of serious adverse event reports, emphasizing the urgent need for PVG frameworks specifically tailored to high-risk therapeutics such as CGTs [207]. RMPs must therefore evolve beyond static documents to become dynamic, data-driven tools that adapt to RWE, survivorship trends, and emerging molecular signals.

To fully realize predictive safety frameworks, RWD must be systematically integrated across the CGT lifecycle, informing both REMS implementation and dynamic RMP adaptation. This includes linking real-time patient outcomes, wearable sensor data, and registry analytics with regulatory-defined risk thresholds to trigger preemptive safety interventions.

Strategic alignment across global regulatory bodies, including the FDA, EMA, and the Japanese Ministry of Health, Labor and Welfare (MHLW)—is fundamental to ensure consistency in safety signal interpretation and rapid risk mitigation responses. This convergence supports international data sharing, accelerates learning from real-world outcomes, and harmonizes long-term safety expectations across jurisdictions.

The following domains offer a practical framework for aligning safety monitoring with the unique complexities of CGTs. Table 5 outlines key domains that support an advanced PVG framework for CGTs. Each pillar, while distinct, operates synergistically to support a multidimensional safety infrastructure, ranging from AI-based signal detection to global regulatory harmonization.

As CGTs expand into genome editing and broader therapeutic areas beyond oncology, they introduce additional layers of safety complexity. Emerging tools such as base editors, prime editors, and next-generation CRISPR systems enable in vivo gene correction but also pose risks including off-target edits, chromosomal instability, epigenetic disruption, and prolonged vector persistence in non-target tissues [208–210]. Recent studies have shown that base editors, which are CRISPR-derived tools enabling targeted nucleotide changes without double-strand breaks, can induce both Cas9-dependent and Cas9-independent off-target mutations [210]. This has prompted the development of ML–based prediction tools such as ABEdeepoff and CBE-deepoff, which are designed to anticipate off-target effects of adenine and cytosine base editors, respectively [210]. These models allow for genome-wide estimation of editing specificity and support preclinical safety evaluation of genome-edited CGTs [210]. In the case of in vivo gene editing, additional concerns around potential germline transmission have prompted the need for long-term reproductive monitoring and counseling, as well as molecular assays that can track integration patterns and clonal expansion over time [211].

At the same time, these therapies are being applied in more clinically diverse and vulnerable populations, including patients with autoimmune, metabolic, or rare pediatric conditions. These groups may respond differently to CGTs, particularly in how their immune systems react or recover [212]. Regulators are adapting to emerging CGT safety concerns, but global alignment remains challenging. Despite initiatives by ICH and others, safety definitions, real-world data management, and registry integration efforts remain fragmented across regions [54]. In addition, a persistent challenge in the global expansion of CGTs is ensuring equitable access to long-term safety infrastructure. Many LMICs lack the infrastructure needed to sustain comprehensive patient monitoring, including registries, digital platforms, and trained pharmacovigilance personnel. Without targeted interventions, disparities in safety oversight will continue to grow as CGTs expand into broader markets, undermining both patient outcomes and regulatory confidence. Practical solutions include mobile-based adverse event reporting, telehealth-enabled follow-up, and increased participation in international safety registries. Global health authorities, regulatory bodies, and industry stakeholders must collaborate to build local capacity, harmonize data systems, and ensure that CGT safety frameworks are inclusive, resilient, and globally sustainable [213].

Furthermore, incorporating patient and caregiver experiences offers critical insight into the real-world impact of CGTs. In pediatric contexts, treatment decisions often involve both the child and caregiver, who must navigate complex emotional, ethical, and logistical challenges. A recent scoping review highlighted recurring themes, including risk–benefit deliberation, timing of trial enrollment, and long-term quality of life considerations [214, 215]. In LMICs, these issues are compounded by limited infrastructure, regulatory variability, and constrained access to care. Engaging patient advocacy groups and integrating their input into trial design and follow-up

Table 5 Strategic domains for evolving pharmacovigilance in cell and gene therapy

Pillar	Description	Goal	Example Tools/Applications
AI-Driven Signal Detection	Uses machine learning (ML), natural language processing (NLP), and causal inference to identify safety signals from diverse sources (e.g., EHRs, registries, social media)	Accelerate detection, reduce manual burden, and support dynamic risk stratification	Bayesian AI, SHAP/LIME, ChatGPT, Genpact, Saama, crispr2vec
Omics-Informed Surveillance	Leverages genomics, transcriptomics, proteomics, and integration site tracking to detect clonal evolution, genotoxicity, and off-target events	Enable early detection of molecular safety risks	Integration site analysis, single-cell RNA-seq, ddPCR, TP53 profiling
Real-World Data Integration	Synthesizes data from registries, EHRs, claims, and patient-reported outcomes to capture atypical or delayed AEs	Extend monitoring beyond clinical trials; inform RMPs	CIBMTR, EBMT, FAERS, VigiBase, Flatiron, TriNetX, DARWIN EU
Global Regulatory Harmonization	Aligns LTFU and PMS frameworks across regions; incorporates real-world safety data into regulatory pathways	Enable global oversight and label harmonization	ICH E2E, EMA RMPs, FDA REMS, WHO-UMC, ISPE guidance
Patient-Centered Monitoring	Uses wearables, ePROs, and telehealth to track patient health remotely and improve adherence	Increase access, retention, and early intervention	Medidata Sensor Cloud, Apple Health, ActiGraph, gamified pediatric wearables
Adaptive Risk Management Plans	Evolves RMPs using RWE, real-time signal detection, and dynamic dashboards; links to biomarker-based alerts	Maintain relevance of safety planning throughout CGT lifecycle	Dynamic RMP platforms, PSURs, Risk MAPs, automated escalation tools

AI artificial intelligence, *AEs* adverse events, *CGT* cell and gene therapy, *ddPCR* droplet digital polymerase chain reaction, *EBMT* European Society for Blood and Marrow Transplantation, *EHR* electronic health record, *EMA* European Medicines Agency, *ePRO* electronic patient-reported outcome, *FAERS* FDA Adverse Event Reporting System, *FDA* US Food and Drug Administration, *ISPE* International Society for Pharmacoepidemiology, *ICH* International Council for Harmonisation, *LIME* local interpretable model-agnostic explanations, *LTFU* long-term follow-up, *ML* machine learning, *NLP* natural language processing, *PSUR* periodic safety update report, *qPCR* quantitative polymerase chain reaction, *REMS* risk evaluation and mitigation strategy, *RMP* risk management plan, *RWE* real-world evidence, *SHAP* SHapley Additive exPlanations, *TP53* tumor protein 53, *VigiBase* WHO Global Individual Case Safety Report Database System, *WHO-UMC* World Health Organization-Uppsala Monitoring Centre

protocols can strengthen ethical oversight and improve enrollment and retention [216, 217].

To remain effective, future PVG in CGT systems must be agile, analytics-enabled, and globally interoperable. Genome editing will require new forms of monitoring, rare disease populations will demand tailored safety frameworks, and global expansion will hinge on equitable infrastructure. Addressing these challenges early will help ensure that innovation in CGTs progresses hand in hand with responsible, inclusive long-term safety oversight.

11 Conclusion: Redefining Pharmacovigilance for a Genomic Era

CGTs are reshaping the therapeutic landscape, offering curative potential across a range of previously intractable conditions. This promise, however, brings with it complex and evolving safety challenges involving immunologic, genomic, and developmental dimensions. As these therapies mature, PVG must evolve from traditional reactive models into proactive, data-driven frameworks that span the entire product lifecycle.

This review outlines a reimagined PVG paradigm anchored in federated, ethically aligned artificial intelligence systems. These systems enable secure, multi-institutional collaboration without compromising patient privacy or data sovereignty. Equally important is the development of pediatric-specific endpoints and structured transition plans that account for long-term developmental trajectories, not only acute toxicities. Expanding PVG infrastructure in LMIC should also be prioritized through global registries, digital monitoring platforms, and scalable training initiatives designed to promote safety equity across regions [218–220].

Independent organizations that operate across clinical development and safety oversight are well positioned to implement these strategies. Their multidisciplinary scope and global reach allow them to facilitate the alignment of registry initiatives, standardize safety signal definitions, and integrate intelligent digital tools to support anticipatory PVG frameworks.

The future of PVG will depend not only on the sophistication of analytics but also on collaborative governance, harmonized safety standards, and biologically informed insight. Embedding PVG across all phases of CGT development, from preclinical research to long-term follow-up, will enable early identification of emerging risks and reinforce patient-centered innovation.

Declarations

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Consent to participate Not applicable. This review does not involve any original research with human participants; thus, no participant consent was necessary.

Consent for publication Not applicable. This article does not include any individual data or images requiring consent for publication.

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