

Annals of Stem Cell Research

Review Article

Long-Term Follow-Up of Patients Receiving Stem Cell-Based Regenerative Therapies

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Received: 10 March 2026; Accepted: 31 May 2026; Published: 16 August 2026; DOI: 10.5281/zenodo.22274944

Citation of this article: Babic L, Barbieri C, Barbu R (2026) Long-Term Follow-Up of Patients Receiving Stem Cell-Based Regenerative Therapies. Ann Stem Cell Res, 9(1): 01-08.

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Abstract

Background: Stem cell-based regenerative therapies are given once and persist, so their adverse events fall outside the window in which conventional pharmacovigilance operates.

Objective: To set the follow-up durations mandated in each jurisdiction beside the events actually observed in published long-term cohorts.

Methods: Narrative review of regulatory documents, gene therapy cohorts and long-term clinical follow-up studies.

Findings: United States guidance recommends fifteen years for integrating vectors and the European Union requires at least five years then yearly follow-up. Seven haematologic cancers occurred among 67 patients given elivaldogene autotemcel, with onset from fourteen to ninety-two months, and 38 suspected secondary T-cell malignancies were reported against approximately 42,500 exposures. No teratoma was seen in 41 recipients of pluripotent-derived grafts.

Conclusions: The evidence supports the mandated durations as proportionate to observed event timing; it does not show what fraction of patients remain in follow-up, since attrition inside these protocols is unpublished.

Keywords: Long-term follow-up; Gene therapy; Regenerative medicine; Insertional oncogenesis; Pharmacovigilance

Introduction

Stem cell-based regenerative therapies are administered once and are intended to persist. That single property, rather than any particular toxicity, is what forces long-term follow-up onto the field. A transduced haematopoietic stem cell carries its integrated vector into every daughter cell for the life of the graft; a cultured limbal or epidermal graft is sustained by a small number of self-renewing clones that must survive for decades [1]; a pluripotent-derived retinal or cardiac graft is a population of cells whose proliferative history cannot be undone once implanted. Adverse events in these products are therefore not confined to the peri-administration window in which conventional pharmacovigilance operates.

The regulatory response has been to impose observation periods measured in years to decades, and the clinical response has been a set of published cohorts, most of them small, that now reach far enough to test whether those periods were set sensibly. This review sets the mandated durations beside the observed events. Two disciplines are imposed throughout. Every duration is given with the document, jurisdiction and date that establish it, because all three major regulators have revised their instruments and a naked number is not usable. Every adverse event is given as events against exposures, because the cohorts differ by vector, transgene, indication and era, and pooling them produces a rate that describes no patient.

Regulatory Clocks and Their Documents

The United States position is set by the Food and Drug Administration's guidance for industry on long-term follow-up after administration of human gene therapy products, issued by the Center for Biologics Evaluation and Research in January 2020 under docket FDA-2018-D-2173 [2]. It recommends fifteen years of observation for integrating vectors, naming gammaretroviral and lentiviral vectors and transposon elements, and up to fifteen years for herpesvirus vectors

capable of establishing latency, for persistent microbial vectors and for genome editing products. For adeno-associated viral vectors it recommends up to five years. The fifteen-year figure survived the most recent regulatory relaxation: when the FDA eliminated the risk evaluation and mitigation strategies for all approved autologous chimeric antigen receptor T-cell products on 26 June 2025, it stated that the change did not alter the requirement for manufacturers to conduct post-marketing observational safety studies with follow-up of patients for fifteen years after product administration [3].

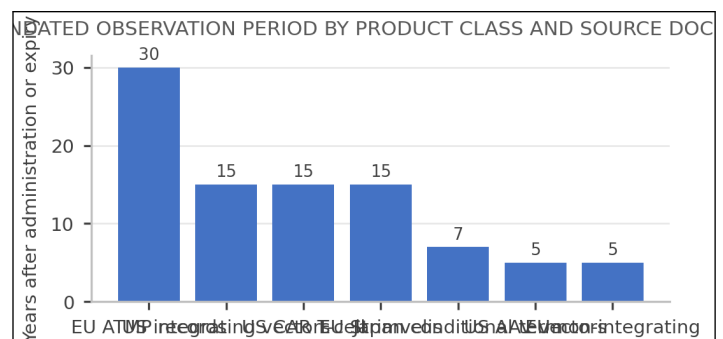


Figure 1: Mandated observation periods as printed in the FDA guidance of January 2020, the FDA communication of 26 June 2025, the EMA guideline effective 1 May 2010, the Strimvelis DHPC of 22 March 2021, Regulation (EC) No 1394/2007 of 13 November 2007 and Japan's law in force from 25 November 2014; N = 7 product classes across three jurisdictions [2,3,4,8,5,6].

The European Union operates two clocks with different objects. The European Medicines Agency guideline on follow-up of patients administered with gene therapy medicinal products, EMEA/CHMP/GTWP/60436/2007, adopted in 2009 and effective from 1 May 2010, prescribes sampling before treatment and at three, six and twelve months, continuing for at least five years and then yearly until data indicate that there is no longer any risk, for vectors capable of integration or of latency and reactivation; a minimum of five years applies to non-integrating viral vectors and a total of five years to plasmid and non-viral vectors [4]. Separately, Article 15(4) of Regulation (EC) No 1394/2007 on advanced therapy medicinal products, dated 13 November 2007, requires

the marketing authorisation holder to keep patient and product traceability data for a minimum of thirty years after the expiry date of the product, with Article 14 obliging the holder to detail measures for follow-up of efficacy and adverse reactions [5]. Thirty years of records is not thirty years of clinic visits, and the two are routinely conflated.

Japan sets its clock at the approval rather than the patient. The Law for Partial Revision of the Pharmaceutical Affairs Law, promulgated 27 November 2013 and in force from 25 November 2014, created a conditional and term-limited approval for regenerative medical products lasting a period within a range of no more than seven years in principle, with obligatory investigation of treatment outcome, periodic infectious disease reporting, and recording and storage of information on treated patients [6]. Full approval must be applied for within that term [7]. Product-specific obligations can be longer and more prescriptive than any class rule: the direct healthcare professional communication for Strimvelis, agreed 25 February 2021 and disseminated 22 March 2021, sets annual visits for the first eleven years and further visits at thirteen and fifteen years [8]. Holoclar, authorised conditionally on 17 February 2015 and converted to a standard authorisation on 22 February 2024, carried the imposed observational studies HOLO-UP and HOLOSIGHT across those nine years [9].

Insertional Oncogenesis in Haematopoietic Gene Therapy

The events that justified these durations are countable and belong to gammaretroviral haematopoietic gene therapy. In X-linked chronic granulomatous disease, 2 of 2 treated adults developed myelodysplasia with monosomy 7 after activation of MDS1-EVI1 and related loci; one died of overwhelming sepsis twenty-seven months after treatment and the other proceeded to allogeneic transplantation [10,11]. In Wiskott-Aldrich syndrome, 7 of 10 treated patients developed acute leukaemia,

comprising one acute myeloid leukaemia, four T-cell acute lymphoblastic leukaemias and two T-ALL with secondary AML, with dominant clones carrying integrations at LMO2, MDS1 or MN1 among more than 140,000 unambiguous integration events [12].

Table 1: Mandated long-term follow-up by jurisdiction, product class and duration, each with the document and date that establishes it; durations quoted without their document and date are not usable [2,3,4,5,6].			
Jurisdiction	Product class	Duration	Document and date
United States	Integrating vectors	15 years	FDA guidance, January 2020
United States	AAV vectors	Up to 5 years	FDA guidance, January 2020
United States	Autologous CAR T-cell	15 years post-marketing	FDA communication, 26 June 2025
European Union	Integrating or latent vectors	At least 5 years, then yearly	EMA guideline, effective 1 May 2010
European Union	All ATMPs, records only	30 years after expiry	Regulation 1394/2007, 13 Nov 2007
Japan	Conditional approval term	No more than 7 years	MHLW law, in force 25 Nov 2014

In the Paris SCID-X1 trial, 4 of 9 successfully treated patients developed acute leukaemia, with onset at thirty-three and sixty-eight months in the two later cases and one death at month sixty [13]. Eight of the nine were alive at a median follow-up of nine years, and transduced T cells remained detectable up to 10.7 years after treatment [14]. In the London cohort of 10 enrolled patients, the index T-ALL presented at twenty-four months, on day 717, and entered remission four months after chemotherapy began [15]. The pattern is that the vector, the transgene and the disease all matter: 0 of 18 ADA-SCID patients treated with a retroviral vector in the Milan series developed leukaemic transformation, with 100% overall survival across 2.3 to 13.4 years of follow-up, median 6.9 years, and infection rates falling from 1.17 to 0.17 events per person-year [16]. A single lymphoid T-cell leukaemia has since been reported against 33 patients treated with Strimvelis, arising 4.7 years after treatment

given in 2016 [8], the same event described in the primary literature as occurring fifty-seven months after infusion and set against 75 ADA-SCID patients reported treated worldwide since 2000 [17].

Lentiviral products have not abolished the problem. Seven haematologic cancers occurred among 67 patients infused with elivaldogene autotemcel for cerebral adrenoleukodystrophy, thirty-two in ALD-102 and thirty-five in ALD-104, an incidence of 2.1 per 100 person-years (95% CI 0.8 to 4.2) over 338 person-years, with onset between fourteen and ninety-two months and ALD-102 patients followed to 8.9 years as of 1 February 2023 [18]. One acute myeloid leukaemia arose roughly 5.5 years after LentiGlobin for sickle cell disease in the HGB-206 Group A cohort; vector insertion was detectable in blasts but the causality assessment concluded that the leukaemia was unlikely to be insertion-related [19]. The interval distribution is the operative finding: fourteen to ninety-two months for eli-cel, sixty-eight months in Paris, 4.7 years for Strimvelis. A five-year window would have missed several of these.

Secondary Malignancy After CAR T-Cell Therapy

The CAR T-cell signal is of a different evidentiary kind and should not be handled as though it were a cohort incidence. The European Medicines Agency evaluated 38 suspected cases of secondary T-cell malignancy after CD19- or BCMA-directed CAR T-cell therapy against approximately 42,500 patients who had received an authorised product in trials or commercially by 11 April 2024, a reporting rate of approximately one case per thousand treated, with 22 of 33 informative cases (67%) diagnosed within twelve months of infusion [20]. The numerator is suspected cases from spontaneous reporting and the denominator is estimated cumulative exposure rather than a followed cohort, so the quotient is a reporting rate and nothing stronger. Regulators on both sides of the Atlantic have treated it as a reason to keep the long observation window rather than as a measured

incidence [21,3].

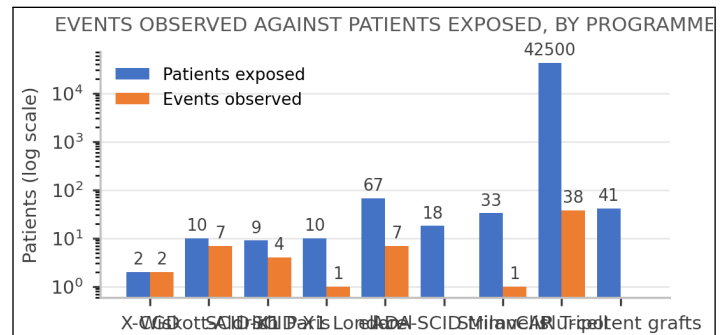


Figure 2: Events observed against patients exposed on a logarithmic scale, showing that the countable events are insertional and clonal while zero teratomas have been seen in the 41 pluripotent-derived graft recipients; N = 42,690 exposures across nine programmes [11,12,13,15,18,16,8,20,26,27,29,30].

The clustering of two-thirds of informative cases within the first year after infusion is nonetheless informative about design. It argues that the intensive phase of surveillance for these products belongs early, where the events are being detected, while the long tail exists to capture what the haematopoietic gene therapy experience shows can arrive at four to eight years. A protocol that spends its resources uniformly across fifteen years matches neither pattern.

Grafts of Pluripotent and Somatic Stem Cells

Non-haematopoietic grafts have generated a different and largely reassuring record. Cultivated autologous limbal grafts, first reported for damaged corneal surfaces in 1997 [22], achieved permanent restoration of a transparent regenerating epithelium in 76.6% of eyes among 112 patients, with failures concentrated in the first year and restored eyes stable over follow-up of up to ten years; success was 78% when cultures contained more than 3% p63-bright cells and 11% below that threshold [23]. Genetically corrected epidermal grafts for junctional epidermolysis bullosa [24] were followed 6.5 years in the phase I/II trial, which showed the transgenic epidermis to be sustained by a small number of long-lasting self-renewing stem cells while transduced transit-amplifying progenitors were lost within the first

few months [1]; near-total epidermal replacement in a child has been reported at five years [25].

For pluripotent-derived products the central point is negative and should be stated plainly. Across the followed cohorts assembled here, zero teratomas have been observed in 41 recipients: 18 patients given subretinal human embryonic stem cell-derived retinal pigment epithelium for Stargardt's macular dystrophy and age-related macular degeneration, followed a median of twenty-two months with no adverse proliferation or rejection [26]; 5 patients given HLA-matched allogeneic induced pluripotent stem cell-derived RPE, of whom 1 had an immune reaction with fluid recurrence resolved by local steroid, grafts present at six months and stable across a one-year observation [27]; 6 patients in ESCORT given an hESC-derived cardiovascular progenitor fibrin patch, with a maximum follow-up of six years, no adverse event attributed to the cells or the patch and no cardiac teratoma or remote tumour on whole-body computed tomography [28,29]; and 12 full-dose recipients of stem cell-derived fully differentiated islets, 10 of whom (83%) were insulin-independent at day 365 with no severe hypoglycaemia between days 90 and 365 and two deaths from cryptococcal meningitis and progression of pre-existing neurocognitive impairment [30]. Forty-one recipients is a small denominator and short of the durations that would exclude a late event; the honest statement is that teratoma risk is theoretically grounded, regulatorily central and, so far, empirically unobserved in followed clinical cohorts. The one documented tumour after stem cell transplantation into the central nervous system was donor-derived and arose in a boy with ataxia telangiectasia treated outside a regulated trial [31]. Immunological rather than neoplastic outcomes dominate what is actually seen, and the immunogenicity of autologous pluripotent derivatives remains an open question in its own right [32].

The longest continuous human experience with a cellular

graft is not a pluripotent one. Among 79 patients receiving islet transplantation alone across 159 infusions between February 2001 and June 2023, Kaplan-Meier graft survival was 86% at one year, 65% at five, 47% at ten, 47% at fifteen and 40% at twenty years, with median graft survival 3.9 years, overall patient survival 92% over a median follow-up of 13.1 years, and immunosuppression-related adverse events in 44% [33]. That series shows what a twenty-year denominator buys: a survival curve with a shape, not a point estimate.

Attrition and the Denominator Nobody Has Published

Every duration above assumes the patient is still being seen. The best verified attrition data come from a related population rather than from gene therapy itself: among 21,990 two-year survivors of haematopoietic cell transplantation reported to the CIBMTR, the ten-year cumulative incidence of loss to follow-up was 13% for adult allogeneic recipients, 15% for adult autologous, 25% for paediatric allogeneic and 24% for paediatric autologous [34]. Paediatric attrition is the higher figure, and paediatric patients are precisely the population in whom SCID-X1, Wiskott-Aldrich, adrenoleukodystrophy and epidermolysis bullosa products are used.

No primary source gives retention or attrition inside sponsor-run fifteen-year long-term follow-up protocols. That absence is the most consequential gap in this literature. Mandated durations run to fifteen years in the United States and to thirty years of records in the European Union, and nobody has published what fraction of gene therapy recipients are still being seen at year ten or year fifteen. Until that is reported, the fifteen-year requirement is a specification of intent whose realised value is unknown.

Conclusion

The durations and the events line up better than one might expect. Insertional events occurred at fourteen to ninety-two months after eli-cel, at thirty-three and

sixty-eight months in Paris, at twenty-four months in London and at 4.7 years for Strimvelis, which is why fifteen years under the FDA guidance of January 2020, retained on 26 June 2025, and the at-least-five-years-then-yearly schedule effective in the European Union from 1 May 2010, are proportionate rather than precautionary. Japan's seven-year conditional term under the 2013 law in force in 2014 and the thirty-year traceability requirement of Regulation 1394/2007 address different objects and should not be quoted as follow-up periods. What is missing is not more rules but the denominator: attrition inside long-term follow-up protocols is unpublished, 41 pluripotent-derived recipients is too few to characterise a late risk, and the CAR T-cell figure of 38 suspected cases against roughly 42,500 exposures remains a reporting rate. Reporting who is still being followed would do more for this field than lengthening the interval over which they are meant to be.

Table 2: Longest-followed published cohorts by indication, with N, observed follow-up and principal finding; N = 303 patients across six cohorts [14,12,18,23,33,26].			
Indication and product	N	Follow-up	Principal finding
SCID-X1, gammaretroviral	9	Median 9 years	4 leukaemias, 1 death
Wiskott-Aldrich, gammaretroviral	10	To 2014 report	7 acute leukaemias
Cerebral ALD, eli-cel	67	338 person-years	7 haematologic cancers
Limbal deficiency, limbal grafts	112	Up to 10 years	76.6% permanent restoration
Type 1 diabetes, islet alone	79	Median 13.1 years	40% graft survival at 20 years
AMD and Stargardt's, hESC-RPE	18	Median 22 months	0 tumours, no rejection

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