Allucent
Helping bring new therapies to light

ADVANCED THERAPY SAFETY MANAGEMENT: Proactive Strategies for Real-World Risk Detection

Advanced Therapy Medicinal Products (ATMPs)

- **Cell & Gene Therapies** (CAR-T, TCR-modified T cells, HSC gene therapy)
- **T-cell Engagers**
- **mRNA Therapeutics**

The Promise of Advanced Therapies

- Durable response
- Curative potential

Unique Safety Challenges in Advanced Therapies

Immediate & Short-Term Risks

- Cytokine release syndrome (CRS)
- Immune effector cell-associated neurotoxicity (ICANS)
- Other acute reactions (e.g., fever, chills, cytopenia, hepatotoxicity)

Potential Long-Term Risks

- Insertional mutagenesis
- Secondary malignancies
- Additional concerns (e.g., off-target effects, waning effect, immunogenicity leading to neutralizing responses)

Complex manufacturing processes can also lead to batch variability and contamination risks

Advanced therapies present unique safety challenges that require careful oversight. This underlines the need for vigorous post-market surveillance and extended follow-up periods.

Long-Term Follow-Up (LTFU) in Real-World Populations

Real-world monitoring beyond clinical trials is essential for fully characterizing the safety profile of ATMPs.

Clinical Trial Limitations

- Small cohorts (50-200 patients)
- Homogeneous populations
- Follow-up ≤2-5 years

Real-World Evidence Goals

- Detect rare/ delayed AEs
- Understand long-term efficacy
- Capture diverse populations
- Identify new indications

Regulatory Mandates

- Extended follow-up requirements
- Patient registries
- Focus on delayed adverse events

Real-World Challenges & the Role of Registries

Challenges

- Older patients with comorbidities
- Fragmented data
- Lack of unified data collection mechanisms

Solutions

- Post-Authorization Safety Studies (PASS)
- Disease & product registries (e.g., EBMT)
- Patient support/ follow-up programs

Structured data collection initiatives provide crucial insights into safety and efficacy profiles in broader patient populations.

LTFU Operational Considerations & Solutions

Shared Burden Between Sponsor, Participants and Sites

- Duration (10-15 years)
- Site staff turnover
- Patient relocation
- Compliance
- Cost & efficiency balance

Fit-for-Purpose Solutions for Participants and Sites

- Patient-centric, decentralized follow-up
- Digital tools: eConsent, telehealth, eCOA, home health
- Aim to increase data points from required to 'nice to have'
- Align visits with the standard of care
- Reimbursement support for patient travel expenses

Alleviating Sponsor Burden with Streamlined Data & Monitoring:
A dedicated LTFU basket protocol streamlines safety monitoring and data collection across studies, reducing operational burden and improving consistency in long-term safety evaluation.

Trial-1 | **Trial-2** | **Trial-3**

LTFU Database

Dedicated Protocol for LTFU: similar product, same data points, streamlined approach

Post-Marketing Challenges & How to Overcome Them

Challenge	Solution
10-15 year patient retention	Loss of patients from trial to registry/PASS
Early patient education and digital reminders	Coordinated transfer of data and consent
Variable site engagement & turnover	Multi-country complexity
Ongoing training	Centralized coordination
Data quality & completeness in registries	Regulatory updates
Define minimum dataset, integrate EHRs	Rapid rollout through cross-functional teams

Effective LTFU management depends on streamlined operations, integrated data systems and active site and patient engagement to sustain compliance.

Safety Monitoring Once Therapy Is Approved

Global PV Requirements and Legal Framework for ATMPs:

Follow guidance provided by FDA (US), EMA (EU), MHRA (UK), PMDA (Japan), NMPA (China), Health Canada (Canada) and early frameworks emerging in LATAM and Middle East

Sources of Safety Data for ATMPs

Spontaneous Reporting
- Cornerstone of PV, despite underreporting
- Critical when patient numbers are very small

Solicited Data
- PASS
- Product-specific & disease registries
- Patient support/follow-up programs

Traceability Systems
- Linking product → batch → patient → outcome
- Accurate signal detection & regulatory compliance

Signal Detection in Advanced Therapies

Unique Challenges of Signal Detection

- Limited patient exposure
- Novel, immune- and gene-mediated risks
- Delayed and long-latency toxicities
- Fragmented, under-reported safety data

Core PV Approaches

ATMP Safety Monitoring

- **Spontaneous & solicited reports** — Well-documented cases are vital
- **Expert clinical adjudication** — Case-level review by cross-functional committees
- **Traceability systems** — Link product, batches and patient outcomes
- **Registries** — Foundation of long-term signal detection

AI as a Signal Detection Tool

- Integration of fragmented data sources
- Multi-dimensional pattern recognition
- Early signal amplification
- Risk prediction

AI is a supportive, not a standalone tool. Transparency and human adjudication are essential.

Risk Management Planning & Regulatory Expectations

From a regulatory perspective, every ATMP must have a risk management plan in place from day zero. The plan evolves as new safety data emerges over time.

Regulators expect risk management plans to include several key elements:

- PASS & long-term patient registries
- Educational materials (HCPs & patients)
- Controlled distribution & prescriber qualification
- DHPCs & other communication tools
- Effectiveness evaluation of risk minimization measures

Key Takeaways & Future Directions

Enhanced Clinical Monitoring
CGTs demand sophisticated long-term follow-up protocols

Specialized Medical Expertise
Interpretation of complex clinical presentations requires multidisciplinary teams

Integrated Data Systems
Must capture long-term outcomes, patient-reported outcomes and early signal detection

Education Initiatives Critical
Educational materials for treating physicians, pharmacists, patients and caregivers

The success of advanced therapies depends not just on their efficacy, but also on effective long-term monitoring and proactive safety management.

Allucent
Helping bring new therapies to light
2000 Centregreen Way, Suite 300
Cary, North Carolina 27513

+1 919-361-2286
www.allucent.com
@Allucent-CRO