

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



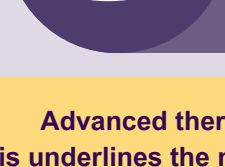
Immediate & Short-Term Risks

- 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)

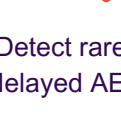


Homogeneous populations

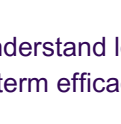


Follow-up
≤2-5 years

Real-World Evidence Goals



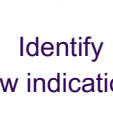
Detect rare/
delayed AEs



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



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

Solutions

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

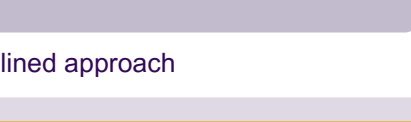
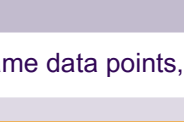
- Duration (10-15 years)
- Site staff turnover
- Patient relocation
- Compliance
- Cost & efficiency balance

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.



LTFU Database

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

Post-Marketing Challenges & How to Overcome Them



10-15 year patient retention



Early patient education and digital reminders



Loss of patients from trial to registry/PASS



Coordinated transfer of data and consent



Variable site engagement & turnover



Ongoing training



Multi-country complexity



Centralized coordination



Data quality & completeness in registries



Define minimum dataset, integrate EHRs



Regulatory updates



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.

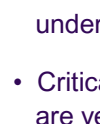
Safety Monitoring Once Therapy Is Approved



Global PV Requirements and Legal Framework for ATMPs:

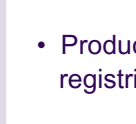
Follow guidance provided by FDA (US), EMA (EU), MHRA (UK), PMDA (Japan), NMPA (China), Health Canada (Canada) and early frameworks emerging in LATAM and Middle East

Sources of Safety Data for ATMPs



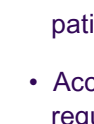
Spontaneous Reporting

- 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



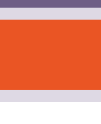
Spontaneous & solicited reports
Well-documented cases are vital



Expert clinical adjudication
Case-level review by cross-functional committees

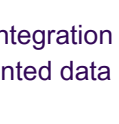


Traceability systems
Link product, batches and patient outcomes

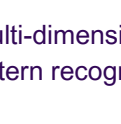


Registries
Foundation of long-term signal detection

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.

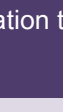
Risk Management Planning & Regulatory Expectations

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.

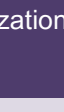
Regulators expect risk management plans to include several key elements:



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.