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Beyond the LVEF: Modernizing Pharmacovigilance and Cardiovascular Risk Management in Early-Phase Clinical Trials

Mario Alejandro Castellanos U*

Principal investigator, Universidad Nacional Autonoma de Mexico, Mexico.

***Correspondence:**
Mario Alejandro Castellanos U, Principal investigator, Universidad Nacional Autonoma de Mexico, Mexico.

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ABSTRACT

Background: *Traditional pharmacovigilance (PV) has historically relied on reactive functional changes, such as a decrease in Left Ventricular Ejection Fraction (LVEF). However, the emergence of targeted therapies demands a shift toward proactive, molecular-level surveillance [1].*

Objective: *This article explores modern strategies for cardiac signal detection in early- phase trials, emphasizing the integration of high-sensitivity biomarkers and advanced imaging [2].*

Conclusion: *Modernizing PV through "Precision Monitoring" enhances participant safety and prevents premature attrition of drug candidates [3].*

Keywords

Pharmacovigilance (PV), Drug safety surveillance, Adverse drug reactions (ADR), Signal detection, Risk management.

Introduction

The landscape of drug development is undergoing a paradigm shift. While the "gold standard" for cardiotoxicity has long been the LVEF, this parameter is notoriously insensitive to early myocardial injury [4]. In the era of Immune Checkpoint Inhibitors (ICIs), cardiac adverse events (AEs) can be fulminant and unpredictable, requiring a shift from compliance-driven reporting to sophisticated clinical strategy [5,6].

Stratified Cardiac Monitoring by Drug Class

Monitoring must be tailored to the specific mechanism of action (MoA) of the investigational product (Table 1).

Regulatory Framework and Data Integrity

Adherence to International Council for Harmonisation (ICH) standards is mandatory

1. **ICH E14 & S7B:** Recent 2022 revisions allow for integrated non-clinical and clinical data to waive formal "Thorough QT" studies [8].
2. **ICH E2F:** Any significant cardiovascular signal must be analyzed in the Development Safety Update Report (DSUR) [9].
3. **MedDRA:** Inaccurate coding can mask life-threatening signals [10].

Table 1: Comparison of Monitoring Protocols (Referenced against ESC and ASCO Guidelines [1,7].

Drug Class	Primary Cardiac Risk	Gold Standard Monitoring	PV Signal
Anthracyclines	Cumulative Cardiomyopathy	Echocardiography (LVEF)	GLS decrease > 15% [7]
Immune Checkpoint	Myocarditis / Arrhythmia	Cardiac MRI / Biopsy	hs-Troponin trend [1]
Small Molecules	QTc Prolongation	12-lead ECG	\Delta QTc > 60 ms [8]

Discussion

The Ethical and Operational Dilemma

Distinguishing drug-induced injury from background noise in multi-morbid populations is critical [11]. The implementation of Cardiovascular Adjudication Committees (CEC) provides independent review to prevent the "False Positive Trap" [12]. Furthermore, AI-enabled wearables allow for 24/7 surveillance, moving beyond the periodic ECG "snapshot" [13].

Conclusion and Future Perspectives

The definition of cardiac safety must shift to molecular injury and structural strain. Future trials will likely utilize Genomic Pharmacovigilance to determine monitoring frequency based on individual polygenic risk scores [14].

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