2026 Volume: 01 Issue: 07 ISSN 1671-2838 Page No: 653-660

Pharmaceutical Care and Research

https://pcrjournal.com

Review Article

Volume: 01
Issue: 07

SYSTEMATIC REVIEW AND CLINICAL EVALUATION OF CAUSALITY ASSESSMENT METHODS FOR ADVERSE DRUG REACTIONS (ADRS) IN PHARMACOVIGILANCE

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Article Received: 23 August 2026
Article Revised: 11 September 2026
Published on: 01 October 2026

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DOI: https://doi-doi.org/101555/ijpcr.2243

ABSTRACT

Adverse Drug Reactions (ADRs) present a massive challenge to global healthcare systems, leading to escalating **morbidity**, prolonged hospital stays, and extensive **socioeconomic burdens**. Assessing whether a suspected drug is clinically responsible for an adverse medical event remains the foundational pillar of robust **post-market surveillance**. This systematic review delivers an exhaustive, critical comparison of traditional and contemporary **causality appraisal frameworks**, including expert clinical judgment schemas (**WHO-UMC system**), standardized algorithmic checklists (**Naranjo Scale**, **Liverpool tool**, and organ-specific **RUCAM framework**), and multi-layered probabilistic models (**Bayesian networks**). The study expands on operational vulnerabilities such as **inter-rater variance**, data-entry bottlenecks, and linguistic ambiguity. Furthermore, it incorporates standard **regulatory reporting workflows** (**CDSCO**, **FDA**, **EMA**) and offers real-world step-by-step **clinical scoring simulations**. Finally, we highlight the paradigm shift toward integrating automated, **No-Code Artificial Intelligence (AI)** and **Large Language Models (LLMs)** to ensure optimized, objective, and real-time **patient safety networks** across modern pharmacy ecosystems.

KEYWORDS: Adverse Drug Reactions (ADRs); Pharmacovigilance; Causality Assessment Methods; Naranjo Algorithm; WHO-UMC System; No-Code Artificial Intelligence (AI).

1. INTRODUCTION

The complete clinical safety footprint of any **novel molecular entity** cannot be realistically established during pre-approval **Phase I-III clinical trial** designs. These structural constraints arise due to highly controlled cohorts, short exposure durations, explicit **exclusion criteria** (such as pediatric, geriatric, or pregnant demographics), and the complete absence of complex **polypharmacy**

environments. Consequently, public safety relies directly on the comprehensive operational integrity of **post-marketing surveillance** and **spontaneous reporting systems**.

1.1 The Clinical Dilemma

In micro-level bedside pharmacy practice and macro-level safety monitoring, healthcare providers face a persistent challenge: distinguishing whether an unexpected medical sign, symptom, or laboratory abnormality is genuinely **drug-induced**, secondary to an underlying pathophysiological disease pathway, or triggered by a complex drug-drug interaction. Misinterpreting this causal link can carry devastating public healthcare consequences. Mistakenly dismissing an actual ADR allows dangerous therapeutics to remain on market shelves, while false positive attributions create undue clinical anxiety, leading to unnecessary discontinuation of critical, life-saving therapies.

Scope and Operational Definitions

Causality assessment is defined as a systematic, validated, and evidence-guided scientific framework engineered to determine the qualitative likelihood or exact quantitative probability that a specific medicinal agent is causally associated with an observed adverse clinical outcome. It provides a standardized data infrastructure for global regulatory agencies, translating subjective clinical intuition into transparent, reproducible, and trackable safety datasets.



2 METHODOLOGICAl CLASSIFICATION OF ASSESSMENT APPROACHES

Over multiple decades of evolution, pharmacovigilance research has produced diverse analytical methodologies to process Individual Case Safety Reports (ICSRs). These modern approaches are globally categorized into three distinct technical paradigms.

1.2 Expert Judgment and Global Introspection (WHO-UMC System)

The World Health Organization–Uppsala Monitoring Centre (WHO-UMC) Causality Assessment System stands as the primary globally adopted expert-driven framework. Rejecting rigid numerical scoring metrics, the WHO-UMC system relies on a holistic, clinical evaluation performed by an expert panel. Practitioners review the case's chronological history, laboratory parameters, and alternative clinical etiologies concurrently.

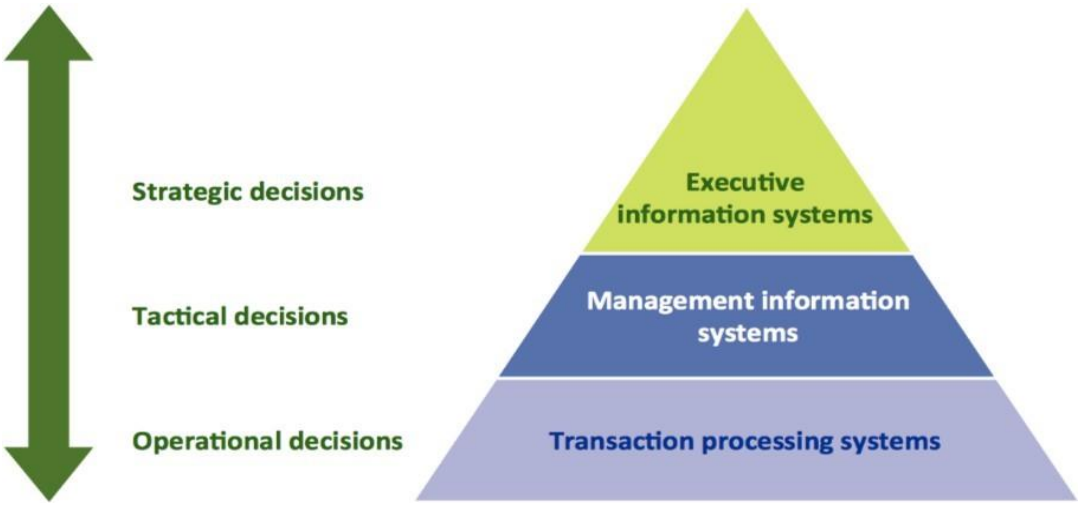
The evaluation categorizes cases into six explicit diagnostic tiers:

Certain: Plausible timeline, confirmed by lab work, explicit dechallenge and positive rechallenge. Probable/Likely: Reasonable timeline, unlikely disease source, positive dechallenge.

Possible: Logical sequence, but easily explained by underlying medical state. Unlikely: Improbable temporal link or a clearer disease explanation exists.

Conditional/Unclassified: More clinical data required.

Unassessable/Unclassifiable: Heavily conflicting or profoundly missing parameters.



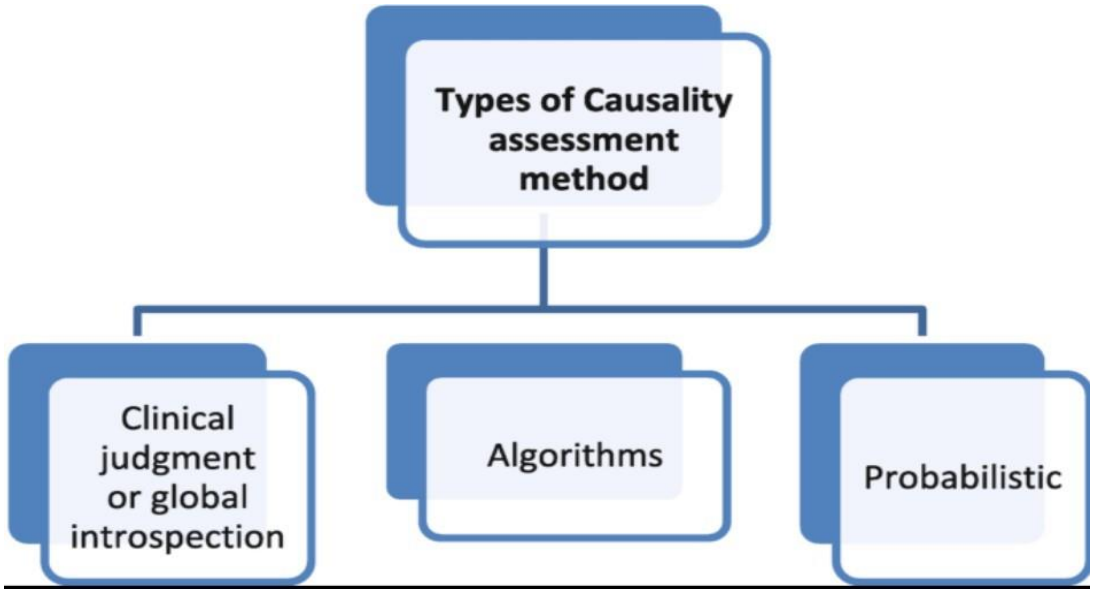
1.2 Standardized Algorithms and Scoring Systems

To reduce human subjectivity and eliminate inter-observer variations, structured questionnaires with assigned quantitative scoring metrics were developed. The Naranjo Algorithm, introduced in 1981, remains the benchmark bedside tool in academic and hospital pharmacy. It comprises a

10-question matrix measuring previous publications, baseline timing, dechallenge behavior, rechallenge outcomes, placebo responses, objective laboratory confirmation, and dose-response kinetics. Total scoring ranges determine categories: >= 9 indicates Definite; 5–8 implies Probable; 1–4 represents Possible; and <= 0 is classified as Doubtful.

Alternative algorithms include the Liverpool Adverse Drug Reaction Causality Assessment Tool, which utilizes a sequential, flowchart-driven binary logic tree designed to enhance reproducibility among bedside nurses and pharmacists. Furthermore, highly specializedframeworks exist for targeted organ injury, most notably the RUCAM Scale (Roussel Uclaf Causality Assessment

Method), optimized exclusively for Drug-Induced Liver Injury (DILI) and Herb-Induced Liver Injury (HILI) by integrating precise hepatocyte enzyme recovery kinetics.



Bayesian Networks (such as the Bayesian Adverse Reactions Diagnostic Instrument - BARDI) utilize complex mathematical probability distributions to manage uncertainty. This system combines background epidemiological data (prior probability) with specific clinical evidence from the current patient case to calculate a definitive posterior mathematical percentage likelihood of causality. While highly precise, these methods require heavy computation and extensive background databases, making them ideal for automated large-scale healthcare data.

1.2 Comparative Methodological Framework

Assessment Method	Primary Mechanism	Core Benefit	Critical Limitation
WHO-UMC System	Global Introspection & Expert Review	Holistic, flexible clinical overview	Low inter-rater reproducibility
Naranjo Algorithm	10-Question Weighted Scoring Check	Rapid bedside triage; highly standard	Rigid; ignores polypharmacy
Liverpool Tool	Flowchart-driven Binary Logic Tree	Extremely high inter-rater consistency	Lacks sensitivity for complex cases
RUCAM Scale	Organ-Specific Kinetic Algorithms	Gold standard for hepatic injury/DILI	Strict limited to liver toxicity
Bayesian Networks	Mathematical Posterior Probabilities	Objective quantitative data integration	Highly complex; requires vast databases

2. CLINICAL CLASSIFICATION AND CRITERIA

Understanding the mechanistic profile of an adverse effect is crucial before attempting to score its causal probability. ADRs are classified into dose-dependent **Type A** (augmented pharmacological responses, such as bleeding from warfarin) and dose-independent **Type B** (bizarre, idiosyncratic, or hypersensitivity immunological responses, such as Stevens-Johnson Syndrome).

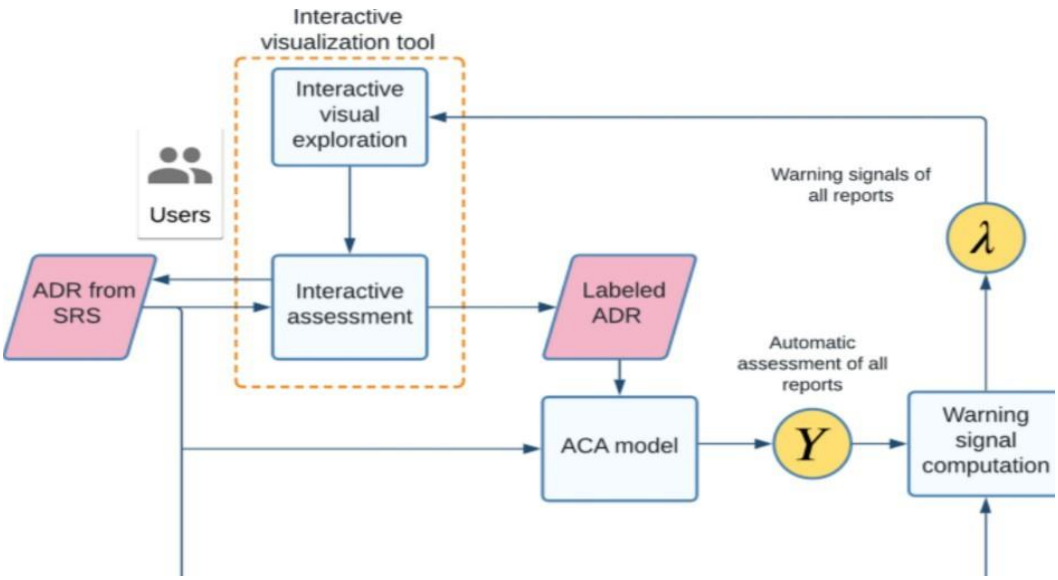
Independent of the selected framework, causality determination fundamentally relies on **four core clinical pillars**:

- **1. Temporal Sequence:** The onset of the clinical presentation must follow a rational chronological window post-drug exposure.
- **2. Dechallenge Resolution:** The mitigation or complete disappearance of toxic signs upon drug cessation or dose down-titration.
- **3. Rechallenge Confirmation:** The direct, visible return of identical pathology upon re-exposure (often restricted due to ethical safety barriers).
- **4. Exclusion of Alternative Etiologies:** A rigorous clinical scan to prove that background pathophysiological diseases or concurrent multi-drug treatments are not the true source of the reaction.

3. REAL-WORLD CLINICAL SIMULATIONS AND APPLICATIONS

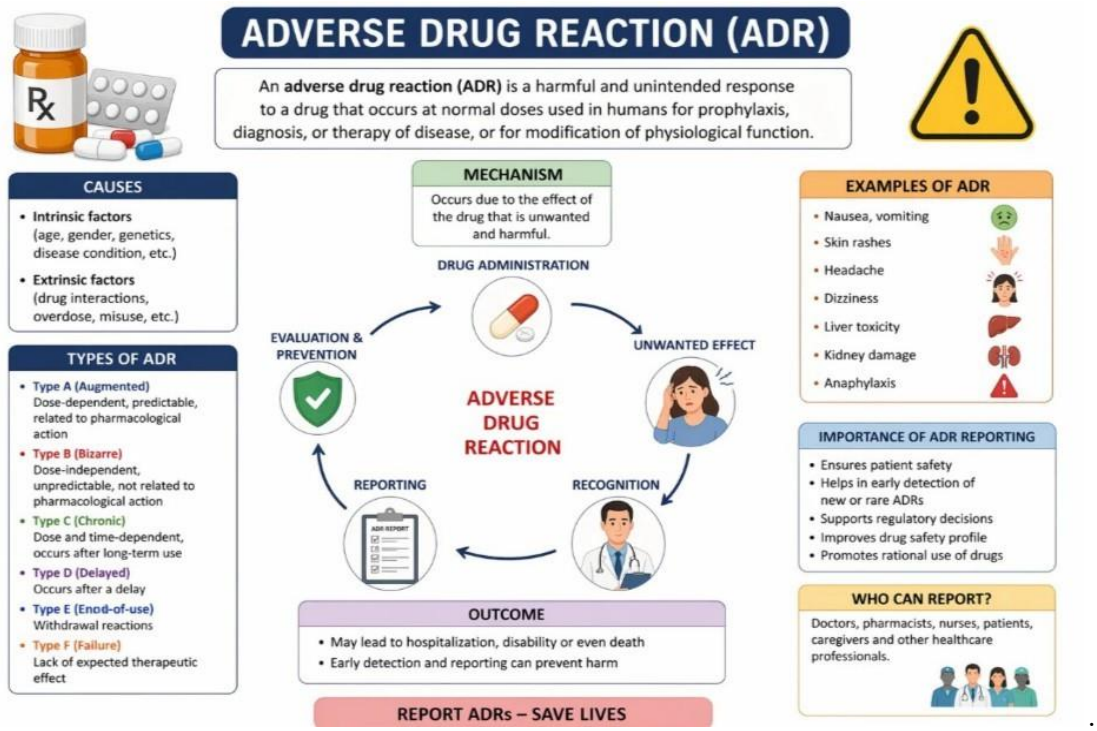
To understand how these methods operate under practical conditions, consider two common clinical scenarios encountered in hospital setups:

- **Case Study 1:** A 45-year-old patient receives Amoxicillin for a respiratory tract infection. On day 5, the patient exhibits elevated alanine aminotransferase (ALT) levels. Applying the RUCAM scale, the chronological window is highly suggestive (+2 points), alternative viral causes are ruled negative (+1 point), and subsequent dechallenge demonstrates a 50% drop in liver enzymes within 8 days (+2 points). The final score maps to a 'Probable' classification, validating rapid therapeutic withdrawal.
- **Case Study 2:** An epileptic patient on Phenytoin exhibits an aggressive maculopapular rash. Utilizing the Naranjo scale, previous literature reports confirm this pattern (+1), the rash appeared post-administration (+2), and cleared upon drug removal (+1). No alternative explanations are presen (+2). The resulting score of 6 firmly establishes a 'Probable' adverse reaction, requiring an alternate anticonvulsant regiment.



4. THE FUTURE PARADIGM: DIGITAL AND NO-CODE AI INTEGRATION

Traditional manual workflows are heavily constrained by data backlogs, high operational costs, and personal clinical biases. Modern global pharmacovigilance is undergoing a paradigm shift toward automated **No-Code Artificial Intelligence (AI)** and **Large Language Model (LLM)** infrastructures. These systems map erratic patient descriptions directly into standardized **MedDRA terminology** with high semantic accuracy. By automating standard **ICSR data fields** and running algorithm questionnaires without human variance, no-code frameworks empower clinicians to launch real-time **safety monitoring workflows** without writing a single line of software code, decreasing institutional review costs drastically



4. CONCLUSION AND REGULATORY PERSPECTIVES

Establishing definite causality links is vital to protect public health and optimize therapeutic drug selections. Data gathered through structured protocols is routinely compiled and forwarded to major regulatory systems, including India's **CDSCO** (**Pharmacovigilance Programme of India - PvPI**), the US **FDA's FAERS** database, and Europe's **EMA EudraVigilance** framework to drive global safety actions.

This review highlights that while **digital automation** represents the future, a balanced methodology linking expert introspection with reproducible **scoring algorithms** remains the current gold standard to preserve **patient safety** across the pharmacy ecosystem.

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