CONFIDENTIAL / PEER-REVIEW DOSSIER

Marginalia red flags

Interrogating the Medical Literature

A clinician's diagnostic framework for critical appraisal and evidence-based practice.

Marginalia red flags

Based on PsychoPharmRef Guidelines | Data current as of May 2026.

Evidence Does Not Simply Exist

The modern literature landscape is not a perfect record of truth. It is generated, published, reviewed, promoted, and sometimes retracted within a complex ecosystem of incentives.

SURFACE APPEARANCE: THE POLISHED RECORD

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

OCTOBER 26, 2023. VOL. 389 NO. 17.

Randomized Trial of Novel Therapy

Global Health Initiative Outcomes

Clinical Case Studies: Cardiology

Editorials and Perspectives

RECEIVED: OFFICIAL RECORD

FORENSIC ANALYSIS: THE UNDERLYING CHAOS

The NEW ENGLAND JOURNAL of MEDICINE

FLAGGED FOR REVIEW

ESTABLISHED IN 1812

Randomized Trial of Novel Therapy

DATA DISCREPANCY - See p. 45, Table 2. Possible P-hacking?

CONFLICT OF INTEREST UNDISCLOSED - Funding Source Questionable. Investigate.

OCTOBER 26, 2023. VOL. 389 NO. 17.

Randomized Trial of Novel Therapy

Global Health Initiative Outcomes

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SELECTIVE REPORTING? Where are negative results?

Original conclusion showed no significant benefit. REVISED per sponsor request.

FORENSIC EVIDENCE: COMPROMISED

[MEDICAL CHART: PATIENT INTAKE FORM]

URGENT REVIEW

The Patient: The Medical Literature

Chief Complaint: Information overload and replication failures — *Symptoms include reproducibility crisis, publication bias, and statistical manipulation.*

Our Objective: Transform clinicians from passive consumers into active investigators. We will perform the History, Anatomy, Physical Exam, and Pathological assessment of modern research.

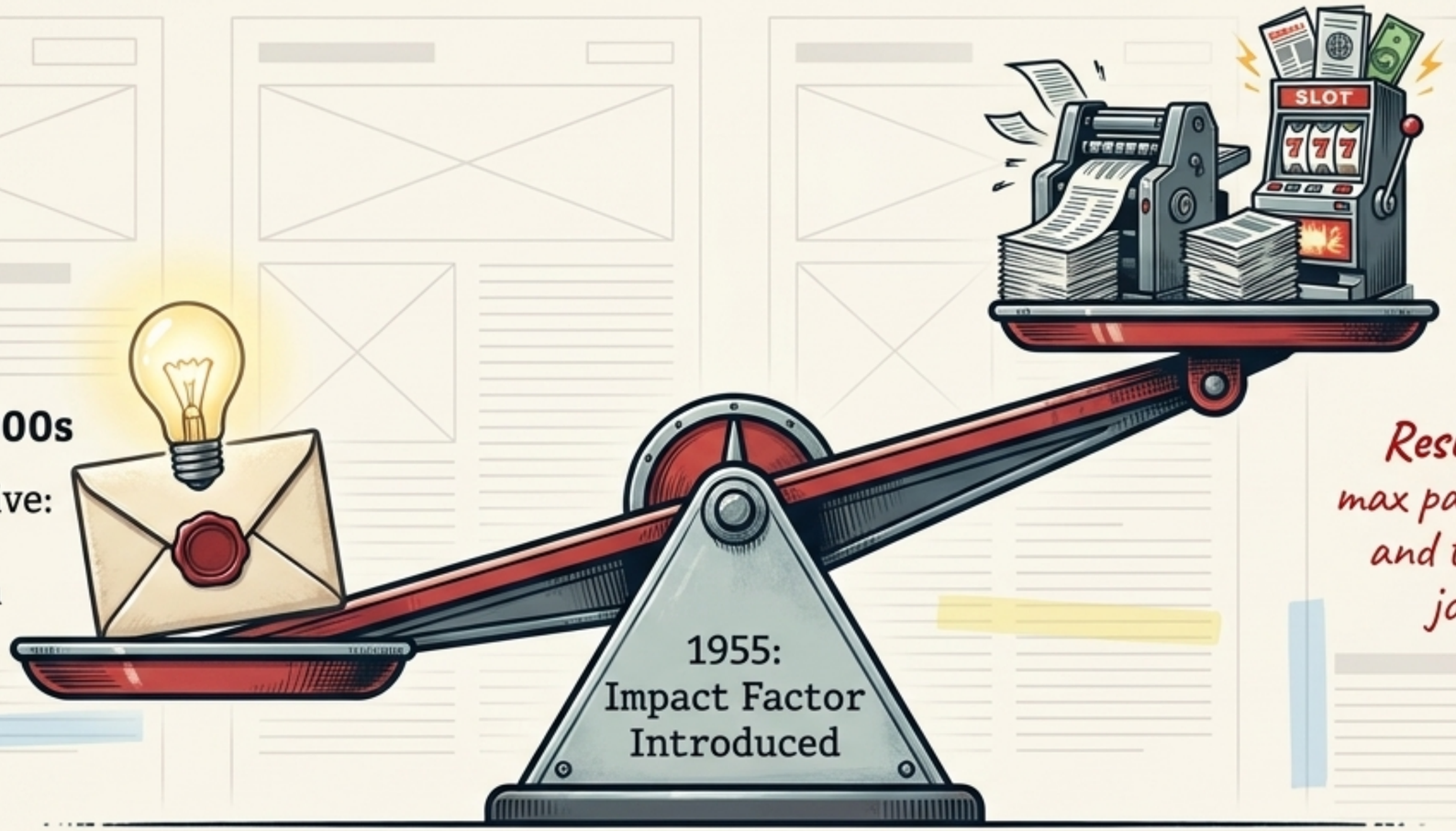
Critical condition. Requires immediate forensic examination.

The History of Present Illness: Shifting Incentives

Margin notes

1665 to mid-1900s

Primary Incentive:
Intellectual Contribution



1970s to Present

Primary Incentive:
Publish-or-Perish

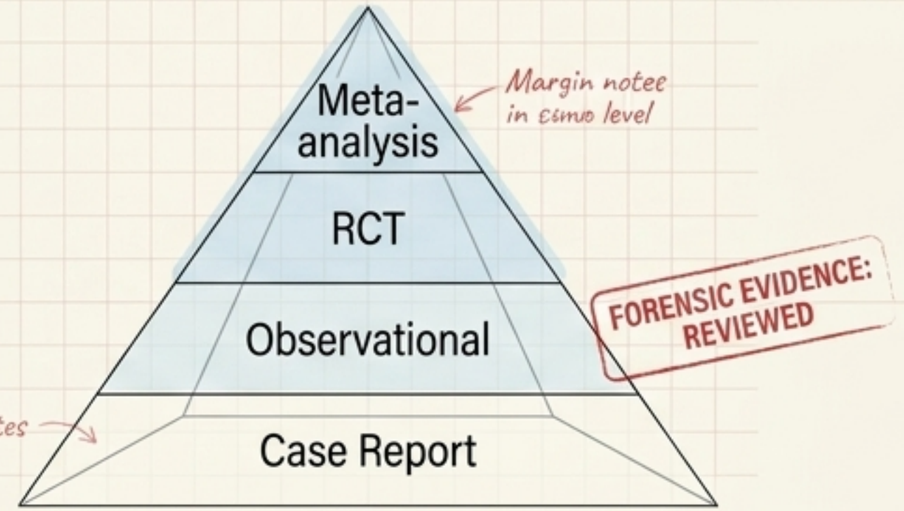
Result: Slicing data for max papers, publication bias, and the rise of predatory journals (2000s).

Clinical notes in margin margins

Mostly note in margin of story

Scientists are increasingly rewarded not necessarily for doing good science, but for publishing science.

The Anatomy: Hierarchy of Evidence



Design Architecture	Diagnostic Strength	Critical Limitations	Optimal Clinical Use
Case Report/Series	Documents rare phenomena.	Anecdotal, no control. Red Flag: Anecdotal	Novel presentations. Red Flag: Anecdotal
Cross-Sectional	Fast, good for prevalence.	Cannot determine causality. Red Flag: No caucality	Epidemiology.
Cohort	Establishes temporal relationship.	Confounding, expensive. Red Flag: Confounding	Risk factors, prognosis.
Case-Control	Efficient for rare outcomes.	Recall bias. Red Flag: Recall bias	Hypothesis testing.
RCT	Gold standard, proves causality.	Expensive, may not reflect real world.	Efficacy.
Systematic/Meta	Highest evidence, pools data.	Garbage in, garbage out. Red Flag: Data Quality	Guideline consensus.

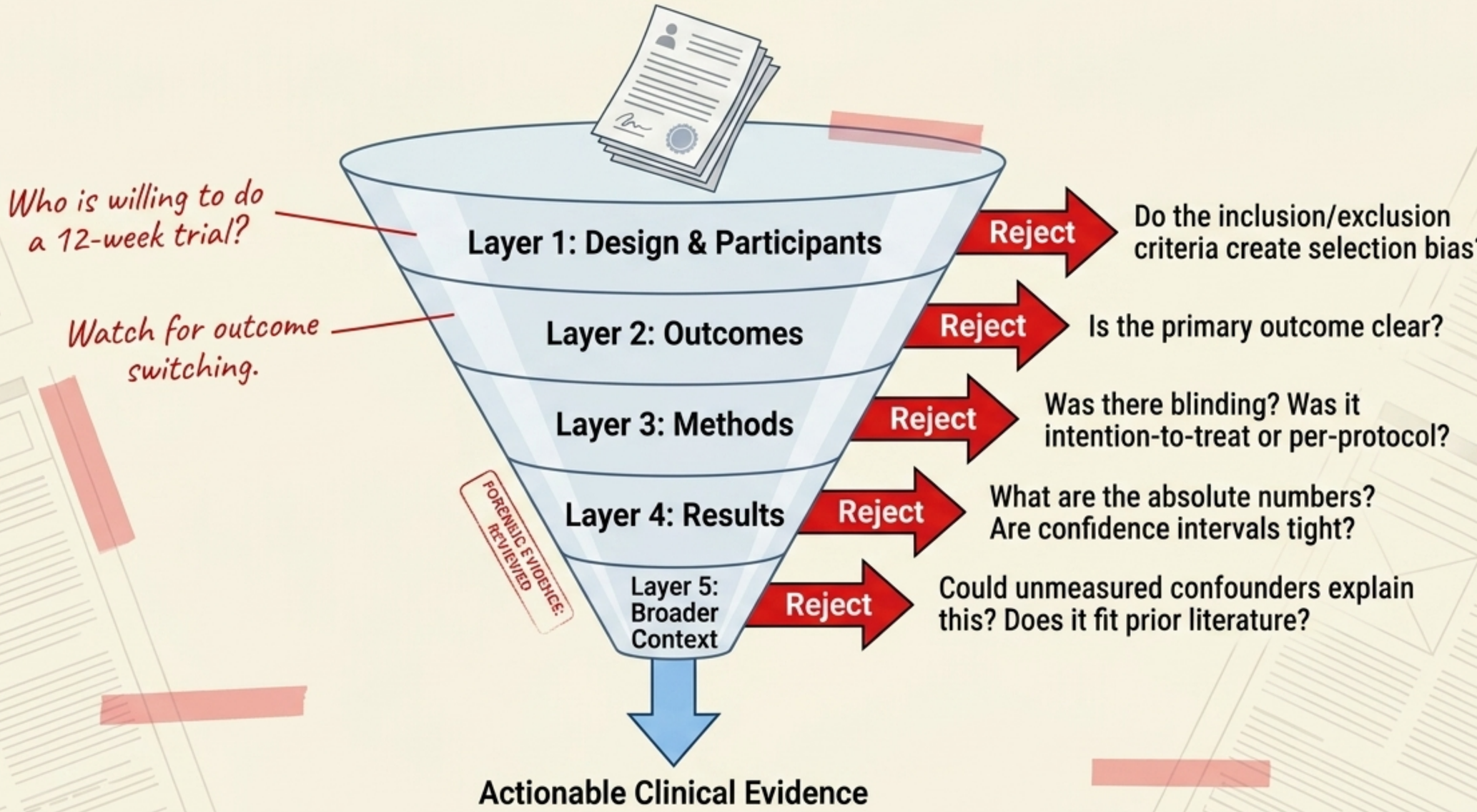
Red Flag: stract

Red Flag: Recall bias

Red Flag: External Validity

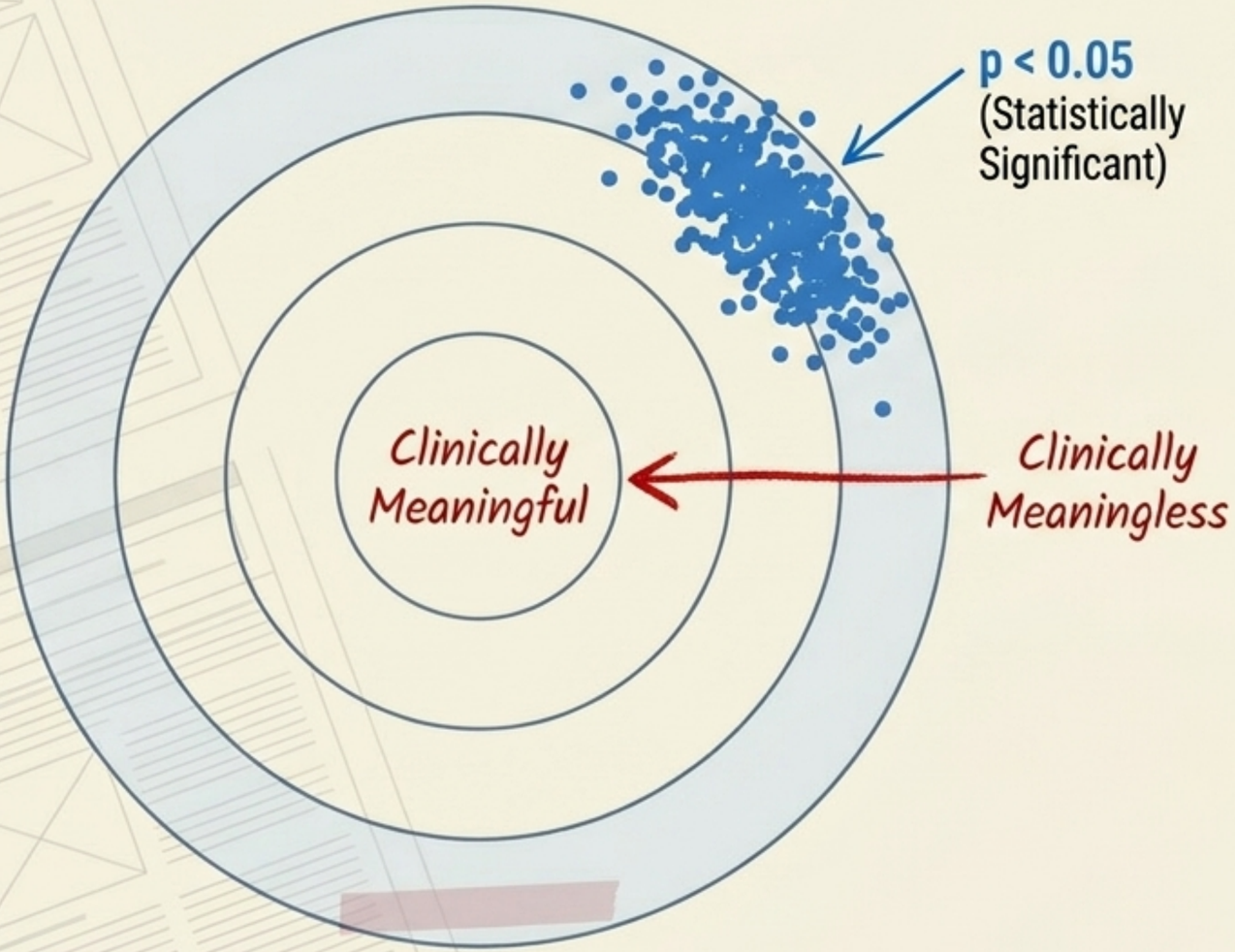
FORENSIC EVIDENCE: REVIEWED

The Physical Exam: The Appraisal Funnel



FORENSIC EVIDENCE: REVIEWED

Pathology I: The Target Illusion



Key distinction!

The P-Value Trap

A *p*-value of 0.04 only indicates the probability of observing the data if the null hypothesis were true. It does not mean the effect size matters in practice.

Clinical Reality

An antidepressant that reduces symptoms by 2 points on a 60-point scale is significant on paper, but invisible to the patient.

Critical example

Flawed Assumptions

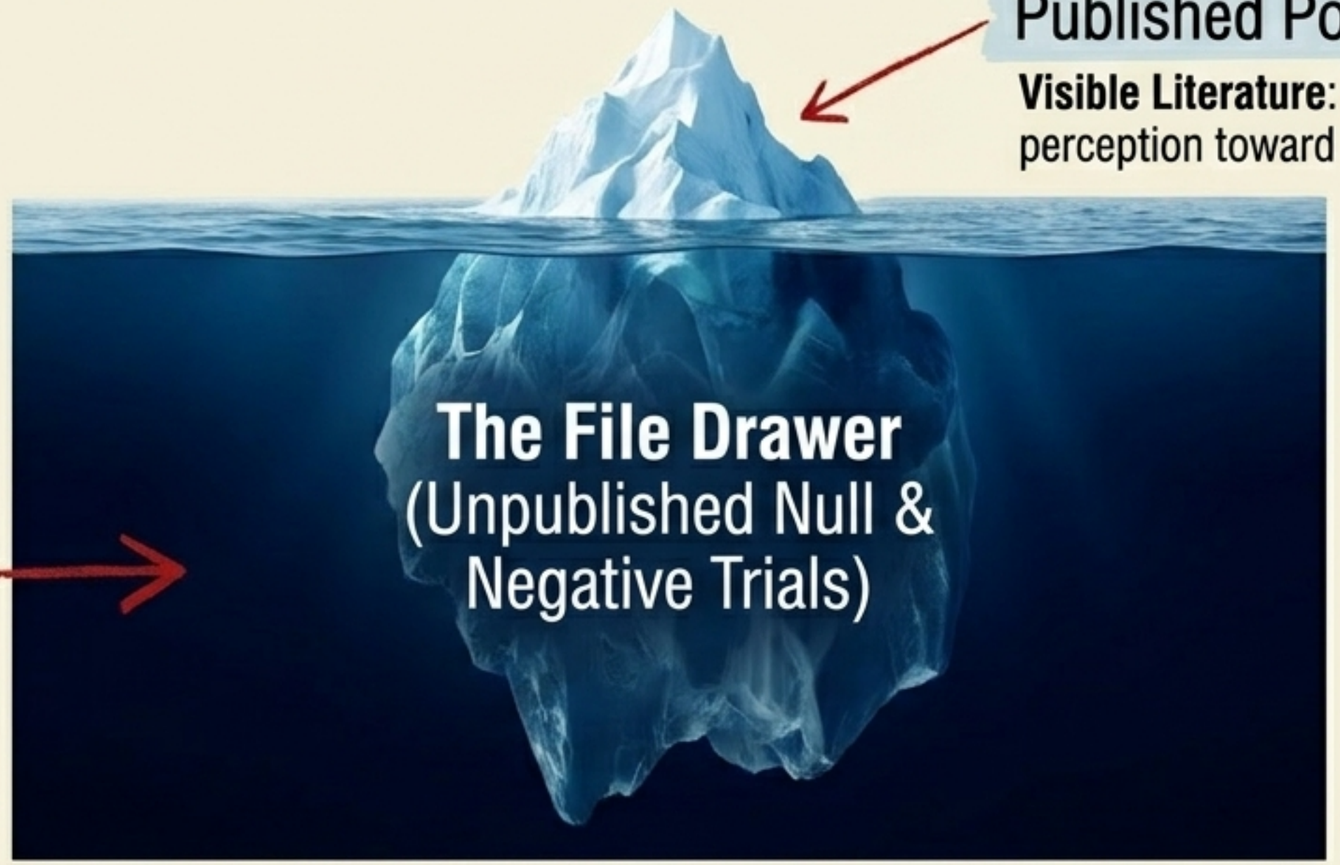
The 1998 Wakefield MMR study (retracted 2010) fell apart because its core assumption—recovering measles virus from intestinal samples—was false.

FORENSIC EVIDENCE: REVIEWED

Pathology II: Publication Bias

Published Positive Trials

Visible Literature: Skews clinical perception toward massive efficacy.



Example: Meta-analyses of FDA submissions reveal the true benefit of SSRIs is much smaller when hidden negative trials are factored in.

Studies with positive or novel results are exponentially more likely to be published. You are diagnosing a patient based on an incomplete medical history.

FORENSIC EVIDENCE: REVIEWED

Pathology III: Structural Toxins in Publishing

Impact Factor Flaws

Metric

Average citations in two years.

The Reality

Red flag: Quality correlation?

High-impact journals suffer high retraction rates. Editors can artificially inflate metrics by rejecting papers that do not cite the journal.

The Open Access Paradox

The Goal

Democratize knowledge by moving from reader-pays to author-pays.

The Unintended Consequence

Critical flaw: Financial incentive overruns quality control.

Predatory Journals. By relying on author fees, journals are financially incentivized to accept nearly any manuscript, creating a cottage industry of spam science.

WARNING: METHODOLOGICAL RED FLAGS

Red flag: Protocol deviation

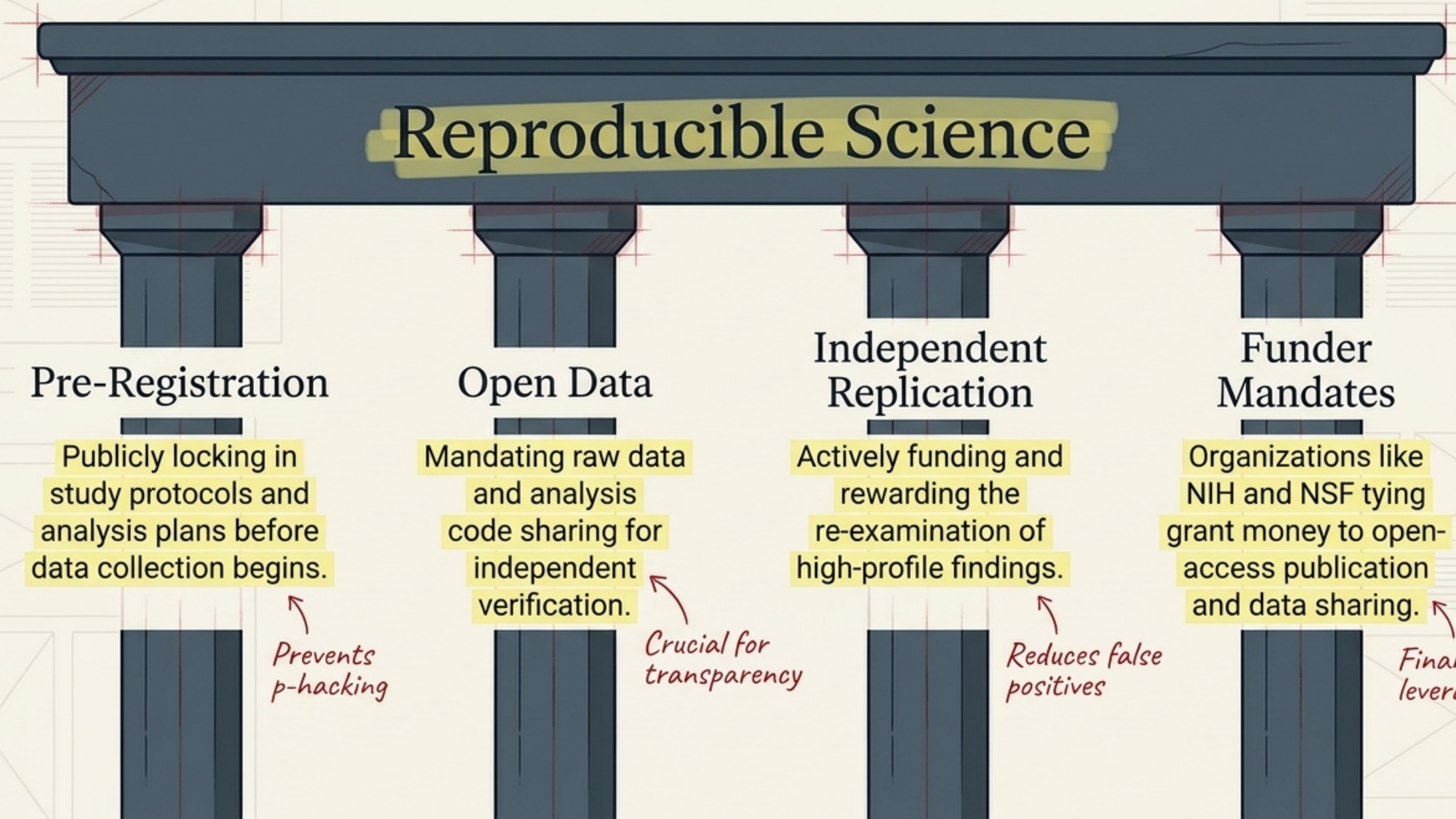
- **OUTCOME SWITCHING:** The reported outcome differs from what was registered a priori.
- **P-HACKING:** Multiple statistical tests were run, but only the positive
- **DROP-OUT EVASION:** Large dropout rates with no analysis of who left the trial or why.
- **POST-HOC SUBGROUPS:** Trumpeting success in a specific demographic that was not pre-specified in the study design.
- **NULL-CROSSING INTERVALS:** Confidence intervals that cross the null, rendering findings ambiguous.
- **SAMPLE SIZE ILLUSIONS:** Massive effect size claims derived from a tiny sample.

Data Dredging

Unreliable precision

The Treatment Plan: Curing the Replication Crisis

FORENSIC EVIDENCE: REVIEWED



Pre-Registration

Publicly locking in study protocols and analysis plans before data collection begins.

Prevents p-hacking

Open Data

Mandating raw data and analysis code sharing for independent verification.

Crucial for transparency

Independent Replication

Actively funding and rewarding the re-examination of high-profile findings.

Reduces false positives

Funder Mandates

Organizations like NIH and NSF tying grant money to open-access publication and data sharing.

Financial leverage

FORENSIC EVIDENCE: REVIEWED

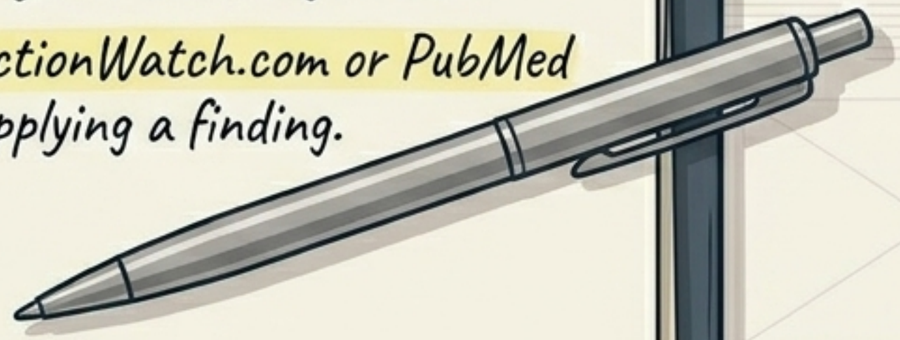
Prescriptions for Practice

Red flag: Premature adoption

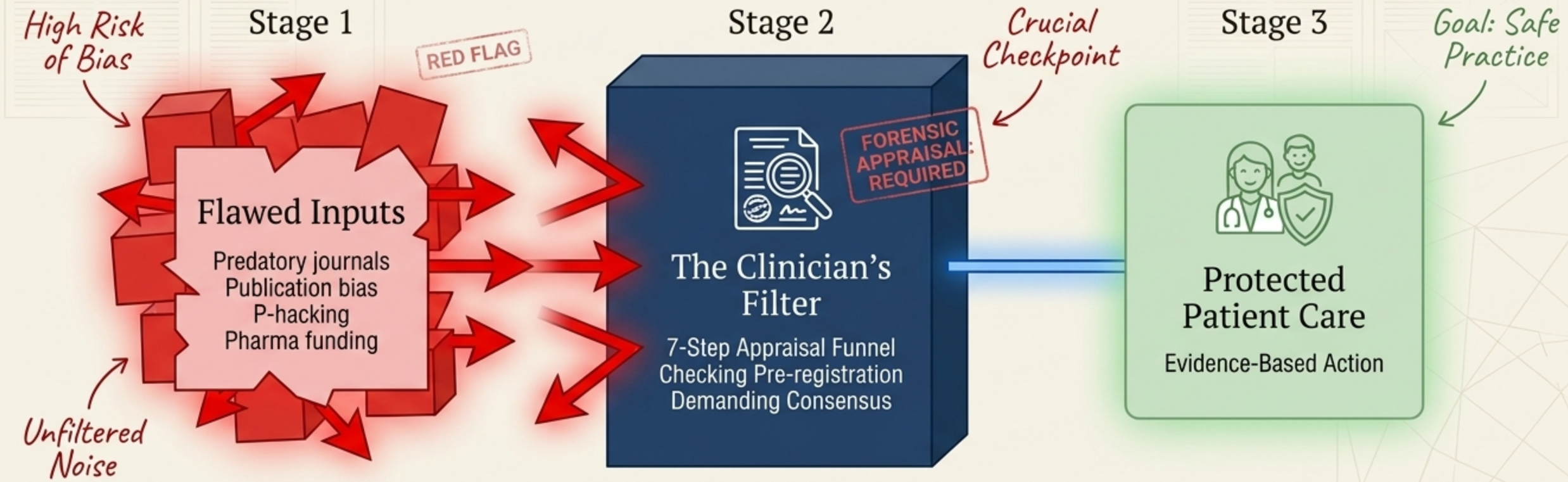
1. **Wait for Consensus:** No single study should change your practice. Demand replication.
2. **Beware the Mechanism:** Blocking a receptor does not automatically mean treating a disease. Skepticism is required for purely mechanistic claims.
3. **Audit the Authors:** Authors often confess the study's flaws in the Limitations section. Read it first.
4. **Follow the Money:** Always trace conflicts of interest. Pharma-funded studies are statistically more likely to show drug benefit.
5. **Verify the Record:** Always check RetractionWatch.com or PubMed for retraction status before citing or applying a finding.

Crucial step for validity

Financial bias indicator



The Ultimate Gatekeeper



The literature is a powerful tool. But without the mindful clinician acting as the final filter, it has as much potential to mislead as it does to illuminate.

— Attriuiin Strvinge

Core Principle