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# Uncovering seeding trials: examining non-scientific purposes in clinical trials

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## Standfirst

*Seeding trials*—clinical studies designed primarily for marketing rather than scientific advancement—pose underappreciated risks to research integrity and patient safety. Sukhun Kang and colleagues argue for stronger transparency measures and coordinated global oversight to address this hidden practice.

Seeding trials are clinical studies that prioritise marketing over science while disguising this commercial purpose as legitimate research.[1 2] The term 'seeding trial' entered the scholarly literature in 1994, when Food and Drug Administration (FDA) Commissioner David Kessler and colleagues described such studies as 'thinly veiled attempts to entice doctors to prescribe a new drug' through trials that 'appear to serve little or no scientific purpose'.[3] Table 1 summarises observable characteristics that can help identify such trials, though definitive classification typically requires access to internal sponsor documents revealing intent. By exposing physicians to new drugs under the guise of data collection, these trials distort prescribing patterns and delay recognition of harms.[4] Their objectives extend beyond efficacy evaluation to include encouraging off-label prescribing, switching patients from established treatments and expanding into market niches of questionable benefit.

Despite three decades of awareness, regulatory systems worldwide remain poorly equipped to identify and prevent seeding trials. Reliance on whistleblowers and internal leaks is untenable: regulators, clinicians and patients require proactive mechanisms to detect and deter these practices. We argue that seeding trials should be treated not as rare aberrations but as a recurring form of commercial bias within pharmaceutical research. Documented cases span across time and multiple therapeutic areas: the ADVANTAGE trial for rofecoxib (1999), the STEPS trial for gabapentin (Neurontin) (1996) and related misconducts include Study 329 for paroxetine (1994).[1 5 6] These cases emerged only because litigation or whistleblowers exposed internal documents; the true prevalence of marketing-driven protocols remains unknown. That such practices persisted across different companies, drug classes and regulatory environments suggests structural incentives rather than isolated misconduct. Proactive detection—through transparency mandates and harmonised oversight—is essential to curtail these practices.

### Seeding trials put marketing above science

Seeding trials violate core principles of research ethics. They compromise autonomy by withholding material information: participants cannot give genuine informed consent when the trial's primary purpose—marketing—is concealed. They breach beneficence and non-maleficence by enrolling individuals in studies designed to serve commercial objectives rather than resolve genuine therapeutic uncertainty, exposing participants to risks without corresponding scientific justification. They offend justice by distributing research burdens unfairly: patients in seeding trials assume risks that generate data serving primarily corporate interests, while trials sited in low-resource settings may exploit populations with limited regulatory protection. These violations are not merely procedural. When participants later discover that their involvement served marketing rather than science, trust in clinical research erodes—making future recruitment more difficult and undermining the social contract that sustains ethical research.

### Intent of trial matters

Some argue that the line between legitimate research and seeding trials is not easily drawn. As London and colleagues note, defenders argue that post-marketing studies are 'a vital tool for addressing numerous evidentiary gaps in comparative effectiveness, drug safety, and real-world utility', and that labelling them as unethical could deter legitimate research.[7] Matheson similarly observes that 'nearly all industry-financed trials serve marketing functions' to some degree, and the challenge lies not in identifying 'fatuous' seeding trials but in recognising 'the coexistence within the same clinical studies of defensible science and subtle marketing spin.[4] This spectrum—from clearly legitimate research to unambiguous marketing—makes bright-line distinctions difficult and underscores the need for transparency about sponsor intent.

Two documented cases exemplify the unambiguous end of this spectrum.

Merck's ADVANTAGE trial with Vioxx was presented as scientific research, but internal company documents revealed that its primary purpose was to introduce physicians to Vioxx prescribing. Meanwhile, participants were exposed to cardiovascular risks that the company downplayed. The fallout was severe: approximately 30 000 lawsuits and nearly $5 billion in compensation followed the drug's withdrawal.[6 8 9] The Study of Neurontin: Titrate to Effect, Profile of



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Table 1 Observable characteristics indicative of seeding trials[11 13]

| Observable characteristic | Explanation |
|---|---|
| Low patient-to-site ratio | Large number of study sites enrolling few patients each |
| Extensive sponsor involvement | Limited independent oversight, heavy company control |
| Investigator selection based on volume | Investigators selected primarily for prescribing volume |
| Emphasis on secondary endpoints | Primary focus on endpoints not directly clinically relevant |
| Minimal scientific rigour | Superficial or minimal scientific data collection |
| Phase 4 (post-marketing) trial | Post-marketing trials less scrutinised by regulators |

Safety trial provides another instructive case.[1 10] Internal documents from Parke-Davis revealed that the trial was designed not to gain FDA approval for new indications but to 'disseminate the information as widely as possible through the world's medical literature", generating market excitement and stimulating off-label prescribing. The company employed 'peer-to-peer selling' by physician speakers and funded studies with 'key customers' to expand gabapentin use in neuropathic pain and bipolar disorder—indications for which the drug lacked approval. Unlike Vioxx, gabapentin remains widely prescribed today, underscoring that seeding trial harms extend beyond withdrawn drugs.

Many trials, however, occupy an ambiguous middle ground—generating useful data while also serving promotional objectives. Barbour and colleagues found that 7% of trials in leading journals fell into a 'MAYBE' category, exhibiting some marketing characteristics but resisting definitive classification.[11] Matheson similarly notes that large outcome trials for angiotensin receptor blockers addressed clinically relevant issues but were also used during their courses to generate interest and product differentiation.[4] Such trials illustrate the spectrum between legitimate research and seeding: they may answer important scientific questions while simultaneously exposing hundreds of physicians to the sponsor's product and generating publications favourable to its market position.

The scarcity of documented borderline cases is itself revealing. Internal documents—the only definitive evidence of sponsor intent—are typically exposed through litigation, which tends to uncover egregious violations rather than ambiguous ones. Without access to such documents, external observers cannot classify individual trials with certainty. This evidentiary gap underscores why proactive transparency about sponsor objectives—not merely retrospective detection—is essential.

### Whistle-blowers should not be our first line of defence

Currently, the detection of seeding trials largely depends on internal leaks or whistle-blower actions, highlighting significant gaps in regulatory oversight.[12] Such trials are adeptly designed to avoid overt indicators of promotional intent, making proactive identification challenging. Without systematic surveillance mechanisms, the research community remains dependent on retrospective exposés rather than prospective prevention.

### Transparency and data can expose hidden marketing

To deter seeding trial practices, transparency is key to stripping away the disguise. Requiring public trial registration, full disclosure of sponsor funding and investigator payments is no longer optional—it is a baseline for ethical research.[13] Observable trial characteristics such as low patient-to-site ratio, extensive sponsor involvement, investigator selection based on volume, emphasis on secondary endpoints, minimal scientific rigour and phase 4 trials should trigger further scrutiny.[14]

Public databases, such as ClinicalTrials.gov, already collect significant information related to clinical trials. However, additional transparency measures, including detailed reporting on investigator remuneration, sponsor contributions and clear articulation of trial objectives, are essential to distinguish legitimate research from promotional activities.[15] Previous analyses have identified observable characteristics that distinguish seeding trials from legitimate research. Barbour and colleagues developed these criteria through a systematic review of documented seeding trials, including internal industry documents exposed through litigation, and validated them against trials in leading medical journals.[11] Martineau and colleagues subsequently applied similar criteria to large prospective antidepressant trials registered on ClinicalTrials.gov.[13] Table 1 synthesises characteristics common to both frameworks: structural features (low patient-to-site ratios, phase 4 timing), governance patterns (extensive sponsor involvement, investigator selection based on prescribing volume) and design choices (emphasis on secondary endpoints, minimal scientific rigour). These criteria function as red flags warranting scrutiny rather than definitive markers of marketing intent.

We analysed 34 398 industry-funded phase 3 and 4 interventional trials with results posted on ClinicalTrials.gov from 1998 to 2024, covering seven therapeutic areas that had a confirmed seeding trial in the prior literature (osteoarthritis, major depressive disorder, epilepsy, asthma, type 2 diabetes, schizophrenia and rheumatoid arthritis).[11 13] Applying criteria from Barbour *et al*—including patient-to-site ratios below 15 and limited independent oversight—204 trials (0.59%) displayed marketing-driven characteristics, with prevalence ranging from 0.15% (osteoarthritis) to 0.98% (rheumatoid arthritis).[13] This figure suggests relative rarity but confirms their existence and the need for vigilance. Yet systematic surveillance of seeding trial characteristics remains underdeveloped: no registry routinely flags trials with suspicious design features, and no regulatory body conducts prospective monitoring for marketing-driven protocols. Future research should validate detection criteria across therapeutic areas, assess their predictive value against confirmed cases and develop computational tools—including machine learning approaches—to identify suspicious patterns in real time. Until such infrastructure exists, the research community will continue to rely on retrospective exposés rather than prospective prevention.

### Global oversight and practical solutions

Effectively addressing the challenge of detecting seeding trials requires not only enhanced national oversight but also a coordinated international response.[16] The global variability in regulatory standards creates vulnerabilities that pharmaceutical companies can exploit to conduct marketing-driven trials unnoticed. While regulatory authorities in the USA, the European Union, Canada and Australia have increased their transparency requirements and post-approval oversight to varying degrees, considerable differences persist. For instance, the European Medicines Agency has mandated extensive trial registration and results reporting through the EudraCT database, and Canada's Health Products and Food Branch has established stricter post-marketing surveillance.[14 17] However, regulatory systems in other jurisdictions—particularly in low- and middle-income countries—often remain less stringent, potentially increasing the risk of seeding trials and subsequent patient harm.



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**Box 1 Action priorities for curbing seeding trials**

**Regulators**
⇒ Require standardised trial reporting templates disclosing funding, investigator payments, enrolment criteria and site selection rationale.
⇒ Fund independent oversight committees through pooled industry levies, with public reporting of audit results.
⇒ Restrict financial incentives tied directly to patient enrolment or prescribing behaviour.

**International bodies (WHO, ICH)**
⇒ Harmonise global standards for trial registration and transparency to prevent 'regulatory havens'.
⇒ Support capacity-building for oversight in low- and middle-income countries.

**Governments and supranational entities (eg, European Commission)**
⇒ Enact regulations to minimise seeding trials and strengthen post-marketing oversight.
⇒ Mandate publicly accessible platforms tracking industry payments to physicians.

**National health systems and health departments**
⇒ Require ethics committee authorisation for all drug studies, including observational research.
⇒ Train ethics committee members to recognise seeding trial characteristics.

**Clinicians and researchers**
⇒ Apply 'red flag' checklists before participating in or citing trials (eg, unusually low patient-to-site ratios, sponsor-dominated oversight, non-clinically relevant endpoints).
⇒ Demand full transparency in trial objectives and investigator compensation.

**Patients and advocates**
⇒ Push for clear disclosure in consent forms when trials serve commercial as well as scientific purposes.
⇒ Actively participate in trial oversight and policy discussions.

**Journals and editors**
⇒ Require protocols, funding details and independent oversight statements before accepting industry-sponsored trials.
⇒ Refuse publication of studies where marketing objectives are concealed.

ICH, International Council for Harmonisation.

International cooperation through organisations such as the WHO and the International Council for Harmonisation can facilitate the adoption of consistent global guidelines.[18] However, given potential conflicts of interest between these bodies and pharmaceutical companies, registry design and oversight standards should involve independent researchers and government representatives, not industry-affiliated organisations alone. WHO's International Clinical Trials Registry Platform provides a foundational framework on which further harmonisation can build. Global standardisation should prioritise uniform trial registration protocols, comprehensive disclosure of funding and investigator incentives, and harmonised ethical review processes.

Transparency must be matched by enforcement. Regulators should mandate standardised reporting templates disclosing trial funding, investigator payments, enrolment criteria and site selection rationale. Independent oversight committees, funded through pooled industry levies, should conduct random audits with publicly available results. Existing transparency initiatives demonstrate feasibility: in the USA, the Open Payments database and ProPublica's Dollars for Docs project allow public tracking of industry payments to physicians. Similar platforms should be mandated in the European Union and other jurisdictions.

Regulation must also address incentives. Payments tied directly to patient enrolment or prescribing behaviour should be restricted, with clear criteria distinguishing legitimate research support from marketing rewards. Pharmaceutical companies and some academic partners may resist these changes, citing administrative burden, but the risks of inaction—compromised science and patient harm—are far greater. Enforcement will require cooperation between industry, regulators, clinicians and patient groups. Public disclosure of investigator compensation, coupled with education campaigns on ethical trial conduct, can help shift cultural norms.[19] The test of any solution is whether it deters commercial misuse while remaining feasible to implement.

Box 1 summarises action priorities for regulators, international bodies, governments, health systems, clinicians, patients and journals.

### We should act now

Protecting patients and preserving trust in clinical research requires immediate steps: stronger disclosure rules, harmonised international oversight and active involvement of clinicians and patients in demanding transparency. Seeding trials are not rare anomalies—they are predictable products of misaligned incentives. Unless regulators and journals act decisively, marketing will continue to masquerade as science, with patients bearing the risks.

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