Review Article

Integrity of Clinical RCTs: Safeguarding Trust, Evidence, and Patient Welfare

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Clinical trials occupy a central position in modern medicine because they generate evidence used to decide whether interventions are effective, safe, and worth implementing. Their social value depends not only on scientific ambition but also on integrity: the assurance that trials are ethically justified, methodologically sound, operationally controlled, statistically credible, transparently reported, and open to scrutiny. Clinical trial integrity is broader than fraud prevention and broader than regulatory compliance. It includes the relevance of the research question, the protection of participants, the precision with which the treatment effect is defined, the faithful execution of the protocol, reliable data governance, prespecified statistical analysis, balanced interpretation, and responsible public communication. This article argues that trial integrity is best understood as a life-cycle concept. It begins with a clinically meaningful question and a design capable of answering it, continues through trial conduct, data management, statistical analysis, interpretation, and transparent reporting, and extends after publication through data sharing, public audit, post-publication review, and correction of the scientific record. Particular attention is given to prespecification, trial registration, statistical analysis plans, the query process, negative trials, early termination, and the interaction between personal, institutional, and community-driven integrity. The central claim is that trustworthy clinical trials require more than procedural compliance. They require a professional culture in which patient welfare, methodological rigor, reproducibility, and public accountability remain aligned throughout the entire trial life cycle.

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Introduction: trial integrity as a public trust

Clinical trials are more than technical instruments for testing medical interventions. They are public acts of trust. Patients agree to participate because they expect that their contribution will be used responsibly. Clinicians rely on trial evidence when advising patients. Regulators, payers, guideline panels, and health systems use trial results to make decisions that affect large populations. If the integrity of a trial is compromised, the consequences are not limited to a single publication. Poorly designed or poorly conducted trials may expose participants to avoidable risks, produce unreliable evidence, mislead future research, distort meta-analyses, and waste scarce resources. The ethical and scientific duties of clinical research are therefore inseparable.

The Declaration of Helsinki states that medical research involving human participants must be governed by ethical standards that protect health, rights, and well-being, and that the rights and interests of individual participants must not be subordinated to the generation of knowledge [1]. This principle is the moral foundation of trial integrity. A trial that violates participant rights cannot be considered scientifically respectable, even if its data appear technically clean. Conversely, a trial that is ethically approved but scientifically weak also lacks integrity because it exposes participants to burdens without a reasonable prospect of producing meaningful knowledge.

Clinical trial integrity can be defined as the set of conditions under which a trial's ethical conduct, methodological validity, operational execution, data quality, statistical analysis, interpretation, and reporting allow its findings to be trusted. This definition has two implications. First, integrity is prospective: it must be built into the trial before recruitment starts. Second, integrity is continuous: it must be maintained from design and registration through conduct, analysis, reporting, data sharing, and correction of the scientific record. Integrity is therefore not a final audit activity. It is a life-cycle property of the trial.

This article organizes trial integrity around that life cycle. It begins with the research question and design, then considers prespecification and public documentation, operational conduct and data governance, statistical interpretation, negative trials, early termination, transparency and accountability, and finally the personal, institutional, and community levels at which integrity is produced. The purpose is not to create another checklist, but to provide an integrated framework for thinking about trustworthy clinical trials.

From PICO to estimands: defining what the trial is meant to learn

The first safeguard of trial integrity is a relevant, answerable research question. A trial should address an uncertainty that matters to patients, clinicians, or public health. It should not be conducted merely because funding, technology, convenience, or commercial opportunity allows it. Integrity requires that the target population, intervention, comparator, endpoint, follow-up, and analysis strategy align with the intended decision. Without this alignment, even a technically well-executed trial may answer the wrong question.

Traditionally, the core question of a clinical trial was often summarized using the PICO structure: population, intervention, comparator, and outcome. PICO remains useful because it gives a compact 'study in a nutshell' description and helps readers understand the basic clinical question. It is particularly helpful in trial protocols, systematic reviews, guideline questions, and teaching. However, for modern clinical trials PICO is no longer sufficiently precise. It does not fully specify what treatment effect is being estimated, especially when patients discontinue treatment, switch therapy, receive rescue medication, die before outcome assessment, withdraw consent, or experience other intercurrent events.

The estimand framework can therefore be understood as a more rigorous extension of PICO, not as a simple replacement. It retains the need to define the population, treatment conditions, comparator, and endpoint, but adds explicit consideration of intercurrent events and the population-level summary measure [2][3]. In this way, the estimand framework transforms a general clinical question into a precise target of estimation and links trial objectives, design, data collection, statistical analysis, and interpretation. PICO describes the trial question; the estimand defines the treatment effect.

This distinction is central for integrity. If a trial claims to estimate the effect of assigning treatment, but then excludes patients who discontinue treatment or receive rescue medication, the analysis may no longer match the clinical question. If death occurs before a patient-reported outcome can be measured, the outcome cannot be treated as merely missing without considering what clinical question is being answered. If non-adherence is handled through a hypothetical strategy [3], the assumptions required for that hypothetical contrast must be made explicit. The estimand framework makes such decisions visible and therefore reduces the risk that analytical convenience quietly changes the meaning of the trial result.

Design integrity also requires avoiding unnecessary complexity. Randomization, allocation concealment, blinding, endpoint adjudication, and standardized outcome assessment are not bureaucratic rituals; they are protections against bias. Their relevance depends on the trial context. Blinding may be essential in

trials with subjective endpoints, whereas non-blinded endpoint assessment may be sufficient in some pragmatic trials where participant blinding is impossible. The key issue is not whether every trial looks identical, but whether the design addresses the most important threats to validity for the question being asked.

Good Clinical Practice [2] now explicitly emphasizes quality by design and proportionate, risk-based quality management. ICH E6(R3) stresses that trial processes and mitigation strategies should focus on factors critical to trial quality and should be proportionate to the importance of the data and the risks to participants [3]. This is an important shift away from a narrow compliance culture. Integrity is not achieved by maximal documentation of every minor activity, but by identifying what could truly compromise participant safety or the reliability of the primary conclusions.

Prespecification, protocols, SAPs, and prevention of bias

A high-quality protocol is the backbone of trial integrity. It should define the objectives, eligibility criteria, interventions, outcomes, follow-up, safety procedures, data collection, monitoring, and analysis principles in sufficient detail. The SPIRIT 2025 statement provides updated guidance on minimum protocol content and emphasizes structured, transparent trial protocols [4]. A protocol is not only an operational document; it is also a public commitment. It prevents ambiguity, limits selective decision-making, and allows reviewers, regulators, journals, and readers to distinguish planned procedures from post hoc reconstruction.

The statistical analysis plan (SAP) has a complementary role. It should be finalized before unblinding or before access to outcome data could influence analytical decisions. It should specify the analysis populations, primary and secondary endpoints, statistical models, covariate adjustment, handling of missing data and intercurrent events, multiplicity procedures, subgroup analyses, sensitivity analyses, and relevant model assumptions. The aim is not to eliminate scientific judgement, but to prevent outcome-driven analysis. Without prospective statistical specification, even sophisticated analyses may become instruments of selective reporting.

Prespecification and public availability should be distinguished. Prespecification means that key design and analysis decisions are fixed before knowledge of trial results can influence them. Public availability means that others can later verify what was prespecified. Both are needed. Trial registration provides an essential public record of the trial and its main design features, but it cannot replace access to the full

protocol, because registry entries usually do not contain the level of detail needed to evaluate important methodological and statistical decisions. Similarly, the SAP is often more detailed than the protocol and should be dated, version-controlled, and publicly accessible through a registry, journal supplement, institutional or open-science repository, or standalone publication.

Trial registration is also a powerful tool for preventing selective emphasis on specific endpoints. By documenting primary and secondary outcomes before results are known, registration makes it more difficult to redefine the main objective of the trial after observing the data. It allows readers to compare the final publication with the originally registered endpoints and to identify outcome switching, selective omission of non-significant endpoints, or disproportionate emphasis on favourable secondary or exploratory findings. However, registration can serve this function only if it is prospective, sufficiently detailed, updated with transparent justification, and interpreted together with the full protocol and SAP.

Protocol amendments are legitimate and often necessary. Recruitment problems, new safety information, external evidence, operational lessons, or changes in standard of care may justify modifications. Amendments become problematic when they are poorly justified, introduced after emerging outcome information, or not clearly reflected in the final report. A transparent amendment history allows readers to judge whether changes were scientifically justified or potentially biased. For integrity, the question is not whether a trial ever changed, but whether changes were documented, justified, and separated from outcome-driven adaptation.

Operational conduct, oversight, and participant protection

Even the best protocol fails if the trial is poorly implemented. Operational integrity concerns the fidelity with which the trial is conducted. This includes recruitment processes, informed consent, eligibility verification, randomization, intervention delivery, adherence monitoring, outcome ascertainment, safety reporting, and retention of participants. Errors in these processes may distort the trial population, compromise comparability, or weaken endpoint validity.

Informed consent is central but should not be reduced to a signed form. Participants must understand the research nature of the trial, relevant risks and benefits, alternatives, confidentiality protections, and their right to withdraw without disadvantage. The Declaration of Helsinki emphasizes special caution when potential participants are in dependent relationships with investigators or may feel pressure to consent [1]. This is particularly important in clinical settings where patients may fear that refusal could affect their care.

Monitoring should be proportionate and risk-based. Traditional monitoring sometimes focused heavily on source-data verification without asking whether the verified data were critical to the trial's conclusions. Modern integrity management should prioritize critical data, critical processes, participant safety, and signals of systematic error or misconduct. Central statistical monitoring, targeted site visits, review of recruitment patterns, unusual endpoint distributions, missing-data rates, delayed adverse-event reporting, and deviations from expected timelines can all help detect problems early. The objective is prevention and correction, not retrospective punishment.

Independent oversight may be necessary, especially in trials with serious risks, vulnerable populations, complex adaptive designs, or major public-health implications. Data monitoring committees can protect participants by reviewing accumulating safety and efficacy data under predefined procedures. Endpoint adjudication committees can improve consistency when outcomes require clinical judgement. Trial steering committees can help preserve scientific independence. These bodies must have clear roles, appropriate independence, access to relevant information, and procedures for documenting recommendations; otherwise, oversight becomes symbolic rather than protective.

Operational integrity also includes learning from recurrent problems. A single missing field may be a data issue; repeated missing fields at one site may reveal a training or workflow problem. Systematic late reporting of adverse events may indicate misunderstanding of safety procedures. Unexpected recruitment patterns may raise concerns about eligibility assessment or informed consent. Trial management should therefore treat operational signals as opportunities to correct the system before they become threats to validity or participant welfare.

Randomization integrity deserves specific attention. The randomization sequence should be generated independently, implemented through a validated and access-controlled system, and protected from prediction or manipulation. Allocation concealment must be maintained until assignment, and emergency unblinding should be documented with reasons, timing, and personnel involved. Randomization errors, ineligible randomizations, duplicate randomizations, and post-randomization exclusions should be reviewed systematically because they may threaten both internal validity and participant protection.

Data integrity, query management, and digital systems

Data integrity is a core component of trial integrity. ICH E6(R3) defines reliable data in terms that include being attributable, legible, contemporaneous, original, accurate, complete, secure, reliable, and fit for

purpose [2]. These criteria are not merely technical. They are epistemic: they determine whether the observed data can support the conclusions drawn from them.

The clinical data query process is a central mechanism for preserving data integrity. Queries are generated when entered data are missing, implausible, inconsistent with other data fields, incompatible with predefined validation rules, or insufficiently supported by source documentation. A well-controlled query process clarifies discrepancies without introducing undocumented changes or retrospective reinterpretation. Each query should be traceable from detection to resolution, including the original value, the reason for the query, the response, any correction made, the person responsible, and the date of resolution.

Query management should be timely, systematic, and proportionate to the importance of the data item. Particular attention should be given to queries affecting eligibility, primary endpoints, safety outcomes, treatment exposure, protocol deviations, censoring, and analysis populations. The query process has a dual integrity function. Operationally, repeated or systematic queries may indicate problems in trial conduct, such as unclear documentation, inconsistent outcome assessment, delayed reporting, or site-specific misunderstandings of the protocol. From the data-management perspective, queries are the controlled mechanism by which discrepancies are clarified, corrected, documented, and made auditable. The query process is therefore a critical bridge between trial conduct, data management, and statistical credibility.

Data governance should cover the full data life cycle: data capture, transfer, cleaning, coding, query resolution, database lock, archiving, and controlled access for reuse. Data cleaning must not become data manipulation. Rules for correcting values, handling outliers, resolving discrepancies, and coding adverse events should be predefined or consistently documented. Any change to source data should remain traceable and should not obscure the original entry. Database lock should represent not merely an administrative milestone, but the point at which the dataset has been cleaned, documented, and protected against outcome-driven modification.

Modern trials increasingly use electronic case report forms, electronic health records, wearable devices, patient-reported outcome apps, remote monitoring, imaging platforms, and algorithmic tools. These technologies can improve efficiency and inclusiveness, but they create new vulnerabilities. Systems must be validated or assessed as fit for purpose. Audit trails, user permissions, data transfer checks, backup procedures, cybersecurity protections, and version control become part of trial integrity. Blinding must

also be protected within digital systems; inappropriate access rights can accidentally reveal treatment allocation.

Artificial intelligence and automated tools may increasingly support screening, monitoring, coding, translation, imaging analysis, or drafting. Their use can be compatible with trial integrity only if their role is documented, validated for the intended purpose, monitored for errors, and subject to human accountability. AI should not become an invisible contributor to trial decisions. Where AI affects eligibility, endpoint classification, safety detection, or analysis, its performance and limitations must be transparent.

Statistical integrity and interpretation

Statistical integrity requires more than correct software code. It requires alignment between the research question, design, estimand, data structure, model, assumptions, and interpretation. A common threat is the mismatch between the clinical question and the reported analysis. Excluding post-randomization events, switching analysis populations, changing endpoint definitions, selecting favourable covariate adjustments, or choosing sensitivity analyses after seeing the data can undermine the randomized comparison. The statistical analysis should implement the trial question, not quietly replace it.

Missing data are a major integrity challenge. They should be prevented where possible through good follow-up procedures, but statistical handling must also be prespecified and justified. Complete-case analysis, multiple imputation, inverse probability weighting, tipping-point analyses, and estimand-based strategies each answer different questions under different assumptions. Integrity does not require that one method be universally preferred. It requires that assumptions be explicit, plausible, and examined through sensitivity analyses.

Multiplicity and selective emphasis are additional concerns. Trials often include many endpoints, time points, subgroups, interim looks, and analysis populations. Without control of multiplicity or a clear hierarchy of interpretation, chance findings may be overinterpreted. Subgroup analyses are particularly vulnerable. They can generate hypotheses, but rarely provide definitive evidence unless prespecified, clinically plausible, sufficiently powered, and supported by formal interaction testing. Registration, protocols, and SAPs help make selective endpoint or subgroup emphasis visible, but interpretation still requires discipline.

Interpretive integrity also requires balanced reporting of benefits and harms. A trial should not celebrate a statistically significant efficacy endpoint while downplaying adverse events, missing data, treatment discontinuation, or limited generalizability. Conversely, a trial that does not show superiority should not be dismissed as uninformative if it was well designed and provides precise evidence against a clinically meaningful effect. Integrity means allowing the results to discipline the narrative. The task of statistical interpretation is not to rescue the preferred conclusion, but to describe what the data do and do not support.

Statistical integrity also depends on reproducible implementation. The derivation of analysis datasets, endpoint variables, censoring indicators, protocol-deviation flags, and analysis populations should be documented and traceable. Statistical code should be version-controlled, reviewed, and, for critical analyses, independently validated. Software versions, package dependencies, random seeds, and deviations from the SAP should be recorded. Reproducibility does not require that every analysis be publicly executable in all settings, but it does require that the path from raw data to reported results can be audited and, where appropriate, independently reproduced.

Negative trials: epistemological and methodological challenges

The following discussion mainly concerns superiority trials. In non-inferiority and equivalence trials, the absence of a statistically significant superiority effect has a different meaning and must be interpreted in relation to the prespecified margin, assay sensitivity, adherence, and analysis population.

Negative clinical trials deserve specific attention in any discussion of trial integrity. They are often described as studies that 'failed' to show a statistically significant treatment effect. This wording is problematic. A trial may fail scientifically because it was poorly designed, underpowered, badly conducted, or analysed inappropriately. But a well-designed trial that does not demonstrate a benefit of the experimental intervention has not failed. It may produce evidence that is highly valuable for clinical decision-making, future research, guideline development, and the avoidance of ineffective or harmful interventions.

The first epistemological challenge is that a negative trial does not automatically prove absence of effect. A non-significant p-value indicates that the observed data did not provide sufficient evidence against the null hypothesis under the chosen statistical model and significance threshold. It does not by itself show that the treatment has no clinically relevant effect. Interpretation depends on the confidence interval, the assumed minimally important difference, endpoint validity, adherence, follow-up completeness, and

credibility of the analysis. A negative trial with a narrow confidence interval excluding clinically meaningful benefit can be highly informative. A negative trial with a wide confidence interval may remain compatible with important benefit, no effect, or harm and is better described as inconclusive.

The key question is what range of treatment effects remains compatible with the data and whether this range includes effects that would matter clinically. A precise null result can change practice, prevent unnecessary exposure to ineffective interventions, and redirect research resources. An imprecise null result should generate caution rather than strong claims of no benefit. A negative trial is informative only to the extent that it was capable of detecting or excluding a clinically meaningful effect.

A second challenge is the distinction between intervention failure and trial failure. A trial may be negative because the intervention truly does not work for the target population or endpoint. But it may also be negative because the trial did not adequately test the intervention. Poor intervention fidelity, inadequate dosing, contamination, cross-over, low adherence, inappropriate timing, insensitive endpoints, short follow-up, high missingness, or recruitment of a population with little room for improvement can all dilute a true effect. In pragmatic trials, this distinction is particularly important. A pragmatic trial may validly show that an intervention is not effective under real-world implementation conditions, even if it might work under more controlled circumstances.

Negative trials are also prone to spin: the tendency to shift attention from a non-significant primary endpoint to favourable secondary, exploratory, per-protocol, subgroup, biomarker, or safety findings. Such findings may be useful for hypothesis generation, but they should not be presented as if they override the primary result unless this interpretation was prespecified and statistically justified. Integrity requires that the primary estimand and endpoint hierarchy remain visible in the interpretation, even when other results appear more attractive. Selective emphasis on favourable secondary findings can be as misleading as selective non-reporting.

Negative trials have an ethical dimension. Participants accept burdens and risks because the trial is expected to contribute to knowledge. If negative results are not published, are reported incompletely, or are reframed in a misleadingly positive way, the contribution of participants is not fully respected. Publication bias against negative trials distorts the evidence base, exaggerates treatment effects in meta-analyses, and may lead to unnecessary further trials. A negative trial conducted with integrity should therefore be registered, reported, interpreted, and made accessible with the same care as a positive trial.

Early termination of clinical trials: integrity under pressure

Clinical trials may have to be terminated before reaching their planned sample size or follow-up duration. Early termination is sometimes ethically necessary, but it is methodologically delicate. It may occur because of clear evidence of benefit, evidence of harm, futility, external evidence that changes equipoise, poor recruitment, operational failure, loss of funding, changes in standard of care, or public-health emergencies. Each situation has different implications for integrity. A trial stopped for safety protects participants from avoidable harm; a trial stopped for futility may avoid exposing further participants to burdens when the trial is unlikely to answer its question; a trial stopped for apparent benefit may accelerate access to an effective intervention. However, early termination can also leave important uncertainty unresolved.

Integrity requires that early-stopping processes be planned as far as possible before the trial begins. Protocols and SAPs should specify whether interim analyses are planned, who will see unblinded interim data, which statistical boundaries or decision criteria will be used, and whether stopping may occur for efficacy, harm, futility, or other reasons. In trials with relevant risks, independent data monitoring committees play a central role by reviewing accumulating data and recommending whether the trial should continue, be modified, or be stopped. Their independence protects the trial from inappropriate influence by investigators, sponsors, or external expectations.

Stopping early for benefit is especially challenging. It may appear ethically compelling, but trials stopped early after few events often overestimate treatment effects and provide limited information on safety, durability of benefit, subgroup consistency, and long-term outcomes. A very large observed effect at an interim analysis may partly reflect random high variability, particularly when the number of outcome events is small. For this reason, early efficacy stopping should usually require stringent statistical evidence, clinical plausibility, consistency across key outcomes, and careful consideration of remaining uncertainties. Empirical work has shown that trials stopped early for benefit can systematically overestimate treatment effects, sometimes substantially [5].

Stopping for futility raises a different set of issues. A futility decision does not necessarily mean that the intervention has no effect. It means that, given accumulating data and prespecified assumptions, the trial is unlikely to achieve its planned objective if continued. This may be scientifically and ethically appropriate, particularly when resources could be redirected or participant burden avoided. However, futility depends on assumptions about the target effect, event rates, adherence, missing data, and future

information. A trial stopped for futility may therefore be informative, but it must be interpreted in relation to the planned effect size and the amount of information actually accrued.

Early termination for operational or feasibility reasons is often less visible but equally important for integrity. Trials may stop because of poor recruitment, excessive missing data, supply problems, site failure, changes in clinical practice, or lack of funding. Such trials should not be treated as if they produced a definitive negative result. Their findings may be exploratory, biased, or underpowered. Nevertheless, they remain part of the evidence base and should be reported transparently. Participants have still contributed data, and non-reporting would increase research waste and publication bias. Where ethically and legally possible, deidentified trial data should therefore be made accessible for responsible secondary use. However, data sharing in this context must be accompanied by sufficient documentation, including the protocol, SAP, data dictionary, reason for early termination, achieved sample size, completeness of follow-up, major protocol deviations, and limitations of interpretation. For small or rare-disease trials, controlled access may be preferable to unrestricted open access because re-identification risks may be higher. The aim is not to give prematurely terminated trials an evidential weight they cannot carry, but to ensure that the information generated by participants is not lost and can be interpreted cautiously in the context of the broader evidence base.

When a trial is terminated early, several practical steps are essential. The reason for stopping should be documented clearly, including whether it was prespecified or ad hoc. The timing of interim analyses, the amount of information available at stopping, the role of the data monitoring committee, and the decision-making process should be described. The trial registry should be updated, ethics committees and regulatory authorities should be informed as required, and participants should be followed for safety whenever appropriate. The database should be cleaned and locked according to a controlled process. If the SAP has to be modified after early termination, this should be dated, justified, and clearly distinguished from the originally planned analysis.

Transparent reporting is crucial. CONSORT 2025 asks authors to report why a trial ended or was stopped [6], and Good Clinical Practice treats premature termination or suspension as a situation requiring appropriate communication and documentation [2]. A publication should therefore not merely state that a trial was 'terminated early.' It should explain who made the decision, on what basis, at what time point, with how many participants and events, and with what implications for interpretation. Early termination may protect participants, but it also changes the evidential meaning of the trial; integrity requires that both aspects are made explicit.

Transparency, reporting, and public accountability

Trial integrity extends beyond conduct to reporting and dissemination. Selective non-publication is a major violation of the social contract of clinical research. Participants contribute under the assumption that their involvement will generate knowledge. If results remain unpublished because they are negative, inconvenient, commercially unattractive, or operationally disappointing, that contribution is wasted and the evidence base is distorted.

Prospective registration is a central transparency safeguard. It records the existence of a trial and key design features before results are known. ClinicalTrials.gov summarizes legal requirements under FDAAA 801 and 42 CFR Part 11, including registration of applicable clinical trials not later than 21 calendar days after enrolling the first participant and, in general, submission of results information not later than one year after the completion date [7]. In Europe, the Clinical Trials Information System and related transparency mechanisms support submission, assessment, supervision, and public access to clinical trial information under the EU Clinical Trials Regulation.

Reporting guidelines are another integrity tool. CONSORT 2025 provides an updated 30-item checklist for reporting randomized trials and includes an open-science section [6]. Such guidelines do not guarantee good science, but they make omissions visible. They help readers assess whether the trial was randomized, how allocation was concealed, who was analyzed, what outcomes were prespecified, how harms were captured, why the trial ended, and whether deviations from the protocol occurred.

Data sharing is a further step toward accountability. The ICMJE requires clinical trial data-sharing statements to specify whether deidentified individual participant data will be shared, what data and related documents will be available, when they will be available, and under what access criteria [8]. Responsible data sharing can enable verification, secondary analyses, individual participant data meta-analyses, and methodological learning. At the same time, it must protect participant privacy, respect consent, and avoid misuse. The goal is not uncontrolled openness, but accountable transparency.

Transparency also requires mechanisms to check whether completed trials make their results publicly available in time. Several initiatives have moved from general appeals for publication toward systematic public audit. In the United States, the FDAAA TrialsTracker monitors whether trials subject to FDAAA reporting requirements have submitted results to ClinicalTrials.gov [9]. In Europe, the EU Trials Tracker monitors whether trials registered in the European Union Clinical Trials Register have reported results within the expected one-year period after completion [10]. These tools transform non-reporting from an

invisible failure into a measurable and publicly attributable integrity problem. They also make clear that transparency is not fulfilled by registration alone. Completed trials must report their results, including negative, inconclusive, or prematurely terminated trials, in a timely manner. Registry result reporting and journal publication should nevertheless be distinguished. Registry reporting provides a structured and often legally required minimum disclosure, whereas peer-reviewed publication allows fuller methodological explanation, clinical interpretation, and integration into the scientific literature. Both are needed for a trustworthy evidence ecosystem.

Post-publication review is another component of transparency and public accountability. Traditional peer review before publication is necessary, but it cannot detect every methodological weakness, reporting inconsistency, statistical error, undisclosed protocol deviation, or interpretive problem. Once a trial is published, the wider scientific community can compare the publication with the registry entry, protocol, SAP, supplementary material, and shared data or code where available. Continuing scrutiny may occur through letters to the editor, formal commentaries, journal correspondence, systematic reviews, replication attempts, post-publication peer-review platforms, or public discussion among methodological experts.

The purpose of post-publication review should not be to undermine trust in clinical research, but to strengthen trust by making correction possible. When relevant concerns are raised, journals and authors have a responsibility to respond transparently and, where necessary, issue corrections, expressions of concern, reanalyses, or retractions. COPE guidance supports the view that post-publication discussion, corrections, expressions of concern, and retractions are mechanisms for maintaining the reliability and transparency of the scientific record [11][12]. Post-publication review therefore extends trial integrity beyond acceptance by a journal: it recognizes that the credibility of clinical evidence depends on its capacity to remain open to criticism, correction, and reinterpretation in light of new information.

Personal, institutional, and community-driven integrity

No checklist can substitute for a culture of integrity. Clinical trials involve many actors: sponsors, investigators, statisticians, trial managers, monitors, ethics committees, regulators, journals, contract research organizations, data managers, patient partners, and participants. Integrity depends on how these actors respond when incentives conflict with good science. Commercial pressure, academic competition, recruitment targets, publication ambitions, regulatory deadlines, and reputational concerns can all distort judgement.

Clinical trial integrity depends on three interacting levels of responsibility. At the personal level, investigators, statisticians, trial managers, monitors, data managers, and authors must act with professional honesty, methodological discipline, and willingness to document uncertainty. This includes respecting the protocol, resisting selective interpretation, reporting errors, protecting blinding, avoiding inappropriate analytical flexibility, and communicating results without spin. Personal integrity is indispensable because many critical decisions in a trial are made in situations where rules cannot specify every detail.

However, trial integrity cannot be left to individual virtue alone. It also requires institutional integrity. Universities, hospitals, sponsors, contract research organizations, ethics committees, data coordinating centres, and trial units must provide structures that make good conduct possible: training, standard operating procedures, independent oversight, quality management systems, secure data environments, version control, audit trails, conflict-of-interest management, publication rights, and protection for researchers who raise concerns. Good Clinical Practice assigns defined responsibilities to sponsors, investigators, and other parties involved in trial conduct, reflecting the fact that reliable trial evidence is produced by systems, not by isolated individuals [2].

A third level is community-driven integrity. Clinical trials are embedded in a wider scientific and public ecosystem that includes registries, reporting guidelines, peer review, journals, regulators, data-sharing platforms, systematic reviewers, post-publication review, patient communities, and public audit initiatives. These actors create external visibility and make selective reporting, delayed result disclosure, undisclosed protocol deviations, or misleading interpretation more difficult to hide. Community-driven integrity does not replace the responsibilities of investigators and institutions, nor should it become informal punishment without fair process. Its value lies in distributed accountability: trial evidence remains open to verification, criticism, correction, and reinterpretation after the original investigators have reported their findings.

Conflicts of interest do not automatically invalidate a trial, but they must be declared, managed, and considered in interpretation. Independence of statistical analysis, publication rights, access to data, and authorship decisions should be secured contractually before the trial begins. Investigators should not be prevented from publishing unfavourable results. Statisticians should have sufficient independence to raise concerns about analysis decisions, data anomalies, selective reporting, or inappropriate interpretation.

Training is essential. Trial integrity should be part of the professional identity of everyone involved in clinical research, not only of principal investigators. Young researchers should learn that protocol deviations, undocumented analyses, poor data handling, and selective narratives are not minor administrative imperfections; they are threats to the validity and ethics of research. The ALLEA European Code of Conduct for Research Integrity emphasizes that research integrity is supported by research culture, responsible practices, research data management, open science, and appropriate governance [13]. A culture of integrity encourages early reporting of errors, open discussion of uncertainty, and correction rather than concealment.

The three levels are mutually dependent. Personal integrity gives ethical direction to day-to-day decisions; institutional integrity creates the conditions under which responsible conduct can be sustained; community-driven integrity ensures that clinical trial evidence remains visible, contestable, and correctable. Trial integrity is strongest when all three levels reinforce one another.

Conclusion

Clinical trial integrity is the condition that allows trial evidence to be trusted. It begins before the first participant is enrolled, with an ethically justified research question, a design capable of answering it, and a precise definition of the treatment effect to be estimated. Traditional descriptions using population, intervention, comparator, and outcome remain useful as compact summaries, but modern trial integrity requires more: the estimand framework links the clinical question to intercurrent events, endpoint definition, population-level summary, and statistical analysis.

Integrity is maintained during trial conduct through informed consent, protocol fidelity, risk-based monitoring, independent oversight, reliable data capture, systematic query resolution, protection of blinding, and participant safety. It is strengthened by prespecified protocols and SAPs that are dated, version-controlled, and publicly accessible. These documents allow readers to distinguish planned analyses from post hoc decisions and to assess whether deviations were justified and transparent.

The integrity of a trial is also tested by interpretation. This is particularly evident in negative trials, where the temptation to overstate secondary findings, rescue an intervention through selective emphasis, or confuse inconclusive evidence with evidence of no effect may be strong. It is also evident when trials terminate early, because stopping may be ethically necessary but may leave the evidential meaning of the trial fragile. A well-conducted negative or prematurely terminated trial is not necessarily a scientific

failure; it may provide essential evidence for clinical practice, future research, and the avoidance of ineffective or harmful interventions, provided that it is interpreted with appropriate caution.

Trial integrity does not end with publication. Registration, timely public reporting of results, access to protocols and SAPs, data and code availability where appropriate, public audit, and post-publication review all contribute to accountability. Corrections, reanalyses, expressions of concern, and retractions should be understood not as threats to science, but as mechanisms for protecting the reliability of the scientific record.

Clinical trial integrity is therefore not a single regulatory requirement or a final audit activity. It is a continuous ethical, methodological, operational, statistical, and editorial commitment. In an era of complex designs, digital systems, real-world data, artificial intelligence, and increasing demands for transparency, trustworthy trials require more than compliance. They require a professional culture in which patient welfare, scientific validity, reproducibility, and public accountability remain aligned throughout the entire life cycle of the trial.

Integrity safeguards across the trial life cycle

Trial phase	Core integrity question	Key safeguards
Question and design	Is the trial asking a meaningful and answerable question?	Clinical relevance; PICO; estimand; bias-resistant design; quality by design.
Prespecification	Can planned decisions be distinguished from post hoc choices?	Protocol; SAP; prospective registration; amendment history; public accessibility.
Conduct and data	Was the trial implemented and documented reliably?	Informed consent; monitoring; oversight; query management; audit trails; database lock.
Analysis and interpretation	Does the analysis answer the intended question?	Estimand-consistent analysis; missing-data assumptions; multiplicity control; balanced benefit-harm interpretation.
Exceptional situations	Are negative or early-terminated trials interpreted with appropriate caution?	Precision-based interpretation; avoidance of spin; documentation of stopping reasons; contextual data sharing.
Public accountability	Can the evidence be scrutinized and corrected?	Results reporting; CONSORT; data sharing; public audit; post-publication review; corrections and retractions.
Research culture	Do individuals, institutions, and communities reinforce integrity?	Training; independence; conflict management; protected reporting; distributed accountability.

References

1. [a], [b] *World Medical Association (2024). "Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Participants." World Medical Association. https://www.wma.net/policies-post/wma-declaration-of-helsinki/.*
2. [a], [b], [c], [d], [e] *International Council for Harmonisation (2025). "ICH E6(R3): Guideline for Good Clinical Practice." International Council for Harmonisation. https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_20250106.pdf.*

3. a, b, cInternational Council for Harmonisation. "ICH E9(R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials." International Council for Harmonisation. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-and-sensitivity-analysis-clinical-trials-guideline-statistical-principles-clinical-trials-step-5_en.pdf.
4. ^Chan AW, et al. (2025). "SPIRIT 2025 Statement: Updated Guideline for Protocols of Randomised Trials." BMJ. https://www.bmj.com/content/389/bmj-2024-081477.
5. ^Bassler D, et al. (2008). "Early Stopping of Randomized Clinical Trials for Overt Efficacy Is Problematic." J Clin Epidemiol. https://pubmed.ncbi.nlm.nih.gov/18226746/.
6. a, bHopewell S, et al. (2025). "CONSORT 2025 Statement: Updated Guideline for Reporting Randomised Trials." BMJ. https://www.bmj.com/content/389/bmj-2024-081123.
7. ^ClinicalTrials.gov. "FDAAA 801 and the Final Rule." ClinicalTrials.gov. https://clinicaltrials.gov/policy/fdaaa-801-final-rule.
8. ^International Committee of Medical Journal Editors. "Recommendations: Clinical Trials - Registration and Data Sharing." International Committee of Medical Journal Editors. https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html.
9. ^FDAAA TrialsTracker. "Who Is Sharing Their Clinical Trial Results?" FDAAA TrialsTracker. https://fdaaa.trialstracker.net/.
10. ^EU Trials Tracker. "Who Is Not Sharing EU Clinical Trial Results?" EU Trials Tracker. https://eu.trialstracker.net/.
11. ^Committee on Publication Ethics. "Post-Publication Discussions and Corrections." Committee on Publication Ethics. https://publicationethics.org/news-opinion/post-publication-discussions-and-corrections.
12. ^Committee on Publication Ethics (2024). "Visibility of Corrections and Retractions." Committee on Publication Ethics. https://publicationethics.org/guidance/cope-position/visibility-corrections-and-retractions.
13. ^ALLEA (2023). "The European Code of Conduct for Research Integrity." ALLEA. https://allea.org/code-of-conduct/.

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