Ethical Oversight in Clinical Innovation: Navigating the Case Report Dilemma

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Learning Point of the Article:

Case reports of innovative clinical interventions highlight a critical ethical gap: Existing frameworks inadequately govern the transformation of clinical practice into published knowledge, underscoring the need for harmonised, risk-stratified standards of oversight to protect patient trust and ensure transparency.

Introduction

Case reports have served as a vehicle for clinical communication for well over a century, predating the formalization of randomized controlled trials and systematic reviews as the dominant epistemic units of evidence-based medicine. Their value is far from merely historical. Case reports describing unexpected drug toxicity, the first identification of novel pathological entities, and the application of off-label therapeutic strategies continue to appear in indexed journals at substantial volume. Gagnier et al., in the foundational paper establishing the CAse Report (CARE) guidelines, noted explicitly that case reports constitute individual, clinical-practice-derived narratives with the potential, when systematically aggregated, to generate early signals of both efficacy and harm that formal trials cannot capture in a timely fashion [1].

The ethical architecture surrounding case reports is, by comparison to that governing prospective trials, underdeveloped. The Declaration of Helsinki, now in its eighth revision following the October 2024 World Medical Association (WMA) General Assembly, provides foundational ethical principles for medical research involving human participants, but its scope and applicability to retrospective clinical documentation remain a point of active interpretive debate [2,3]. The International Committee of Medical Journal Editors (ICMJE) mandates patient consent and transparency but stops short of requiring ethics committee approval for all case reports [4]. Committee on Publication Ethics (COPE), in guidance published in 2022, explicitly acknowledged "many grey areas" in how ethical approval for case reports should be handled and offered conditional rather than prescriptive direction [5].

The problem sharpens considerably when the reported intervention is innovative (that is, when it departs in a clinically meaningful way from the standard of care). At this juncture, the question of whether formal ethics review is required is not merely procedural; it touches on foundational issues of patient safety, institutional accountability, and the integrity of the published medical record. This paper examines these tensions through the lens of established regulatory frameworks, empirical data on present reporting practices, and guidance from relevant bodies, with the intent of proposing a coherent, clinician-facing approach to ethical oversight in the publication of innovative case reports.

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Case Reports: Value, Scope, and the Innovation Problem

A case report is, in definitional terms, a narrative that describes a medical problem experienced by one or more patients for scientific, clinical, or educational purposes [1]. This deceptively simple description encompasses a wide range of outputs: Descriptions of rare disease presentations, documentation of unexpected adverse events, reports of diagnostic uncertainty, and, critically for present purposes, accounts of therapeutic innovations applied in clinical practice. The CARE guidelines, developed through a three-phase consensus process involving 27 clinicians, researchers, and journal editors, produced a 13-item checklist intended to improve the completeness and transparency of published case reports and have been endorsed by multiple international journals [1,6].

Case reports have historically been the first published record of interventions that later became standard of care. Propranolol for infantile hemangiomas, for instance, was introduced through observational case-level reporting before prospective data were available. Off-label drug use, defined as prescribing for an unapproved indication, age group, dosage, or route of administration, is extraordinarily common and frequently precedes the generation of level I evidence. Published estimates suggest that off-label prescribing accounts for 12–38% of all prescriptions in general practice and up to 56% in oncology, with rates in pediatric inpatient settings are approaching 97% [7,8]. These therapeutic practices enter the medical literature predominantly through case-level reports before any formal evaluative apparatus catches up.

It is precisely this zone, between clinically motivated innovation and knowledge dissemination, where ethical complexity is greatest. The clinical imperative to act in the patient's best interest drives the application of novel treatments. The scientific imperative to share outcomes drives their publication. Neither impulse, individually, requires formal ethics review under most institutional or regulatory frameworks. Their combination, however, creates a situation functionally analogous to a prospective uncontrolled trial: A clinician applies an intervention outside validated parameters, observes the outcome, and places that outcome in the permanent record. Whether this constitutes research, and therefore whether it requires oversight, is neither a trivial nor a settled question.

Ethical Oversight: The Practice-Research Distinction and Its Limits

The conceptual boundary between clinical practice and research was formally articulated in the 1979 Belmont Report, produced by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Report defined practice as interventions "designed solely to enhance the well-being of an individual patient or client" with a reasonable expectation of success, and research as "an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge" [9]. Critically, the Report acknowledged that the two may occur simultaneously and stated: "If there is any element of research in an activity, that activity should undergo review for the protection of human subjects" [9].

The Belmont report further noted that the experimental character of an intervention, its novelty or departure from standard practice, does not, in and of itself, constitute research. However, it simultaneously stated that "radically new procedures of this description should, however, be made the object of formal research at an early stage to determine whether they are safe and effective" [9]. This creates a structural tension for innovative case reporting: The treating clinician acts within the scope of practice, yet the decision to document and publish the outcome transforms the activity into one that contributes to generalizable knowledge, the defining criterion of research under Belmont.

The Declaration of Helsinki, in its 2024 revision, maintains that all human research must be evaluated by an independent, competent ethics committee before commencement and that informed consent is a non-negotiable requirement for research involving identifiable participants [2,3]. The 2024 revision strengthened several protections, including explicit requirements for informed consent covering biological material and identifiable data, dual review for cross-border research, and new guidance on community engagement [3,10]. It continues to apply primarily to prospective research, but the boundary with retrospective clinical reporting remains, as before, incompletely demarcated.

Institutional Review Boards (IRBs) in the United States operate under 45 CFR 46 and Food and Drug Administration (FDA) regulations (21 CFR 56), both of which define research as a systematic investigation designed to develop or contribute to generalizable knowledge [11]. Under these definitions, a single case report arising from routine clinical care is generally not considered research and does not require IRB approval. The University of North Carolina's Office of Human Research Ethics has formally stated that "an anecdotal report on one or a series of patients seen in one's own practice and a comparison of these patients to existing reports in the literature is not research and does not require IRB approval," while specifying that seeking out cases from other clinicians does cross into research territory [11]. Similarly, the University of Pittsburgh Human Research Protection Office has stated that innovative or newly

introduced clinical procedures "do not require IRB review and approval except when they meet the definition of research" [12].

These institutional positions, however, address the narrow legal question of whether IRB approval is required. They do not resolve the broader ethical question of whether such oversight is appropriate given the nature of the intervention. The American College of Physicians Ethics Manual advises that physicians considering an unprecedented off-label indication or dosage "should consult with peers, an institutional review board, or other expert group to assess the risks, potential adverse outcomes, potential consequences of foregoing a standard therapy, and whether the innovation is in the patient's best interest" [13]. This consultative recommendation falls short of a formal approval requirement but clearly contemplates that substantive ethical consideration precedes the act, not merely its documentation.

The parallel question from IRBs themselves is equally nuanced. A retrospective determination of IRB exemption, a formal statement from an ethics committee that a case report does not constitute research, does not function as ethical approval, and COPE has explicitly noted that such exemption statements should not be construed as permitting publication without patient consent [5,14]. As stated in a European Heart Journal Case Reports editorial, "the fact that some IRBs do not consider case reports to constitute research does not alter the ethical standard for informed patient consent being required for publication" [14].

The Dilemma in Practice: When Innovation Meets Publication

Off-label prescribing and procedural innovation occupy different ethical terrain than the documentation of incidental findings or rare genetic phenotypes. When a clinician administers a biologic agent outside its licensed indication, uses a surgical device in an unapproved configuration, or applies an emerging regenerative intervention without prospective trial data, the risk exposure to the patient is real and potentially uncharacterized. Publishing the outcome serves knowledge, but it also retroactively frames the encounter as informative, lending a scientific legitimacy to a decision made under therapeutic uncertainty.

The ethical concerns in this context are several. First, patient safety: Innovative interventions carry unknown risk profiles, and the absence of trial data means that neither the clinician nor the patient can fully appreciate what adverse events are plausible. Second, therapeutic misconception: Patients who receive an innovative treatment in the context of clinical care may conflate their individual interests with any perceived research agenda, particularly if the treating clinician is known to have research interests. Third, publication bias: Case reports of innovative treatments are disproportionately more likely to report positive outcomes, creating a distorted view of treatment efficacy in the literature [15]. Fourth, institutional accountability: If adverse outcomes follow an innovative intervention that was reported without ethics consultation, institutions face significant governance exposure.

The scale of the problem is measurable. A 2024 systematic review by Tran et al. examining ethical reporting in case reports and case series across 12 consecutive years found that ethical reporting practices remained "consistently suboptimal" throughout the study period. Informed consent reporting improved modestly over time, but ethics committee involvement was inconsistently reported and often absent [16]. A cross-sectional meta-research study examining publications from 2021 found that only 46% of case reports mentioned ethics committee involvement and that 79% reported informed consent, with considerable variability in how exemptions were justified [17]. A PLOS ONE trial in 2022, in which pre-review ethics documentation was requested for a cohort of submitted manuscripts, found that nearly two-thirds of submissions in one cohort did not meet human subjects research requirements, problems that would have gone undetected without this additional scrutiny [18].

The Jeyaraman et al. PMC-indexed review specifically addressing off-label and experimental treatments in case reports characterized this as an "imperative of ethical integrity," observing that the anecdotal nature of case reports creates conditions for pre-mature adoption of unproven therapies, and called for a collaborative approach among clinicians, researchers, ethicists, and regulatory bodies to establish comprehensive, field-specific ethical guidelines [15].

Patient Autonomy and Informed Consent: Treatment, Publication, and the Gap between Them

Informed consent for treatment and informed consent for publication are legally and ethically distinct acts. The former is a clinical obligation: The patient must understand the nature, purpose, risks, benefits, and alternatives of any proposed intervention, and must agree voluntarily and competently before the intervention proceeds. When the proposed intervention is innovative, departing from standard care in a clinically meaningful way, the information owed to the patient is necessarily more extensive, not less. The treating clinician must communicate the evidentiary basis (or lack thereof) for the proposed treatment and acknowledge its experimental

character.

Publication consent is a separate matter. The ICMJE requires that patients who are identifiable in case reports, even in the presence of de-identification efforts, be shown the manuscript before submission and provide written consent for publication [4]. This requirement extends to details that might permit re-identification, including indirect descriptors, such as occupation, geographical region, or the combination of multiple clinical features. The ICMJE further requires that this consent be documented and archived with the journal or the authors in accordance with local law [4]. COPE echoes this position, recommending that journals establish explicit policies specifying both when ethics approval is required and what documentation of patient consent is expected [5].

The practical challenge is that consent processes are frequently treated as formalities. A retrospective review of the published literature by Tran et al. demonstrated persistent shortfalls in the documentation of both consent and ethics review, despite sustained guidance from international bodies [16]. Authors may obtain consent forms but fail to disclose to patients that de-identification is imperfect, that material may be accessible online permanently, or that their consent, once publication occurs, is irrevocable [14]. The European Heart Journal Case Reports has taken a notably principled position on this, explicitly distinguishing between IRB exemption and adequate publication consent and noting that "anonymization of a case report is not sufficient to eliminate the need for consent" [14].

For innovative treatments specifically, the consent burden is compounded by the need to explain that the treatment itself may not have a robust evidence base. A patient being treated with an off-label biologic or an experimental surgical technique is, in a meaningful sense, in a different position from a patient receiving established care. The treating clinician owes this patient not only clinical transparency but also a frank acknowledgement that the planned documentation and dissemination of the clinical outcome constitutes a form of knowledge generation, one that could influence future clinical decisions made about other patients. The American College of Physicians guidelines suggest that physicians prescribing for innovative off-label uses should "tell patients about the unknowns, monitor outcomes" and consider consulting oversight bodies [13].

Regulatory Landscape and the Inconsistency of Editorial Policy

The regulatory framework governing case report publication is segmented and inconsistent across jurisdictions, institutions, and journals. In the United States, federal regulations (45 CFR 46 and 21 CFR 56) establish a clear definition of human subjects research but create a zone of ambiguity around single case reports of clinical practice outcomes. IRBs vary substantially in their interpretation of where this boundary falls. Some institutions require formal exemption determination letters even for single-patient case reports; others leave this entirely to authorial or departmental discretion [17].

Journal editorial policies compound this inconsistency. COPE's 2022 guidance note acknowledged wide variation in how journals handle ethics approval requirements for case reports, observing that some require explicit ethics committee determination (approval or exemption) while others require only patient consent, and others still accept author declarations without documentation [5]. A COPE forum case addressing a situation where authors claimed that IRB approval "was not required as patients were treated with approved diagnostic and therapeutic procedures according to generally accepted standards of care" illustrates the dilemma editors face: The majority of COPE forum members recommended declining to publish when ethics documentation could not be verified [19].

The PLOS ONE experience with enhanced ethics checks is instructive. Following a 2022 trial in which ethics documentation was requested before peer review, journal staff discovered that in one cohort, nearly two-thirds of submissions failed to meet human subjects research requirements, problems that peer review alone had failed to catch. The journal implemented a mandatory pre-review ethics documentation policy effective March 2023, resulting in a 30% increase in manuscripts rejected at the staff editor stage [18]. This experience strongly suggests that the present norm, relying on author declarations during submission, is inadequate as an oversight mechanism.

The ICMJE recommendations, updated to align with the 2024 Declaration of Helsinki, state that all investigators should ensure their work accords with Helsinki principles and that they should be prepared to provide documentation of ethics committee review when requested by editors [4]. The recommendations further specify that identifying information should not be published without written informed consent, that patients should be shown the manuscript to be published, and that this consent should be documented [4]. These are concrete, operational requirements, but their enforcement rests with journal editorial boards, which apply them unevenly.

European institutions and journals are generally more prescriptive. Several European journals of case reports explicitly require either ethics committee approval or a formal exemption determination, irrespective of the routine character of the intervention reported. Oxford Medical Case Reports and similar platforms state that they follow both COPE and ICMJE

recommendations on patient privacy and consent and require written informed consent for publication [20]. These policies reduce ambiguity for authors but do not address the upstream question of when, during the clinical encounter itself, ethics consultation should be sought for an innovative intervention.

Recommendations: Toward a Risk-Stratified, Harmonized Framework

The practical path forward requires disaggregating the problem into its component parts: The ethics of applying the innovative intervention itself, and the ethics of publishing the resulting clinical experience. These are sequential but distinct obligations, and conflating them as present guidance often does, obscures what is owed to the patient at each stage.

With respect to the intervention: Clinicians applying innovative treatments outside established standards of care should seek prospective ethics consultation, ideally from a formal committee but at minimum from institutional colleagues with relevant expertise. The Belmont Report's instruction that "radically new procedures should be made the object of formal research at an early stage" [9] is not merely aspirational; where the innovation is sufficiently novel, this is a substantive ethical obligation, not a bureaucratic suggestion. Where formal research incorporation is not feasible, documentation of the rationale, the patient's understanding of the experimental nature of treatment, and any institutional committee review should be created contemporaneously.

With respect to publication: All case reports involving innovative interventions should require a documented statement addressing three questions: (1) Whether ethics committee consultation was sought for the intervention, (2) Whether informed consent for publication was obtained from the patient after the patient was shown the manuscript, and (3) Whether the reporting adheres to the CARE checklist, which includes an item specifically addressing ethical compliance [1, 6]. Where ethics committee approval or exemption was not sought, authors should be required to explain why not. This explanation should be published as part of the manuscript.

Journals should adopt tiered policies rather than binary approval/exemption dichotomies. A report of a rare adverse reaction to a licensed drug used on-label carries different ethical weight than a report of an unlicensed surgical innovation in a pediatric patient. Editorial policies that treat these equivalently, or fail to distinguish them at all, serve neither authors nor patients well. Tiered policies might require full ethics committee documentation for innovative interventions substantially outside standard care, formal exemption determination for routine clinical care reports, and patient consent documentation as a universal requirement regardless of intervention type.

At the institutional level, hospital credentialing committees, pharmacy and therapeutics committees, and new technology review bodies should develop prospective mechanisms for tracking and documenting innovative interventions before they are applied. Ansani et al. proposed precisely such a model, a multidisciplinary policy process for innovative off-label medication use that incorporates formulary review, peer expertise input, and prospective safety surveillance, as an institutionally implementable framework [21]. Embedding ethical documentation into this prospective institutional process would substantially reduce the retrospective ambiguity that currently characterizes publication ethics for innovative case reports.

Finally, the international research community needs harmonized standards. The fragmentation of present guidance, spanning the Declaration of Helsinki, the Belmont Report, ICMJE, COPE, FDA regulations, European directives, and individual journal policies, creates a compliance environment that is genuinely difficult to navigate in good faith. A coordinated initiative among COPE, ICMJE, and the WMA to develop a specific instrument addressing the ethics of innovative treatment reporting in case studies would fill a gap that has persisted for too long.

Conclusion

The ethical oversight of publishing case reports on innovative clinical interventions remains inadequately governed, despite foundational frameworks, such as the Belmont Report and the 2024 revision of the Declaration of Helsinki. While the latter strengthens protections for informed consent and institutional review, its principles risk dilution if left to individual interpretation rather than embedded in enforceable journal policies and institutional protocols. Empirical evidence consistently shows poor reporting of ethics committee involvement and informed consent in case reports, reflecting systemic design flaws rather than clinician negligence. Present guidance is fragmented, inconsistently applied, and insufficiently sensitive to the ethical weight of novel treatments. Addressing this gap requires coordinated, risk-stratified standards across journals, ethics bodies, and institutions, ensuring that innovative interventions – often uncertain in evidentiary foundation – are subject to transparent and harmonized oversight. Patient trust, the cornerstone of both practice and science, demands more than formal consent; it requires a documented, continuous ethical commitment from clinical decision-making through to publication.

Clinical Message

1. Clinicians must secure informed consent for both treatment and publication, with clear disclosure of uncertainties in innovative interventions.
2. Innovative treatments reported in case studies should trigger prospective ethics consultation and documentation, not rely solely on exemption policies.
3. Journals, institutions, and ethics bodies must coordinate to enforce harmonized standards, ensuring ethical integrity in case report publication.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given the consent for his/ her images and other clinical information to be reported in the journal. The patient understands that his/ her names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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