Commentary

The Unregulated Majority: Who Ensures Quality in Non-Submission Real-World Studies?

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Real-world evidence (RWE) is increasingly central to healthcare decision-making, with regulatory and health technology assessment (HTA) authorities formalising standards for data reliability, relevance, and transparency. Yet the vast majority of industry-sponsored RWE studies are not designed for submission to authorities. Instead, they are produced for scientific communication, disease awareness, medical education, or exploratory purposes. This "non-submission RWE" dominates the evidence ecosystem but often proceeds without prespecified protocols, adequate comparators, or peer-reviewed oversight. While many non-submission RWE studies lack prespecified protocols or independent oversight, it is important to note that a substantial number are conducted rigorously and provide valuable insights into natural disease history, treatment patterns, and unmet needs. The result is a body of evidence that appears scientific but lacks safeguards against bias, selective reporting, and promotional drift.

This commentary examines recurring flaws in non-submission RWE, including protocol shortcuts, descriptive overreach, weak peer review, and selective dissemination. It highlights the risks these shortcomings pose for clinicians, patients, and policymakers by distorting perceptions of treatment value and eroding trust in RWE as a credible scientific field. Drawing on regulatory pilots, harmonisation efforts, and methodological innovations such as target trial emulation and transparency templates, it argues that the tools to improve quality already exist but remain underused in non-submission contexts.

A pragmatic framework is proposed around three pillars: protocol registration, analytical transparency, and internal governance boards. These measures, adapted from existing regulatory and trial practices, would raise the floor of quality across all RWE. Extending accountability to non-submission studies is not a compliance burden but a professional responsibility. If real-world data are

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to guide real-world decisions, all studies—regulatory or not—must meet baseline standards of validity, transparency, and integrity.

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Introduction

Real-world evidence (RWE) has become an increasingly prominent element of modern healthcare decision-making, moving from a marginal complement to randomised controlled trials (RCTs) into a central pillar of regulatory, reimbursement, and clinical deliberations. The European Medicines Agency (EMA), the United States Food and Drug Administration (FDA), and the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) have all released frameworks to encourage the use of real-world data (RWD) under conditions of relevance, reliability, and transparency [1][2]. Recent initiatives such as the EMA pilot on regulatory use cases [3] and multi-country lifecycle evidence generation programmes [4] demonstrate that when RWE is generated under regulatory oversight, it can meaningfully inform safety surveillance, paediatric and rare disease research, and trial feasibility. Complementing these regulatory initiatives, the EMA's *Clinical Evidence 2030* perspective envisions a system where patient voice, transparency, and advanced analytics drive evidence generation across the lifecycle [5].

At the same time, methodological innovation has expanded the credibility of observational research. Target trial emulation approaches [6], harmonisation pilots in oncology [7][8], and innovative external comparator strategies such as blinded expert video review in rare diseases [9] illustrate how RWE can approach trial-level rigour. Parallel efforts to improve reporting and transparency—such as the STaRT-RWE and HARPER templates, the REQueST tool, and the EU push toward registry qualification—further show that tools to strengthen trust in RWE are already available [10][11]. International harmonisation initiatives, including those led by Duke Margolis and the International Council for Harmonisation (ICH), have sought to align definitions of reliability, relevance, and quality across agencies [12]. Industry stakeholders, through EFPIA and other consortia, have also called for clear good practice principles in the conduct of non-interventional studies (NIS), including mandatory registration, bias reduction strategies, and adherence to FAIR data standards [13].

Despite these advances, however, a paradox remains. The majority of RWE produced in the pharmaceutical sector is not designed for submission to regulatory or health technology assessment (HTA) authorities. Instead, it is generated for scientific communication, burden-of-disease description, medical education, or indirect support of product positioning [13]. Such studies—which dominate conference abstracts, poster presentations, and local registry analyses—frequently lack prespecified protocols, comparator groups, or peer-reviewed oversight. Recent reviews confirm that even in leading journals, over a quarter of observational studies fail to report key quality elements such as missing-data handling, residual confounding, or falsification tests [14]. Audits in dermatology and other therapeutic areas have demonstrated persistent weaknesses in reporting sample size justification, attrition, and data completeness, despite the availability of STROBE guidelines [15]. From a reviewer's standpoint, weaknesses in question specification, study design, and data fitness remain common, even when target trial reconstruction is attempted [16].

Evidence from comparative analyses of RWE versus RCTs reinforces the scale of the challenge. For example, work comparing diabetic kidney disease trial populations with real-world cohorts revealed minimal overlap, highlighting how unadjusted comparisons can be misleading when data generation mechanisms differ fundamentally [17]. In oncology, broadening trial eligibility criteria and integrating real-world populations has been championed to enhance representativeness and external validity [18]. Similarly, proposals for adaptive and biomarker-driven designs, pragmatic registries, and digital endpoints underscore how high-quality RWE can complement trials in precision medicine [19]. Yet these methodological insights remain largely confined to high-stakes regulatory or academic settings. In the broader landscape of non-submission industry-sponsored RWE, study quality is often compromised by speed, feasibility considerations, or promotional intent.

The contrast is stark: while regulators and academic consortia invest heavily in improving the credibility of RWE, the vast majority of studies produced for communication, education, or awareness operate with little to no structured oversight. This "unregulated majority" presents not only a scientific shortfall but also an ethical challenge. Patients contribute data—directly or indirectly—without assurance that the resulting evidence meets minimal standards of validity or transparency. The time has come to extend governance and quality safeguards beyond the narrow scope of regulatory submissions, ensuring that all RWE intended to influence clinical understanding or decision-making meets basic principles of scientific integrity.

The Blind Spot: Recurring Quality Issues in Non-Submission RWE

The dominance of non-submission RWE within the pharmaceutical ecosystem is both striking and underappreciated. These studies include disease burden descriptions, treatment pattern analyses, pragmatic registry reports, and exploratory effectiveness comparisons that rarely proceed to formal submission. Yet they form the majority of the evidence landscape encountered by clinicians at congresses, in medical affairs slide decks, and in peer-reviewed but low-impact journals (typically those with an impact factor <2 or not indexed in major bibliographic databases)[13][14]. Their prevalence makes their weaknesses all the more concerning.

Several recurring flaws characterise this body of work:

1. **Protocol shortcuts**: Many non-submission studies advance with little more than a concept slide or one-page outline rather than a detailed, prespecified protocol. In reviews of congress abstracts, up to one-third of non-submission studies are based only on concept notes or short outlines rather than full protocols. without proper adjustment, comparators, or sensitivity analyses. This absence of planning limits reproducibility and increases the risk of selective analytic choices [1][13].
2. **Descriptive overreach**: Studies intended to be descriptive—such as treatment pattern reviews—are often stretched to make causal inferences about effectiveness or safety without proper adjustment, comparators, or sensitivity analyses. Even when causal inferences are attempted, confidence intervals and sensitivity analyses are rarely presented to contextualize findings. In oncology, proxy endpoints like time-to-next-treatment (TTNT) are commonly used in place of validated outcomes, yet rarely accompanied by a discussion of their limitations [16].
3. **Selective reporting**: Non-submission RWE is disproportionately channelled into congress abstracts and posters. Positive findings are highlighted, while neutral or negative analyses are quietly omitted. As an example, the dermatology field offers repeated examples of registry data being presented selectively, emphasising supportive comorbidity profiles without rigorous confounder adjustment [15].
4. **Methodological issues:** Other recurrent flaws include poor data quality and governance, unaddressed selection bias, intercurrent confounding, and immortal time bias—all of which compromise reliability if not explicitly managed.
5. **Weak peer review**: Weak peer review is a common problem, since the majority of these outputs are confined to conference proceedings where peer review is minimal, if it occurs at all, while many

observational studies published in low-threshold journals also fail to meet transparency and reproducibility standards [13][14]. By weak peer review we refer to acceptance processes without statistical or methodological scrutiny, typical of many conference proceedings and lower-tier journals.

6. **Promotional drift:** Many studies are designed not primarily to answer clinical questions but to support the positioning of therapies within treatment algorithms. Registries created in parallel with product launches often highlight unmet needs or under-treatment patterns that subtly reinforce the sponsor's value proposition, rather than generating neutral insights. Evidence also shows that physicians participating in non-interventional post-marketing studies tend to prescribe the studied drug more frequently: a large German cohort study found a **7–8% increase in prescriptions during the study** and a **6–7% increase in the following year** [1][13][20]. While it is acceptable that physicians adapt prescribing practices during formal trials, poor-quality RWE alone is unlikely to drive this behaviour. Nevertheless, the selective framing of registry data to highlight unmet needs can blur the line between education and promotion.
7. **Capability gaps:** In many pharmaceutical companies, RWE functions are underdeveloped at global headquarters or local affiliate level, where resources may be concentrated in medical affairs teams without formal analytical training or spread thin across therapeutic areas. Affiliates and medical affairs teams often lack dedicated epidemiology or biostatistics expertise, relying instead on external vendors or adapting clinical trial–style approaches to observational settings. This can result in studies with weak design, inadequate adjustment for confounders, or superficial analyses that prioritise feasibility over validity. Industry reflections confirm that limited internal capacity remains a barrier to robust non-interventional research [13].

Comparative analyses illustrate the risks of such practices. For instance, in diabetic kidney disease, comparisons between trial and real-world cohorts highlight mismatched populations; in oncology, restrictive inclusion criteria often reproduce biases seen in trials, reducing generalisability [17]. Similarly, in oncology, expanding eligibility criteria has been shown to improve external validity, yet non-submission real-world oncology studies often fail to mirror such inclusivity, restricting populations in ways that serve feasibility or sponsor convenience rather than scientific rigour [18][19].

The cumulative effect of these shortcomings is a large body of evidence that looks scientific but lacks the safeguards necessary for credibility. Unlike regulatory-grade RWE, these studies are not subject to systematic bias assessment, independent review, or transparency requirements. This blind spot risks

perpetuating low-quality evidence under the guise of scientific legitimacy and erodes trust among clinicians, patients, and policymakers alike.

Why It Matters: Implications for Science, Policy, and Patients

The shortcomings of non-submission RWE are not a minor methodological concern; they have tangible consequences across the healthcare ecosystem.

For **clinicians**, the widespread dissemination of non-submission RWE shapes perceptions of treatment effectiveness, safety, and disease burden. When studies are poorly designed or selectively reported, they can reinforce misconceptions, bias prescribing behaviours, or create misplaced confidence in therapeutic strategies. In dermatology and oncology, for example, registry analyses with inadequate adjustment have been cited in promotional contexts as evidence of systemic disease burden or unmet need, subtly influencing treatment adoption without providing robust support [15][18]. Alongside these risks, many rigorously conducted non-submission RWE studies have provided critical insights—for example, clarifying natural histories of rare diseases, mapping treatment pathways, and generating foundational evidence that informs guideline development.

For **patients**, the implications are equally concerning. Patients often participate indirectly, by contributing data through electronic health records, registries, or claims, with the expectation that their information will advance knowledge and improve care. When that data is used in studies of limited quality or promotional intent, it represents a breach of trust [5][13]. Worse still, weak evidence can slow progress if it crowds out higher-quality analyses, or if misleading conclusions seep into guidelines and shared decision-making tools [14].

For policymakers and payers, the proliferation of low-quality RWE muddies the evidence base used to inform healthcare resource allocation. While HTA bodies and regulators apply increasingly strict filters to submission-grade evidence [3][4], non-submission RWE often circulates freely in scientific and policy discourse without similar safeguards [13]. This creates asymmetry: evidence intended to support reimbursement decisions is tightly regulated, while the much larger body of RWE that frames disease narratives and clinical practice remains unchecked.

At a broader level, these practices **erode trust in the credibility of RWE as a field**. Initiatives such as target trial emulation, transparency templates, and international harmonisation seek to raise standards and demonstrate that observational research can match RCTs in credibility under the right conditions [6]

[10][12]. Yet the coexistence of high-quality regulatory RWE with a vast volume of unregulated, non-submission studies risks undermining those efforts. If clinicians and policymakers perceive RWE as inconsistent or biased, the legitimacy of the entire enterprise suffers.

Finally, there is an **ethical dimension**. Generating RWE consumes resources—patients' data, clinicians' time, and public trust. Using those resources to produce evidence of questionable validity is not a neutral act; it represents an opportunity cost. Each weakly designed registry analysis or selective congress poster displaces the potential for a more rigorous study that could genuinely inform practice. In this light, the unregulated majority of RWE is not merely an academic blind spot but a barrier to the responsible use of real-world data in healthcare.

Proposed Framework for Oversight

Addressing the credibility gap in non-submission RWE does not require replicating the entire machinery of regulatory science. Instead, it calls for pragmatic safeguards that raise the floor of quality without paralysing legitimate scientific communication. Three pillars are proposed:

1. **Protocol Registration**

   All non-interventional studies, whether intended for submission or not, should be registered in publicly accessible databases such as the EU PAS Register, ClinicalTrials.gov, or ENCePP. Registration of objectives, endpoints, and analysis plans would create a transparent record that reduces selective reporting and strengthens accountability. Industry statements, such as those from EFPIA, already support this step for hypothesis-evaluating treatment effect (HETE) studies [13]. Extending this expectation to all RWE, regardless of regulatory intent, would be a modest but impactful reform.

2. **Analytical Transparency**

   Transparency does not require open-sourcing every line of proprietary code, but it does require clarity on methods, assumptions, and definitions as well as explicit attention to data quality, governance, database provenance, and use of a prespecified statistical analysis plan (SAP). Initiatives like STaRT-RWE, HARPER, and REQueST provide structured templates for reporting study design, endpoint definitions, and data provenance [10]. Companies should adopt these tools routinely for non-submission studies, ensuring that clinicians, reviewers, and policymakers can assess credibility. Where possible, code snippets, variable definitions, and sensitivity analyses should be made available, particularly when studies are published in peer-reviewed outlets.

3. **RWE Governance, Accountability, and Capability Building**

   Most pharmaceutical companies already operate Global Review Committees (GRCs) or equivalent structures to review clinical trial outputs and major publications. Expanding these committees to review all non-submission RWE, however, risks creating an unmanageable bottleneck. Experience shows that assigning every abstract, poster, or local registry analysis to a central review body leads to delays, reviewer fatigue, and superficial oversight.

A more effective model is to establish **study-specific governance and accountability**. Dedicated study teams—comprising epidemiologists, biostatisticians, medical leads, data managers, and statistical programmers—should be accountable for the statistical analysis plan (SAP), the study report, and all downstream communication materials. Communication materials would then undergo an additional, focused review by scientific communication teams to ensure consistency and quality, without duplicating full methodological review at the committee level.

This model also addresses a broader structural issue: **capability gaps at global and local levels**. Too often, non-submission studies are initiated and "owned" by functions without adequate analytical expertise, leading to weak or inconsistent design. To mitigate this, companies should invest in **capability building and resource hubs**. Locating study teams in countries with strong talent pools and lower operating costs can provide scalable access to skilled epidemiologists, statisticians, and programmers, while maintaining global oversight. This dual approach—study team accountability combined with strengthened analytical capacity—provides assurance that non-submission studies are conducted to a consistent scientific standard, without overwhelming senior committees or relying on ad hoc vendor support. In parallel, there is a case for robust monitoring structures—whether industry-wide or academic consortia—to minimise dissemination of low-quality RWE. Educating clinicians and decision-makers on how to critically appraise such evidence is equally important to ensure that only high-quality, actionable findings influence practice.

Implementing this framework would require investment, but it is not without precedent. Registries such as ENCePP already facilitate protocol transparency, while internal medical review boards are a familiar feature of trial governance. Moreover, structured templates and harmonisation efforts are proliferating, providing a ready-made toolkit for industry adoption [12]. The challenge is not a lack of methodology but the absence of expectation. By making these three safeguards routine for all RWE—whether destined for HTA dossiers, congress posters, or awareness campaigns—the industry can raise credibility standards without stifling scientific productivity.

Conclusion

The debate about the role of real-world evidence in healthcare has too often focused on regulatory submissions and HTA processes, leaving the much larger corpus of non-submission studies underexamined. These studies—produced for awareness, communication, education, or exploratory purposes—represent the bulk of what clinicians encounter at congresses and in medical affairs materials. Yet their methodological safeguards are minimal, and their oversight is inconsistent at best. This imbalance creates a credibility gap that threatens to undermine the legitimacy of RWE as a whole.

High-quality examples from regulatory pilots, harmonisation initiatives, and innovative methodological programmes demonstrate that observational research can achieve rigour comparable to RCTs when supported by governance and transparency. However, without extending even basic safeguards to non-submission studies, the scientific community risks perpetuating a two-tier system: rigorous, auditable evidence for regulators, and an unregulated majority for everyone else.

The reforms proposed here—protocol registration, analytical transparency, and governance boards—are not radical innovations but pragmatic adaptations of existing practices. Implemented consistently, they would raise the floor of quality across all RWE, aligning the expectations for non-submission studies with those already recognised for regulatory evidence. More importantly, they would protect patients' contributions, clinicians' trust, and the credibility of RWE as a field.

Ultimately, the value of RWE lies not only in the data itself but in the integrity of its generation and use. Extending accountability to the unregulated majority is therefore not a matter of compliance, but of professional responsibility. If real-world data are to guide real-world decisions, then all real-world studies —submission or not—must meet a baseline standard of quality and transparency.

Statements and Declarations

Conflicts of Interest

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