SONATA SOFTWARE

The Modernization Engineering Company

Whitepaper

TECHNOLOGY AND POLICY FRAMEWORK | **2026**

Integrated and **holistic evidence generation 2.0**

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Executive summary

We are living through an extraordinary moment for medicine. The convergence of real-world data networks, artificial intelligence, blockchain infrastructure, and connected patient devices is creating conditions that make it possible — for the first time — to build a drug evidence ecosystem that is continuous, comprehensive, transparent, and genuinely patient-centered. Congressional recognition of this moment came with the 21st Century Cures Act of 2016, which directed the FDA to develop frameworks for integrating real-world evidence (RWE) into regulatory decision-making [1][2] — a mandate whose technical fulfilment is now within reach.

The pharmaceutical industry has built extraordinary science. Regulatory agencies like the FDA have protected public health under enormous complexity and resource constraints. Academic researchers have advanced clinical knowledge. And yet structural patterns in how evidence is generated, funded, and published — documented across multiple therapeutic areas in the peer-reviewed literature[3][4] — create gaps between what science knows and what the evidence record reflects. Technology is now uniquely positioned to close those gaps.

This paper offers a concrete, technology-grounded framework for doing so: Evidence 2.0. It is organized around three pillars — holistic real-world evidence generation, end-to-end transparency and traceability, and technology-enabled regulatory modernization and is grounded in existing FDA programs, published research, and implementable technology standards.

The Core Opportunity

Technology now makes it possible to move from a drug evidence system that is episodic, siloed, and static — to one that is continuous, integrated, and dynamically updated. This is not incremental improvement. It is a generational upgrade in our ability to understand what medicines do in the real world — for all patients, not just those who met trial eligibility criteria.[1][5]

PART I: Understanding the current landscape Where technology can make the greatest difference

1.1 How drug evidence is currently generated

The dominant model for pharmaceutical evidence generation has served medicine well for decades. Randomized controlled trials (RCTs) — carefully designed, rigorously executed, statistically powered — have validated countless therapies and protected patients from ineffective or harmful treatments. Regulatory frameworks built around these trials have produced a drug approval system that is among the most rigorous in the world. The FDA's guidance on the considerations for use of real-world data and real-world evidence, finalized in 2023[5], itself acknowledges RCTs as the historical foundation while charting the expansion of the evidentiary toolkit.

And yet this same system has structural patterns — rooted in its pre-digital design — that limit the completeness of the evidence record. Turner et al.'s landmark 2008 analysis in the New England

Journal of Medicine[3] examined 74 FDA-registered antidepressant trials involving 12,564 patients and found that 31% were not published, inflating apparent drug effect sizes by 32% in the published literature overall. Anderson et al.[4] similarly found significant non-compliance with ClinicalTrials.gov result reporting requirements. These are systemic patterns driven by structural incentives, not individual failures — and they are the patterns that technology can most directly address.

The structural characteristics that create these patterns include:

- Episodic evidence generation: concentrated around regulatory milestones rather than continuous, creating knowledge gaps between approval and the accumulation of real-world use data.
- Compressed trial durations: relative to the lifetime of therapy use, meaning long-term safety and effectiveness signals may not emerge until post-approval, if they emerge through formal evidence channels at all.
- Homogeneous trial populations: typically younger, healthier, and more protocol-adherent than the complex, comorbid patients who receive drugs in clinical practice — limiting the generalizability of trial-based conclusions.
- Publication patterns: influenced by outcome, creating systematic asymmetry in the publicly available evidence base that misleads clinicians and the research community alike.

1.2 What has changed and why 'now' is the moment

The convergence of several transformative technologies has created conditions that make a fundamental upgrade to the drug evidence system achievable within a five-to-ten year horizon. The ONC's 2020 Final Rule implementing the 21st Century Cures Act[6] mandated FHIR R4-based APIs across certified EHR systems — creating the foundational interoperability infrastructure that real-world evidence generation at scale requires. By 2022, over 90% of U.S. hospitals were using APIs to enable patient access to EHR data.[7]

EHR | Electronic Health Records at scale

Over 96% of U.S. hospitals now use certified EHR systems, and the 2020 ONC Cures Act Final Rule mandated FHIR R4 APIs across all certified platforms, creating the foundational interoperability infrastructure for real-world evidence generation at population scale. The CMS Interoperability and Patient Access Final Rule (CMS-9115-F) further requires FHIR-based APIs from all major payer types, enabling longitudinal patient data flows that were previously technically impossible.[6][7]

AI | Artificial Intelligence and Machine Learning

Machine learning models can now identify safety signals in complex, high-dimensional health data with sensitivity and speed that traditional pharmacovigilance cannot match. The FDA's Sentinel System has begun deploying AI-powered signal detection algorithms — TreeScan statistical analyses were piloted in 2022 with semaglutide, erenumab, and filgrastim-sndz — demonstrating proof-of-concept for continuous, automated signal identification across approved therapies.[8][9]

Blockchain and distributed ledger technology

Benchoufi and Ravaud, writing in Trials (2017), proposed blockchain as a mechanism to ensure historicity and inviolability of clinical trial data addressing the core problem of after-the-fact modifications to trial protocols and endpoints. Wong, Bhattacharya, and Butte at UCSF demonstrated a working prototype of blockchain-based clinical trial management in Nature Communications (2019), showing that the technology can create durable, transparent logs of trial events in real-world settings.[10][11]

IOT | Wearables, sensors, and connected devices

Continuous patient monitoring through wearable devices and digital biomarkers captures health data between clinical visits the 95% of patient experience that traditional trials never observe. The FDA's Patient-Focused Drug Development initiative has progressively elevated patient-generated data, and published guidance on incorporating digital health technologies into clinical investigations is now available, creating regulatory pathways for this data stream.[12]

API | Interoperability standards and federated health data networks

The Sentinel System, a federated network now covering approximately 138.7 million members, demonstrates the feasibility of privacy-preserving population-scale safety analysis. Since 2016, more than 120 Sentinel drug studies have contributed to FDA regulatory actions or discussions, with 260 scientific papers published from the network since its founding in 2009.[13][14]

PART II: Real-world evidence as the foundation of a learning evidence system

2.1 Moving from point-in-time approval to continuous evidence generation

The FDA's 2018 Framework for the Real-World Evidence Program[1] established the conceptual architecture for a continuous learning model defining RWD as 'data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources,' and RWE as 'the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.' The framework identified electronic health records, medical claims, registries, and patient-generated data as primary RWD sources. Building on this framework, the following components constitute the technical implementation of continuous evidence generation:

Drug-specific patient registries built on modern data infrastructure

Modern registry architectures can draw data automatically from EHR systems through FHIR R4 APIs without requiring clinicians to manually enter information, a design principle now technically enabled by the ONC Cures Act Final Rule.[6] The Sentinel Innovation Center's development of the Real-World Evidence Data Enterprise (RWE-DE), a federated network linking EHR data from 25 million patients across commercial and

academic health systems[15] provides a working model for what drug-specific registry infrastructure can look like at population scale.

Technical enabler: FHIR-Native Registry Design

FHIR R4 APIs, mandated by the 2020 ONC Cures Act Final Rule, enable registry data capture directly from EHR documentation workflows. The PCORnet (Patient-Centered Outcomes Research Network) framework already demonstrates this capability across hundreds of health systems — with data standardized through the PCORnet Common Data Model enabling federated analysis without centralizing sensitive patient records.[6][16]

Federated real-world data analysis and privacy-preserving population safety

Platt, Brown, Robb, and colleagues described the Sentinel Initiative's federated architecture in the New England Journal of Medicine [13]: data remain with the data owner, patient identifiers are removed, and analyses travel to the data rather than requiring data centralization. Since 2022 to 2024, the Sentinel System expanded EHR integration, piloted AI-based signal detection analyses, and conducted active surveillance analyses that contributed to multiple FDA safety labeling decisions.[9] This federated model resolves the tension between population-scale analytical power and individual patient privacy a resolution that makes real-world evidence generation politically and practically viable across health systems.

Pragmatic clinical trials embedded in real-world care

The FDA's framework explicitly identifies pragmatic clinical trials conducted in real healthcare settings with broader eligibility criteria and real-world comparators as a key component of the RWE program.[1][5] Published FDA guidance on pragmatic trial design elements describes how such trials can generate evidence of effectiveness for regulatory decisions. The PCORnet infrastructure, spanning over 11 million research-consented patients across academic health centers and health plans, already provides the distributed trial capability to execute such trials at scale.[16]

2.2 Patient-generated evidence

The FDA's Patient-Focused Drug Development (PFDD) initiative established under PDUFA VI and codified in the 21st Century Cures Act has progressively elevated the formal role of patient experience data in benefit-risk assessments.[2][12] Published FDA guidance on patient-focused drug development describes how patient experience data, including patient-reported outcomes (PROs) and digital health

technology-derived data, can be incorporated into regulatory decision-making. The technical infrastructure for collecting such data at scale validated PRO instruments administered digitally, wearable continuous monitoring, structured patient community data now exists and is rapidly maturing.

Real-world patient data in action

The FDA's Digital Health Center of Excellence, established in 2020, has published guidance on the use of Digital Health Technologies (DHTs) including wearables, sensors, and software as medical devices in clinical investigations creating regulatory pathways for continuous patient-generated data to contribute formally to drug evidence generation. This guidance represents a tangible step toward the patient-centered evidence ecosystem described in this framework.[12]

PART III: Technology-enabled transparency and end-to-end traceability

3.1 The traceability opportunity

The structural pattern identified by Turner et al. [3] in which trial outcomes influence publication probability, systematically distorting the evidentiary record is fundamentally an information architecture problem. The published evidence base is a subset of the total generated evidence, with the subset selected by processes that are not fully visible to downstream users. Technology can make those processes visible.

Anderson et al.'s 2015 analysis of ClinicalTrials.gov reporting compliance [4] found that even the regulatory requirement to report results introduced by the FDA Amendments Act of 2007 was not consistently met. Compliance was significantly higher when financial penalties were in place, demonstrating both the limitations of voluntary disclosure and the effectiveness of structured accountability. A technology-enabled traceability architecture makes compliance verifiable in real time, rather than discoverable only through retrospective audit.

3.2 A proposed Unified Evidence Traceability Platform (UETP)

We propose the development of a Unified Evidence Traceability Platform, a modern, API-first, cloud-native system that creates and maintains a complete, publicly accessible record of the evidence genealogy for every drug. The UETP would be built on four technical pillars:

Immutable protocol registry on distributed ledger

Benchoufi and Ravaud, in a foundational 2017 paper in Trials, proposed blockchain as a mechanism for clinical trial data transparency, identifying timestamping, time-ordering, and smart contracting as three core functionalities that blockchain provides for quality control in clinical studies. Wong, Bhattacharya, and Butte's 2019 Nature Communications paper demonstrated a working blockchain prototype for running clinical trials in ways that make retroactive data manipulation technically detectable. A permissioned blockchain-based UETP protocol registry would extend these proofs-of-concept into operational infrastructure.[10][11][17]

Structured financial provenance disclosure

The CMS Open Payments database, created under the Physician Payments Sunshine Act, already captures all financial transfers from pharmaceutical manufacturers to physicians and teaching hospitals publicly, in structured, machine-readable format. The UETP would integrate Open Payments data with trial registration records to create an automated, query-able map of financial relationships surrounding any registered study. Rather than disclosures buried in journal appendices, the UETP enables any stakeholder to query: 'What financial relationships do the investigators on this study have?'

AI-powered evidence synthesis and anomaly detection

Machine learning models running continuously against the UETP dataset can identify patterns that warrant additional scrutiny: studies where pre-specified primary endpoints changed after enrollment began; publication patterns where negative studies in a particular therapeutic area appear systematically absent; or clusters of studies where a single funding source dominates the evidence base. The FDA's Sentinel system has already demonstrated that AI-powered signal detection in large federated datasets is technically feasible and operationally deployable at scale.[8][9]

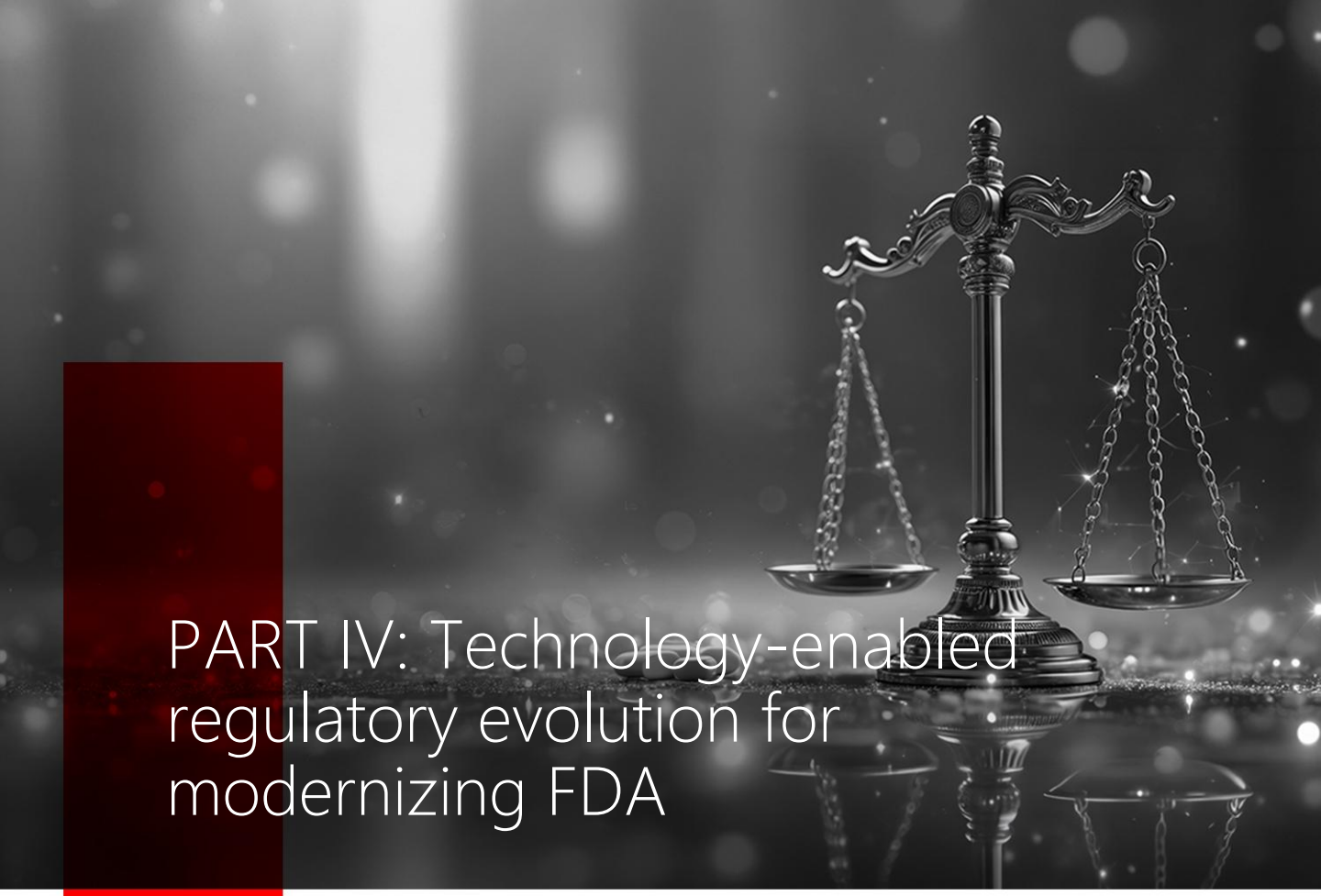
Regulatory decision lineage and linking

Every major regulatory decision would be linked in the UETP to the specific studies that supported it, the financial relationships of the investigators involved, and any independent analyses or expert opinions that contributed. This creates an end-to-end chain of custody from evidence to decision that can be audited as new data emerges, enabling a learning regulatory system. The FDA's existing regulatory submission systems provide the source data; the UETP provides the linking and querying infrastructure.[1]

3.3 Making transparency useful from disclosure to insight

Transparency is only valuable if it is actionable. The UETP is designed not just to store transparency information, but to make it actively useful to its different audiences:

- For regulators: Automated flags when submitted evidence packages have significant funding concentration, when study designs changed materially after enrollment began, or when published evidence diverges from registered endpoints delivered as structured analytical reports.
- For clinicians: A plain-language 'evidence label', analogous to a drug label, summarizing the evidence quality profile of any approved therapy: how many trials, who funded them, what the balance of trial versus real-world evidence is, and what the most recent safety signals show.
- For patients: Plain-language summaries integrated into patient-facing platforms answering the questions patients ask: 'How was this drug tested? In people like me? How long have people been using it?'
- For researchers: Open access to structured evidence metadata enables systematic research on evidence quality patterns across therapeutic areas creating a publicly funded research program focused on the health of the evidence ecosystem itself.



PART IV: Technology-enabled regulatory evolution for modernizing FDA

4.1 The FDA's opportunity to lead a technology transformation

The FDA has already demonstrated meaningful capacity for technology-driven innovation. Commissioner Gottlieb's 2018 congressional testimony [19] described the FDA's active investment in integrating electronic health records, registries, and claims data into regulatory decision-making, and the development of frameworks to evaluate RWE for new drug indications and post-approval study requirements. The Sentinel System's evolution from a claims-based safety surveillance network to an EHR-integrated, AI-capable pharmacovigilance platform [8][13][14] demonstrates that the FDA can build and operate sophisticated real-world data infrastructure.

The opportunity now is to accelerate this trajectory — to move from piloting real-world evidence frameworks to operationalizing them; from building Sentinel toward activating Sentinel as a primary pharmacovigilance tool; and from accepting digital health data in some contexts to establishing robust standards for how it contributes to benefit-risk assessments across the full regulatory lifecycle.

4.2 Five technology-enabled regulatory capabilities

Capability 1: Continuous safety signal monitoring with AI

The FDA's FAERS (Adverse Event Reporting System) currently captures spontaneous adverse event reports — valuable but well-documented as incomplete. Ball, Robb, Anderson, and Dal Pan's 2016 description of the Sentinel Initiative as 'a comprehensive approach to medical product surveillance'[14] identified active surveillance — proactively querying existing health data rather than waiting for voluntary reports as the key paradigm shift. Maro and colleagues' 2023 analysis of six years of the Sentinel ARIA system [20] described how the system has supported safety labeling changes, REMS evaluations, and NDA reviews through active safety data querying. AI-powered NLP models that analyze clinical notes, patient community posts, and published case reports can further extend this surveillance capability, dramatically expanding the signal capture surface beyond what claims-based analyses alone can detect.

Capability 2: Independent evidence re-analysis infrastructure

The FDA's 2023 guidance on considerations for real-world data and real-world evidence[5] describes the methodological criteria by which RWE can support regulatory decisions — criteria that equally apply to the independent re-analysis of submitted trial data. A standing infrastructure for rapid, independent re-analysis of patient-level data from pivotal trials using cloud-based analytical environments, CDISC-standardized data formats, and a network of qualified independent statistical teams would systematize what is currently an exceptional practice into a routine capability, providing an additional layer of analytical validation for major regulatory actions.

Capability 3: Proactive conflict mapping using open data

The CMS Open Payments database which captures all financial transfers from pharmaceutical manufacturers to physicians and research institutions, publicly, in structured machine-readable format is a powerful transparency resource that currently sits largely disconnected from FDA regulatory review processes. An automated system that queries Open Payments data and links it to registered trial investigators, advisory panel nominees, and published meta-analysis authors would give FDA reviewers complete, at-a-glance situational awareness of the financial context surrounding submitted evidence a capability that requires no new data collection, only new data integration and query tooling.

Capability 4: A living label infrastructure

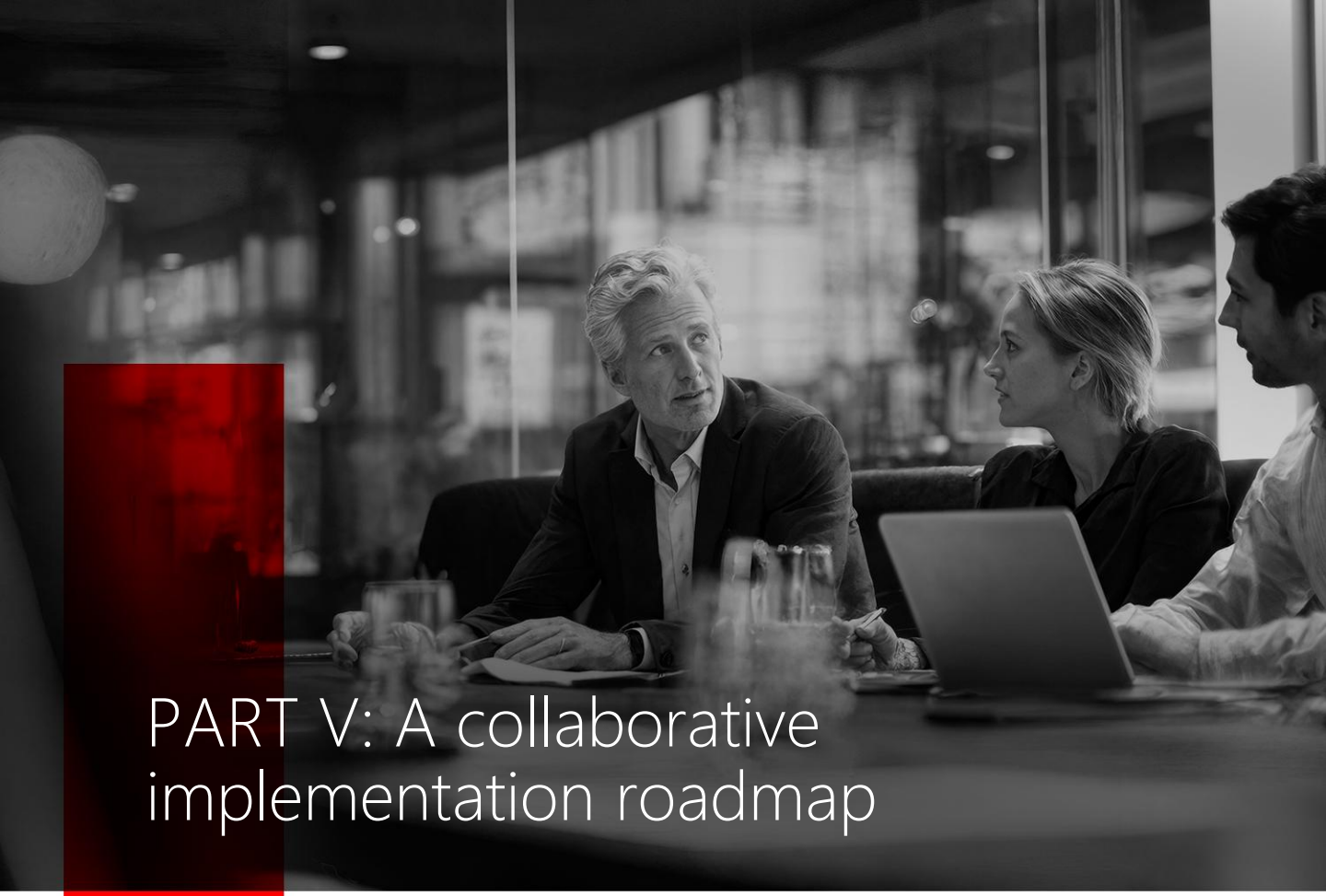
Drug labels — the official summaries of a drug's approved uses, benefits, risks, and appropriate populations — are currently static documents, updated through a formal process that lags significantly behind accumulating real-world evidence. The FDA's existing Structured Product Labeling (SPL) standard provides a machine-readable XML foundation for a living label architecture. Extended to incorporate structured sections for trial evidence, real-world evidence, patient-reported outcomes, and known subgroup effects, each tagged with the evidence base supporting it and the UETP financial provenance data, the living label could provide clinicians and patients with a continuously updated, evidence-grounded profile of each approved therapy.

Living clinical practice guidelines

Living systematic reviews and guidelines are continuously updated as new evidence emerges, with explicit versioning have been successfully implemented across major specialty societies including the Cochrane Collaboration and WHO. The FDA's living label infrastructure would apply the same principle to official regulatory documentation, powered by the real-world evidence streams and UETP transparency data described in this framework. The technical infrastructure (FHIR, SPL XML, cloud-based publishing) already exists; the workflow and governance model requires development.[5][16]

Capability 5: Adaptive regulatory pathways powered by real-world evidence

The FDA's accelerated approval pathway and REMS programs already represent steps toward adaptive regulatory frameworks — approvals conditioned on post-market evidence generation. The FDA's 2018 RWE Framework [1] explicitly identified post-approval study requirements as a priority use case for real-world evidence. Building on this foundation, a more comprehensive adaptive framework would use pre-defined evidence thresholds derived from continuous registry, Sentinel, and patient-generated data streams to trigger structured benefit-risk re-evaluations throughout a drug's lifecycle, enabling regulatory decisions that are genuinely responsive to accumulating clinical knowledge rather than locked in at the moment of first approval.



PART V: A collaborative implementation roadmap

5.1 Collaboration, not confrontation

The transformation described in this paper cannot be implemented by any single actor. It requires active collaboration among pharmaceutical companies, academic research institutions, health systems, technology companies, patient organizations, and the FDA. The interests of these actors are more aligned than they might appear. The Manhattan Institute's 2025 analysis[21] estimated that accelerating the use of RWE in drug regulation with a goal of incorporating RWE into half of all supplemental drug applications by 2030 could dramatically reduce regulatory costs while maintaining evidentiary standards. A more trustworthy, comprehensive evidence system reduces costs for everyone: regulatory uncertainty for industry, pharmacovigilance burden for regulators, and clinical decision-making uncertainty for prescribers.

5.2 Phased implementation roadmap

Phase	Timeline	Lead actors	Key technology and policy actions
FOUNDATION	0–12 months	FDA + CMS + ONC + NIH	Mandate FHIR R4 APIs for research use across certified EHR systems (building on 2020 ONC Final Rule); expand Sentinel to include full EHR data integration; launch UETP pilot in 10 therapeutic areas; issue FDA guidance on blockchain-based protocol registration standards
BUILD	12–24 months	FDA + Industry + Academic Health Systems	PDUFA reauthorization incorporates UETP submission requirements; blockchain-based protocol registration piloted for all new Phase III trials; AI-powered signal monitoring deployed in expanded Sentinel; Open Payments integration with FDA reviewer workflows
SCALE	24–48 months	FDA + Congress + international partners	UETP becomes mandatory for all regulatory submissions; living label infrastructure deployed for new approvals; pragmatic trial RWE formally recognized as primary evidence in FDA guidance; ICH harmonization of UETP standards initiated with EMA
MATURE	48–72 months	Full ecosystem	Adaptive regulatory pathways operational for defined therapeutic areas; patient-generated evidence formally integrated into benefit-risk assessments; international UETP harmonization complete; AI-powered continuous safety monitoring fully operational across Sentinel network

5.3 The role of each stakeholder group

Pharmaceutical industry

The industry's role is to invest in the evidence infrastructure that makes its products' true value visible throughout the product lifecycle committing to pre-registration of all trials including those testing combination or comparative approaches, funding independent data custodianship for pivotal studies, building FHIR-native data collection into clinical development programs, and participating in collaborative UETP standard design. Companies that lead on evidence quality will build durable clinical trust a competitive advantage that outlasts any individual product.

Academic research institutions

Academic researchers are the backbone of independent scientific inquiry in medicine. Their role in Evidence 2.0 is to champion rigorous, structured conflict-of-interest management not as a bureaucratic requirement but as a scientific standard recognizing that the perception of independence is as important as independence itself for the credibility of findings. Academic health systems are also uniquely positioned to contribute EHR data to federated research networks like

PCORnet and Sentinel, and to build the methodological toolkit for real-world evidence analysis that the field urgently needs.

The FDA

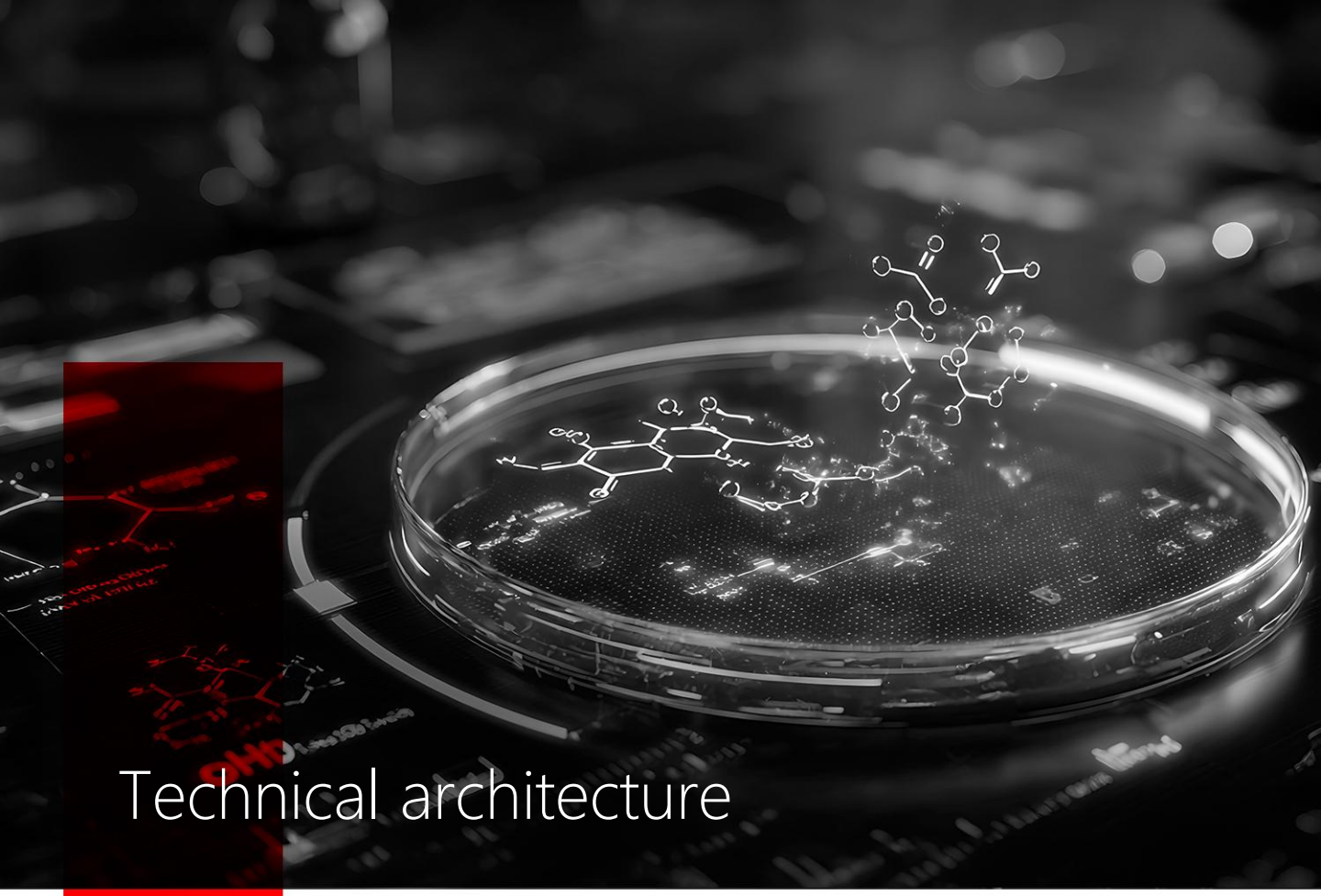
The FDA's role is to provide the regulatory framework that makes Evidence 2.0 operational through guidance documents, PDUFA negotiations, and proactive technology investment. The agency should position itself not as a passive receiver of industry-submitted evidence packages, but as an active participant in a collaborative evidence ecosystem: setting standards, providing analytical infrastructure, and continuously learning from the real-world evidence streams that technology makes available. The Sentinel Innovation Center provides an institutional model for this kind of proactive regulatory technology investment.

Health technology companies

Technology companies — EHR vendors, cloud providers, AI firms, and digital health platforms — are the builders of the technical infrastructure that Evidence 2.0 requires. Their most important contribution is adherence to open standards: FHIR R4 APIs, open-source analytical tools, and interoperable data architectures that prevent the evidence ecosystem from becoming locked into any single proprietary platform. The ONC's Cures Act Final Rule creates regulatory pressure for this openness; the UETP should build on and reinforce it.

Patient organizations

Patient advocacy organizations are the voice of the ultimate beneficiaries of this transformation. Their role is to ensure that patient-generated evidence is incorporated with appropriate rigor, that transparency tools are designed for accessibility rather than just technical completeness, and that the evidence system remains anchored to outcomes that matter to patients' functional status, quality of life, symptom burden, and not just the biomarkers that are easiest to measure in trials.



Technical architecture

The diagram illustrates layers, key services, and trust boundaries.

Evidence 2.0 – Solution Reference Architecture

Experience & Trust layer
EHR plug-ins, CDS hooks | Regulator workbench | Patient portals | Public transparency portal

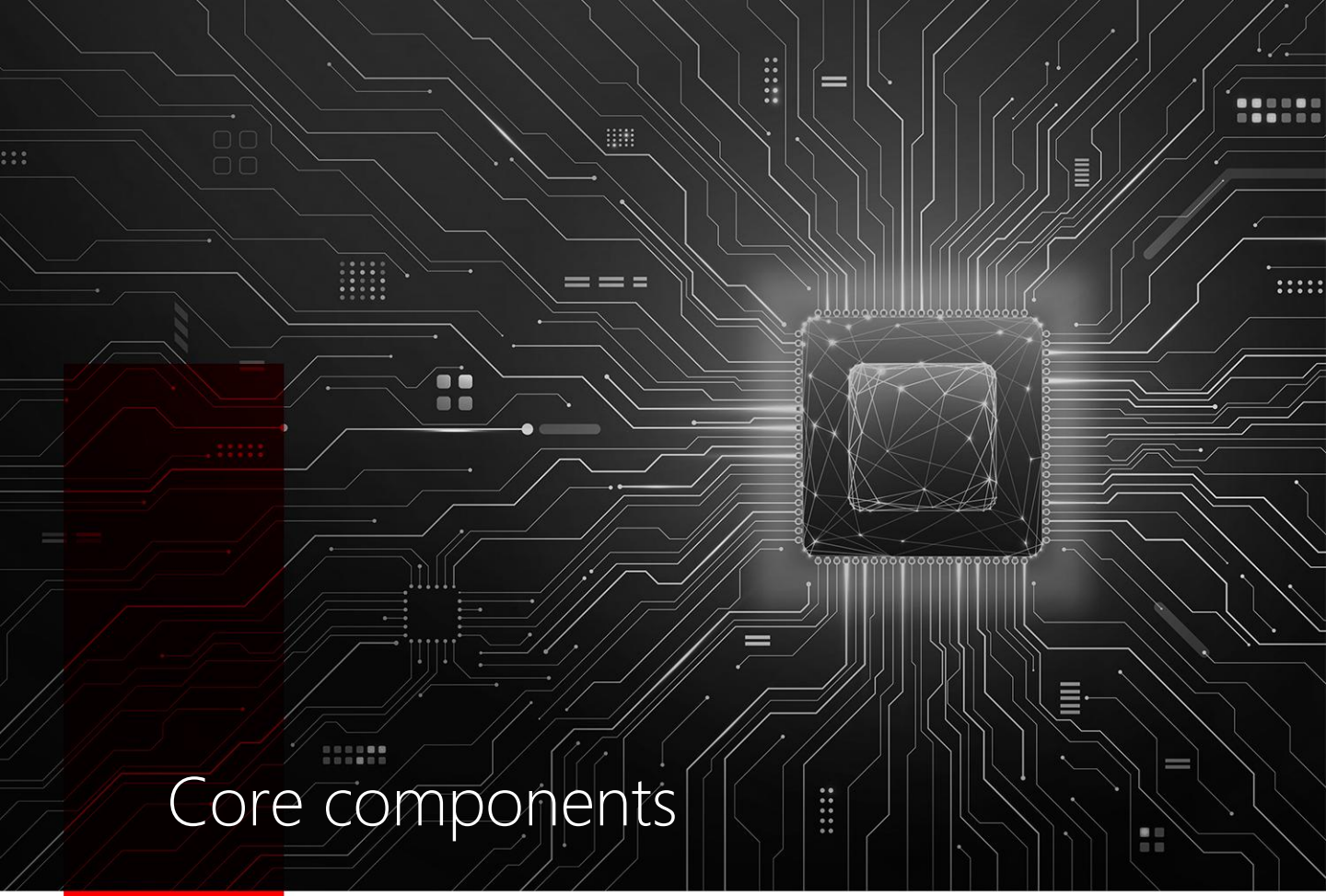
Policy, Governance & Metadata
UETP lineage | Consent & Data use | Model registry | Audit traceability

Analytics & Intelligence
Safety signals | RWE Cohorts | Pragmatic Trials | Living Label

Federated Compute & Access
Query Orchestrator | Secure Research Enclaves | Incentives management

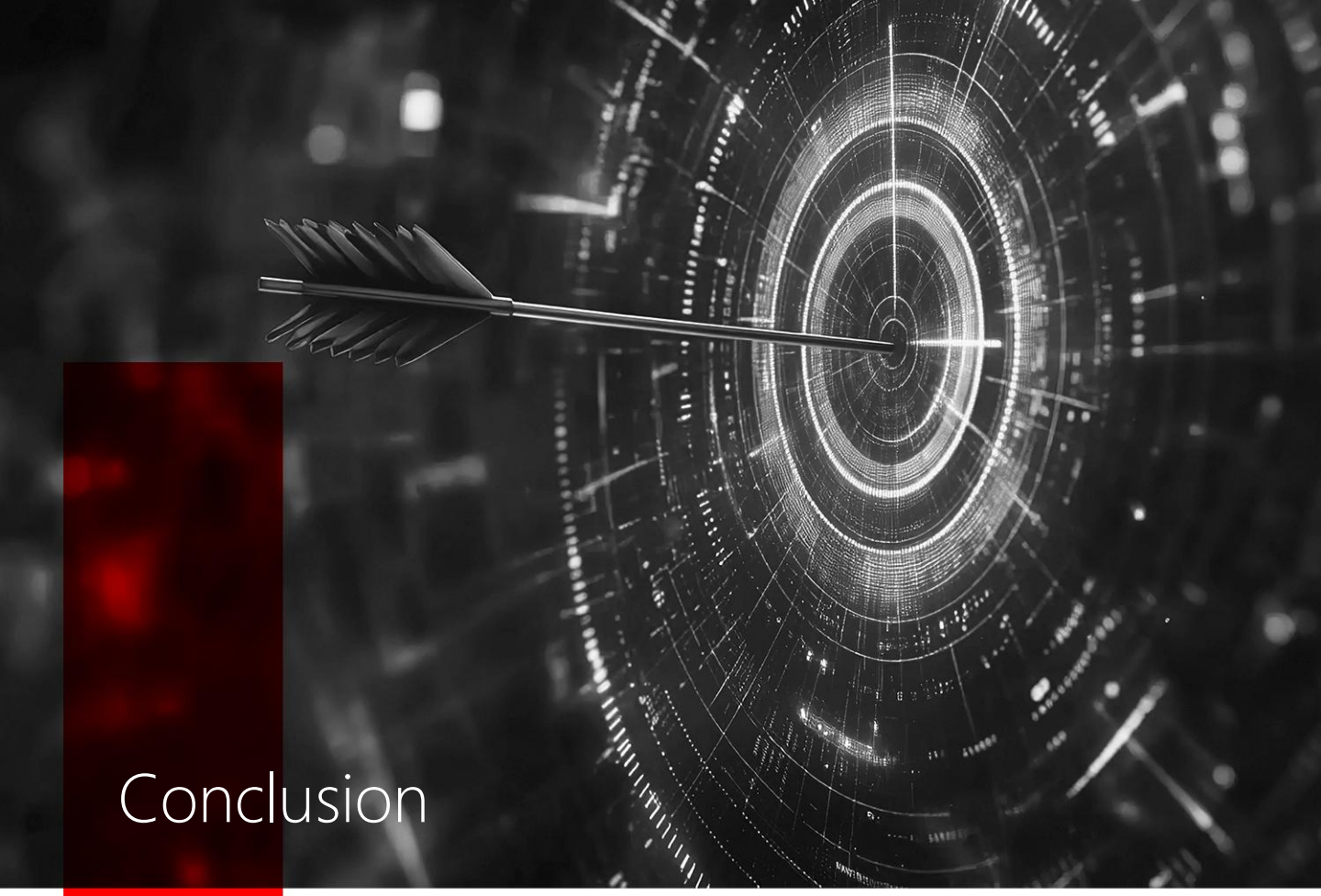
Data & Integration
EHR records | Claims | Registries | Wearables | FAERS/Literature | Event bus | Provenance

Security & Platform Foundations
Identity (OIDC/SMART) | KMS/HSM | Zero-Trust | GitOps | MLOps | Observability



Core components

- UETP: lineage APIs, funding provenance, anomaly detection, decision linkage.
- Federated analytics orchestrator: standardized queries, PPRL, privacy budgets.
- FHIR-native registries: auto-enrollment, PRO/wearables, Provenance/Consent.
- Safety signal service: NLP, disproportionality, causal refinement, reviewer console.
- Pragmatic trial engine: CQL phenotypes, eConsent, randomization, SAE adapters.
- Living label service: evidence grading, triggers, SPL/FHIR outputs.
- Identity and consent: SMART on FHIR, OAuth2/OIDC, fine-grained policy enforcement.
- MLOps and security: registry, drift, zero-trust, KMS (Key management) /HSM (hardware security), audit-ready logging.



Conclusion

Evidence 2.0 is ultimately about patients. It is about a person with a chronic condition who deserves to know not just that a therapy worked in a trial, but how well it has worked in thousands of people who look like them, live like them, and take the other medications they take. It is about a clinician who deserves an evidence base comprehensive enough to support genuinely informed prescribing. It is about a regulator who deserves the data infrastructure to identify emerging safety signals before they become clinical crises.

The technology to build this system exists today and is increasingly mandated into place. The ONC's FHIR requirements[6][7], the FDA's Sentinel expansion[9][13], published blockchain clinical trial frameworks[10][11][17][18], and the FDA's own RWE program[1][5] together constitute a substantial foundation on which Evidence 2.0 can be built. What is needed now is the coordination, the investment, and the collaborative governance to connect these components into a unified, patient-serving system.

The pharmaceutical industry, academic medicine, and the FDA have a genuine opportunity to build something that will benefit patients for generations. An evidence system as sophisticated as the science it evaluates, as continuous as the health it monitors, and as transparent as the public trust it must earn. The tools are here. The framework exists. The opportunity is now.

References

Policy documents and regulatory guidance

[1] U.S. Food and Drug Administration. Framework for the Real-World Evidence Program. December 2018. Federal Register, Docket No. FDA-2018-N-4000. Available at: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

[2] 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (December 13, 2016). Signed into law requiring FDA to establish a program to evaluate the potential use of real-world evidence for drug approvals and post-approval study requirements.

[3] Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy. New England Journal of Medicine. 2008;358(3):252–260. doi:10.1056/NEJMsa065779. [74 FDA-registered trials; 31% unpublished; effect sizes inflated 32% overall in published literature.]

[4] Anderson ML, Chiswell K, Peterson ED, Tasneem A, Topping J, Califf RM. Compliance with Results Reporting at ClinicalTrials.gov. New England Journal of Medicine. 2015;372(11):1031–1039. doi:10.1056/NEJMsa1409364.

[5] U.S. Food and Drug Administration. Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products. Guidance for Industry. August 2023. Available at: https://www.fda.gov/media/171667/download

[6] Office of the National Coordinator for Health Information Technology (ONC). 21st Century Cures Act: Interoperability, Information Blocking, and the ONC Health IT Certification Program. Final Rule. Federal Register. May 1, 2020; 85 FR 25642. Mandated FHIR R4 APIs across all certified EHR systems.

[7] ONC/ASTP. Hospital Use of APIs to Enable Data Sharing Between EHRs and Apps. Data Brief. 2023. Available at: https://healthit.gov/data/data-briefs/hospital-use-apis-enable-data-sharing-between-ehrs-and-apps/ [Reported 90%+ of hospitals using APIs for patient EHR access.]

FDA sentinel system

[8] U.S. Food and Drug Administration. An Assessment of the Sentinel System (2022 to 2024). PDUFA VII Commitment Report. September 2025. Available at: https://www.fda.gov/media/189028/download

[9] Sentinel Initiative. Drug Studies and Key Database Statistics. sentinelinitiative.org. Accessed February 2026. [~138.7 million members; 260 scientific papers published; 120+ drug studies contributing to FDA regulatory actions since 2016.]

[10] Desai RJ, Gagne JJ, Choudhry NK, et al. The FDA Sentinel Real World Evidence Data Enterprise (RWE-DE). Pharmacoepidemiology and Drug Safety. 2024;33(10):e70028. doi:10.1002/pds.70028. [EHR-claims linked network covering 25 million lives.]

[11] Platt R, Brown JS, Robb M, et al. The FDA Sentinel Initiative — An Evolving National Resource. New England Journal of Medicine. 2018;379(22):2091–2093. doi:10.1056/NEJMp1809643.

[12] Ball R, Robb M, Anderson SA, Dal Pan G. The FDA's Sentinel Initiative — A Comprehensive Approach to Medical Product Surveillance. Clinical Pharmacology & Therapeutics. 2016;99(3):265–268. doi:10.1002/cpt.320.

[13] Maro JC, Nguyen MD, Kolonoski J, et al. Six Years of the US Food and Drug Administration's Postmarket Active Risk Identification and Analysis System in the Sentinel Initiative: Implications for Real World Evidence Generation. Clinical Pharmacology & Therapeutics. 2023;114:815–824.

Blockchain and clinical trial data integrity

[14] Benchoufi M, Ravaud P. Blockchain Technology for Improving Clinical Research Quality. Trials. 2017;18(1):335. doi:10.1186/s13063-017-2035-z. [Foundational theoretical framework for blockchain in clinical trials; identifies timestamping, time-ordering, and smart contracting as core functionalities.]

[15] Wong DR, Bhattacharya S, Butte AJ. Prototype of Running Clinical Trials in an Untrustworthy Environment Using Blockchain. Nature Communications. 2019;10(1):917. doi:10.1038/s41467-019-08874-y. [UCSF proof-of-concept on Ethereum network.]

[16] Hang L, Kim B, Kim K, Kim D. A Permissioned Blockchain-Based Clinical Trial Service Platform to Improve Trial Data Transparency. BioMed Research International. 2021;2021:5554487. doi:10.1155/2021/5554487. [Hyperledger Fabric implementation with 12 endorser peer nodes.]

[17] Benchoufi M, Porcher R, Ravaud P. Blockchain Protocols in Clinical Trials: Transparency and Traceability of Consent. F1000Research. 2017;6:66. doi:10.12688/f1000research.10531.5. [Application to informed consent and data traceability.]

[18] Nugent T, Upton D, Cuesta M. Improving Data Transparency in Clinical Trials Using Blockchain Smart Contracts. F1000Research. 2016;5:2541. doi:10.12688/f1000research.9756.1. [Early smart contract application for clinical trial result transparency.]

FDA commissioner testimony and policy context

[19] Gottlieb S. Implementing the 21st Century Cures Act: A 2018 Update from FDA and NIH. Testimony before the House Committee on Energy and Commerce, Subcommittee on Health. June 6, 2018. Available at: https://www.fda.gov/NewsEvents/Testimony/ucm614607.htm

[20] Maro JC, et al. Six Years of the US FDA's Postmarket Active Risk Identification and Analysis System (ARIA) in the Sentinel Initiative. Clinical Pharmacology & Therapeutics. 2023;114:815–824. doi:10.1002/cpt.2975.

[21] Manhattan Institute. Expanding the Use of Real-World Evidence Can Make FDA Regulatory Decisions Faster, Cheaper, and Just as Safe. Report. 2025. Available at: https://manhattan.institute/article/expanding-the-use-of-real-world-evidence-can-make-fda-regulatory-decisions-faster-cheaper-and-just-as-safe

PCORnet and pragmatic trials infrastructure

[22] PCORnet (Patient-Centered Outcomes Research Network). PCORnet Common Data Model (CDM) and Federated Research Infrastructure. pcornet.org. Accessed February 2026. [Spanning 11+ million research-consented patients across academic health centers and health plans.]

[23] Baigent C, Harbers M, et al. Making Clinical Trials More Efficient and Effective. New England Journal of Medicine. 2017;376(14):1382–1392. doi:10.1056/NEJMsa1604821. [Evidence framework for pragmatic trial design embedded in real-world clinical settings.]

Publication bias — Additional references

[24] Dwan K, Altman DG, Arnaiz JA, et al. Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias. PLOS ONE. 2008;3(8):e3081. doi:10.1371/journal.pone.0003081. [Comprehensive systematic review establishing publication bias as a documented, pervasive phenomenon across medical specialties.]

[25] Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG. Empirical Evidence for Selective Reporting of Outcomes in Randomized Trials: Comparison of Protocols to Published Articles. JAMA. 2004;291(20):2457–2465. doi:10.1001/jama.291.20.2457.

[26] Hart B, Lundh A, Bero L. Effect of Reporting Bias on Meta-Analyses of Drug Trials: Reanalysis of Meta-Analyses. BMJ. 2012;344:d7202. doi:10.1136/bmj.d7202. [Quantified the downstream impact of reporting bias on meta-analytic conclusions.]

Interoperability standards and FHIR

[27] Centers for Medicare & Medicaid Services. CMS Interoperability and Patient Access Final Rule (CMS-9115-F). March 9, 2020. Available at: https://www.cms.gov/priorities/burden-reduction/overview/interoperability/policies-regulations/cms-interoperability-patient-access-final-rule-cms-9115-f. [Required FHIR R4-based APIs from all major payer types.]

[28] HL7 International. FHIR Release 4 Specification. October 30, 2019. Available at: https://hl7.org/fhir/R4/. [Foundational technical standard for healthcare data exchange; mandated by ONC 2020 Final Rule.]

Patient-focused drug development and digital health

[29] U.S. Food and Drug Administration. Patient-Focused Drug Development: Methods to Identify What Is Important to Patients. Guidance for Industry, Researchers, Patient Advocacy Groups, and Other Interested Parties. October 2021. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-methods-identify-what-important-patients

[30] U.S. Food and Drug Administration. Digital Health Center of Excellence. Guidance Documents on Digital Health Technologies for Remote Data Acquisition in Clinical Investigations. 2021. Available at: https://www.fda.gov/science-research/science-and-research-special-topics/digital-health-center-excellence

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