

Integrated Prospective Regulatory Governance: A Quality-by-Design Operating Model for High-Risk Class III Medical Device Clinical Investigations

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Research Article

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Additional Declarations: Competing interest reported. S.S.P. is employed by Encore Medical Inc., a medical device manufacturer engaged in high-risk cardiovascular device development, and holds stock options in Encore Medical Inc. The described implementation experience was derived from a regulatory-governance context involving the author's employer. The author declares no other competing financial or non-financial interests.

Abstract

High-risk (Class III) medical device clinical investigations under the U.S. Investigational Device Exemption (IDE) framework are recurrently delayed by preventable regulatory failures: documentation deficiencies triggering clinical holds, authorization gaps during investigator transitions, fragmentation between regulatory and clinical functions, and reactive compliance postures. This paper describes Integrated Prospective Regulatory Governance (IPRG), a four-component operating model that embeds regulatory requirements as prospective design constraints across the clinical investigation lifecycle. The model was derived from U.S. and international regulatory requirements governing IDE investigations and quality systems, and refined through prospective application within an FDA-authorized IDE investigation of a transcatheter structural-heart closure device. The implementation setting was a ClinicalTrials.gov-registered IDE investigation (NCT05537753); no patient-level data are reported. Each component—Prospective Compliance Architecture, Cross-Functional Regulatory Integration, Investigator Lifecycle Management, and Risk-Stratified Submission Strategy—is mapped to its governing regulatory basis and positioned against the contemporary regulatory inflection represented by the Quality Management System Regulation (QMSR) and ICH E6(R3) Good Clinical Practice. Applied prospectively, the model maintained regulatory authorization continuity across investigator and site transitions, with deviations confined to minor procedural events having no effect on subject safety or data integrity. These observations illustrate feasibility rather than comparative effectiveness. IPRG operationalizes the quality-by-design and risk-proportionality principles formalized in ICH E6(R3) and the QMSR. Built on requirements common to every Class III sponsor, it is structurally transferable and offers a candidate template for prospective compliance governance. Controlled, multi-program evaluation is warranted.

Introduction

The clinical evaluation of high-risk medical devices is one of the most regulated activities in applied science. In the United States, a Class III device that does not qualify for an alternative pathway is studied under an Investigational Device Exemption (IDE) governed by 21 CFR Part 812 and ultimately reviewed for marketing authorization under the premarket approval (PMA) provisions of 21 CFR Part 814 [1, 2]. The sponsor's quality system is held to the Quality Management System Regulation (QMSR), which as of February 2, 2026 amends 21 CFR Part 820 to incorporate ISO 13485:2016 by reference [3, 4].

Despite the maturity of this architecture, device programs continue to experience preventable disruption. Clinical holds, documentation deficiencies, delegation-of-authority gaps during personnel transitions, and post hoc corrective action consume time and capital [5, 6]. A survey of over 200 medical technology companies found that regulatory processes add an average of 30–54 months to the U.S. device development cycle, with compliance challenges accounting for a substantial share of IDE-related delays [6]. A recurring structural cause is functional fragmentation: regulatory affairs, clinical operations, and quality assurance operate as sequential silos, with compliance treated as a downstream checkpoint rather than an upstream design input.

The structural heart device sector exemplifies these challenges. The growing volume of transcatheter interventional trials—for patent foramen ovale closure, atrial septal defect repair, left atrial appendage occlusion, and other indications—has placed increasing demands on device sponsors, many of which are small-to-mid-size companies operating with lean regulatory teams. These sponsors must satisfy the full scope of IDE obligations—annual reports, safety communications, supplement filings, site-specific authorizations, and multi-site investigator oversight—with limited personnel and without the institutional memory that larger organizations accumulate over decades of trial conduct.

The regulatory environment has recently shifted in a way that makes the reactive posture increasingly untenable. ICH E6(R3) Good Clinical Practice, adopted at Step 4 on January 6, 2025, and issued by the FDA as a final guidance in September 2025, reorients GCP toward quality by design (QbD) and risk proportionality: sponsors are expected to identify and mitigate risks to trial quality from the earliest design stages [7, 8]. In parallel, the QMSR and the new Compliance Program 7382.850 expand inspection scope from subsystem sampling to lifecycle-focused, process-oriented examination [3, 4, 9]. Together, these developments reward sponsors who can convert regulatory principle into a concrete operating model.

This paper describes such a model. Integrated Prospective Regulatory Governance (IPRG) is a four-component operating system (Fig. 1) that (i) embeds regulatory requirements as prospective design constraints, (ii) integrates regulatory, clinical, and quality functions, (iii) manages the investigator lifecycle as a controlled process, and (iv) ties each regulatory submission to a prospective readiness assessment. The contribution is not a new set of requirements; it is an integration architecture that translates QbD and risk-proportionality principles into day-to-day trial governance for high-risk device investigations.

Materials and Methods

Model Development

The IPRG model was developed through structured analysis of regulatory, quality, and clinical-operational requirements governing IDE investigations. Primary sources included 21 CFR Part 812 [1], 21 CFR Part 814 [2], the QMSR incorporating ISO 13485:2016 [3, 4], ISO 14971:2019 [10], and ICH E6(R3) and E8(R1) [7, 8, 11]. Each requirement was decomposed into operational implications, and common failure modes were identified from published literature [5, 6], FDA guidance [1], and direct operational experience. Four recurrent failure modes were identified: (a) documentation deficiency triggering clinical holds; (b) discontinuity at investigator and site transitions; (c) functional fragmentation between regulatory, clinical, and quality functions; and (d) reactive compliance management where CAPA functions as the principal control rather than prospective risk elimination.

Model Architecture

The model comprises four interdependent components (Table 1, Fig. 1). Their integration—not any single element—produces the prospective governance effect.

Table 1

Summary of the IPRG model: components, targeted failure modes, mechanisms, and regulatory basis.

Component	Failure Mode	Mechanism	Regulatory Basis
1. Prospective Compliance Architecture	Documentation deficiency / clinical holds	Part 812 obligations decomposed into anticipatory controls, checklists, and gating criteria	21 CFR 812; ICH E6(R3)
2. Cross-Functional Regulatory Integration	Functional fragmentation	Traceability spine linking protocol, design history file, and risk management file	QMSR/ISO 13485; ISO 14971
3. Investigator Lifecycle Management	Transition discontinuity	Structured transition protocol with predefined documentation and verification	21 CFR 812; ICH E6(R3)
4. Risk-Stratified Submission Strategy	Reactive compliance	Submissions gated on readiness assessment stratified by data criticality	21 CFR 814; ICH E8(R1); E6(R3)

Component 1: Prospective Compliance Architecture. Embeds regulatory requirements as design constraints from trial activation. Each Part 812 obligation—submission content, reporting timelines, recordkeeping—is decomposed into anticipatory controls: checklists, gating criteria, and document templates instantiated before the activity they govern, with a defined owner and evidence artifact. For example, the IDE annual report obligation is managed through a prospective documentation calendar that accumulates required data elements throughout the reporting period rather than assembling the report retroactively at the filing deadline. Regulatory basis: 21 CFR Part 812 [1]; ICH E6(R3) [7].

Component 2: Cross-Functional Regulatory Integration. Eliminates fragmentation via a traceability spine linking the clinical protocol, design history file, and risk management file. A change in any one propagates a controlled review in the others; regulatory strategy is a standing input to clinical and quality decision-making rather than a downstream sign-off. The spine ensures that a protocol amendment simultaneously triggers updates to the clinical evaluation plan, risk management file, and informed consent documents, with each update verified for consistency before site-level implementation. Regulatory basis: QMSR/ISO 13485:2016 [3, 4]; ISO 14971:2019 [10].

Component 3: Investigator Lifecycle Management. Manages site and investigator transitions through a structured protocol treating each activation, investigator change, and closure as a controlled sub-process with predefined documentation, sequencing, and verification. The protocol specifies which documents must be in place before enrollment can begin or resume at a transitioning site, the sequence in which regulatory, IRB, and financial-disclosure steps must be completed, and the verification artifacts confirming completion. Regulatory basis: 21 CFR Part 812 [1]; ICH E6(R3) [7].

Component 4: Risk-Stratified Submission Strategy. Gates each submission milestone on a readiness assessment stratifying risk by data criticality and consequence of error. Higher-risk submissions (e.g., PMA modules, pivotal safety analyses) receive multi-layer review; lower-risk filings (e.g., routine site additions) follow a streamlined but documented process. Regulatory basis: 21 CFR Part 814 [2]; ICH E8(R1) and E6(R3) [7, 11].

Implementation Setting

The model was refined through prospective application within an FDA-authorized IDE investigation of a transcatheter structural-heart closure device conducted across multiple U.S. sites. The investigation evaluates a device for percutaneous closure of a cardiac septal defect for prevention of recurrent ischemic stroke and is registered with ClinicalTrials.gov (NCT05537753) under IDE G220115. The sponsor is a small, publicly traded medical device company with a lean regulatory team. This study describes a regulatory-governance model and does not report human-subjects research; no ethics approval was required.

Outcome Assessment

The model was assessed descriptively against four operational indicators: (a) continuity of regulatory authorization without clinical holds attributable to documentation deficiency; (b) documentation integrity during investigator and site transitions; (c) deviation profile; and (d) cross-functional documentation alignment. These indicators were assessed qualitatively and were not prespecified endpoints in a comparative design. No attempt was made to compare outcomes against investigations conducted without the model, and the assessment is a feasibility demonstration, not an efficacy study.

Results

Under prospective application of the IPRG model, the IDE investigation maintained the continuity of regulatory authorization throughout the implementation period. No clinical holds were imposed attributable to documentation deficiency or compliance gaps.

Multiple investigator and site transitions occurred, including site activations, principal investigator changes, and site closures. Each was managed through the Component 3 lifecycle protocol. Delegation-of-authority documentation, financial-disclosure records, IRB authorizations, and GCP training records were maintained without interruption. No enrollment authorization gaps occurred at active sites.

Protocol deviations were confined to minor procedural and interval-related events—such as scheduling variances in follow-up windows—each documented in real time and assessed as having no effect on subject safety or data integrity. No major or critical deviations were recorded.

Multiple IDE supplement and annual report submissions were preceded by structured readiness assessments in which the completeness of the evidentiary record, the consistency of the regulatory narrative with the design history file, and the alignment of reported outcomes with the risk management file were verified before filing. No submission was rejected or returned by the FDA for deficiency.

The Component 2 traceability spine was tested most rigorously during a planned protocol amendment requiring simultaneous updates across the clinical evaluation plan, design history file, risk management file, and informed consent documents at all active sites. The amendment triggered an automated review cascade: each linked document was flagged for update, the responsible owner identified, and updated documents verified for internal consistency before site-level implementation. The cascade was completed without introducing misalignment—a common failure mode that, under fragmented governance, often surfaces only during regulatory inspection and requires expensive retroactive reconciliation.

These observations are offered as an existence proof that the model is operable in a live, federally regulated investigation. They are not evidence of comparative effectiveness; the absence of a comparator precludes causal attribution.

Discussion

The individual requirements IPRG addresses are well established; the model invents none of them. Its novelty is integrative. Existing instruments operate at adjacent but distinct levels: ISO 14971 governs device-safety risk management but is not a trial-operations model [10]; ICH E6(R3) and E8(R1) supply principles but stop short of prescribing a sponsor-side operating system [7, 11]; FDA programs such as TAP and the Breakthrough Devices Program act on the agency–sponsor interface rather than inside the sponsor’s workflow [12, 13]. IPRG occupies the gap between principle and practice. Prior collaborative work between industry and FDA demonstrated the value of prospective quality planning in clinical trials [14]; IPRG extends that logic from a planning exercise to a continuous governance architecture for high-risk device investigations.

The QMSR’s incorporation of ISO 13485 and the expanded inspection scope of CP 7382.850—which shifts FDA inspection from subsystem sampling to lifecycle-focused evaluation, with management review records and internal audit findings no longer categorically exempt [9]—reward integrated, prospective quality systems. ICH E6(R3) makes quality by design the explicit expectation [7, 8]. A model designed around prospective, integrated control is aligned with the direction in which both regulatory regimes have moved.

Because every IPRG component rests on requirements applying identically to all Class III sponsors, the model is not contingent on any single device or sponsor. It is structurally transferable and offers a candidate template for the broader structural-heart device sector. The model also reduces fragility in lean regulatory teams by encoding governance rules into explicit protocols and traceability structures

rather than relying on individual institutional knowledge—an important consideration for sponsors whose regulatory departments may number only one or two individuals.

Limitations

This is a single-program, single-operator account without a comparator. The framework was implemented by its designer, confounding the model with the individual. Outcomes are observational, not prespecified, and no quantitative metrics (time-to-activation, deviation rate per patient-year, documentation-cycle time) are reported. Prospective multi-program, multi-operator application with prespecified process endpoints is needed. Demonstrated adoption beyond a single organization would convert the transferability argument from inference to evidence.

Conclusion

Integrated Prospective Regulatory Governance is an operating model targeting four preventable failure modes in high-risk device investigation: documentation deficiency, transition discontinuity, functional fragmentation, and reactive compliance. Its contribution is to operationalize, at the sponsor level, the quality-by-design and risk-proportionality principles now formalized in ICH E6(R3) and the QMSR. Built on obligations common to every Class III sponsor, it is structurally transferable and offers a testable template for prospective compliance governance. Controlled, multi-program evaluation is the appropriate next step.

Declarations

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Conflict of Interest

The author is employed by Encore Medical Inc., a medical device manufacturer engaged in high-risk cardiovascular device development, and holds stock options in Encore Medical Inc. The author declares no other competing financial interests.

Author Contributions

S.S. Pandya conceived and designed the model, conducted the regulatory analysis, implemented the model in the described investigation, and wrote the manuscript. The author read and approved the final manuscript.

References

1. U.S. Food and Drug Administration. Investigational Device Exemptions. 21 CFR Part 812. <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-812>. Accessed June 3, 2026.
2. U.S. Food and Drug Administration. Premarket Approval (PMA). 21 CFR Part 814. <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-814>. Accessed June 3, 2026.
3. U.S. Food and Drug Administration. Medical Devices; Quality Management System Regulation. Final Rule. 89 FR 7496. February 2, 2024. Effective February 2, 2026.
4. International Organization for Standardization. ISO 13485:2016—Medical devices—Quality management systems—Requirements for regulatory purposes. Geneva: ISO; 2016.
5. Van Norman GA, Drugs. Devices, and the FDA: Part 2: An Overview of Approval Processes: FDA Approval of Medical Devices. JACC Basic Transl Sci. 2016;1(4):277–87.
6. Makower J, Meer A, Denend L. FDA Impact on U.S. Medical Technology Innovation: A Survey of Over 200 Medical Technology Companies. Stanford, CA: California Healthcare Institute; 2010.
7. International Council for Harmonisation. ICH Harmonised Guideline. Good Clinical Practice E6(R3). Step 4 version. Adopted January 6, 2025.
8. U.S. Food and Drug Administration. E6(R3) Good Clinical Practice—Guidance for Industry. Silver Spring, MD: FDA; September 2025.
9. January. Food and Drug Administration. Inspection of Medical Device Manufacturers. Compliance Program 7382.850. Volume 30. Silver Spring, MD: FDA; 2026.
10. International Organization for Standardization. ISO 14971:2019—Medical devices—Application of risk management to medical devices. Geneva: ISO; 2019.
11. International Council for Harmonisation. ICH E8(R1)—General Considerations for Clinical Studies. Step 4 version. 2021.
12. U.S. Food and Drug Administration. Total Product Life Cycle Advisory Program (TAP). <https://www.fda.gov/about-fda/cdrh-offices/total-product-life-cycle-advisory-program-tap>. Accessed June 3, 2026.
13. U.S. Food and Drug Administration. Breakthrough Devices Program—Guidance for Industry and Food and Drug Administration Staff. Silver Spring, MD: FDA; December 2018 (updated 2023).
14. Norden-Zfoni A, Gal P, Luke R, et al. Quality by Design in Clinical Trials: A Collaborative Pilot With FDA. Ther Innov Regul Sci. 2019;53(3):405–13.

Figures



Figure 1

Integrated Prospective Regulatory Governance (IPRG) operating model. The four components—Prospective Compliance Architecture, Cross-Functional Regulatory Integration, Investigator Lifecycle Management, and Risk-Stratified Submission Strategy—operate as an integrated, continuous governance loop around a central quality-by-design trial governance function. Arrows indicate cyclical interdependence. Each component is mapped to its targeted failure mode and governing regulatory basis (21 CFR Part 812, ICH E6(R3), QMSR/ISO 13485, ISO 14971, ICH E8(R1), 21 CFR Part 814).