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Reducing Protocol Deviations in IRD Ophthalmology Trials Through Criticality Checklists and Escalation Pathways

A Comprehensive Framework for Deviation Classification, Prevention, and Management

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Abstract

Protocol deviations in inherited retinal disease (IRD) ophthalmology trials represent a multifaceted operational challenge threatening participant safety and primary endpoint data integrity (Getz, 2011; Cilley, 2025). These deviations span imaging acquisition, functional testing, investigational product handling, and visit scheduling. Unlike conventional pharmacological trials, IRD gene therapy involves irreversible surgical interventions where deviations cannot be recovered through repeat visits (Russell, 2017).

This article presents a comprehensive framework for classifying protocol deviation types in IRD trials and identifies strategic intervention points enabling proactive prevention through structured pre-visit preparation and real-time escalation protocols.

The Procedure Criticality Checklist (PCC) system applies risk-based monitoring principles (International Council for Harmonization, 2023) by severity and implementing targeted prevention mechanisms. The framework integrates evidence from surgical safety science (Haynes, 2009), quality-by-design methodology (TransCelerate Biopharma, 2023), IRD trial operations literature (Thompson, 2020).

The framework comprises: (1) a deviation taxonomy, (2) criticality-stratified pre-visit checklists, (3) tiered escalation pathways with predefined decision authorities, and (4) electronic integration mechanisms real-time monitoring.

Implementation is anticipated to reduce preventable deviations, improve data integrity, strengthen regulatory submissions, and accelerate approval timelines for ATMP ophthalmology programs.

This framework addresses a critical gap in IRD trial operations by providing standardized, operationalizable deviation prevention methodology suitable for adoption across national research networks (Igoe, 2024).

Keywords: advanced therapy medicinal products, clinical trial management systems, deviation taxonomy, inherited retinal disease, procedure criticality checklist, protocol deviations, pre-visit checklists, procedural complexity, quality by design, real-time escalation, risk-based monitoring, risk-based quality management

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1. Introduction

1.1 The IRD Trial Landscape and Procedural Complexity

Inherited retinal diseases represent a genetically diverse group of rare disorders affecting over one million individuals worldwide (Daiger, 2013). The past decade has brought unprecedented clinical trial expansion driven by molecular diagnostic advances and development of adeno-associated virus (AAV)-mediated gene therapies. Regulatory approvals of voretigene neparvovec for RPE65-associated dystrophy catalyzed subsequent trials in choroideremia, X-linked retinoschisis, and achromatopsia (Russell, 2017; Tuohy, 2021).

Contemporary IRD trials investigating advanced therapy medicinal products (ATMPs) involve complex procedural elements: (a) surgical interventions requiring precise anatomical targeting to delicate intraocular structures (Thompson, 2020), (b) multimodal imaging protocols sensitive to acquisition parameters and environmental conditions (Taylor, 2023), (c) specialized functional assessments requiring specific participant states and operator expertise (Yang, 2021), and (d) complex investigational product logistics involving chain-of-custody, temperature control, and timing-critical administration (Nuzbrokh, 2020).

1.2 Protocol Deviations as a Distinct Clinical Trial Problem

Protocol deviations - departures from protocol-specified procedures, timelines, or assessments—exist on a continuum of severity and consequence (Chodankar, 2023). Contemporary trial operations literature categorizes deviations using multiple dimensions: timing (when relative to target event), reversibility (whether the deviation can be corrected or assessment repeated), impact (effects on safety, endpoint validity, regulatory compliance), and preventability (whether deviations result from modifiable factors) (TransCelerate BioPharma, 2023).

In IRD trials, deviations acquire distinctive significance for several reasons. First, participant rarity means each individual contributes substantial statistical weight; a single compromised primary endpoint may noticeably affect statistical power (Igoe, 2024). Second, many outcome assessments anchored to a single treated eye are genuinely non-recoverable; repeat visits risk confounding from learning effects, adaptation changes, or disease progression (Lacy, 2020). Third, some procedural deviations—such as incorrect vector volume in subretinal delivery—cannot be remediated post-hoc because the intervention is irreversible (Nuzbrokh, 2020). Fourth, the intersection of surgical complexity and specialized functional testing creates multiple failure points where deviations originate.

1.3 Existing Deviation Management Paradigm and Its Limitations

Current clinical trial deviation management follows predominantly reactive patterns(Cilley, 2025): deviation occurs, is identified through verification or monitoring, is classified and documented, undergoes root-cause analysis via sponsor query, and triggers corrective and preventive actions (CAPA) implementation and tracking. While necessary for quality assurance, this approach proves structurally inadequate for IRD trials where deviations frequently become permanent data liabilities by detection time.

The regulatory landscape increasingly emphasizes proactive quality management. The International Council for Harmonization's E6(R3) Good Clinical Practice guideline explicitly requires that quality be built into trial design and conduct, advocating risk-based quality management (RBQM) emphasizing prospective identification and control of critical-to-quality (CtQ) factors (International Council for Harmonization, 2023). The FDA similarly emphasizes risk-based monitoring targeting highest-risk study activities. However, implementation tools specifically designed for visit-level deviation prevention in IRD trials remain underdeveloped. Existing RBQM frameworks and CAPA systems focus on reactive management rather than prospective prevention (USFDA, 2023). This framework advances beyond existing approaches by combining procedure-specific criticality classification, tripartite pre-visit checklists creating decision-making opportunity

at prevention points, and real-time escalation pathways enabling rapid resolution before deviations occur.

1.4 Study Purpose and Scope

This article presents a comprehensive framework for understanding, classifying, and preventing protocol deviations in IRD ophthalmology trials. Rather than an empirical outcomes study, this work constitutes systematic framework development informed by: (a) evidence on deviation types in complex clinical trials (Getz, 2011), (b) surgical safety science and human factors engineering principles (Haynes, 2009; Borchard, 2012), (c) regulatory requirements for risk-based quality management (International Council for Harmonization, 2023), and (d) published literature on IRD trial procedures (Thompson, 2020; Igoe, 2024).

The framework targets IRD trial sponsors, contract research organizations, site clinical research coordinators and investigators, quality assurance personnel, institutional review boards, and national research networks overseeing multi-site rare disease trials. Design emphasizes operational implementation within current regulatory and resource constraints, with focus on practical feasibility and adaptability across diverse site settings.

2. Framework Development Methodology

2.1 Approach and Rationale

This framework development employed narrative synthesis methodology integrating evidence from three primary sources: (1) clinical trial operations literature on deviation types, frequency, and management strategies, (2) surgical safety science demonstrating effectiveness of checklist-based interventions, and (3) regulatory guidance documents emphasizing risk-based quality management principles.

Table 1 presents a visual representation of how deviation types map across functional domains and consequence levels. This taxonomy organizes deviations into seven primary categories, each with distinct prevention opportunities

Table 1 *Functional Domain Framework for Classifying and Preventing Protocol Deviations in Inherited Retinal Disease Trials*

Functional Domain	Consequence Level	Typical Deviation Examples	Prevention Entry Point
Imaging Procedures	Major	Wrong modality; critical parameter deviation; laterality error; file corruption	Pre-visit: equipment calibration verification; parameter checklist
	Minor	Suboptimal quality; documentation gaps; timing delays	Morning-of: quality assurance verification; documentation templates
Functional Testing	Major	Wrong eye; dark adaptation interrupted; invalid reliability indices; wrong sequence	Pre-visit: staff competency; environment readiness; participant factors
	Minor	Data entry error; incomplete calibration log; stimulus parameter documentation	Immediate pre-procedure: parameter verification; equipment check

Functional Domain	Consequence Level	Typical Deviation Examples	Prevention Entry Point
Procedural (Surgical)	Major	Wrong site/laterality; incorrect volume; technique deviation; unplanned deviations	Pre-visit: surgical team briefing; protocol review; equipment readiness
Investigational Product Handling	Major	Temperature excursion; timing error; accountability gap; dosing error	Pre-visit: storage verification; logistics confirmation; staff training
Visit Window/Timing	Major	Visit outside protocol window; missed visit; unplanned visit outside schedule	Pre-visit (72hr+): participant scheduling; feasibility assessment
Eligibility Confirmation	Major	Inclusion/exclusion criteria not re-confirmed; protocol version mismatch; amendment not implemented	Pre-visit: eligibility re-verification; protocol amendment tracking
Safety Labs/Assessments	Major	Missing required safety lab; incorrect sample handling; collection window violation	Pre-visit: lab order verification; collection kit preparation
Source Documentation	Minor	Missing source note; incomplete signature; illegible documentation; missing timestamp	Immediate post-visit: documentation review; source-to-EDC reconciliation

Note. Consequence level reflects the severity of a deviation within each functional domain. Prevention entry point indicates the workflow stage at which the corresponding safeguard is applied. EDC = electronic data capture.

2.2 Evidence Source Selection Criteria

Literature sources were selected using the following criteria: (a) direct relevance to protocol deviations, quality management, or procedural complexity in clinical trials; (b) established evidence base from peer-reviewed publications or regulatory guidance; (c) applicability to rare disease or gene therapy trial contexts; and (d) recent publication (primarily 2009-2025) ensuring contemporary relevance. Key regulatory documents included ICH E6(R3), FDA risk-based monitoring guidance, and EMA advanced therapy guidance. Surgical safety literature focused on checklist science, with particular emphasis on the WHO Surgical Safety Checklist and its adaptations. IRD-specific sources emphasized procedural complexity, endpoint sensitivity, and trial operational challenges.

2.3 Framework Construction Process

The framework development followed a systematic process: First, existing deviation management frameworks (CAPA, RBQM) were reviewed to identify gaps specific to IRD trials. Second, deviation types encountered in IRD trials were identified from published trial literature and regulatory submissions. Third, a four-tier criticality classification system was developed based on consequence severity (safety impact, endpoint validity impact) and reversibility. Fourth, prevention mechanisms targeting each deviation category were identified from surgical safety and trial operations literature. Fifth, a tripartite pre-visit checklist architecture was designed with temporal phases enabling detection and corrective action at multiple points before deviations occur. Sixth, escalation pathways were structured with pre-specified decision authorities and response timeframes. Finally, electronic integration mechanisms enabling real-time monitoring were incorporated.

2.4 Imaging Procedure Deviations

Imaging procedures in IRD trials—optical coherence tomography (OCT), fundus autofluorescence (FAF), fundus photography, infrared imaging—are foundational to primary and secondary endpoint assessment (Taylor, 2023). Deviations in imaging fall into several categories: (1) modality deviations (scanning with wrong device, missing required modality), (2) parameter deviations (incorrect field size, focus depth, illumination settings, or zoom level), (3) acquisition quality deviations (motion artifact, inadequate signal, segmentation failure exceeding protocol thresholds), (4) laterality deviations (imaging wrong eye or documenting incorrect eye), and (5) data handling deviations (file naming errors, upload failures, reading center miscommunication).

Prevention mechanisms for imaging deviations include: (a) pre-visit equipment calibration verification with documented logs, (b) parameter checklist review 48–72 hours before visit, (c) morning-of-visit quality control scan, (d) immediate pre-procedure parameter confirmation by lead technician, and (e) real-time file verification before participant departure from imaging area. Electronic integration enabling automated parameter recording and reading center feedback loops strengthens prevention at multiple stages.

2.5 Functional Testing Deviations

Functional assessments in IRD trials—including full-field stimulus testing (FST), dark-adapted perimetry, modified lighted maze testing (MLMT), and microperimetry—measure visual capacity under specific, protocol-defined conditions. These assessments are sensitive to deviations in: (1) participant preparation (dark adaptation duration and completeness, pupil dilation status, refractive correction), (2) test parameters (stimulus intensity, size, duration, frequency), (3) environment conditions (ambient light, background luminance, fixation monitoring), (4) operator technique (instruction clarity, response validation, test sequencing), and (5) outcome validation (reliability indices, attention checks).

Functional testing deviations are particularly consequential because they cannot be remediated through repeat testing within the same visit window—repeated testing introduces habituation and learning effects that compromise validity (Lacy, 2020). Prevention requires: (a) pre-visit participant communication confirming dark adaptation instructions, (b) environmental readiness verification (lighting control, equipment functioning, backup devices available), (c) staff competency validation through competency checklists and periodic refresher testing, (d) immediate pre-test participant state verification (dark adaptation status, pupil dilation, visual acuity confirmation), and (e) real-time quality monitoring during testing with pre-established stopping rules for invalid data.

2.6 Surgical/Procedural Deviations

In IRD gene therapy trials involving subretinal or intravitreal vector injection, procedural deviations include: (1) laterality errors (operating on wrong eye), (2) anatomical errors (wrong injection site or location), (3) technical execution errors (incorrect volume, injection rate, needle gauge, or trajectory), (4) timing errors (injection timing relative to anesthesia or other perioperative medications), and (5) monitoring failures (inadequate intraoperative imaging, missed safety monitoring steps) (Nuzbrokh, 2020).

These deviations are uniquely irreversible—a wrong-eye injection or incorrect dose cannot be corrected post-hoc. Prevention mechanisms include: (a) comprehensive pre-operative verification of protocol requirements, participant identity and medical history, (b) operating room checklist immediately before procedure commencement (WHO Time-Out equivalent), (c) confirmation of critical parameters (laterality, site, volume, technique) before incision, (d) continuous monitoring against protocol specifications during procedure, and (e) immediate post-operative verification that procedure was completed as specified before anesthesia reversal.

2.7 Investigational Product Handling and Administration Deviations

Advanced therapy medicinal products, particularly gene therapy vectors, require specialized handling with strict chain-of-custody, temperature control, and timing requirements (European Medicines Agency, 2022). Deviations include: (1) temperature excursions during storage or transport, (2) timing errors (preparation not completed in required timeframe, administration outside acceptable window), (3) dose administration errors (wrong participant, wrong eye, wrong dose), (4) accountability gaps (missing documentation, unclear chain of custody), and (5) technique errors (incorrect preparation method, non-sterile handling).

Prevention mechanisms include: (a) pre-visit verification of product availability, storage conditions, and expiration dating, (b) pharmacy/product team readiness confirmation, (c) detailed preparation protocol review with all staff involved in handling, (d) real-time monitoring of preparation steps with checklist verification, (e) immediate pre-administration patient identification and confirmation procedures, and (f) complete documentation of all handling steps with timestamps and observer signatures.

2.8 Visit Window and Timing Deviations

Protocol-specified visit windows define the acceptable time range relative to a reference event (baseline, last visit, procedure) within which assessments must occur. Deviations occur when visits are scheduled or completed outside the protocol window. These deviations often reflect logistical constraints (participant scheduling, staff availability, site capacity) rather than intentional non-compliance (Cilley, 2025).

Prevention strategies include: (a) long-lead participant scheduling and communication (multiple reminder contact attempts), (b) site capacity planning ensuring adequate staff and equipment availability, (c) real-time window monitoring with automated alerts when visits approach window boundaries, (d) escalation pathways for visits at risk of missing the window, and (e) protocol flexibility (where permitted) offering alternative visit types or partial visit options when complete adherence to original window becomes infeasible.

2.9 Eligibility Confirmation and Protocol Amendment Deviations

Eligibility deviations occur when inclusion or exclusion criteria are not re-confirmed at required timepoints, or when protocol amendments are not properly implemented. These deviations can result in ineligible participants proceeding through visits or critical protocol changes not being reflected in trial execution (TransCelerate BioPharma, 2023).

Prevention mechanisms include: (a) structured eligibility re-verification checklists at protocol-specified intervals, (b) automated alerts when re-verification is due, (c) protocol amendment tracking systems ensuring all staff are notified and trained on changes before implementation, (d) version control of protocols and forms at site level, and (e) escalation to sponsor medical monitor when eligibility status becomes uncertain.

3. Protocol Deviation Taxonomy for IRD Ophthalmology Trials

3.1 Conceptual Framework for Classification

Protocol deviations in IRD trials are understood across multiple classification dimensions. The functional domain perspective examines the trial procedure or assessment type in which deviation occurred. The consequence perspective considers potential impact on participant safety or endpoint validity. The temporal perspective identifies when the deviation originated and when prevention was possible. This multidimensional understanding enables targeted prevention strategies.

Table 2 presents how deviation types map across functional domains and consequence levels, organizing deviations into seven primary categories.

Table 2 *Deviation Types in IRD Ophthalmology Trials: Functional Domains and Consequence Levels*

Functional Domain	Consequence Level	Typical Deviation Examples	Prevention Entry Point
Imaging Procedures	Major	Wrong modality; parameter deviation; laterality error; file corruption	Pre-visit: equipment calibration; parameter checklist
	Minor	Suboptimal quality; documentation gaps; timing delays	Morning-of: quality assurance; documentation templates

Functional Domain	Consequence Level	Typical Deviation Examples	Prevention Entry Point
Functional Testing	Major	Wrong eye; interrupted dark adaptation; invalid reliability indices	Pre-visit: staff competency; environment readiness
	Minor	Data entry error; incomplete calibration log	Immediate pre-procedure: parameter verification
Procedural (Surgical)	Major	Wrong eye/site; incorrect volume; technique deviation	Pre-visit: surgical team briefing; protocol review
Investigational Product	Major	Temperature excursion; timing error; dosing error	Pre-visit: storage verification; logistics confirmation
Visit Window/Timing	Major	Visit outside protocol window; missed visit	Pre-visit (72hr+): scheduling; feasibility assessment
Eligibility Confirmation	Major	Criteria not re-confirmed; amendment not implemented	Pre-visit: eligibility re-verification; amendment tracking

Note. Abbreviated version of the framework presented in

Table 1, retaining the highest-frequency deviation types and their primary prevention entry points.

3.2 Imaging Procedure Deviations

Imaging procedures—optical coherence tomography, fundus autofluorescence, fundus photography, infrared imaging—form the foundation for primary and secondary endpoint assessment. Imaging deviations span modality errors (incorrect device, missing required modality), parameter errors (wrong field size, focus depth, illumination, zoom), acquisition quality errors (motion artifact, inadequate signal, segmentation failure), laterality errors (wrong eye or incorrect documentation), and data handling errors (file naming, upload failures, reading center miscommunication).

Prevention requires multi-point strategies: pre-visit equipment calibration verification with documented logs, parameter checklist review 48–72 hours before visit, morning-of quality control scanning, immediate pre-procedure parameter confirmation by lead technician, and real-time file verification before participant departure. Electronic integration with automated parameter recording and reading center feedback strengthens prevention at multiple stages.

3.3 Functional Testing Deviations

Functional assessments in IRD trials—full-field stimulus testing, dark-adapted perimetry, modified lighted maze testing, microperimetry—measure visual capacity under protocol-defined conditions. These assessments are sensitive to deviations in participant preparation (dark adaptation duration, pupil dilation, refractive correction), test parameters (stimulus intensity, size, duration, frequency), environment conditions (ambient light, background luminance, fixation monitoring), operator technique (instruction clarity, response validation, test sequencing), and outcome validation (reliability indices, attention checks).

Functional testing deviations cannot be remediated through repeat testing within the same visit window—repeated testing introduces habituation and learning effects compromising validity. Prevention requires pre-visit participant communication confirming dark adaptation instructions, environmental readiness verification, staff competency validation through competency checklists and refresher testing, immediate pre-test participant state verification, and real-time

quality monitoring during testing with pre-established stopping rules for invalid data.

3.4 Surgical/Procedural Deviations

In IRD gene therapy trials with subretinal or intravitreal vector injection, procedural deviations include laterality errors (operating on wrong eye), anatomical errors (wrong injection site), technical execution errors (incorrect volume, injection rate, needle gauge, trajectory), timing errors (injection timing relative to anesthesia), and monitoring failures (inadequate intraoperative imaging, missed safety steps).

These deviations are uniquely irreversible—a wrong-eye injection or incorrect dose cannot be corrected post-hoc. Prevention mechanisms include comprehensive pre-operative verification of protocol requirements and participant identity, operating room checklist immediately before procedure, confirmation of critical parameters before incision, continuous monitoring against protocol specifications during procedure, and immediate post-operative verification before anesthesia reversal.

3.5 Investigational Product Handling Deviations

Advanced therapy medicinal products require specialized handling with strict chain-of-custody, temperature control, and timing requirements. Deviations include temperature excursions during storage or transport, timing errors (preparation not completed in required timeframe, administration outside acceptable window), dose administration errors (wrong participant, wrong eye, wrong dose), accountability gaps (missing documentation, unclear chain of custody), and technique errors (incorrect preparation method, non-sterile handling).

Prevention mechanisms include pre-visit verification of product availability, storage conditions, and expiration dating, pharmacy team readiness confirmation, detailed preparation protocol review with all staff involved, real-time monitoring of preparation steps with checklist verification, immediate pre-administration patient identification and confirmation, and complete documentation of all handling steps with timestamps and observer signatures.

3.6 Visit Window and Timing Deviations

Protocol-specified visit windows define acceptable time ranges relative to reference events within which assessments must occur. Deviations occur when visits are scheduled or completed outside the protocol window, often reflecting logistical constraints (participant scheduling, staff availability, site capacity) rather than intentional non-compliance.

Prevention strategies include long-lead participant scheduling with multiple reminder contact attempts, site capacity planning ensuring adequate staff and equipment availability, real-time window monitoring with automated alerts at boundary approach, escalation pathways for visits at risk of missing the window, and protocol flexibility offering alternative visit types or partial visit options when complete adherence becomes infeasible.

4. Procedure Criticality Classification and Deviation Prevention Framework

4.1 Four-Tier Criticality Classification System

The framework stratifies trial procedures into four tiers based on consequence severity and reversibility, enabling proportionate allocation of prevention resources (International Council for Harmonization, 2023).

Table 3 Tier-Based Classification of Trial Procedures by Endpoint Criticality and Prevention Intensity

Tier	Definition	Characteristic Procedures	Prevention Intensity	Key Mechanisms
Tier 1: Mission-Critical	Direct impact on participant safety and endpoint validity; irreversible if deviation occurs	Subretinal/intravitreal vector injection; intraoperative OCT guidance;	Maximum intensity: 48–72h pre-visit preparation; PI-level oversight; operating	Early identification of prerequisites; role clarity; real-time decision support

Tier	Definition	Characteristic Procedures	Prevention Intensity	Key Mechanisms
		investigational product administration	room checklist; post-procedure verification	
Tier 2: High-Impact	Primary endpoint assessment; sensitive to technique; limited recoverability	Dark-adapted perimetry; FST; MLMT; microperimetry (primary endpoint)	High intensity: 48h pre-visit verification; assessor sign-off; environment verification; quality monitoring during assessment	Staff competency verification; environment readiness; participant preparation
Tier 3: Moderate-Impact	Secondary endpoints or supportive assessments; partially recoverable	Best-corrected visual acuity (BCVA); OCT imaging (structural); FAF; fundus photography	Standard intensity: visit-level checklist; documentation verification; routine quality assurance	Protocol adherence; basic quality control; timely documentation
Tier 4: Routine	Administrative or low-complexity assessments with minimal impact	Informed consent; safety labs; PRO questionnaires; demographic updates	Standard intensity: inclusion in routine visit workflow; standard verification procedures	Workflow integration; standard documentation

Note. Tiers are ordered by decreasing impact on participant safety and endpoint validity. BCVA = best-corrected visual acuity; FAF = fundus autofluorescence; FST = full-field stimulus testing; MLMT = multi-luminance mobility test; OCT = optical coherence tomography; PI = principal investigator; PRO = patient-reported outcome.

4.2 Tripartite Pre-Visit Checklist Architecture

The Procedure Criticality Checklist operates across three temporal phases, each targeting different failure modes and enabling corrective action at prevention points rather than after deviations occur.

Table 4 Three-Phase Pre-Visit Verification Framework for Deviation Prevention

Phase	Timing	Responsible Party	Key Focus Areas	Deviation Types Targeted
Phase 1: Pre-Visit Preparation	48–72 hours before visit	Clinical research coordinator, site manager	Equipment status verification; eligibility confirmation; participant readiness; staff availability; protocol version check; any unresolved issues escalation	Visit window violations; eligibility errors; equipment failures; investigational product readiness; procedural knowledge gaps

Phase	Timing	Responsible Party	Key Focus Areas	Deviation Types Targeted
Phase 2: Morning-of-Visit Readiness	2 hours before scheduled procedures	Lead technician, coordinator, PI (for Tier 1–2)	Equipment calibration confirmation with logs; imaging parameters verification; environment checks (lighting, temperature); staff briefing; participant-specific factors affecting feasibility; final readiness declaration	Imaging parameter deviations; functional testing environment issues; late protocol amendments; participant non-compliance; staff unavailability
Phase 3: Immediate Pre-Procedure Verification	At point of care (immediately before procedure/assessment begins)	Investigator/lead assessor, operating room coordinator	Participant identity and laterality confirmation; procedure-specific parameter confirmation; equipment functioning; emergency equipment availability; team role assignment; escalation contact availability; informed consent active status	Laterality errors; wrong patient; critical parameter deviations; equipment malfunction; missing informed consent; inadequate team preparation

Note. Phases proceed sequentially from advance preparation to point-of-care verification. PI = principal investigator.

4.3 Escalation Pathway Design for Real-Time Risk Management

When checklist findings reveal unresolved risks, pre-specified escalation pathways enable rapid decision-making and corrective action before deviations occur.

Table 5 Three-Level Escalation Pathway for Unresolved Pre-Visit Issues

Level	Escalation Triggers	Escalation Authority	Decision Options	Response Timeframe	Documentation
Level 1: Site-Level	Single unresolved Tier 3–4 item; resolvable logistical issue with sufficient lead time (>12 hours)	Site investigator, clinical research coordinator	(1) Resolve issue and proceed with visit; (2) Reschedule visit to resolved window; (3) Modify visit scope if permitted	30 minutes during clinic hours	Documented in CTMS with decision and rationale

Level	Escalation Triggers	Escalation Authority	Decision Options	Response Timeframe	Documentation
Level 2: Sponsor/CRO-Level	Unresolved Tier 1–2 item; eligibility uncertainty; visit window at critical boundary; investigational product issue; protocol interpretation question	Sponsor medical monitor, trial manager, CRO operations lead	(1) Proceed with full visit as scheduled; (2) Proceed with partial visit (deferred assessments); (3) Reschedule entire visit; (4) Reschedule with pre-notification to IRB	2 hours (same-day for visit-critical decisions)	CTMS escalation ticket with decision documentation; email confirmation to site
Level 3: Regulatory/Ethics-Level	Imminent participant safety risk; potential serious adverse event; protocol deviation with reportability implications; eligibility question affecting informed consent validity	Sponsor regulatory/medical affairs lead; institutional review board/independent ethics committee; data safety monitoring board (if convened)	(1) Halt visit pending safety assessment; (2) Modify visit procedures to address safety; (3) Withdraw participant from trial; (4) Expedited protocol amendment	Initiation within 24 hours; ongoing communication until resolution	Full audit trail in CTMS; regulatory submission file; IRB/IEC correspondence

Note. Escalation level is determined by the criticality of the unresolved item and its regulatory implications. CRO = contract research organization; CTMS = clinical trial management system; IEC = independent ethics committee; IRB = institutional review board.

4.4 Hypothetical Implementation Scenario: Imaging Endpoint Visit

Consider a Tier 2 primary endpoint visit requiring dark-adapted perimetry and specialized OCT imaging. Seventy-two hours before the scheduled visit, the clinical research coordinator completes Phase 1 pre-visit preparation checklist. During this check, the OCT equipment calibration log reveals that calibration was last performed eight days earlier, exceeding the five-day protocol requirement. Rather than discovering this post-visit, the coordinator immediately contacts the equipment service vendor and obtains expedited recalibration, completed successfully two days before the visit.

Two hours before the visit (Phase 2), the lead technician performs morning-of readiness verification. The OCT calibration is confirmed current. Ambient lighting in the dark adaptation room is verified at protocol-specified levels. Backup perimetry equipment is confirmed functional. During Phase 3 immediate pre-procedure verification, the participant undergoes formal dark adaptation status confirmation, and the technician and investigator verbally confirm all perimetry parameters before testing begins.

This scenario illustrates the framework's operational value: the calibration gap was detected and resolved 72 hours before it could have compromised the assessment. Without the pre-visit checklist, calibration would likely

have been discovered only when morning-of checks revealed the lapsed date, creating time pressure and potential visit delay. Had the gap gone undetected, it would have been discovered post-visit through source data verification, at which point the imaging data would be compromised and non-recoverable.

4.5 Comparative Analysis: Framework Advancement Beyond Existing Approaches

Existing deviation management frameworks operate primarily through reactive paradigms. Corrective and Preventive Actions (CAPA) systems detect deviations after occurrence, analyze root causes, and implement corrective measures—essential for continuous improvement but incapable of preventing irreversible deviations. Risk-Based Quality Management (RBQM) frameworks identify critical-to-quality factors and establish monitoring approaches, but do not typically provide procedure-specific, visit-level prevention mechanisms with defined action authorities and timeframes.

This framework advances beyond existing approaches in four dimensions. First, it applies procedure-specific criticality classification stratifying prevention intensity proportionate to consequence severity, rather than applying uniform monitoring to all procedures. Second, it creates a temporal prevention window (48–72 hours pre-visit) enabling corrective action before the irreversible event, rather than attempting detection and remediation after deviations have occurred. Third, it specifies decision authorities and timeframes at each escalation level, enabling rapid authorization of corrective actions rather than prolonged query-and-response cycles. Fourth, it integrates electronic systems enabling automated alerts and centralized monitoring, rather than relying on manual compliance tracking. Together, these elements shift the paradigm from reactive deviation documentation to prospective deviation prevention—a fundamental reorientation particularly necessary for irreversible procedural interventions in rare disease trials.

5. Implementation Considerations and Integration

5.1 Workflow Integration and Operational Burden

The framework is designed to integrate into existing site workflows rather than creating additional visits or substantially increasing staff burden. Pre-visit preparation activities—equipment verification, eligibility confirmation, participant scheduling—largely consolidate tasks already performed informally at most sites. Morning-of readiness checks formalize existing procedures. Immediate pre-procedure verification mirrors surgical safety checklists already used at many institutions.

Experience from surgical safety checklist implementation demonstrates that operationally mature institutions adopt new checklists with minimal resistance when perceived as supporting existing safety goals. Site engagement and leadership endorsement are critical success factors. Training should emphasize that the PCC functions as a communication and safety tool supporting team coordination, not as a compliance burden.

Table 5 presents an integrated model showing how the PCC framework, escalation pathways, and tier classification work together to prevent specific deviation types. The model illustrates that prevention requires: (a) early identification (pre-visit detection of risks), (b) decision-making authority (clear specification of who decides when issues cannot be resolved), (c) action capability (resources and authority to implement corrective actions), and (d) documentation (audit trail enabling learning and regulatory confidence)

Table 6 Deviation Prevention Pathway: From Risk Identification to Corrective Action

Deviation Type	Detection Points	Prevention Actions	Escalation Trigger
Imaging	Pre-visit equipment audit → morning-of calibration verification → pre-procedure parameter confirmation	Equipment repair authorization; parameter override protocols; reading center pre-notification	Equipment downtime >4 hr OR critical parameter out-of-range

Deviation Type	Detection Points	Prevention Actions	Escalation Trigger
Functional Testing	Environmental readiness assessment → staff competency verification → participant preparation state	Environment modification; staff retraining; participant rescheduling; test modification	Dark adaptation prerequisites unmet OR participant fatigue/visual symptoms precluding valid testing
Procedural	Surgical team briefing → time-out confirmation → intraoperative protocol compliance monitoring	Team reassignment; procedure delay for further review; anesthesia adjustment	Equipment limitation OR surgeon/anesthesia concern regarding participant safety or procedure feasibility
Investigational Product	Pre-visit product status → storage/transport verification → preparation step-by-step checklist	Product replacement; preparation restart; timing adjustment	Temperature excursion OR inability to meet preparation timing requirement
Visit Window	Participant scheduling confirmation → window boundary monitoring → escalation at T–7 days if at risk	Participant contact intensification; schedule modification; window exception request	Visit outside acceptable window imminent despite interventions
Eligibility	Eligibility re-verification checklist → protocol version confirmation → amendment implementation audit	Eligibility re-assessment; protocol training; documentation correction	Eligibility status uncertain OR protocol amendment not implemented
Safety Assessment	Lab order verification → sample collection kit readiness → collection window monitoring	Lab order placement; kit replacement; collection timing coordination	Lab capacity unavailable OR collection window infeasible

Note. Detection points occur across a five-stage temporal pathway: pre-visit preparation (T–72 to T–48 hr) → morning-of readiness (T–2 to T–0 hr) → immediate pre-procedure (T = 0) → execution (T + visit) → documentation (T + post-visit). Arrows (→) denote sequential detection checkpoints; OR denotes alternative escalation conditions. T = time relative to the scheduled procedure; hr = hours.

5.2 Domain-Specific Prevention Strategies

5.2.1 Preventing Imaging Deviations

Imaging deviations originate from multiple sources: equipment malfunction, parameter drift, human error, or communication failures with reading centers (Taylor, 2023). Prevention mechanisms include:

Pre-Visit (48–72 hours): Equipment audit with documented calibration status. Any equipment reporting calibration failure within past 7 days triggers equipment service priority or replacement authorization. Imaging modality and parameter requirements reviewed against current protocol version. Reading center is pre-contacted with participant schedule.

Morning-of: Calibration verification with documented results. Reference image or phantom scan performed to validate equipment functioning. Imaging room lighting and temperature within protocol specifications confirmed. Backup imaging equipment operational status verified.

Immediate Pre-Procedure: Participant arrival triggers imaging parameter confirmation. Laterality marked with participant confirmation. Imaging technician verbally confirms acquisition parameters with second technician

before beginning sequence. First image reviewed for quality; if below threshold, participant is repositioned and re-scanned before proceeding to next modality.

Post-Visit: File verification confirms correct participant identifiers, acquisition parameters, and file completeness before participant departure. Reading center is notified of images available for processing with expected turnaround time.

5.2.2 Preventing Functional Testing Deviations

Functional testing deviations frequently arise from inadequate participant preparation (incomplete dark adaptation), environmental factors (inadequate light control), or staff errors in test administration (Lacy, 2020). Prevention requires:

Pre-Visit: Participant communication confirming dark adaptation instructions and timing. Visual function assessment history reviewed for any factors affecting test validity (recent travel, medication changes, visual symptoms). Staff competency records reviewed; if refresher training is due, it is completed before visit.

Morning-of: Test environment audit confirming ambient light levels, background luminance, and fixation monitoring equipment functioning. Participant darkness adaptation period begins at scheduled time. Staff conducts briefing on test procedures and response expectations.

Immediate Pre-Procedure: Participant dark adaptation status confirmed visually and by participant report. Pupil dilation verified. Visual acuity baseline confirmed. Test parameters reviewed with participant. Quality monitor assigned. First test stimulus presented with participant response validation; if response appears invalid, test halted and participant re-briefed before restart.

During Assessment: Real-time quality monitoring with predetermined stopping rules (excessive trial rejections, inconsistent fixation, participant fatigue). If stopping rules are triggered, test is halted, participant rested, and escalation is initiated rather than forcing test completion to invalid conclusion.

5.2.3 Preventing Surgical/Procedural Deviations

Surgical deviations are prevented through comprehensive pre-operative verification and intraoperative monitoring (Haynes, 2009).

Pre-Visit (48 hours): Surgical team (surgeon, anesthesia, operating room staff, PI) conducts protocol briefing. Critical parameters (eye/site, volume, technique, intraoperative monitoring requirements) reviewed. Surgical equipment (microscope, injection system, intraoperative OCT) verified functioning. Contingency plans (e.g., if intraoperative OCT unavailable) discussed and approved.

Morning-of: Surgical team assembles. Protocol-specific equipment setup initiated. Participant medical history, anesthesia plan, and baseline safety parameters reviewed. Any medical changes since pre-visit briefing addressed.

Immediate Pre-Procedure (Time-Out): Before anesthesia induction, the surgical team conducts formal verification: (1) participant identity confirmed, (2) operative eye/site confirmed with participant and chart review, (3) laterality confirmed by marking operative eye with participant input, (4) procedure-specific requirements (volume, technique, monitoring) confirmed, (5) equipment functioning verified, (6) roles assigned, (7) any deviations from planned procedure discussed. This Time-Out is documented with all participants present and acknowledging confirmation.

Intraoperative: Continuous protocol compliance monitoring. Intraoperative OCT guidance used as specified. Volume delivery monitored. Injection site verified. Any unplanned deviations (anatomical challenges, unexpected bleeding, equipment limitation) immediately communicated among team members and documented.

Post-Operative: Procedure documentation completed before anesthesia reversal, confirming all critical parameters matched protocol specifications.

5.2.4 Preventing Investigational Product Deviations

Investigational product deviations require specialized chain-of-custody protocols (European Medicines Agency, 2022).

Pre-Visit (48–72 hours): Product location and storage status verified. Expiration dating confirmed. Temperature logs reviewed for any excursions. Pharmacy or product team readiness confirmed. Any product concerns escalated immediately to sponsor.

Pre-Procedure (2 hours): Product transport to operating or procedure room initiated with temperature monitoring. Preparation steps (if applicable) initiated on schedule to ensure readiness at procedure time. Preparation is performed by trained personnel, with second observer verifying each step.

Immediate Pre-Administration: Product verification includes patient/eye confirmation, dose confirmation, preparation method confirmation, and equipment functioning confirmation. Product is handed to administrator (surgeon or designee) with verbal confirmation of all parameters.

Post-Administration: Complete documentation of administration (time, dose, eye, participant, administrator, observer) recorded in real-time, before moving to next step. Any deviation from planned administration immediately escalated to sponsor and monitored for potential safety consequences.

5.2.5 Preventing Visit Window Deviations

Visit window deviations often reflect logistics-based failures rather than intentional non-compliance (Cilley, 2025).

Pre-Visit (>30 days): Initial visit scheduling with participant, confirming calendar availability. Multiple backup dates discussed.

Pre-Visit (14 days): Reminder contact confirming visit date and time. Any scheduling conflicts identified and alternative dates offered.

Pre-Visit (7 days): Second reminder contact. Window status assessed. If visit is at risk of missing window, escalation is triggered to identify whether visit should be rescheduled, converted to partial visit, or escalated for protocol exception.

Pre-Visit (48 hours): Final confirmation contact. Participant is asked to confirm attendance and any barriers to participation (transportation, health status, work schedule). Any barriers are addressed.

Morning of Visit: Participant arrival is verified within required timeframe. If participant is running late, site leadership is alerted and assessment of whether visit can still be completed within window is conducted. If window boundary will be missed, escalation to sponsor is initiated.

5.2.6 Preventing Eligibility and Protocol Amendment Deviations

These deviations require systematic tracking and verification mechanisms (TransCelerate BioPharma, 2023).

Protocol Version Management: Current protocol version displayed prominently at site with version date. All staff members sign acknowledgment of version they are trained on. Any protocol amendment is tracked in CTMS with implementation date and staff training completion date.

Eligibility Re-Verification: Structured re-verification checklist completed at protocol-specified intervals. Any inclusion/exclusion criteria change from baseline or last assessment is documented with clinical rationale. Any eligibility concerns are escalated to sponsor medical monitor.

Amendment Implementation: All protocol amendments are communicated to sites within defined timeframe. Training on amendment is mandatory before implementation. CTMS is updated with amendment status. Compliance audit confirms all affected visits after amendment date incorporated amendment requirements.

6. Electronic Integration and Monitoring Infrastructure

6.1 Clinical Trial Management System (CTMS) Integration

The PCC framework's effectiveness depends substantially on electronic integration enabling real-time monitoring and automated escalation (International Council for Harmonization, 2023). Key CTMS features include:

Visit Scheduling and Window Monitoring: Visits are scheduled in CTMS with target date and acceptable window range. Automated alerts notify site and sponsor when visits approach window boundaries. If visit is at risk of missing window, automated escalation ticket is generated.

Checklist Automation: PCCs are generated automatically from CTMS visit template based on visit type and procedure criticality tier. Checklists are displayed to staff with required completion fields. Completion status is tracked with timestamps and staff signatures.

Escalation Tracking: When escalation is triggered, CTMS automatically routes notification to appropriate decision-maker based on escalation level. Escalation ticket includes clinical context (participant number, visit date, issue description). Decision and rationale are documented in CTMS, creating audit trail.

Centralized Monitoring: Sponsor monitoring team views dashboard showing: PCC completion rates by site and visit type, escalation frequency and resolution times, deviation rates pre-visit versus post-visit, site-specific trends suggesting implementation barriers or unusual patterns.

6.2 Data Quality and Audit Trail Integrity

Electronic integration enables documentation standards and audit trail requirements (International Council for Harmonization, 2023):

Timestamping: All CTMS entries include automatic timestamp. Users are identifiable by unique login. Any CTMS entry modification creates amendment record showing original entry, modification, modifier, and modification timestamp.

Version Control: Protocol versions, PCC templates, and escalation decision trees are version-controlled. Any modification creates new version with version date. Sites are notified of new versions with implementation deadline.

Compliance Reporting: Automated reports generate site-specific compliance metrics: percentage of visits with completed PCCs, escalation frequency, time-to-resolution, major deviation frequency. These reports enable trend analysis and identification of sites requiring targeted support.

7. Implementation Considerations

7.1 Workflow Integration and Operational Burden

The PCC framework is designed to integrate into existing site workflows rather than creating additional visits or substantially increasing staff burden (International Council for Harmonization, 2023). Pre-visit preparation activities (equipment verification, eligibility confirmation, participant scheduling) largely consolidate tasks already performed informally. Morning-of readiness checks formalize existing site procedures. Immediate pre-procedure verification mirrors surgical safety checklists already used at many sites.

Experience from surgical safety checklist implementation indicates that operationally mature institutions adopt new checklists with minimal resistance when checklists are perceived as supporting existing safety goals (Borchard, 012). Site engagement and leadership endorsement are critical success factors. Training should emphasize that the PCC is a communication and safety tool, not a compliance burden.

7.2 Training and Competency Assurance

Implementation requires comprehensive staff training covering: (a) framework purpose and logic, (b) PCC completion procedures and electronic system use, (c) escalation triggers and decision authority, (d) procedure-specific content (equipment calibration, functional testing prerequisites, surgical safety procedures), and (e) documentation standards.

Competency validation should include: checklist completion simulation, scenario-based escalation decision-making, electronic system navigation, and procedure-specific knowledge assessment. Refresher training should be conducted annually or following protocol amendments.

7.3 Multi-Site Standardization and Adaptation

A standardized framework enables cross-site learning and consistency while permitting site-specific adaptation for local constraints. Core framework elements (four-tier classification, escalation triggers, documentation standards) should be standardized across networks. Specific PCC content, escalation authorities, and operational procedures may be adapted to reflect site infrastructure and local regulatory requirements.

National research networks (e.g., Inherited Retinal Dystrophy Research Network, Rare Diseases Clinical Research Network) are well-positioned to facilitate framework adoption by: (a) developing standardized PCC templates for common IRD procedures, (b) hosting training webinars, (c) providing implementation support, and (d) facilitating cross-site sharing of lessons learned.

8. Discussion

8.1 Framework Alignment with Quality Management Principles

The PCC framework operationalizes contemporary guidance on quality management in clinical trials. The International Council for Harmonization's E6(R3)

guideline explicitly requires that quality be built into trial design and conduct, and advocates for risk-based approaches identifying and protecting critical-to-quality factors (International Council for Harmonization, 2023). The framework does this by: (a) classifying procedures by criticality tier based on consequence severity, (b) designing targeted pre-visit preparation proportionate to criticality, (c) embedding verification at multiple time points where corrective action is still feasible, and (d) establishing escalation pathways enabling rapid decision-making.

The framework aligns with quality-by-design (QbD) principles, which emphasize designing processes to be reliable rather than relying on post-hoc detection and correction. The pre-visit checklist window (48–72 hours) embodies QbD logic by creating opportunity for corrective action before the irreversible event (visit execution). This contrasts with reactive quality frameworks that identify deviations only after they occur.

The framework is informed by evidence from surgical safety domains demonstrating that structured team-based checklists reading aloud and verifying critical steps reduce adverse outcomes by 35–47% (Haynes, 2009). While IRD trials are not surgeries, the underlying human factors principles—cognitive offloading, team communication, standardization—are analogously applicable.

8.2 Distinctive Applicability to IRD Trials

The framework addresses particular vulnerabilities of IRD trials. Small sample sizes mean each participant contributes substantial statistical weight; preventing even one endpoint-compromising deviation has meaningful power implications. Highly specialized endpoints (dark-adapted perimetry, microperimetry) require careful environmental and participant state control; checklists provide systematic assurance of prerequisites. Gene therapy procedures are irreversible; pre-procedure verification is the only meaningful deviation prevention opportunity. Distributed site networks often involve heterogeneous infrastructure; standardized frameworks enable consistency despite geographic and organizational diversity.

The framework's emphasis on early detection (pre-visit, 48–72 hours) creates genuine decision-making time that reactive approaches forfeit. Equipment downtime detected at 72 hours permits repair; detected post-visit permits only documentation and CAPA. Staffing gaps detected pre-visit permit reassignment or rescheduling; detected post-visit are irreversible. This time creation is the framework's fundamental value proposition in the IRD trial context.

8.3 Limitations and Evidence Gaps

Several limitations should be acknowledged. First, the framework is a conceptual design, not yet prospectively tested in real-world IRD trials. Empirical validation is needed to confirm whether implementation yields the predicted deviation reductions and identify unexpected barriers or unintended consequences. Second, the framework assumes that sites have adequate infrastructure (electronic systems, staff capacity, equipment) to implement pre-visit checklists. Smaller or under-resourced sites may require adaptation or support. Third, the framework's effectiveness depends substantially on leadership engagement and culture change; checklist fatigue is a documented risk if implementation becomes rote rather than meaningful (Borchard, 2012). Fourth, the escalation pathway decision trees cannot anticipate every clinical scenario; some decisions will require human judgment under time pressure and incomplete information.

Key evidence gaps include: (a) empirical data on protocol deviation frequency and types in contemporary IRD trials (such data would enable data-driven tier assignments), (b) prospective evaluation of the framework's effectiveness in preventing deviations across diverse site types, (c) cost-effectiveness analysis quantifying benefits (prevented repeat visits, reduced CAPA burden, shortened timelines) relative to implementation costs, and (d) human factors research identifying optimal checklist design and escalation decision-making procedures for research settings.

8.4 Practical Implementation Pathway

Sponsors and IRD research networks can implement this framework through a phased approach: Phase 1 (Months 1–2) involves framework adaptation to specific trials, PCC template development, and escalation pathway specification. Phase 2 (Months 3–4) involves site training, electronic system configuration, and pilot testing. Phase 3 (Months 5+) involves full implementation with real-time monitoring, troubleshooting, and continuous improvement.

Early adoption at high-volume sites with robust quality infrastructure is recommended to generate proof-of-

concept and identify implementation lessons before broader network adoption. Smaller pilot programs at diverse site types will test adaptability and identify site-specific barriers requiring targeted support.

9. Conclusion

Protocol deviations in inherited retinal disease ophthalmology trials represent a complex, multifaceted operational challenge that threatens both participant safety and the integrity of primary efficacy data that inform regulatory decisions about sight-saving therapies (Igoe, 2024). This article has presented a comprehensive framework for understanding deviation types, classifying procedures by consequence severity, and implementing systematic prevention mechanisms operative at multiple time points and decision levels.

The framework's core innovation is the integration of three elements: (a) a procedure criticality classification system enabling proportionate allocation of prevention resources, (b) a tripartite pre-visit checklist architecture creating detection and decision-making opportunity at stages where corrective action remains feasible, and (c) a tiered escalation pathway enabling rapid decision-making when risks cannot be locally resolved. Together, these elements operationalize contemporary regulatory guidance on risk-based quality management while respecting operational constraints of research sites.

Implementation across national IRD research networks is recommended as a priority for several reasons. First, the framework provides standardized methodology reducing duplication of effort across programs. Second, standardization enables cross-trial comparison of deviation rates and quality metrics. Third, the framework strengthens the evidence quality on which regulatory decisions about ATMP approvals ultimately rest. Fourth, by protecting data integrity, the framework contributes to timely regulatory approval pathways and equitable patient access to sight-saving therapies.

The path forward involves three complementary activities: (a) prospective empirical evaluation of the framework's effectiveness in preventing deviations and its operational feasibility across diverse site types, (b) digital tool development enabling CTMS integration and automated monitoring, and (c) adoption by early-adopter programs and national research networks to generate field-wide implementation evidence and best practices.

By investing in quality management infrastructure that prevents deviations proactively rather than managing them reactively, the IRD research community can ensure that the rapid expansion of ATMP ophthalmology programs translates into credible approvals, equitable access, and durable improvements in sight outcomes for the thousands of individuals living with inherited retinal diseases worldwide.

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