# Standard Operating Procedure

## Conduct of Multicenter Clinical Trials – GCP Compliance

Protocol NX-2214-301

*A Phase III, Randomized, Double-Blind, Placebo-Controlled Multicenter Study Evaluating the Efficacy and Safety of NX-2214 in Adults with Moderate-to-Severe Plaque Psoriasis*

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| **SOP Number** | SOP-CT-014 |
| **Version** | 4.0 |
| **Effective Date** | 01 June 2026 |
| **Supersedes** | Version 3.2 (12 November 2024) |
| **Next Scheduled Review** | 01 June 2027 |
| **Sponsor** | Nexa Therapeutics, Inc. |
| **Coordinating Center** | Vertex Clinical Trials Unit |
| **Governing CRO** | Meridian Clinical Research Network |

### Approval Signatures

| Role | Name | Signature | Date |
|---|---|---|---|
| Sponsor Medical Director | Dr. Elena Vasquez, Nexa Therapeutics | _____ | _____ |
| Coordinating Investigator | Dr. Michael Chen, Vertex Clinical Trials Unit | _____ | _____ |
| Head of Clinical Operations | Sarah Okonkwo, Meridian CRN | _____ | _____ |
| QA/QC Director | Dr. Priya Nair, Meridian CRN | _____ | _____ |

## 0.1 Purpose and Scope

This Standard Operating Procedure (SOP) defines the mandatory processes for planning, initiating, conducting, monitoring, and closing out multicenter interventional clinical trials sponsored by Nexa Therapeutics, Inc. and operationally managed by Meridian Clinical Research Network. It establishes uniform expectations for all personnel – sponsor staff, contract research organization (CRO) staff, Principal Investigators, and site personnel – engaged in Protocol NX-2214-301 and any subsequent multicenter protocol referencing this SOP.

This procedure applies to all 42 participating investigator sites across 9 countries and covers the full trial lifecycle from site feasibility assessment through database lock and archiving. It does not supersede local regulatory requirements, institutional policies, or the approved protocol; where a conflict exists, the more stringent requirement governs.

ICH E6(R2) Good Clinical Practice • 21 CFR Parts 50, 54, 56 and 312 (US FDA) • Regulation (EU) No 536/2014 on Clinical Trials • Declaration of Helsinki (2013, Fortaleza revision) • Applicable local data protection and health privacy law at each participating site.

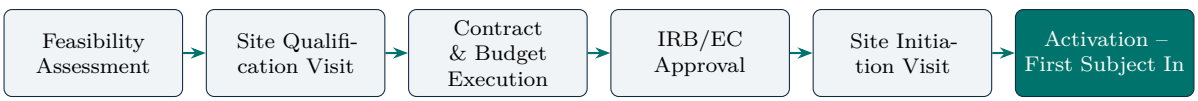
## 0.2 Roles and Responsibilities

Each role below carries defined accountability under this SOP. Delegation of tasks at site level must be recorded on the study-specific Delegation of Authority (DoA) log and is limited to individuals with documented training and qualifications.

| Role | Key Responsibilities | Reports To |
|---|---|---|
| Sponsor (Nexa Therapeutics) | Overall trial accountability, protocol authorship, safety determinations, regulatory submissions | Board of Directors |
| Coordinating Investigator | Scientific leadership across sites, protocol interpretation queries, publication oversight | Sponsor |
| Principal Investigator (per site) | Subject safety, informed consent, protocol adherence, supervision of delegated staff | Coordinating Investigator |
| Clinical Research Associate | Site monitoring, source data verification, regulatory document maintenance | Clinical Operations Lead |
| Data Management Team | eCRF design, query resolution, database lock readiness | Head of Clinical Operations |
| Pharmacovigilance Unit | SAE triage, expedited reporting, aggregate safety review | Sponsor Medical Director |
| IRB / Independent Ethics Committee | Protocol and consent approval, ongoing ethical oversight | Institution (independent) |
| Site Study Coordinator | Visit scheduling, consent logistics, IP dispensing records | Principal Investigator |

## 0.3 Site Selection, Initiation, and Activation

Sites are selected based on feasibility survey results, prior trial performance, patient population access, and infrastructure adequacy (pharmacy, biosample handling, emergency equipment). Activation follows a fixed sequence; no site may enroll subjects prior to completion of every step below.



The target interval from feasibility confirmation to activation is 45 calendar days. Sites exceeding 75 days without activation are escalated to the Steering Committee for a go/no-go re-evaluation. The Site Initiation Visit (SIV) must cover protocol training, IP handling, electronic data capture (EDC) system access, and safety reporting pathways, and must be documented on the SIV attendance log retained in the Trial Master File (TMF).

## 0.4 Informed Consent Process

Informed consent is obtained by the Investigator or a qualified, delegated sub-investigator prior to any protocol-specific procedure. The consent discussion must occur in a private setting, in the subject's preferred language, and allow adequate time for questions.

**Mandatory Elements**

- Current IRB/EC-approved consent version
- Voluntary participation and right to withdraw
- Foreseeable risks and expected benefits
- Alternative treatments available
- Confidentiality and data-sharing scope

**Re-Consent Triggers**

- Substantive protocol amendment
- New safety information affecting risk profile
- Change to biological sample use or retention
- Extension of study duration

Signed and dated consent forms are filed in the subject's source record; the process must be documented contemporaneously in the source notes, including the date, time, and version of the consent form used. Non-English-speaking subjects must receive a certified translated consent form – verbal translation alone is not acceptable except under emergency exception provisions defined in the protocol.

## 0.5 Investigational Product Management

### 0.5.1 Storage and Temperature Monitoring

Investigational product (IP) NX-2214 and matching placebo must be stored at 2°C–8°C in a dedicated, access-controlled pharmacy refrigerator with continuous calibrated temperature logging. Logs are reviewed by site pharmacy staff daily and by the CRA at every monitoring visit.

### 0.5.2 Accountability and Reconciliation

Drug accountability logs must record every receipt, dispensing, return, and destruction event, reconciled against subject dosing records at each visit. Discrepancies exceeding one dosing unit must be investigated and documented within 5 business days.

**Temperature Excursion Handling**

Upon any excursion outside 2°C–8°C: (1) quarantine affected product immediately and label *DO NOT USE*; (2) record duration and temperature range from the logger; (3) notify the CRA and Sponsor Pharmacovigilance within 24 hours; (4) do not dispense or destroy quarantined product until written disposition is received from the Sponsor.

## 0.6 Safety Reporting

All adverse events are recorded in the eCRF regardless of causality. Serious adverse events (SAEs) follow expedited timelines independent of routine visit schedules.

| Event Type | Reporting Timeline | Recipient |
|---|---|---|
| SAE – fatal or life-threatening | Within 24 hours of awareness | Sponsor Pharmacovigilance, IRB/EC |
| SAE – other serious | Within 24 hours of awareness | Sponsor Pharmacovigilance |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) | Within 7 or 15 calendar days per expectedness | Regulatory Authorities, all sites |
| Pregnancy during study exposure | Within 24 hours of awareness | Sponsor Pharmacovigilance |
| Overdose (with or without associated AE) | Within 24 hours of awareness | Sponsor Pharmacovigilance |

*Reference: ICH E2A, Clinical Safety Data Management – Definitions and Standards for Expedited Reporting.*

## 0.7 Monitoring and Quality Oversight

Monitoring combines on-site visits with centralized statistical data review to detect outliers, site drift, and data integrity concerns between visits.

| Visit Type | Frequency | Primary Focus |
|---|---|---|
| Site Initiation Visit (SIV) | Once, pre-activation | Training, readiness, regulatory binder completeness |
| Interim Monitoring Visit (IMV) | Every 6–8 weeks | Source data verification, consent compliance, IP accountability |
| Remote / Centralized Monitoring | Continuous | Query trends, enrollment pace, safety signal detection |
| Close-Out Visit (COV) | Once, post-database lock | Reconciliation, IP return, archiving confirmation |
| For-Cause Audit | As triggered | Root-cause investigation of significant findings |

## 0.8 Protocol Deviations and CAPA

Deviations are classified as **Minor** (no impact on subject safety or data integrity), **Major** (potential impact requiring corrective action), or **Critical** (direct impact on subject safety, rights, or primary endpoint reliability).

**Reporting and CAPA Requirement**

Major and Critical deviations must be reported to the CRA within 3 business days and to the IRB/EC per local requirements. A Corrective and Preventive Action (CAPA) plan is mandatory for all Major and Critical deviations, with root-cause analysis, assigned owner, and a verification-of-effectiveness date logged in the Quality Issue Tracker.

## 0.9 Records Retention and Archiving

Essential documents, including signed consent forms, source records, monitoring visit reports, and the completed regulatory binder, are retained for a minimum of 15 years following trial completion, or longer where local law requires. Site archiving is confirmed at the Close-Out Visit and documented in the TMF Index prior to final site release.

## Appendix A – Revision History

| Version | Date | Summary of Changes |
|---|---|---|
| 1.0 | 04 Feb 2022 | Initial issue for protocol NX-2214-101 (Phase I). |
| 2.0 | 19 Sep 2022 | Expanded to multicenter scope; added CRA monitoring cadence table. |
| 3.0 | 22 Jan 2024 | Added centralized/remote monitoring; revised SAE timelines to align with amended ICH E2A guidance. |
| 3.2 | 12 Nov 2024 | Clarified temperature excursion quarantine procedure; added pregnancy reporting pathway. |
| 4.0 | 01 Jun 2026 | Full rewrite for Protocol NX-2214-301; added deviation classification matrix and CAPA requirement; updated retention period to 15 years. |

## Appendix B – Regulatory References

- ICH E6(R2) – Good Clinical Practice: Integrated Addendum
- ICH E2A – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
- US Code of Federal Regulations, Title 21, Parts 50, 54, 56, and 312
- Regulation (EU) No 536/2014 on Clinical Trials on Medicinal Products for Human Use
- World Medical Association Declaration of Helsinki (2013, Fortaleza revision)