1. SPONSOR INFORMATION

- **Sponsor Name**: NovaCura Pharmaceuticals, Inc.
- **Sponsor Address**: 123 Innovation Way, BioTech Park, Metropolis 10001
- **Sponsor Contact**:
    - Name: Dr. Jade Nicholson
    - Title: Director, Clinical Development
    - Phone: +1 (800) 123-4567
    - Email: jade.nicholson@novacura-pharma.com

NovaCura Pharmaceuticals, Inc. is responsible for the design, management, and financing of the trial. A Contract Research Organization (CRO), **Apex Clinical Services**, will be overseeing day-to-day monitoring and data management under a written transfer of obligations.

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2. PROTOCOL OVERVIEW

- **Protocol Title**: A Phase II, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of **NVX-101** in Adult Patients with Migraine.
- **Protocol Number**: NVX-101-2025-P2
- **Study Phase**: II
- **Study Design**:
    - Randomization: 2:1 (NVX-101 : Placebo)
    - Blinding: Double-blind (subject, investigator, sponsor)
    - Estimated Enrollment: 150 subjects
    - Number of Sites: ~10 in two countries (USA, Canada)

2.1 Study Objectives

1. **Primary Objective**: To evaluate the efficacy of NVX-101 (100 mg, once daily) versus placebo in reducing the frequency of migraine attacks over 12 weeks.
2. **Secondary Objectives**:
    - To assess NVX-101's safety profile, including incidence of adverse events, vital signs changes, and laboratory abnormalities.
    - To evaluate the impact of NVX-101 on patient-reported outcomes (quality of life, headache-related disability).

2.2 Study Population

- **Key Inclusion Criteria**:
    - Male or female, 18–65 years old.
    - History of migraines (per International Headache Society criteria) for at least one year.
    - Minimum of 4 migraine days per month in the last 3 months.

- **Key Exclusion Criteria**:
    - Any serious uncontrolled comorbid conditions (e.g., severe cardiovascular disease).
    - Use of other investigational drugs within 30 days.
    - Known hypersensitivity to the IP or placebo excipients.

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3. INVESTIGATIONAL PRODUCT (IP)

- **Name**: NVX-101 (100 mg oral tablets)
- **Comparator**: Placebo tablets (matching color, shape, packaging)
- **Manufacturing & Labeling**:
    - Manufactured in compliance with GMP by NovaCura's facility (Lot #NVX101-22A for active, Lot #PLB101-22B for placebo).
    - IP labels to include: protocol ID, randomization code, "For Clinical Trial Use Only," storage conditions (20–25°C), expiry date, and unique kit number.
- **Storage & Accountability**:
    - Stored at clinical sites in locked, temperature-controlled cabinets.
    - Site pharmacist or designated unblinded coordinator maintains IP logs (receipt, dispensing, returns).
    - Temperature monitored daily; excursions documented and reported to Sponsor QA.

3.1 Repackaging/Blinding Procedures

- NovaCura's unblinded supply manager handles randomization codes and kit labeling.
- Investigators and site staff remain blinded; the kit's external packaging does not reveal the treatment assignment.

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4. MONITORING & OVERSIGHT

4.1 Risk-Based Monitoring

- Sponsor and CRO, Apex Clinical Services, will use a **risk-based monitoring plan** per ICH E6(R2) Section 5.18.
- **Central Monitoring**: Real-time data review for key safety/efficacy endpoints.
- **On-Site Monitoring**: Baseline, monthly, and closeout visits.
- **Key Focus Areas**:
    - Randomization integrity
    - IP accountability
    - Informed consent documentation
    - Critical data points (migraine attack frequency, AE reporting)

4.2 Quality Management & Serious Breach Assessment

- NovaCura has a **Quality Management System** to assess protocol deviations, identify potential serious breaches, and implement CAPAs.
- All protocol deviations are documented in a **Deviation Log**, escalated as needed to Sponsor QA.

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5. DATA MANAGEMENT & SOURCE DOCUMENTS

- **Data Capture**:
  - Electronic Data Capture (EDC) system: eCRFs created by Apex Clinical Services.
  - ePRO: subjects use a migraine diary app to record daily headache details.
- **Audit Trail & ALCOA+ Compliance**:
  - EDC system logs user, date, time, reason for any data changes.
  - ePRO includes time stamps for each diary entry, with monthly site staff reviews.
- **Source Documents**:
  - Paper medical charts for physical exams and lab results, ePRO diaries for headache data.
  - All changes or corrections initialed/dated, with no use of correction fluid.

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6. INFORMED CONSENT PROCESS

- **Process**:
  - Consent must be obtained by a locally licensed investigator or sub-investigator authorized by the PI (signed Delegation Log).
  - Consent is performed **before** any study procedures.
- **ICF Versions**:
  - English version 1.0 dated 01 Jan 2025 (IRB-approved).
  - French version 1.0 dated 15 Jan 2025 (for Canadian French-speaking sites).
- **Subjects Unable to Read**:
  - Impartial witness required, present for entire consenting discussion.
- **ICF Tracking**:
  - Maintain a log referencing date of IRB approval and version number.
  - Each site to file signed ICF copies in Investigator Site File and participant's medical record.

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7. SAFETY REPORTING & PHARMACOVIGILANCE

- **Adverse Event (AE) Collection**:
  - Sites capture AEs during each visit and via subject diaries.

- **Serious Adverse Events (SAEs)**:
    - Immediately notified to the Sponsor within 24 hours of awareness.
    - Sponsor to assess relatedness/expectedness and file expedited reports to IRB/HSA/Health Canada as required.
- **Safety Monitoring Committee**:
    - An independent Data Safety Monitoring Board (DSMB) will review unblinded safety data at mid-point and final.

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8. INVESTIGATOR RESPONSIBILITIES & STAFF TRAINING

- **Delegation of Duties**:
    - Each site maintains a Delegation Log, signed by the PI, indicating staff members authorized for tasks like informed consent, IP dispensing, data entry.
- **Protocol Training**:
    - All site staff must attend sponsor-led initiation visit or complete online training modules.
    - Document GCP certification within the last 2 years.
- **Ongoing Communication**:
    - PI leads monthly site team meetings, documents them in meeting minutes.
    - CRAs and the PI promptly address any findings from monitoring visits.

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9. REGULATORY SUBMISSIONS & ESSENTIAL DOCUMENTS

- **Regulatory Authorities**:
    - Clinical Trial Notifications (CTNs) submitted to HSA (Singapore) and to Health Canada.
    - Protocol amendments also require IRB and regulatory authority approvals before implementation.
- **Trial Master File**:
    - Maintained electronically by Apex Clinical Services; includes all essential documents (protocol, IB, approvals, monitoring reports).
    - Sites maintain Investigator Site File (ISF) with local records (signed ICFs, local approvals, delegation logs).

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10. SIGNATURES & COMMITMENTS

By signing, the Sponsor commits to conducting this trial in compliance with ICH E6(R2) GCP guidelines, local regulations, and the approved protocol.

- **Sponsor Representative**:
    - *Name*: Dr. Jade Nicholson, Director of Clinical Development
    - *Signature*: _____
    - *Date*: 05 Feb 2025
- **Principal Investigator**:
    - *Name*: Dr. [TBD by site]
    - *Signature*: _____
    - *Date*: [Site-specific date]