APPENDIX C: INVESTIGATOR BROCHURE FOR NIMSAI HERBAL

Protocol Title: Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Trial to Evaluate the Efficacy and Safety of Nimsai Herbal Capsules in Participants with Grade 2-3 Internal Hemorrhoids

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1. INTRODUCTION TO NIMSAI HERBAL

Nimsai Herbal is a novel, proprietary oral herbal formulation developed by Nimsai Academia for the systemic management of hemorrhoidal disease. It is hypothesized to target underlying venous congestion, a critical factor in hemorrhoid pathogenesis according to the War-Drill Model. This brochure provides investigators with essential information regarding the composition, mechanism of action, preclinical and clinical data, and safety profile of Nimsai Herbal.

2. COMPOSITION AND FORMULATION

- Formulation: Oral capsules
- Strength: 600 mg per capsule
- Composition: Proprietary herbal blend.
- Appearance: Beige, oblong capsule

3. RATIONALE AND MECHANISM OF ACTION (Based on War-Drill Model)

The War-Drill Model posits that hemorrhoids are primarily a manifestation of systemic and/or local venous congestion, which precedes and drives vascular deformation. Nimsai Herbal is designed to address this fundamental etiology.

Proposed Mechanism: Nimsai Herbal is believed to exert its therapeutic effects by primarily preventing and resolving venous congestion (blood accumulation), which is the root cause of hemorrhoid formation according to the War-Drill Model. This is achieved through:

- Targeted Delivery via DRcaps®: Ensuring active ingredients bypass gastric acidity and are released in the intestine for optimal absorption and systemic effect.
- Modulating Vascular Tone: Influencing neuro-peptides (NPY) and endothelin (ET-1) to directly improve venous return and reduce blood accumulation in the hemorrhoidal plexus.
- Improving Blood Rheology: Facilitating smoother blood flow and preventing stasis that contributes to chronic congestion and subsequent vascular deformation.
- Addressing Hormonal Influences (Drill Mode): Counteracting specific hormonal shifts that induce venous congestion in Drill Mode hemorrhoids.
- Reducing Inflammation: Targeting inflammatory cytokines (IL-6, TNF-α) to alleviate secondary inflammation and tissue damage associated with chronic congestion.

4. PRECLINICAL DATA

- In Vitro Studies: Mechanistic in vitro studies were conducted to elucidate the molecular underpinnings of the War-Drill Model's proposed mechanisms for hemorrhoid pathogenesis. These investigations demonstrated that stimulation of human endothelial cells with pro-inflammatory cytokines (TNF-α, IL-1β) increased NPY and ET-1 expression (associated with War Mode), and estrogen exposure upregulated NOS3 expression (associated with Drill Mode).
- No animal studies have been conducted for Nimsai Herbal.

5. CLINICAL DATA (Summary of Current RCT)

- Study Design: Double-blind, placebo-controlled RCT (NA-2024-01).
- Population: 300 participants with Grade 2-3 hemorrhoids.
- Intervention Duration: 10 days (600 mg QD).
- Primary Endpoint: Hemorrhoid regression (≥75% reduction in composite hemorrhoid severity score from baseline), further substantiated by a reduction of at least one Goligher grade, at Day 10.
- Key Findings: The ongoing RCT has demonstrated significant efficacy for Nimsai Herbal in achieving hemorrhoid regression and symptom resolution compared to placebo. Detailed findings across hemorrhoid types are as follows:
    - Drill Mode Hemorrhoid: Complete recovery from pain, discomfort, bleeding, itching, inflammation, and complete disappearance of the external hemorrhoid (pile) is observed after 10-day oral use.
    - War Mode Hemorrhoid: After 10-day oral use, pain, discomfort, bleeding, itching, and inflammation cease; however, the external hemorrhoid (pile) significantly shrinks but does not disappear completely. This condition serves as evidence that the individual has War Mode hemorrhoids, indicating the likely presence of serious underlying pathologies such as Crohn's, proctitis, polyps, fissures, or fistulas. Complete disappearance of the external hemorrhoid cannot be expected unless the underlying disease is treated. An urgent colonoscopy and endoscopic evaluation are strongly recommended in such cases.
- Safety: Nimsai Herbal has shown a favorable safety profile with no serious adverse events reported to date; mild GI discomfort (4%) was comparable to placebo (2%).

6. DOSAGE AND ADMINISTRATION

- Dosage: 600 mg (one capsule)
- Frequency: Once daily
- Route: Oral
- Duration: 10 days

7. SAFETY INFORMATION

- Adverse Events: As summarized above, mild gastrointestinal discomfort is the most frequently reported adverse event, with an incidence comparable to placebo. No serious adverse events attributed to Nimsai Herbal have been observed in clinical trials.
- Contraindications: Known hypersensitivity to any component of Nimsai Herbal.
- Drug Interactions: No significant drug interactions have been identified. However, in a small number of cases (2-3 day duration), diarrhea has been observed when Nimsai Herbal was taken concomitantly with medications used by diabetic patients.
- Special Populations / Contraindicated Use: Nimsai Herbal takes a highly cautious and strict approach to patient safety, prioritizing absolute certainty even for a natural product with no anticipated negative interactions. Therefore, its use is contraindicated and not recommended for the following populations:
    - Pregnant and lactating women.
    - Patients undergoing chemotherapy.
    - Patients who have undergone organ transplant surgery.
    - Individuals with a history of high allergic symptoms.
    - Individuals aged 17 years and younger.

8. HANDLING AND STORAGE

- Storage: Store at room temperature, away from direct sunlight and moisture.
- Handling: Standard precautions for oral medication.

9. REGULATORY AND ETHICAL STATUS

- Ethics Approval: Protocol NA-2024-01 approved by Nimsai Academia Ethics Committee on October 10, 2021.

10. Dissemination Plan

The findings of this trial will be submitted for publication in peer-reviewed medical journals and presented at relevant scientific conferences, regardless of the outcome. Participant confidentiality will be maintained throughout the dissemination process. De-identified data and statistical code will be made available upon reasonable request from the corresponding author. Requests for data will be reviewed by the Nimsai Academia Ethics Committee.

11. Appendices

- Appendix A: Informed Consent Form
- Appendix B: Case Report Forms (CRFs)