RESEARCH PROTOCOL

National Multicenter Prospective Registry of Venous Ulcer of the Lower Limbs (RENUVI-Mexico)

RENUVI — Prospective, Multicenter, Observational Cohort

Item	Information
Unique identifier	RENUVI-001-CMN
Protocol Date	July 20, 2026
Expected duration	60 months
Scope	Public and private institutions in Mexico

Master document for review by the Coordinating Committee, local research and ethics committees, and institutional authorities. Pending administrative fields must be completed prior to activation of the first center.

VERSION CONTROL

Version	Date	Sections	Change	Justification
1.0	20-Jul-2026	All	Initial protocol of the national registry.	Creation of the project.

STATEMENT OF COMPLIANCE

Registration will be conducted in accordance with the approved protocol, the General Health Law, the Regulations of the General Health Law on Health Research, NOM-012-SSA3-2012, the ethical principles of the Declaration of Helsinki, the Good Clinical Practices applicable to observational research, the Mexican data protection legislation and the policies of each participating institution. Each center will begin activities only after obtaining the required local approvals.

The study does not assign treatments or modify clinical care. Diagnostic and therapeutic decisions will remain under the responsibility of the treating physician. The national database will store encrypted data; the re-identification key will remain in the exclusive custody of each center.

CONTENTS

Note: In Word, select the table of contents and choose "Update Field" to display the final pagination.

1. SUMMARY OF THE PROTOCOL

1.1 Synopsis

Field	Description
Abbreviated title	National Registry of Venous Ulcer of the Lower Limbs (RENUVI-Mexico)
Design	Prospective, multicenter, observational, and longitudinal registry, with a cohort of active ulcers and a cohort of recurrence after healing.
Problem	Absence of standardized national data on disease burden, diagnostic patterns, treatment, healing, recurrence, quality of life, and resource use.
Population	Adults with at least one active leg ulcer of confirmed venous or predominantly venous etiology, cared for at participating centers in Mexico.
Primary Objective	Describe the cumulative proportion of index ulcers with complete healing at 24 weeks and the time to healing.
Primary outcome	Complete healing: 100% epithelialization, absence of drainage and no need for dressing, confirmed by clinical evaluation; if feasible, sustained or confirmed ≥14 days later.
Secondary outcomes	Percent area change at 4 and 12 weeks; healing at 12 and 52 weeks; recurrence; pain; quality of life; infection; hospitalization; amputation; mortality; adherence; venous interventions; adverse events; resources and direct costs.
Follow-up	Basal, week 4, week 12, week 24 and week 52; additional contact at the time of healing and confirmation ≥14 days.
Target sample	2,000 participants, with competitive recruitment and regional representation goals.
Duration	48 months of recruitment and up to 12 months of follow-up; estimated total duration of 60 months.
Platform	REDCap or equivalent platform with traceability, validations, access control and auditable export.

1.2 Study outline

1. Consecutive identification of potentially eligible patients at each facility.
2. Confirmation of eligibility, informed consent and assignment of the RENMUV code.
3. Baseline patient record, limb, index ulcer, additional ulcers, venous hemodynamics, photograph, and usual treatment.
4. Scheduled follow-up and capture of therapeutic modifications, adherence, complications, healing and use of resources.
5. Admission to the recurrence cohort when index ulcer heals; follow-up up to week 52.
6. Closure, validation, resolution of discrepancies and national analysis with models adjusted by patient and center.

1.3 Calendar of activities

Activity	Basal	Week 4	Shem 12	Sem 24	Sem 52	Not scheduled
Consent and Eligibility	X					
Demographics and social determinants	X					
Venous history/comorbidities	X	Act.	Act.	Act.	Act.	Act.
Exploration, CEAP and VCSS	X	X	X	X	X	X
ITB or finger pressure where applicable	X	According to clinic		According to clinic		According to clinic
Venous duplex	X/≤90 d	According to clinic		According to clinic		According to clinic
Index ulcer: area, bed, exudate, and skin	X	X	X	X	X	X
Calibrated Photography	X	X	X	X	X	X
NRS Pain 0–10	X	X	X	X	X	X
Quality of life (CCVUQ or VEINES-QOL/Sym)	X		X		X	X
Treatment and adherence	X	X	X	X	X	X
Infection/antibiotics/adverse events		X	X	X	X	X
Resource use and hospitalizations	6 months previous	X	X	X	X	X
Healing state		X	X	X	X	X
Recurrence after healing				X	X	X

Recommended windows: week 4 ±7 days; week 12 ±14 days; week 24 ±21 days; week 52 ±30 days. An unscheduled visit may be used to document healing, recurrence, infection, hospitalization, or intervention.

2. INTRODUCTION

Theoretical framework

Chronic venous disease comprises persistent morphological and functional alterations of the venous system that produce signs or symptoms and require evaluation or treatment. Its clinical spectrum ranges from telangiectasias and varicose veins to edema, skin changes, healed ulcer, and active ulcer. The CEAP classification allows the description of the clinical class, etiology, anatomical distribution, and

pathophysiology; in this framework, C6 identifies active venous ulcer and C6r indicates recurrence. In Mexico, a primary care study found chronic venous disease in 71.3% of the participants evaluated and demonstrated progressive deterioration in quality of life as the clinical class increased; only a minority received early referral to the specialist. [1]

Venous ulcer is a loss of skin continuity, usually located in the gaiter or malleolar region, whose predominant etiology is ambulatory venous hypertension. This hypertension may result from superficial, deep or perforating reflux; venous obstruction; dysfunction of the calf muscle pump; or combinations of these mechanisms. The sustained transmission of pressure to the microcirculation promotes endothelial activation, leukocyte adhesion, extravasation of erythrocytes and proteins, hemosiderin deposition, edema, persistent inflammation and remodeling of the extracellular matrix. The result is relative hypoxia, impaired nutrient exchange, glycocalyx damage, fibrosis, lipodermatosclerosis and skin vulnerability. Once the wound is established, the inflammatory load, metalloproteinase imbalance, cellular senescence, biofilm and comorbidities can perpetuate the inflammatory phase and prevent orderly repair. Bull 2.3

The actual frequency of venous ulcers remains uncertain. A recent systematic review and meta-analysis estimated pooled prevalence of 0.32% and incidence of 0.17%, but documented extreme heterogeneity related to definitions, population, source of cases, and methodology. [4] This variability limits extrapolation to Mexico, where specific information on active ulcer, duration, recurrence, and longitudinal outcomes is scarce. The clinical burden exceeds the size of the wound: pain, exudate, odor, pruritus, sleep disturbance, limitation of walking, isolation, anxiety, job loss, and dependence for cures deteriorate well-being. Prolonged and recurrent episodes demand consultations, materials, antibiotics, hospitalizations, and procedures, with substantial direct and indirect costs for patients, families, and institutions. [5]

The diagnosis must establish the venous etiology and rule out arterial, neuropathic, inflammatory, neoplastic or pressure causes. The evaluation includes clinical history, pulses, characteristics of the wound and perilesional skin, ankle-brachial index or digital pressure when calcification, CEAP classification, Venous Clinical Severity Score and duplex ultrasound. The latter characterizes reflux, obstruction and superficial, deep and perforating anatomy, and guides interventions. Current guidelines recommend compression to promote healing, as long as arterial perfusion allows its safe application. Compression reduces venous diameter, edema and capillary filtration, improves return and muscle pump function; however, its real effectiveness depends on pressure, technique, tolerance, mobility, education, access and adherence. [3,6]

Local care includes cleaning, debridement when indicated, exudate control, perilesional protection, and dressings selected according to clinical needs. No dressing is a substitute for correction of venous hypertension. In patients with treatable superficial reflux, early intravenous intervention combined with compression may accelerate healing and reduce recurrence; deep vein obstruction should also be considered in refractory or recurrent ulcers. [3] After closure, sustained compression, physical activity, limb elevation, skin care, and venous correction are components of prevention, although long-term adherence is problematic. [7,8]

The evolution does not depend exclusively on vascular treatment. Age, obesity, diabetes, malnutrition, heart or kidney failure, concomitant arterial disease, joint limitation and social conditions can modify healing and

adherence. The infection must be diagnosed clinically, avoiding equating bacterial colonization with invasive infection. The indiscriminate use of cultures or antibiotics favors costs, toxicity and resistance. Therefore, care requires coordination between vascular surgery, angiology, nursing, family medicine, rehabilitation, nutrition and wound teams, with shared education and sufficient follow-up to detect closure, complications and recurrence.

Outcome measurement requires reproducible definitions. Complete healing should represent 100% epithelialization, absence of drainage, and lack of need for dressing, ideally confirmed in a subsequent evaluation. The area can be measured using calibrated digital planimetry or documented geometric methods; early percentage change provides prognostic information, but does not replace complete closure. Time to healing, recurrence, ulcer-free days, pain, quality of life, infection, hospitalization, adverse events, resource utilization, and costs are also relevant. An international eDelphi consensus proposed five essential domains: healing, pain, quality of life, resource use, and adverse events, and recommended privileging the patient as the primary reporting unit. [9]

Prospective registries complement clinical trials because they describe heterogeneous populations, treatments actually received, and institutional variation. Their validity depends on consecutive inclusion, common definitions, temporal follow-up, quality control, transparent handling of missing data, and adjustment for confusion. RENMUV adopts a multilevel structure that differentiates patient, limb, ulcer, and center, designates an index ulcer, and documents additional lesions. The integration of clinical, hemodynamic, therapeutic, patient-centered, and economic variables will allow characterizing the natural history, recognizing inequalities, generating hypotheses, and establishing a national infrastructure for pragmatic research and continuous improvement.

Length: 835 words

Scientific basis

Venous ulcer is the advanced clinical expression of sustained venous hypertension caused by muscle pump reflux, obstruction, or dysfunction. High ambulatory pressure is transmitted to the microcirculation and promotes endothelial activation, leukocyte adhesion, macromolecule extravasation, edema, persistent inflammation, degradation of the extracellular matrix, and deterioration of the skin barrier. [2,3] This pathophysiology explains why treatment must simultaneously address the wound and the underlying hemodynamic mechanism.

Contemporary guidelines recommend structured etiological evaluation with CEAP classification, VCSS, arterial assessment, and duplex ultrasound to identify reflux or obstruction. [3] Compression continues to be the therapeutic basis because it reduces hypertension and edema, improves venous return, and can promote healing, pain, and quality of life. [6,10] When there is superficial venous incompetence that can be corrected, early intervention combined with compression accelerates closure and decreases recurrence. [3] However, the clinical response varies according to duration and initial area, post-thrombotic disease, arterial perfusion, mobility, infection, comorbidities, compression technique, adherence, and access to specialists.

The available evidence shows considerable heterogeneity in participant selection, etiology definitions, area measurement, confirmation of closure, duration of follow-up, and recurrence report. [4,9] This inconsistency limits comparisons between centers, quantitative syntheses, and transfer of results to different health systems. A recent international group recommends measuring scarring, pain, quality of life, resource utilization, and adverse events, considering the patient as the main reporting unit. [9]

RENMUV responds to these limitations through a prospective cohort with uniform definitions, index ulcer, serial measurement, confirmation of healing, follow-up of recurrence and capture of CEAP, VCSS, hemodynamics, treatment, adherence, and patient-reported results. Its design will allow estimating clinical trajectories, identifying prognostic factors, and quantifying variation between institutions. The multilevel structure will distinguish patient, limb, ulcer, and center, while temporal follow-up will allow for the analysis of closure, recurrence, and clinical changes using methods that consider censorship, competitive risks, missing data, and institutional clustering. Therapeutic comparisons will be interpreted as adjusted associations, recognizing confusion by indication and avoiding automatic causal attribution. Thus, the registry will produce contextualized evidence for Mexico and a methodological platform for pragmatic studies, quality assessment, and national health planning.

Length: 350 words

Problem statement

Venous ulcers generate a considerable burden; however, Mexico does not have prospective, standardized information to determine their magnitude, distribution, etiologic characteristics, and outcomes. Available data on chronic venous disease demonstrate high prevalence and deterioration in quality of life, but insufficiently describe patients with active ulcers and document limited reference to the specialist. [1] International estimates show extreme heterogeneity and cannot be extrapolated to the Mexican population. [4]

The fragmentation of the health system can lead to differences in access to arterial evaluation, duplex ultrasound, adequate compression, specialized care, and venous intervention. In addition, the absence of shared definitions of healing, recurrence, infection, adherence, and resource utilization makes it difficult to compare centers, assess quality, and recognize inequalities. It is unknown what proportion heals at 12, 24, or 52 weeks, how long closure takes, how often the ulcer recurs, and what clinical, hemodynamic, therapeutic, or social factors are associated with unfavorable outcomes.

The central problem is the lack of a national system that transforms daily care into reliable longitudinal evidence. Without this infrastructure, resource planning, intervention evaluation, indicator development, and policy formulation remain based on incomplete information or information from other contexts.

Justification

The creation of the Mexican National Registry of Venous Ulcers is justified by the need to produce its own, comparable, and longitudinal evidence on an advanced complication that causes pain, disability, recurrence, and sustained consumption of resources. Chronic venous disease is common in Mexico and its impact on quality of life increases with clinical severity; however, there is still low specialized reference and scarcity of specific information on active ulcers. [1] International prevalence and incidence figures are heterogeneous and do not necessarily represent the demographic, epidemiological, and institutional diversity of the country. [4]

RENMUV will make it possible to describe patients seen in public and private institutions, identify regional variations, and uniformly document etiology, area, duration, hemodynamics, comorbidities, compression, local care, interventions, adherence, and patient-centered outcomes. The 52-week follow-up will make it possible to estimate healing, time to closure, recurrence, clinical events, quality of life, and resource utilization with contemporary definitions. [9] This information will allow recognizing risk groups and potentially modifiable factors, without confusing observational association with causality.

The registry will also provide indicators to assess essential processes, such as arterial assessment, duplex ultrasound, CEAP/VCSS classification, compression reception, and post-closure follow-up. Accurate and confidential comparison between centers can guide quality improvement, training, and referral pathways. The inclusion of social determinants, rurality, insurance, and care sector will allow for the examination of inequalities and support equity strategies.

From a scientific perspective, a REDCap platform with a standardized dictionary, auditing, adjudication, and statistical plan will facilitate multicenter studies, prognostic analysis, economic evaluation, and future pragmatic research. Standardization will also reduce methodological heterogeneity, allow for the validation of instruments, favor national and international publications, and facilitate the participation of centers with different capacities, without imposing treatments outside of routine practice. From a health perspective, the results will support personnel planning, materials, vascular services, and recurrence prevention programs. Together, RENMUV will turn dispersed clinical data into actionable national knowledge, strengthen collaboration between centers, and provide an objective basis for recommendations, policies, and resource allocation tailored to Mexico. In addition, it will strengthen the culture of measurement, transparency, collaborative learning, and accountability of clinical results.

2.3 Risk-benefit assessment

Expected risk: minimal. Additional risks are mainly limited to loss of confidentiality, discomfort with questionnaires and photographing of the wound. No testing outside of clinical practice is required, except for non-invasive measurements authorized by the local committee. Photography will exclude face, tattoos or other identifiers where possible.

Direct benefit: not guaranteed. The use of a structured assessment may facilitate continuity of care, but participation does not ensure improvement. Social benefits include national information for research, quality of care, health planning, and design of future studies.

3. OBJECTIVES AND OUTCOMES

Type	Objective	Outcome/estimating
Primary	Estimate the complete healing of the index ulcer at 24 weeks and the time to healing.	Confirmed healing; date of first closure; time from baseline; death as a competitive risk in sensitivity analysis.
Secondary	Describe early response.	Absolute and percentage area change at 4 and 12 weeks; reduction ≥40% at 4 weeks as an exploratory indicator.
Secondary	Determine long-term scarring and recurrence.	Closure at 12 and 52 weeks; ulcer-free days; recurrence at the same site or limb up to week 52.
Secondary	Characterize patient-centered outcomes.	NRS pain; quality of life; mobility; return to activities; satisfaction and burden of treatment.
Secondary	Describe safety and use.	Infection, antibiotics, dermatitis/compression injury, bleeding, hospitalization, amputation, mortality, consultations, healings, and disability.
Exploratory	Identify factors associated with scarring, recurrence, and resources.	Patient variables, wound, hemodynamics, compression, adhesion, center, and procedures; adjusted associations, without automatic causal interpretation.
Health system	Quantify regional and institutional variation.	Process and outcome indicators, adjusted for case mix where appropriate.

4. STUDY DESIGN

4.1 Overall Design

Prospective observational, open-label, multicenter, nationwide cohort. The primary unit will be the participant and an index ulcer will be designated for longitudinal analysis. Additional ulcers will be documented in a repeatable module. There will be no randomization, blinding, or protocol-mandated treatment.

4.2 Index ulcer selection

If there is only one eligible ulcer, it will be the index. If there are several, the one with the largest area that can be measured reproducibly will be chosen. If the areas are similar, the one with the longest duration will be selected. The choice will be frozen after the baseline visit. Healing of other lesions will not replace the outcome of the index ulcer.

4.3 Key operational definitions

Term	Definition
Active venous ulcer	Loss of skin continuity in the leg or malleolar region, clinically compatible with venous hypertension, with clinical evidence and, preferably, reflux duplex or obstruction.

Term	Definition
Predominantly venous etiology	Venous component considered main by the investigator; concomitant arterial disease is recorded and stratified.
Area	Preferential calibrated digital planimetry; alternative: maximum length × maximum width × 0.785, leaving the method recorded.
Complete healing	100% epithelialization, without drainage and without the need for dressing; clinical or photographic confirmation and, if feasible, persistence ≥14 days.
Recurrence	New skin loss at the previously healed site or on the limb itself after closure has been confirmed.
Clinical infection	Diagnosis of the treating person based on local or systemic signs that motivates systemic antibiotic, culture or intervention; isolated colonization does not equate to infection.
Compression adhesion	Days per week and hours per day reported; Predefined high adherence: use ≥5 days/week for most of the day, with continuous alternative analyses.
Loss of Tracking	No assessment of ulcer status within the 52-week window following documented contact attempts.

4.4 Completion of the study

The study will end when the last participant completes the 52-week visit, withdraws their clearance or is declared lost, and the cleanup and closure of the base is complete. The Steering Committee may suspend registration due to operational impossibility, unforeseen risk, persistent low quality, or regulatory mandate.

5. STUDY POPULATION

5.1 Inclusion criteria

- Age ≥18 years.
- Residence or habitual care in Mexico.
- At least one active ulcer below the knee, present ≥2 weeks, considered venous or predominantly venous by the investigator.
- Evidence of chronic venous disease by clinical findings and, preferably, duplex ultrasound performed within 90 days prior to or scheduled as part of care.
- Ability to give informed consent, or legal representative when the local committee allows it.
- Reasonable possibility of completing at least one in-person or remote follow-up assessment.

5.2 Exclusion Criteria

- Ulcer whose main etiology is arterial, neuropathic/diabetic, vasculitic, neoplastic, pressure, traumatic, or pyoderma gangrenosum.
- Severe ischemia that requires urgent revascularization or that, in the opinion of the investigator, prevents classification of the lesion as predominantly venous.

- Simultaneous participation in a trial that prevents the sharing of minimum data or determines the primary outcome by protocol, unless approved by the Steering Committee.
- Failure to obtain consent or applicable authorization.
- Security risk or circumstance that makes monitoring unfeasible, according to the researcher's documented judgment.

Diabetes, treated infection, mild or moderate peripheral artery disease, kidney failure, obesity, immobility, previous thrombosis, and recurrent ulcer are not automatic exclusions; they must be recorded to represent actual practice.

5.3 Recruitment strategy and representativeness

The centers will carry out consecutive screening and will maintain a minimum selection record with the number of evaluated, eligible, included and reason for non-inclusion, without national identifiers. Participation will be sought from the Northwest, Northeast, Central-West, Central, South and Southeast regions, as well as from public, private and academic institutions. Competitive recruitment will be accompanied by limits per center to avoid excessive concentration.

5.4 Retention

- Confirm at least two means of contact and one authorized alternate person.
- Schedule the next visit before concluding the current one.
- Allow remote assessment with calibrated photography and interview when face-to-face visits are not possible.
- Make at least three attempts on different days/times before classifying a visit as lost.
- Record reasons for withdrawal or loss without affecting usual care.

6. EXPOSURES, DIAGNOSIS AND TREATMENT

6.1 Observational principle

The protocol does not prescribe compression, dressings, drugs, antibiotics, debridement, or venous intervention. The exposure actually received will be recorded, with onset date, intensity, changes, interruptions, adherence, and clinical reason.

6.2 Treatment variables

Domain	Minimum data
Compression	Type (bandage, stocking, adjustable device, pneumatic), components/layers, target pressure if known, supplier, frequency, tolerance and adhesion.
Local Care	Cleaning, debridement, primary/secondary dressing, exudate control, skin barrier, frequency of change and responsible professional.
Drugs	Venoactives, analgesics, antibiotics, antiplatelet agents, anticoagulants and other relevant factors; dose, dates and reason.

Domain	Minimum data
Superficial venous intervention	Thermal/non-thermal ablation, sclerotherapy, phlebectomy; segment, date and technical result.
Deep intervention/perforators	Stent, reconstruction, perforator treatment; indication, date and result.
Co-interventions	Exercise, elevation, nutrition, metabolic control, physical therapy, grafting, or skin substitutes.

6.3 Minimum Recommended Vascular Evaluation

- Pulses, temperature, capillary filling and signs of ischemia.
- Ankle-brachial index; if diabetes, calcification or non-compressible result is present, digital pressure or finger-brachial index when available.
- Venous duplex with documented position, maneuvers, and evaluated segments; reflux and superficial, deep, and perforating obstruction.
- Clinical and etiological/anatomical/pathophysiological CEAP classification when possible; VCSS by limb.
- Do not delay necessary care due to the absence of proof of the record.

7. DISCONTINUATION, WITHDRAWAL AND DEVIATIONS

The participant may withdraw his/her consent at any time without affecting his/her care. The participant will be asked, without pressure, if he/she authorises the storage of data already obtained and/or to receive a final confirmation of the vital state and the ulcer. Where permitted by law and consent, data previously anonymised or incorporated into analyses may be retained.

Change of facility, treatment, or insurer does not imply withdrawal. Deviations will be classified as minor or major. Major include: inclusion without valid consent, non-compliance with eligibility that compromises security or interpretability, exposure of identifiers in the national database, and deliberate fabrication or alteration of data.

8. EVALUATIONS AND PROCEDURES

8.1 Baseline Assessment

- Identifier of the centre and participant; date of consent and inclusion.
- Age, sex registered at birth, gender where applicable, state, partial zip code, urban/rural area, schooling, occupation, insurance, and barriers to access.
- Smoking, BMI, mobility, diabetes, arterial, heart, or kidney disease, venous thrombosis, surgery/trauma, previous pregnancy, arthritis, neuropathy, and medications.
- History of ulcer: date of onset, first episode/recurrence, number of episodes, previous treatments, hospitalizations, and absenteeism.
- Limb, site, area, depth, tissue, edge, exudate, odor, perilesional skin, edema, lipodermatosclerosis, atrophie blanche, and clinical infection.
- Photograph with ruler/caliper, participant code and date, without identifiable data.

- CEAP, VCSS, pain and quality of life questionnaire.
- Vascular studies available and current therapeutic plan.

8.2 Standardized wound measurement

7. Clean the wound and remove non-adhered material before measuring, according to safe practice.
8. Always use the same method when possible; record any method changes.
9. For photography, maintain consistent distance and angle, include metric scale and color card if available.
10. Digital planimetry will be the preferred method. Do not estimate depth if it cannot be measured reliably.
11. In circumferential lesions, use planimetry or tracing; avoid length × width if it distorts the area.

8.3 Confirmation of Healing

Closure should be documented by face-to-face examination or interpretable photograph. A second evaluation is recommended ≥14 days later. A central committee may review a random sample and all doubtful cases. If there is no confirmation, the case may be classified as "reported unconfirmed closure" and analyzed separately.

8.4 Safety and Clinical Events

Although there is no study intervention, relevant clinical events will be captured: infection requiring systemic antibiotic, cellulitis, sepsis, bleeding requiring attention, skin injury due to compression, allergy/dermatitis, venous thrombosis, hospitalization, amputation, and death. Institutional care and reporting will follow local practice; registration is not a substitute for pharmacovigilance or technovigilance systems.

8.5 Recommended Instruments

Instrument	Application
CEAP 2020	Clinical and etiological/anatomical/pathophysiological classification.
VCSS	Venous severity per extremity; training and uniform rules.
NRS 0–10	Average ulcer-related pain in the past 7 days.
CCVUQ o VEINES-QOL/Sym	Quality of life; use validated version in Spanish and document instrument/license.
Digital planimetry	Area in cm^2; locally validated software or central method.
Operational adherence scale	Days/week and hours/day of compression; interruptions and reasons.

9. DATA MANAGEMENT AND QUALITY CONTROL

9.1 Platform and structure

The capture will be carried out in REDCap or equivalent system hosted in approved infrastructure. The model will include screening instruments, basal, index wound, additional wounds, vascular studies, treatment, visits,

events, healing and recurrence. Each modification will be in an audit log with user, date and previous/new value.

9.2 Identification and confidentiality

The national identifier will have a CENTRE-PARTICIPANT structure. Name, CURP, RFC, file number, telephone number, full address or photographs with visible identifiers will not be transferred. Each centre will locally keep the correspondence table in a separate encrypted file. The analytical sets will use encoded or anonymised data depending on the purpose.

9.3 Quality rules

Dimension	Indicator/Action
Completeness	Critical fields ≥95% per center; monthly review.
Opportunity	Ideal capture ≤7 days and close of queries ≤14 days.
Validity	Automated ranges, logic, dates, and dependencies.
Concordance	eCRF–source comparison in risk-based sample.
Images	Random audit of quality and healing concordance.
Training	Initial and annual certification of measurement, CEAP/VCSS, consent and data.
Performance	Quarterly dashboard with feedback and corrective plan.

9.4 Monitoring and auditing

Risk-based central monitoring will be applied: missing data, extreme values, duplicates, impossible time sequences, atypical inclusion or scarring rates, and retrospective changes. Remote or face-to-face monitoring of a sample of records, consents, and photographs may be performed, subject to agreements and confidentiality. Critical findings will be escalated to the Steering Committee and the local committee.

9.5 Retention and Access

The retention period will be defined in accordance with applicable regulations, institutional requirements and consent; it will not be less than that necessary to verify publications and audits. Access will follow the principle of least privilege, individual authentication and periodic review. Backups and recovery will be tested in accordance with the data management plan.

10. STATISTICAL CONSIDERATIONS

10.1 General principles

The detailed statistical plan will be approved before the base is frozen. Estimates will be presented with 95% confidence intervals. The distribution, gaps, and number of participants at risk will be described. Primary analyses will follow the participant and the index ulcer; secondary analyses may use all ulcers with models that consider intrapatient and center-based correlation.

10.2 Sample Size

It is proposed to include 2,000 participants. In a conservative 50% scarring ratio scenario, this size offers an approximate accuracy of ±2.2 percentage points for a bilateral confidence interval of 95% before considering losses and pooling. With 15% incomplete follow-up, about 1,700 evaluable participants would retain an approximate accuracy of ±2.4 points. The goal is pragmatic and also seeks to allow multivariate models and regional analyses; it does not constitute a guarantee of potency for specific therapeutic comparisons.

10.3 Analysis of the primary outcome

- Cumulative proportion healed at 24 weeks with 95% CI.
- Kaplan-Meier for time until healing; those who do not heal will be censured in the last interpretable evaluation.
- A model of competitive risks or sensitivity that considers death before healing.
- Cox models with shared effects or robust errors per center for prognostic factors; verification of proportionality.
- Cumulative recurrence incidence curves since the date of confirmed closure.

10.4 Observational Adjustment and Comparisons

Treatment comparisons will be prespecified exploratory or analytical. It will be adjusted for clinical and center confounders using multivariate regression, propensity score, weighting, or matching as appropriate. Balance, positivity, extreme values, and unmeasured confounding sensitivity will be evaluated. Results will be expressed as associations and not as causal effects unless explicitly supported by the design and assumptions.

10.5 Missing Data

The number and pattern of shortages will be reported. The primary analysis will not impute unobserved scarring as an event. For covariates, multiple imputation will be considered if the assumption of random shortages is reasonable. Best/worst-case scenario sensitivity analyses, follow-up probability weighting, and alternative definitions of confirmed closure will be performed.

10.6 Prespecified subgroups

- First episode vs. recurrence.
- C6 vs. C6r and duration <6 vs. ≥6 months.
- Basal area <10, 10–<20 and ≥20 cm^2.

- Superficial, deep, perforating, or combined venous disease.
- Concomitant arterial component by ABI/digital pressure categories.
- Diabetes, obesity, immobility and post-thrombotic history.
- Public vs. private sector; region; level of care.
- Documented compression and adhesion; early vs. non-early venous intervention, with adjustment for confusion.

10.7 Interim Analysis and Reporting

Descriptive quality and recruitment reports will be issued on a semi-annual basis, without repeated evidence of efficacy. An annual national analysis may describe aggregate indicators. Centres will not be publicly classified without adjustment methodology, sufficient size, centre review and governance authorisation.

11. ETHICS, REGULATION AND GOVERNANCE

11.1 Risk classification

It is envisaged as a no-risk or minimal-risk investigation, depending on the authorised activities and the determination of the competent committee. Photography and questionnaires add a risk of confidentiality and a limited burden. The final classification is for each local committee and may vary if a centre incorporates additional procedures.

11.2 Informed consent

Written consent will be obtained prior to procedures exclusive to registration. The document will explain purpose, voluntariness, risks, handling of photographs, transfer of encrypted data, possible secondary uses, publications, conservation, removal and contacts. When a committee authorizes dispensation or alternative consent for routine data, it must be documented by center and will not be assumed applicable to photographs or future contact.

11.3 Governance Committees

Organ	Liability
National Steering Committee	Strategy, approval of centers, policies, budget, conflicts and final decisions.
Scientific Committee	Questions about research, analysis, publications, and data access.
Data and Quality Committee	Dictionary, rules, queries, auditing, freezing, and security.
Adjudication Committee	Blind review when possible of scarring, recurrence, and selected events.
National Coordination	Daily operation, training, contracts, reports and communication.
Local Researcher	Approvals, consent, quality, source, tracking, and local security.

11.4 Ownership, Access and Publications

The governance policy will define institutional custody, use licenses, access, secondary requests, acknowledgment, and authorship. Each analytical proposal will require question, variables, plan, responsible parties, timeline, and approval. Publications will follow STROBE and international authorship criteria; the inclusion of centers and collaborators will be based on verifiable contribution, quality, and compliance, not just recruitment volume.

11.5 Conflicts of Interest and Financing

All members shall declare financial and non-financial relationships. Any industrial support shall be formalized without control over data ownership, analysis, interpretation, or publication. The sources of funding and their function shall be disclosed in reports and manuscripts.

12. MULTI-CENTER OPERATION

12.1 Requirements for activating a centre

- Letter of participation and institutional responsible.
- Research and ethics approval; contract or data agreement where applicable.
- Trained staff and individual accounts on the platform.
- Ability to consent, measure, and follow-up; access to vascular evaluation or referral.
- Simulated case capture test and quality approval.
- Local file, privacy, photography, and incident response plan.

12.2 Training

The initial package will include protocol, Operations Manual, data dictionary, eCRF, photography guide, measurement rules, CEAP/VCSS, consent, privacy, and certification exercises. Refresher sessions will be conducted when the protocol changes or relevant variability is detected.

12.3 Closure of the centre

A center may be closed due to termination, institutional withdrawal, prolonged absence of recruitment, regulatory non-compliance or unacceptable quality. Prior to closure, inquiries will be resolved, possible follow-up will be completed, essential files will be verified, access will be revoked and the availability of data and materials will be documented.

13. MINIMUM DATA DICTIONARY

Domain	Variable	Type	Definition/rule
Identification	record_id	Text	CENTRE-PARTICIPANT code; without direct identifiers.
Center	center_id	List	National code of the centre.
Consent	consent_date	Date	Date of signature; not later than exclusive capture.

Domain	Variable	Type	Definition/rule
Demographics	age_years	Whole	Age at consent, 18–110.
Demographics	sex_birth	Category	Sex registered at birth.
Access	insurance_type	Category	IMSS, ISSSTE, SSA/IMSS-Welfare, private, other.
Clinic	BMI	Decimal	kg/m²; range and alertness.
Clinic	diabetes	Yes/No	Previous diagnosis.
Venous	prior_dvt	Yes/No/Unknown	Prior DVT objectively confirmed if known.
Venous	ceap_c	Category	C6 or C6r for index limb.
Venous	vcss_total	Whole	0–30; register components preferably.
Arterial	abi_index	Decimal	ABI of extremity index and date.
Ulcer	ulcer_onset	Date/partial	Date or month/year; estimate flag.
Ulcer	ulcer_location	Category	Medial/lateral malleolar, gaiter, anterior, posterior, other.
Ulcer	area_cm2	Decimal	Area in cm² and method.
Ulcer	depth_cm	Decimal/NA	Maximum safe depth.
Ulcer	Get out of it	Ordinal	Null, low, moderate, high.
Ulcer	infection_clinical	Yes/No	Clinical diagnosis; associated criteria.
Symptom	pain_nrs	0–10	Average last 7 days.
Treatment	compression_type	Multiple Category	Main type received.
Treatment	compression_days	0–7	Days of use in the last week.
Intervention	venous_procedure	Repeatable	Type, segment, date, indication.
Result	healed_status	Category	Open, unconfirmed close, confirmed close.
Result	healed_date	Date	First complete closure.
Result	recurrence	Yes/No	New ulcer after closure.
Security	hospitalization	Repeatable	Date, cause, clinical relationship.
Follow-up	visit_date	Date	Actual date and type of visit.
Quality	photo_usable	Yes/No/NA	Interpretable calibrated image.

The full dictionary must specify label, field name, type, encoded options, units, range, jump logic, obligation, source, time, identifiable data, derivation rules, and version control.

14. REGISTRY INDICATORS

Type	Indicators
Structure	Active centres by region and sector; certified staff.
Process	ITB/documented digital pressure; duplex available; complete CEAP and VCSS; compression prescribed and received; adhesion evaluation; etiological assessment.
Result	Healing at 12/24/52 weeks; median time; area reduction; recurrence; pain and quality of life.
Security	Infection, hospitalization, compression injury, amputation, and death.
Equity	Results and access by region, rurality, insurance, sex, age and social vulnerability.
Data	Completiency, timeliness, consultations, loss of follow-up and photographic concordance.

15. ABBREVIATIONS

Abbreviation	Meaning
CCVUQ	Charing Cross Venous Ulcer Questionnaire
CEAP	Clinical–Etiologic–Anatomic–Pathophysiologic classification
eCRF	Electronic Case Report Form
95% CI	95% confidence interval
ITB	Ankle-brachial index
NRS	Numerical pain scale
RENMUV	Mexican National Registry of Venous Ulcers
REDCap	Research Electronic Data Capture
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
VCSS	Venous Clinical Severity Score
DVT	Deep vein thrombosis

16. REFERENCES

1. Chamber of Deputies of the Congress of the Union. General Health Law. Text in force accessed on July 20, 2026.

2. Chamber of Deputies of the Honorable Congress of the Union. Regulations of the General Health Law on Health Research. Last amendment published in the Official Gazette on April 2, 2014.

3. Ministry of Health. Official Mexican Standard NOM-012-SSA3-2012, which establishes the criteria for the execution of research projects for health in human beings. Official Gazette of the Federation. January 4, 2013.

4. World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants. Versión vigente aplicable al momento de aprobación.

5. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453-1457.

6. Lurie F, Passman M, Meisner M, et al. The 2020 update of the CEAP classification system and reporting standards. J Vasc Surg Venous Lymphat Disord. 2020; 8(3):342-352.

7. Vasquez MA, Rabe E, McLafferty RB, et al. Revision of the Venous Clinical Severity Score: venous outcomes consensus statement. J Vasc Surg. 2010; 52(5):1387-1396.

8. Hallas K, et al. Development of a core outcome set for research evaluating interventions for venous leg ulcer treatment. J Tissue Viability. 2024.

9. O'Donnell TF Jr, Passman MA, Marston WA, et al. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg. 2014; 60(2 Suppl):3S-59S.

10. EQUATOR Network. STROBE Statement—checklist for cohort studies. Consultado el 20 de julio de 2026.

Before regulatory submission and publication, the bibliography must undergo documentary verification and updating of regulatory versions.

ATTACHMENT A. ELIGIBILITY CHECKLIST

☐ Age ≥18 years

☐ Active leg ulcer ≥2 weeks

☐ Venous or predominantly venous etiology

☐ Compatible vascular evaluation without critical ischemia that invalidates inclusion

☐ Valid consent

☐ Selected and frozen index ulcer

☐ Assigned code; separate local key

☐ Photograph/baseline measurement performed or documented reason

ANNEX B. SET OF ESSENTIAL DOCUMENTS

- Protocol and amendments approved.

- Research and ethics opinions; institutional authorizations.
- Consent and Participant Materials.
- Delegation of functions, training and curricula.
- Confidentiality, data and financing agreements.
- Operations Manual, dictionary, eCRF and statistical plan.
- Screening, inclusion, consultation, monitoring, incident, and closure records.

ANNEX C. PENDING DECISIONS BEFORE ACTIVATION

Theme	Decision required
Legal Sponsor/Custodian	Define responsible institution and contracts.
Platform	Confirm server, location, backup, and administrator.
Quality of life	Choose validated instrument, language and licenses.
Biobanco	Not included; it would require specific amendment, consent, and governance.
Photographs	Define application, encrypted transfer, retention, and allocation.
Sample by center/region	Approve recruitment goals and limits.
Financing	Approve platform budget, coordination, monitoring and support.
Committees	Appoint members, quorum, recusal and terms of reference.

STATISTICAL ANALYSIS PLAN

National Prospective Multicenter Registry of Venous Leg Ulcers in Mexico (RENUVI-Mexico)

Document field	Details
Protocol identifier	RENUVI-001-CMN
SAP version	1.0 — Draft for review and approval
Underlying protocol	Version 1.0; July 20, 2026
Study design	Prospective, multicenter, observational longitudinal cohort registry
Target sample	2,000 adult participants
Follow-up	Baseline; weeks 4, 12, 24, and 52
Intended use	Supporting document for ClinicalTrials.gov registration and prospective statistical specification

Status: This SAP operationalizes the statistical principles in the source protocol. Choices not explicitly fixed by that protocol are identified as proposed specifications requiring approval before database lock. No investigator names are included.

1. Purpose, scope, and governing principles

This Statistical Analysis Plan (SAP) specifies the principal estimands, analysis populations, statistical methods, handling of incomplete observations, and reporting conventions for RENUVI-Mexico. The registry observes routine care and does not randomize participants or mandate treatment. Analyses will prioritize descriptive epidemiology, longitudinal outcomes, and prognostic associations. Any comparison between treatments will be interpreted cautiously because confounding by indication and time-dependent treatment selection may remain.

The protocol and approved amendments take precedence over this SAP in case of conflict. The final SAP should be dated and approved before database lock and before investigators inspect definitive outcome comparisons. Any departures from prespecified analyses will be documented and identified in reporting.

2. Study design, units, and analysis populations

Eligible adults with at least one active below-knee ulcer of confirmed or predominantly venous etiology will be consecutively screened and enrolled at public, private, and academic centers across Mexico. A single index ulcer is selected at baseline: the largest reproducibly measurable eligible ulcer, with longest duration as a tie-breaker. Its identity remains fixed throughout follow-up. Additional ulcers are captured separately. The primary reporting unit is the participant/index ulcer; secondary analyses may account for clustering of ulcers within participants and participants within centers.

Population	Operational definition
Enrolled cohort	All consented participants assigned a valid registry code.

Population	Operational definition
Primary analysis cohort	Enrolled eligible participants with a defined index ulcer and baseline date, irrespective of subsequent treatment or visit attendance.
Evaluable endpoint subset	Participants with sufficient documented healing status and follow-up for a specified visit/window; denominators and reasons for non-evaluability reported.
Recurrence cohort	Participants whose index ulcer has confirmed complete healing, followed from first documented closure to week 52.
Safety/utilization cohort	Enrolled participants with available post-baseline clinical event or resource-use information.

These population labels are proposed implementation definitions; the protocol establishes the participant/index-ulcer unit and recurrence cohort but does not name formal analysis sets. Eligibility violations and withdrawals will be tabulated. A sensitivity analysis may exclude major eligibility violations without replacing the primary analysis.

3. Endpoints and estimands

3.1 Primary endpoint

Complete index-ulcer healing by 24 weeks. Healing requires 100% epithelialization, no drainage, and no further need for a dressing, documented clinically or through an interpretable photograph; confirmation at least 14 days later is preferred when feasible. Record first complete-closure date, verification method, and confirmation status. Report the cumulative proportion healed by 24 weeks and time from baseline to first complete closure. A reported but unconfirmed closure will not be counted as confirmed healing in the strict endpoint definition.

Primary estimand: the probability of confirmed complete healing of the prespecified index ulcer by day 168 after baseline in the enrolled eligible registry population under routine-care management, with death before healing treated as a competing event in a prespecified complementary analysis. The source protocol calls for a cumulative proportion and Kaplan–Meier time-to-healing analysis; a competing-risk analysis is also specified. The exact primary estimator and treatment of unconfirmed closure require final sign-off before database lock.

3.2 Secondary and exploratory endpoints

Domain	Outcome and assessment
Early response	Absolute and percentage change in index-ulcer area at weeks 4 and 12; at least 40% reduction by week 4 as an exploratory response threshold.
Healing	Confirmed healing at weeks 12 and 52; time to healing; ulcer-free days.
Recurrence	New skin breakdown at the previously healed site or in the same limb following confirmed closure, through week 52.
Patient-reported	Ulcer-related pain (0–10 numerical rating scale), quality of life using selected validated instrument, mobility, activities, satisfaction, and treatment burden.
Safety	Clinical infection, antibiotic use, dermatitis/compression injury, bleeding, venous thrombosis, hospitalization, amputation, and death.
Care and utilization	Compression receipt and adherence, venous procedures, wound-care visits, consultations, hospitalization, direct resources/costs and disability.
Health-system	Regional/institutional variation in assessment, treatment processes and outcomes, with case-mix adjustment where appropriate.

4. Analysis conventions and descriptive statistics

All statistical tests will be two-sided. Estimates will be accompanied by 95% confidence intervals (CIs), with nominal p-values reported for exploratory inferential analyses where relevant. No formal multiplicity adjustment is planned for exploratory secondary or subgroup analyses; findings will be labeled hypothesis-generating. Continuous variables will be summarized using mean and standard deviation or median and interquartile range, as appropriate; categorical variables using counts and percentages. Report denominator for each variable, missingness, and the number of participants/centers contributing data.

Time origin is the baseline enrollment assessment. Follow-up visit windows are week 4 ±7 days, week 12 ±14 days, week 24 ±21 days, and week 52 ±30 days. Event dates take precedence over visit labels. Calendar time will be expressed in days from baseline; 24 weeks corresponds to 168 days and 52 weeks to 364 days. Participants enrolled at different times will contribute observed follow-up only.

5. Sample size and precision

The target sample is 2,000 participants. Assuming 50% healing, the protocol estimates approximately ±2.2 percentage points precision for a two-sided 95% CI before accounting for attrition and clustering. With 15% incomplete follow-up, about 1,700 evaluable participants would retain approximate precision of ±2.4 percentage points under simple binomial assumptions. The sample is pragmatic and is not powered for any particular nonrandomized treatment contrast. Precision estimates will be revisited using actual center clustering, event frequency, and missingness.

6. Primary analysis

6.1 Healing proportion and time to event

Provide the number and percentage with confirmed index-ulcer healing by week 24, together with a 95% CI and a participant flow diagram. Display cumulative healing over time and estimate time to healing using Kaplan–Meier methods, censoring participants without documented healing at their last interpretable ulcer-status assessment. Report median time to healing if estimable, survival/healing curves, numbers at risk, and event counts. Because conventional Kaplan–Meier censoring of deaths may overestimate the real-world probability of healing, report cumulative incidence of healing with death before healing as a competing event; include its 24-week estimate and 95% CI.

Proposed clarification for final approval: designate the competing-risk cumulative incidence estimate as the preferred population-level 24-week probability and present the protocol-specified Kaplan–Meier estimate as a complementary time-to-event summary. If governance instead designates Kaplan–Meier as primary, this must be recorded prospectively and the competing-risk estimate retained as sensitivity analysis.

6.2 Event adjudication and censoring

The first documented date of full closure is the event date if subsequently confirmed when feasible. A case lacking confirmation is labeled “reported, unconfirmed closure” and examined in sensitivity analyses. Participants who withdraw or are lost to follow-up are censored at the last interpretable assessment; they are not assumed healed. Death before healing is a competing event. Other post-baseline treatments, transfer between centers, and insurance changes do not censor participants if outcomes remain observable. Report how event dates are handled when closure is only known to occur between assessments; interval-censoring sensitivity methods may be considered if frequent.

7. Secondary analyses

7.1 Change in wound area

Calculate absolute area change as follow-up area minus baseline area (cm^2) and percentage reduction as 100 × (baseline area − follow-up area)/baseline area for positive baseline area. Report distributions at weeks 4 and 12, including the proportion achieving at least 40% reduction at week 4. Use paired descriptive summaries and 95% CIs; exploratory longitudinal mixed-effects models may include time, baseline ulcer area, and center-level effects. Specify handling of healed ulcers as area zero and distinguish unmeasured from healed wounds.

7.2 Healing at weeks 12 and 52, ulcer-free days

Estimate healing at weeks 12 and 52 using the same endpoint definitions and event-time conventions as the primary outcome. Ulcer-free days will be calculated from documented confirmed healing until recurrence, death, loss of observation, or week 52, with the observation period and censoring clearly reported. Alternative calculations treating recurrent wounds and subsequent rehealing as episodes will be exploratory.

7.3 Recurrence

Among participants entering the recurrence cohort, measure time from confirmed closure to first new ulceration at the same site or in the same limb. Estimate recurrence cumulative incidence by week 52, treating death before recurrence as a competing event. Report recurrence rates with observed follow-up and distinguish the recurrence cohort from the full enrollment cohort. Participants without recurrence are censored at last interpretable assessment or administrative end of follow-up.

7.4 Pain, quality of life, safety, and resource use

Summarize pain scores at each visit and within-participant change from baseline. For quality of life, follow the scoring manual of the selected validated Spanish-language instrument (CCVUQ or VEINES-QOL/Sym), reporting instrument and direction of scoring; the source protocol does not select one final instrument. Describe complications using participant-level incidence and event counts, with exposure time where useful. Summarize visits, hospitalizations, procedures, and costs using suitable skew-resistant descriptive methods; report the cost perspective, currency, price year, and unit-cost sources when a formal economic analysis is undertaken.

8. Prognostic models and center effects

Use Cox proportional hazards models to investigate associations with time to healing, accounting for clustering by center through shared frailty or center-robust standard errors. Candidate covariates include baseline ulcer area, ulcer duration, recurrent versus first episode, CEAP C6/C6r, VCSS, venous reflux/obstruction pattern, arterial perfusion, diabetes, obesity, mobility, post-thrombotic history, compression adherence, and treatment exposure. Select a parsimonious set based on clinical relevance, availability, and event counts; avoid indiscriminate data-driven selection. Report adjusted hazard ratios, 95% CIs, number of events, and diagnostics for proportional hazards and influential observations.

Where treatment is initiated after enrollment, account for timing explicitly (for example, time-varying covariates or an appropriately defined landmark) to avoid immortal-time bias. Model center heterogeneity and, where appropriate, participant-level clustering for analyses involving multiple ulcers. Results are associations and must not be described as causal effects without additional justified assumptions.

9. Observational treatment comparisons

Comparisons of compression modalities, adherence categories, early versus later venous intervention, and other treatments are exploratory unless a separate prespecified analysis protocol is approved. Confounding by indication, baseline severity, access to care, and time-dependent treatment decisions will be considered. Depending on the comparison, methods may include covariate adjustment, propensity-score matching or weighting, and time-dependent exposure models. Assess propensity-score overlap, covariate balance, extreme weights, positivity, and sensitivity to unmeasured confounding. No protocol-assigned treatment groups or randomized efficacy hypotheses are defined.

10. Missing data, deviations, and sensitivity analyses

Describe missingness by variable, visit, center, and reason, including withdrawals, deaths, and losses to follow-up. Never impute an unobserved healing event as confirmed closure in the primary analysis. Multiple imputation may be used for missing covariates when missing-at-random assumptions are plausible; specify variables in the imputation model and combine estimates using standard rules. Use inverse probability-of-follow-up weighting where appropriate, with diagnostics and sensitivity analyses for informative loss to follow-up.

Sensitivity analyses will include: (a) strict confirmed healing versus inclusion of reported but unconfirmed closure; (b) competing-risk versus Kaplan–Meier estimates; (c) best-case/worst-case assumptions for unknown healing status; (d) exclusion of major eligibility violations; (e) alternative modeling of missing covariates and follow-up; and (f) center-level heterogeneity. All deviations from the protocol or SAP, including major data-quality exclusions, will be documented before final analysis.

11. Prespecified subgroups

Descriptive and exploratory analyses will examine first versus recurrent ulcers; CEAP C6 versus C6r; duration under 6 versus at least 6 months; baseline area under 10, 10 to under 20, and at least 20 cm^2; superficial, deep, perforator, or combined venous disease; concomitant arterial disease by ankle-brachial index or toe-pressure categories; diabetes, obesity, immobility, and post-thrombotic history; public versus private sector; geographical region; level of care; compression receipt/adherence; and early versus non-early venous intervention. Avoid strong inference from small subgroups or multiple comparisons. Interaction testing, if performed, will be exploratory.

12. Interim reporting, quality controls, and reproducibility

Semiannual reports will summarize recruitment and data quality without repeated formal efficacy testing. Annual national reports may present aggregated indicators. Quality metrics include at least 95% completeness for critical fields per center, preferred data entry within 7 days, and query closure within 14 days. Monitoring will flag duplicates, implausible values, impossible date sequences, atypical recruitment/healing patterns, and discrepancies between wound photographs and recorded closure. Public center rankings are not planned without sufficient case-mix adjustment, sample size, review, and governance approval.

Analyses will be conducted in validated statistical software (software and version recorded in the final report). Programming code, derivation rules, data dictionaries, and output logs will be version-controlled. The final analysis dataset will be locked following query resolution and documented adjudication. Tables, figures, and listings will be generated reproducibly from coded data. Any data sharing will follow consent, local law, institutional approvals, and registry governance.

13. Planned tables and figures

Planned outputs: participant screening and follow-up flowchart; baseline demographic/clinical characteristics; index-ulcer and vascular characteristics; compression and intervention exposure; healing at 12/24/52 weeks; Kaplan–Meier time-to-healing curve with risk table; cumulative incidence curves for healing and recurrence; early wound-area change; pain and quality-of-life trajectories; adverse events and resource use; multivariable prognostic models; missingness and center-quality summaries; and prespecified subgroup estimates with confidence intervals.

14. Open specifications requiring prospective approval

Before database lock, the governing scientific/statistical committee should confirm: (1) primary 24-week estimator and death handling; (2) operational hierarchy for clinical versus photographic healing confirmation; (3) treatment of interval-known healing dates; (4) final quality-of-life instrument and scoring; (5) covariate selection and model complexity; (6) operational definitions of “early” intervention and cost variables; (7) missing-data sensitivity thresholds; and (8) software/version and final table shells. These are implementation decisions not fully determined in protocol version 1.0.

15. Source document and reporting framework

Source: National Prospective Multicenter Registry of Venous Leg Ulcers in Mexico (RENUVI-Mexico), research protocol RENUVI-001-CMN, Version 1.0, July 20, 2026, especially sections 1, 3–6, 8–10, 13, and 14. Observational study reporting should follow STROBE as specified in the protocol. This SAP is a proposed companion document, not evidence of committee approval or study results.

INFORMED CONSENT

National Multicenter Prospective Registry of Venous Ulcer of the Lower Limbs (RENUVI-Mexico)

Invitation

You are invited to voluntarily participate in a national registry whose objective is to know the characteristics, treatment and evolution of venous ulcers of the lower limbs to improve medical care in Mexico.

Purpose

To collect clinical, ultrasound, photographic and follow-up information on patients with venous ulcers to generate scientific evidence and improve the quality of care.

Procedures

If you agree to participate, your medical history, physical examination, duplex ultrasound studies, clinical photographs of the ulcer, treatments received, and follow-up visits will be recorded. Your treating physician's treatment decisions will not be changed by participating in the registry.

Risks

The risks are minimal and relate mainly to the possible loss of confidentiality, which will be minimized by security measures. Photographs and studies are part of routine care or will be obtained without additional invasive procedures.

Benefits

It may not have a direct benefit; however, the information obtained will contribute to improving the knowledge and care of future venous ulcer patients.

Confidentiality

Your information will be identified by a unique code. Your name or other personal identifiers will not be used in databases for analysis or publication. Only authorized personnel will have access to identifiable information when necessary.

Using Photographs

Authorizes the collection of clinical photographs of the ulcer for documentation purposes, evaluation of evolution and scientific analysis. The images will be de-identified and will not be used for purposes other than those described without additional authorization.

Future Use of Data

The data may be used in future projects related to venous disease, subject to approval by the corresponding committees and maintaining their confidentiality.

Voluntary participation

Your participation is completely voluntary. You can withdraw at any time without affecting the medical care you receive.

Costs and compensation

There is no additional cost to you to participate. No financial compensation is offered for participating, unless otherwise established by the participating center in accordance with its regulations.

Contact

If you have questions about the study or your rights as a participant, you may contact the Principal Investigator of the participating center, Dr. Alejandro José Gonzalez Ochoa, at (653) 849 7372 or by email: dralejandro@glezochoavascular.com, or with the Research Ethics Committee of CHSISI SALUD S.A.P.I. de C.V. (Hospital H+) / Centro de Estudios Clínico de Querétaro. Privada Ignacio Zaragoza Poniente 16-B, Colonia Centro, C.P. 76000, Querétaro, Querétaro, Mexico. Phone: +52 442 215 3067. Name of the President: Carlos Garcini Pablos Vélez

Participant's Statement

I declare that I have read (or have been read to) this document, that I had the opportunity to ask questions, and that all of them were satisfactorily answered. I understand that my participation is voluntary and I agree to participate in the National Multicenter Prospective Registry of Venous Ulcer of the Lower Limbs (RENUVI-Mexico).

Participant's Name	
Signature	
Date	
Name of the researcher obtaining consent	
Signature of the researcher	
Witness (if applicable)	

Specific consents

□ I accept the registration of my clinical data.

□ I agree to the collection and storage of clinical photographs.

□ I agree to the storage of data for future research related to venous disease.

□ I agree to be contacted for follow-up registration visits.