Study Protocol

FREEZing-of-Gait Etiology–Phenotype–Outcome Pathway Cohort (FREEZE-Path Cohort)

NCT number：Not yet assigned

Protocol Version: V1.0

Date: October 20, 2025

1. Study Title

FREEZing-of-Gait Etiology–Phenotype–Outcome Pathway Cohort (FREEZE-Path Cohort)

2. Study Design

This study is a prospective, observational, multicenter cohort study designed to investigate the etiology, phenotypic heterogeneity, and longitudinal outcomes of freezing of gait (FOG) across different neurological conditions.

Participants will be followed for 36 months with repeated standardized clinical, gait, and functional assessments. The study does not assign any intervention and does not influence routine clinical management.

3. Study Objectives

3.1 Primary Objective

To establish a multicenter, cross-etiology FOG cohort and to characterize longitudinal changes in FOG burden across different underlying diseases.

3.2 Secondary Objectives

To identify etiological and phenotypic differences in FOG progression and outcomes.

To determine risk factors and predictors for incident FOG in patients at high risk.

To describe associations between real-world treatment exposures (pharmacological, neuromodulation, rehabilitation) and changes in FOG burden.

To develop and validate multimodal prediction and risk-stratification models based on clinical, gait, video, neuroimaging, electrophysiological, and speech features.

4. Study Population

4.1 Study Groups

FOG Group (n ≈ 500):

Patients with established freezing of gait.

High-Risk Group (n ≈ 200):

Patients with Parkinson's disease (PD) presenting gait or balance impairment but without FOG at baseline.

Total planned enrollment: 700 participants

Study centers: 1 coordinating center and 4 participating centers

4.2 Inclusion Criteria

1) Age 30–85 years
2) Presence of freezing of gait or non-freezing gait or balance impairment
3) Diagnosis of Parkinson's disease or related parkinsonian disorders according to established international criteria (including PD, PSP, MSA, DLB, CBD, vascular parkinsonism, or idiopathic normal pressure hydrocephalus)
4) Ability to complete gait and balance assessment tasks independently or with assistance
5) Ability and willingness to provide written informed consent

4.3 Exclusion Criteria

1) Severe dementia (Mini-Mental State Examination score < 10)
2) Severe psychiatric disorders interfering with study participation
3) Severe cardiopulmonary, musculoskeletal, or other medical conditions significantly affecting gait safety
4) Stroke, fracture, or other major medical events within the past 3 months
5) Inability to comply with follow-up procedures
6) Refusal of video or speech data collection

5. Recruitment and Sampling

Participants will be recruited consecutively from neurology, neurosurgery, and rehabilitation clinics at participating centers. A consecutive sampling strategy will be used to minimize selection bias.

6. Study Procedures and Data Collection

6.1 Follow-Up Schedule

Participants will be assessed at:

Baseline

3, 6, 12, 18, 24, 30, and 36 months

Triggered visits will occur within one week after major events (e.g., first FOG episode, fall, surgery).

6.2 Core Data Collection (All Centers)

Demographics and disease history

Motor and non-motor symptoms

Medication and treatment exposure

Standardized clinical scales:

New Freezing of Gait Questionnaire (NFOG-Q)

MDS-UPDRS II & III

MMSE, MoCA

PDQ-39

Berg Balance Scale, Mini-BESTest

Standardized gait-provoking tasks with synchronized video recording

Speech tasks using a fixed protocol

6.3 Extended Data Collection (Optional Centers)

Instrumented gait analysis parameters

Quantitative balance measurements

Structural MRI (3.0T)

Functional MRI

EEG or fNIRS

PET imaging (if clinically available)

6.4 Biospecimens

No biospecimens will be collected, stored, or retained for this study. Only results from routine clinical laboratory tests, if already available, may be extracted from medical records.

7. Outcome Measures

7.1 Primary Outcome

Longitudinal change in FOG burden, measured by annualized change in NFOG-Q

total score over 36 months.

7.2 Secondary Outcomes

Time to first FOG occurrence (high-risk group).

Frequency of falls and fall-related injuries.

Changes in quality of life (PDQ-39).

Changes in gait parameters.

Changes in balance parameters.

Changes in functional brain network connectivity, assessed by resting-state functional MRI (fMRI)

8. Statistical Analysis

8.1 General Principles

All analyses will be conducted using two-sided tests with a significance level of 0.05.

Statistical analyses will be performed using R or SPSS.

8.2 Primary Analysis

Linear mixed-effects models will be used to evaluate longitudinal changes in FOG burden and to compare trajectories across etiological subgroups.

8.3 Secondary Analyses

Cox proportional hazards models will be used to analyze time-to-event outcomes (e.g., incident FOG, first fall).

9. Ethics and Regulatory Considerations

This study will be conducted in accordance with the Declaration of Helsinki and relevant national regulations. Approval will be obtained from the institutional ethics committee at each participating center prior to initiation.

All participants will provide written informed consent prior to enrollment.

10. Privacy and Data Protection

All data will be de-identified using coded participant IDs.

Data will be stored in encrypted systems with role-based access control.

Results will be reported only in aggregate form, without any personally identifiable information.

11. Data Retention

Study data will be retained for a minimum of 5 years after study completion, in accordance with institutional and regulatory requirements.