

Evaluation of the Diagnostic Efficacy of the Electronic Psychometric Hepatic Encephalopathy Score (PHES) Based on a Randomized Crossover Design

Date: 30th September, 2026

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Clinical Study Protocol

Funding: Self- funded
Study ID: Not applicable
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Version: 1.0
Version Date: 30th September 2026

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Protocol Summary

Item	Content
Study Title	Evaluation of the Diagnostic Efficacy of the Electronic Psychometric Hepatic Encephalopathy Score (PHES) Based on a Randomized Crossover Design
Study Objectives	Primary Objective: To determine whether total scores obtained from the electronic- version PHES are equivalent to total scores from the paper- version PHES among cirrhotic patients who complete both assessments. Secondary Objectives: 1. To compare the agreement between electronic- version and paper- version PHES for classification of minimal hepatic encephalopathy (MHE). 2. To compare the agreement of individual sub- test results between electronic- version and paper- version PHES. 3. To analyze the effects of testing time window and test- administration sequence on PHES results.

Study Design	Prospective, multicenter, randomized crossover trial
Target Sample Size	A total of 80 participants are planned for enrollment.
Inclusion Criteria	1. Aged 18- 70 years old. 2. Confirmed liver cirrhosis (established by clinical manifestations, laboratory tests, imaging, or liver biopsy). 3. Preserved cognitive function without overt hepatic encephalopathy (OHE, West- Haven grade $\geq$ II); capable of completing neuropsychological tests. 4. Voluntarily provides written informed consent with adequate study compliance and full understanding of the research.
Exclusion Criteria	1. Coexisting uncontrolled neuropsychiatric disorders that may impair cognitive function (e.g., Alzheimer's disease, Parkinson's disease, sequelae of stroke, severe depression/anxiety disorder, schizophrenia, etc.). 2. Use of hypnotics, sedatives, or psychotropic medications within the preceding one month. 3. Severe alcohol dependence or substance abuse; inability to maintain alcohol or drug abstinence. 4. Lactulose use at screening.
Observation Schedule	Cirrhotic patients will be recruited across participating centers between April 15, 2026 and June 15, 2026. Demographic characteristics, educational background, current therapeutic regimens, liver disease severity scores (Child- Pugh and MELD), and prior experience using smartphones/tablets/computers will be collected. Using a random- number table, participants will be allocated in a 1:1 ratio to Sequence A (paper- version PHES on Day 1, electronic- version PHES on Day 2) or Sequence B (electronic- version PHES on Day 1, paper- version PHES on Day 2). Both tests will be performed at identical time- of- day with a 1- day washout interval. Test duration and error rates will be recorded, and final PHES scores will be calculated.
Outcome Measures	Efficacy Outcomes

	Primary Outcome: Within- patient difference in total PHES score (electronic- version score minus paper- version score). Secondary Outcomes: MHE classification results; individual sub- test scores. Safety Outcomes: Adverse events occurring during testing (e.g., dizziness, nausea, emotional lability).
Statistical Methods	SPSS 26.0 or higher will be used for statistical analyses. Normally- distributed continuous variables will be expressed as mean $\pm$ standard deviation; non- normally- distributed data will be presented as median (interquartile range). Categorical variables will be summarized as frequency (percentage). The two- one- sided t- test (TOST) will be applied to assess equivalence; equivalence will be claimed if the 90 % confidence interval of the mean paired difference falls within -1 to $+1$ points. Kappa statistics will evaluate categorical agreement for MHE classification. Intraclass correlation coefficients (ICC) will assess consistency of sub- test results. Linear mixed- effects models will examine effects of testing time and test sequence. A two- sided P- value < 0.05 will be considered statistically significant.
Study Period	15 April 2026 – 15 June 2026

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List of Abbreviations

Abbreviation	Full English Term	Chinese Term
HE	Hepatic encephalopathy	肝性脑病
OHE	Overt hepatic encephalopathy	显性肝性脑病
CHE	Covert hepatic encephalopathy	隐匿性肝性脑病
MHE	Minimal hepatic encephalopathy	轻微肝性脑病
PHES	Psychometric Hepatic Encephalopathy Score	肝性脑病心理测试评分

1. Background

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome caused by severe acute or chronic liver dysfunction or portosystemic shunting, representing one of the most frequent complications of end-stage liver disease. According to the West-Haven classification, HE ranges from grade 0 to grade 4. Overt hepatic encephalopathy (OHE, West-Haven grade ≥ 2) manifests as somnolence, disorientation, asterixis, severe neuropsychiatric disturbance, or coma. Covert hepatic encephalopathy (CHE) encompasses minimal hepatic encephalopathy (MHE) and West-Haven grade 1 HE. Patients with CHE lack overt disorientation but exhibit neuropsychological or neurophysiological abnormalities including subtle cognitive impairment, inattention, euphoria or anxiety.

Reported prevalence of MHE among cirrhotic patients ranges from 30 % to 84 %, with rates as high as 56.1 % in Child-Pugh C patients. Surveys show that only 6.3 % of physicians screen all at-risk patients for MHE; among North American

hepatologists, 38 % never perform MHE screening due to time burden, costs, and requirements for specialized personnel and equipment. Large retrospective studies have identified MHE as an independent predictor of subsequent OHE occurrence and transplant-free survival in cirrhosis. Current Chinese clinical guidelines recommend universal MHE screening for patients with liver cirrhosis.

The Psychometric Hepatic Encephalopathy Score (PHES) is a widely- validated diagnostic tool for CHE, consisting of five sub- tests: Number Connection Test A (NCT- A), Number Connection Test B (NCT- B), Digit Symbol Test (DST), Line- Tracing Test (LTT), and Serial Dotting Test (SDT). Chinese diagnostic cut- off values have been established for local cirrhotic populations. Nevertheless, conventional paper- based PHES requires trained personnel, consumes substantial time, suffers limited portability, and results are susceptible to age and educational background. Cumbersome workflows, manual data- entry errors, and low analytical efficiency restrict its wider adoption in primary- care settings and large- scale clinical studies.

Mobile- health applications provide new opportunities for chronic- disease management. Smartphone- based tools offer high accessibility, convenient operation, and support repeated testing, making them suitable for home- based cognitive monitoring in patients at risk for HE. Digital neuropsychological assessments and patient- reported symptom scales may enable a closed- loop care pathway: home self- screening → automated risk alert → clinical intervention. For instance, EncephalApp (Stroop- test based) has demonstrated satisfactory sensitivity and specificity for CHE screening.

Our research team has developed an electronic PHES mini- program / application. Test content and scoring algorithms are identical to the paper- version PHES; only the mode of operation is digitized to streamline workflows and improve data- management efficiency. No published studies have compared diagnostic agreement between electronic- version and paper- version PHES. This prospective randomized crossover equivalence study aims to compare test performance in cirrhotic subjects, generate evidence supporting clinical implementation of electronic PHES, and facilitate improved accessibility of CHE screening.

2. Study Objectives

1. **Primary Objective:** To determine whether total scores obtained from the electronic- version PHES are equivalent to total scores from the paper- version PHES among cirrhotic patients completing both assessments.
2. **Secondary Objectives**
 - a. Compare agreement between electronic- version and paper- version PHES for classification of minimal hepatic encephalopathy (MHE).
 - b. Compare agreement of individual sub- test results between electronic- version and paper- version PHES.
 - c. Analyze the influences of testing time window and test- administration

sequence on PHES results.

3. **Study Hypothesis:** Equivalence will be established if the 90 % confidence interval for the mean paired difference (electronic- version PHES score minus paper- version PHES score) lies entirely within the equivalence margin of -1 to $+1$ points.

3. Study Design, Principles and Study Procedures

3.1 Study Design

This is a prospective, multicenter, randomized crossover analytical study. Core principles include randomization, controlled comparison, crossover administration, and outcome- assessor blinding to minimize confounding and ensure data validity.

3.1.1 Study Population

Participants are cirrhotic patients recruited from participating centers between April 2026 and June 2026. Enrolled subjects must be capable of completing two consecutive days of PHES assessments under conditions free of major interference.

3.1.2 Outcome Variables

- **Primary outcome:** Within- subject difference in total PHES score: electronic- version PHES total score minus paper- version PHES total score (continuous variable).
- **Secondary outcomes:** MHE classification (binary: yes / no); individual sub- test scores (continuous); PHES total scores stratified by test sequence (A/B) and testing day (Day 1 / Day 2) (continuous).

3.1.3 Independent Variables

The mode of PHES administration (electronic- version versus paper- version). Test sequence and testing time window are additional independent variables for effect- size estimation.

3.1.4 Confounding Variables

Potential confounders include:

1. Demographics: age, sex, educational attainment.
2. Baseline clinical features: etiology of liver disease, Child- Pugh class, prior history of hepatic encephalopathy.
3. Treatment- related factors: recent exposure to HE- directed therapies (lactulose, rifaximin), sedative or antidepressant agents affecting cognition.
4. Situational factors: mental status, sleep quality, and dietary status at the time of testing.

Confounders will be adjusted for in statistical analyses.

3.1.5 Study- type Rationale

Randomized crossover equivalence design eliminates inter- individual variability by having each participant receive both test modalities, thus improving statistical power. Equivalence testing addresses the research question of whether electronic- PHES yields results comparable to the established paper- based standard.

3.2 Study Procedures

After enrollment, baseline demographic and laboratory data are collected. Eligible participants are randomly assigned (1:1) to Sequence A or Sequence B using a random- number table.

- Sequence A: paper- version PHES on Day 1; electronic- version PHES on Day 2 at matched time- of- day.
- Sequence B: electronic- version PHES on Day 1; paper- version PHES on Day 2 at matched time- of- day.

All assessments are performed under supervision by trained study personnel. Investigators correct participant errors during the Number Connection Test, record sub- test completion time, document adverse events, and compute final PHES scores according to predefined algorithms. Statistical analyses are performed to test equivalence and secondary endpoints.

4. Participant Selection

Planned sample size: 80 participants (40 per sequence).

Inclusion Criteria

1. Age between 18 and 70 years.
2. Diagnosis of liver cirrhosis confirmed by clinical, laboratory, imaging findings or liver biopsy.
3. Intact cognitive status; no overt hepatic encephalopathy (West- Haven grade $\geq$ II); ability to cooperate with neuropsychological testing.
4. Voluntary signed informed consent; adequate comprehension and adherence to study requirements.

Exclusion Criteria

1. Uncontrolled co- morbid neuropsychiatric disorders impairing cognition (Alzheimer's disease, Parkinson's disease, stroke sequelae, severe depression/anxiety, schizophrenia, etc.).
2. Use of hypnotic, sedative, or psychotropic drugs within one month prior to

screening.

3. Severe alcohol dependence or substance abuse with inability to maintain abstinence.
4. Lactulose use at screening.

Discontinuation- from- analysis Criteria

1. Ineligibility discovered after enrollment.
2. Failure to complete tests per protocol (missing sub- tests, non- compliant timing).
3. Severe incomplete or corrupted test data precluding statistical analysis.
4. Voluntary participant withdrawal.
5. Serious adverse event prompting investigator- determined early termination.

Study- wide Stopping Criteria

The whole study may be stopped prematurely if any of the following occurs:

1. Serious adverse events during testing (syncope, severe dizziness, manic agitation) endangering participant safety.
2. Acute clinical deterioration (HE episode, gastrointestinal hemorrhage, liver failure) rendering further testing impossible.
3. Persistent participant non- cooperation preventing data collection.

5. Study Methods and Technical Flowchart

5.1 Study Instruments

- **Paper- version PHES:** Standard validated paper- and- pencil Psychometric Hepatic Encephalopathy Score battery containing all five canonical sub- tests; scoring follows established clinical standards.
- **Electronic- version PHES:** In- house- developed mini- program application. Test content, sub- test composition and scoring rules are identical to the paper- version PHES. The application automates score computation and data recording. System debugging is completed before study initiation to guarantee stable performance and accurate scoring.

5.2 Study Flowchart

Screen cirrhotic patients against inclusion / exclusion criteria

→ Inclusion: age 18- 70 y; liver cirrhosis; no overt HE; capable of neuropsychological testing

→ Exclusion: co- morbid neuropsychiatric disease; recent psychotropic medication;

alcohol/substance abuse; lactulose at screening

→ Enroll 80 eligible participants, randomize 1:1

→ Sequence A (n = 40): Day 1 paper- PHEs; Day 2 electronic- PHEs

→ Sequence B (n = 40): Day 1 electronic- PHEs; Day 2 paper- PHEs

→ Primary endpoint: within- subject difference in total PHEs score

→ Secondary endpoints: MHE classification; individual sub- test scores

5.3 Laboratory and Clinical Assessments

1. Baseline laboratory panel: liver function tests (ALT, AST, total bilirubin, albumin, prothrombin time), complete blood count, electrolytes, serum ammonia for evaluation of hepatic disease severity.

2. Liver function stratification: Child- Pugh scoring.

3. Neuro- mental observation: Consciousness and mental status are documented to exclude gross cognitive impairment.

5.4 Standard Operating Procedures

1. All testers receive unified training on administration and scoring for both PHEs modalities.

2. Tests on Day 1 and Day 2 are scheduled at identical time- of- day to minimize circadian influences on cognition.

3. Testing environments are quiet and free of external distractions.

4. Outcome assessors remain blinded to participant randomization sequence to reduce measurement bias.

5. Brief operational orientation is provided for participants before electronic- PHEs administration.

6. Observation Items and Assessment Time- points

6.1 Efficacy Assessments

6.1.1 Primary Efficacy Outcome

Within- subject total- score difference of PHEs

Definition: Electronic- version PHEs total score minus paper- version PHEs total score. Raw total scores for both modalities are separately recorded.

Time- point: Immediately upon completion of testing on Day 1 and Day 2.

6.1.2 Secondary Efficacy Outcomes

1. **MHE classification result:** Each PHEs modality yields a binary MHE diagnosis according to predefined cut- offs. Recorded immediately post- test on Day 1 and Day 2.

2. **Individual sub- test scores:** Raw scores from each of the five PHES sub- tests for both versions, captured at the time of each test session.

6.2 Safety Assessments

Adverse event incidence

Definition: Any untoward symptom temporally associated with test completion including dizziness, nausea, mood disturbance, or eye strain and vertigo from prolonged screen exposure.

Time- window: Throughout testing and for 72 hours after each test session.

7. Adverse Event Monitoring

Adverse events will be closely monitored from informed- consent signature until study completion or early withdrawal. Vital signs, physical findings, and laboratory changes are evaluated.

Both paper- based and electronic PHES are non- invasive assessments without pharmaceutical or procedural interventions performed on participants. Tests are conducted under investigator supervision; therefore direct physiological harm or alteration of underlying disease course is not anticipated. Potential minor complaints may include visual fatigue or dizziness from prolonged reading or screen viewing. Rare theoretical risk of seizure may exist in photosensitive individuals; the application interface avoids high- frequency flashing visual elements to mitigate this risk.

All adverse events observed or reported must be documented in medical records and case- report forms. Documentation includes event description, onset date, resolution date, severity, corrective measures taken, clinical outcome, and causality assessment.

8. Quality Control and Quality Assurance

Potential sources of bias:

1. Selection bias: inadequate adherence to eligibility criteria.
2. Measurement bias: inter- rater variability among study staff.
3. Confounding bias: age, gender, educational level and other participant characteristics.

Quality- assurance measures:

1. All research personnel follow standardized operating procedures.
2. Uniform training for study staff.
3. Rigorous application of inclusion and exclusion criteria.
4. Known confounders (etiology of liver disease, sex, education) will be incorporated into multivariable analytical models.
5. Minimize missing data; outcome data will be collected even for participants who

withdraw prematurely.

9. Data Safety Monitoring

Adverse events are documented, managed, and followed until resolution or clinical stability. Serious adverse events and unexpected events are promptly reported to the Institutional Review Board and relevant regulatory authorities per local requirements. The principal investigator performs periodic cumulative review of adverse- event profiles to evaluate benefit- risk balance and determine whether study continuation is appropriate.

10. Statistical Considerations

10.1 Sample- size Justification

For this randomized crossover equivalence trial, assuming within- subject standard deviation of PHES total scores of 2.0- 2.5 points, equivalence margin ± 1.0 points, power = 80 %, $\alpha = 0.05$, approximately 25- 39 evaluable subjects are required. To accommodate variance uncertainty and permit evaluation of sequence effects in a two- sequence crossover design, 70 evaluable participants are targeted. Accounting for anticipated drop- out, 80 participants (40 per sequence) will be enrolled.

10.2 Statistical Analyses

Analyses will be performed using SPSS 26.0 and GraphPad Prism 9. Normality is assessed via the Kolmogorov- Smirnov test. Normally- distributed continuous variables are reported as mean $\pm$ standard deviation; non- normal variables as median (interquartile range). Categorical variables are summarized as frequency (percentage). Between- group comparisons employ independent- samples t- test or Mann- Whitney U test; categorical comparisons use χ^2 or Fisher's exact test as appropriate.

Primary- endpoint analysis: Two- one- sided t- test (TOST) for equivalence. Equivalence is concluded if the 90 % confidence interval for the mean paired difference (electronic- PHES minus paper- PHES) falls fully within -1 to $+1$ points.

Secondary- endpoint analyses:

1. MHE categorical agreement: Kappa statistic. $\text{Kappa} \geq 0.75$: good agreement; $0.4 \leq \text{Kappa} < 0.75$: moderate agreement; $\text{Kappa} < 0.4$: poor agreement.
2. Sub- test consistency: Intraclass correlation coefficient (ICC). $\text{ICC} \geq 0.75$ represents good consistency.
3. Sequence and time- window effects: Linear mixed- effects model with PHES total score as dependent variable; test modality and test sequence as fixed effects; participant ID as random effect.
4. Within- participant comparison of test modalities: paired t- test (normal

distribution) or Wilcoxon signed- rank test (non- normal distribution).

Confounder adjustment: Analysis of covariance (ANCOVA) or multivariable linear regression incorporating age, educational level, and Child- Pugh class as covariates to verify equivalence after adjusting for baseline factors.

10.3 Safety Analysis

Descriptive summaries of adverse- event frequency, severity, type, outcome, and causality assessment. Fisher's exact test compares adverse- event rates between the two randomization sequences.

10.4 Missing Data

The per- protocol (PP) set serves as the primary analysis population: PP includes participants satisfying eligibility criteria, completing all required tests per protocol without major data loss. Variables with >20 % missing values will not be statistically analyzed and this limitation will be stated in study reports.

11. Data Collection and Management

Two distinct data streams are maintained: clinical source data and mini- program test data, with logical separation of storage and access to protect participant privacy.

Clinical data (demographics, laboratory values, imaging, endpoints) are manually entered into electronic case- report forms by study staff with double- data- entry and cross- verification. Paper- version PHES results are recorded immediately after testing and transcribed to structured electronic spreadsheets within 48 hours to guarantee traceability. Electronic- PHES raw outputs are exported from the application backend upon principal- investigator approval.

Data review is performed intermittently to verify accuracy and traceability. After validation and database lock, files are archived with redundant backup across multiple media. All records are retained for required regulatory periods. No study data will be transferred outside of China.

12. Ethical Principles

This study complies with the Declaration of Helsinki. Study initiation occurs only after formal Institutional Review Board approval. Prior to enrollment, investigators fully explain study purpose, procedures, foreseeable risks and participant rights including the right to withdraw at any time. Signed informed- consent documents are preserved. Participant confidentiality and data privacy are protected throughout the study.

13. Biospecimen Collection and Storage

No biological specimens are collected or stored for this research. Laboratory test

results used are derived from routine clinical workup; no additional sample acquisition is performed for study purposes.

14. Study Timeline

- April 2026 – May 2026: Finalize protocol, obtain ethical approval, complete debugging of electronic- PHES.
- May 2026 – July 2026: Participant enrollment and data collection.
- July 2026 – September 2026: Data cleaning, statistical analysis, manuscript drafting and submission.

15. References

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16. Investigator Statement and Protocol Signature Page

Investigator Statement

I agree to abide by decisions of the Institutional Review Board. I will obtain renewed ethical approval for any protocol amendments or unanticipated events that pose risks to subjects before implementation.

I will strictly follow this clinical- study protocol. I understand that I may suspend or terminate this research at any time to maximize participant safety.

I will personally supervise study conduct and ensure that all co- workers are aware of their study duties. All study activities will comply with current GCP principles and the Declaration of Helsinki, following ethical and scientific standards.

I will maintain complete and accurate source documentation available for regulatory inspection and audit.

\\ \\\ \\\

Name (printed)

Signature

Date
