STUDY PROTOCOL INCLUDING STATISTICAL ANALYSIS PLAN

Development of a Portable Autonomic Sensing System for Physiological-Psychological Health Risk Prediction

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Co-principal investigator: Chien-Tai Hong

English edition and registration specifications: 19 October 2026

Document Contents

Part I contains the English protocol text, corresponding to the 21-page Chinese protocol, with terminology and assessment details aligned to the IRB application.

Part II contains registration and analysis specifications dated 19 October 2026, including the participant-level comparisons, baseline normalization, statistical test, and actual study status.

The original protocol planned enrollment of 50 participants. Actual enrollment was 51, with 50 completing the study.

Study Title and Investigators

Development of a Portable Autonomic Sensing System for Physiological-Psychological Health Risk Prediction

Principal investigator: Lung Chan. Overall responsibility, study design, and participant recruitment.

Co-principal investigator: Chien-Tai Hong. Study design and participant recruitment.

Project Content: Background

Chronic stress, insufficient sleep, and emotional problems, including anxiety and depression, are increasingly common in modern society and substantially affect individual health and work performance. Through its sympathetic and parasympathetic branches, the autonomic nervous system regulates cardiovascular and physiological states and is significantly affected by psychological stress and emotional fluctuations (Bourdillon, Jeanneret et al. 2021; Krieger, Rhein et al. 2024). Healthcare professionals, such as physicians and nurses, work under sustained pressure and rotating shifts, often resulting in poor sleep, accumulated chronic stress, and impaired physical and mental health and work performance. High occupational stress can cause autonomic dysfunction and, over time, increase burnout and staff turnover. Real-time monitoring and management of healthcare workers' stress and sleep have therefore become important occupational-health issues.

Heart rate variability (HRV) is a physiological indicator of autonomic function. Variation in the intervals between heartbeats can be analyzed to assess sympathetic-parasympathetic balance. Studies associate reduced HRV with adverse health conditions, including increased cardiovascular risk and mental-health problems. People with anxiety or depression often have lower HRV, indicating impaired autonomic function; this is also associated with higher risks of cardiac disease and all-cause mortality (Gorman and Sloan 2000).

Research also indicates an inverse relationship between psychological stress and HRV: HRV measures decrease as stressors increase. Short-term mental stress or increased perceived stress can reduce HRV. Conversely, lower HRV is often accompanied by greater anxiety and cardiovascular risk (Thayer, Yamamoto et al. 2010; Kim, Cheon et al. 2018). Sleep quality is closely related to HRV. Poor sleepers have been found to have lower HRV and faster heart rates, suggesting that poor sleep adversely affects autonomic recovery (Sajjadieh, Shahsavari et al. 2020). HRV is therefore considered a useful physiological indicator of stress and fatigue and a potential warning biomarker for occupational burnout and health risks.

HRV can reflect current physiological stress load and has been shown to provide an objective measure of psychological stress responses (Peabody, Ryznar et al. 2023). Although HRV is clearly associated with stress under laboratory conditions, studies suggest that the relationship may be weaker when subjective stress in daily life is predicted solely from wearable HRV measurements (Martinez, Grover et al. 2022; Velmovitsky, Lotto et al. 2023).

Background (Continued)

Objective HRV data should therefore be combined with subjective questionnaires to improve the accuracy and interpretability of stress assessment. Traditional mental-health monitoring relies heavily on self-completed questionnaires or subjective scales. Although these quantify perceived experience, they lack real-time information and are susceptible to subjective bias.

Recent advances in wearable devices and the Internet of Things have made real-time HRV monitoring for stress and fatigue possible (Singh, Chung et al. 2023; Xian 2023). Wearable sensors are noninvasive and support continuous measurement. Compared with self-report or blood testing, they offer higher-frequency monitoring and greater temporal resolution. Leadtek's H2 Plus wearable ECG watch can measure heart rate and HRV and upload data to a cloud platform in real time. This makes continuous physiological-stress monitoring of healthcare workers in actual clinical settings feasible, beyond reliance on subjective questionnaires alone.

The Leadtek H2 Plus wearable ECG recorder used in this project offers medical-grade physiological-signal measurement and clinical application advantages, including more accurate HRV measurement than typical consumer products. Its ECG sensor measures R-R intervals directly, whereas most mainstream devices use optical photoplethysmography (PPG), which is vulnerable to movement and ambient-light interference. Missed or misidentified beats can impair HRV calculation. Research reports that smartwatch PPG HRV measurements, including Apple Watch measurements, slightly underestimate standard ECG measurements, with mean SDNN underestimated by approximately 8 milliseconds, or nearly 30% (O'Grady, Lambe et al. 2024). Direct ECG measurement may therefore provide more reliable autonomic data and identify clinically important irregular rhythms.

Using Bluetooth Low Energy, the Leadtek device can upload physiological data to the amor health-management platform for cloud storage and analysis and can be integrated with hospital smart-care systems. Consumer products commonly store information locally and synchronize periodically through mobile applications to proprietary cloud services, rather than supporting clinical real-time monitoring. Their cloud platforms are generally confined to vendor ecosystems and lack interfaces for integration with healthcare institutions. Leadtek's established business-to-business medical cloud platform supports real-time review and aggregation from multiple sites, helping clinical teams monitor patients.

The autonomic indices supplied by the Leadtek device, including the SDNN-based vitality index, fatigue index, and physical-stress index, have interpretable physiological meanings. Algorithms can be calibrated during research and raw HRV data can be analyzed for specific clinical needs. By contrast, consumer devices generally use closed proprietary algorithms. The weights and details behind stress or sleep scores are not disclosed, preventing adjustment for particular populations or situations. Such scores lack an academically accepted common standard, raising questions about comparisons between devices and use in clinical assessment.

The Leadtek HRV wearable also holds formal medical-device authorization.

Background and Rationale (Continued)

The device's Taiwan medical-device manufacturing license is No. 006790. It has undergone safety and effectiveness testing, can be used professionally, and has received a Taiwan Excellence Award. Apple Watch ECG software has received FDA and TFDA authorization for functions such as atrial-fibrillation detection, but most other health functions remain nonmedical. Garmin, Fitbit, Oura, and Whoop devices are general health or exercise products that have not undergone equivalent medical certification. Consumer monitoring data are informational and cannot directly support clinical diagnosis.

The Leadtek wearable has advantages in clinical research and smart-care applications. The collaborating clinical team has integrated it into a smart-care platform to collect HRV and other physiological data in real time for decision support. An earlier trial at a Taiwanese medical center used H2 Plus monitoring after discharge in cardiovascular patients, with data-informed medication adjustments, and reported a 75% reduction in rehospitalization, supporting the value of extended monitoring. Leadtek products can record ECG and HRV in real time, completing an autonomic measurement within 30 seconds to 3 minutes and providing measures such as SDNN. They also support prolonged monitoring for risk warnings in situations such as fatigued driving or night-shift care. Medical-grade measurements and cloud integration facilitate incorporation into hospital smart-care systems and complement field validation in this project.

Consumer wearables generally lack validation against standard psychological instruments such as the Perceived Stress Scale (PSS) or Pittsburgh Sleep Quality Index (PSQI). Their stress and sleep scores may consequently be difficult to interpret clinically. Their focus on general daily wellness also limits adaptation to extreme clinical situations. Reversed sleep-wake patterns in shift workers or HRV changes during prolonged high stress may fall outside the training conditions of built-in algorithms. The reliability of consumer stress and fatigue assessments in night work and fatigued driving is therefore limited, representing an implementation gap.

An intervention capable of modulating HRV may help healthcare workers reduce stress and improve sleep. With industry partner Leadtek, this project introduces the BtNPN botanical nano-curcumin patch as a potential HRV-modulating intervention. Curcumin, turmeric's principal component, has potential anti-inflammatory and physiological-stress-regulating properties (Tuong, Moniruzzaman et al. 2023). Preliminary Leadtek testing suggests possible improvements in autonomic indices and general health after use of the patch.

Objectives

The medical-center team and Leadtek will jointly evaluate the practical potential of the medical-grade amor H2 Plus wearable in high-pressure work environments and use clinical evidence to support product optimization and expansion of application modules.

Objectives (Continued)

The amor H2 Plus holds Taiwan medical-device manufacturing license No. 006790 and measures ECG and HRV in real time. It is one of Taiwan's autonomic-sensing devices with a clinical-grade validation foundation.

Wearable HRV monitoring and psychological assessments will be analyzed together to establish relationships between HRV and subjective stress, sleep, anxiety, and depression measured by PSS, PSQI, PHQ-9, and GAD-7. This will strengthen clinical interpretation of HRV and the basis for explanatory product modules. A nonpharmacological intervention, such as a curcumin patch, will be introduced in a randomized crossover trial to observe short-term HRV and psychological responses and assess the sensitivity of HRV for monitoring intervention effects.

Clinical healthcare and shift-working populations will wear H2 Plus for extended periods in real settings, enabling high-frequency noninvasive data collection. Data will support model development and provide feedback on application scenarios, parameter refinement, and cloud-service design for future smart-care platforms, employee-health systems, and B2B uses.

The specific objectives are:

- Validate the stability and user acceptance of the Leadtek H2 Plus HRV wearable in high-pressure clinical settings.

- Establish dynamic relationships between HRV and clinical mental-health scales and develop an integrated physiological-psychological sensing model.

- Evaluate modulation of HRV and subjective symptoms by a nonpharmacological intervention, such as the curcumin patch, and validate HRV tracking sensitivity.

- Provide clinical evidence and application data for product upgrades, modular development, and market expansion.

The project aligns with the National Science and Technology Council's engineering-sector strategy of industry-academia collaboration centered on clinical application settings and technical modules. It combines device validation, user feedback, and integrated data analysis to advance commercialization and clinical implementation together.

Significance: Addressing Gaps in Consumer Wearables

Most consumer wearables, such as Apple Watch, Garmin, and Oura Ring, focus on wellness and everyday tracking. Their HRV technologies commonly use optical PPG, closed algorithms, and no integration with standard psychological scales, with limited clinical validation and healthcare-system integration. Their accuracy and interpretability may be insufficient in high-risk populations experiencing shift work, night duty, and chronic stress. Using a medically certified Leadtek device, this project integrates real-time HRV monitoring with psychological scales to develop risk-warning technology for clinical and smart-care settings.

Significance (Continued)

Clinical field validation will strengthen the translational feasibility of HRV systems. The crossover trial in clinical and shift-working populations will collect HRV together with PSS, PHQ-9, PSQI, and GAD-7, establishing dynamic correspondence between objective and subjective information. This evaluates real-world usability and data stability and quantifies relationships with mental-health status. The aim is to move HRV from physiological monitoring alone toward practical decision support and health-risk warnings.

Combining a domestically developed, CE- and TFDA-certified wearable with a controllable nano-curcumin patch intervention may create industrial applications and international differentiation. Besides ensuring measurement accuracy and system stability, the study will evaluate the device's clinical value for tracking physiological changes and assessing health interventions. Integrated wearable sensing, psychological evaluation, and nonpharmacological intervention may support commercialization of smart-care modules for healthcare institutions, workplace health, and international remote-care markets.

Domestic and International Research

Most studies support an inverse association between HRV and psychological stress or impaired well-being: greater stress, anxiety, or depression is associated with lower indices such as SDNN and RMSSD (Jo, Lee et al. 2024). Reduced HRV has, for example, been associated with higher PSS scores and anxiety (Carnevali, Thayer et al. 2018). Findings vary by setting. Associations are clearer under controlled laboratory conditions and often weaker in everyday life (Martinez, Grover et al. 2022). Population differences also exist. A healthcare-worker study did not find significant associations of HRV with PHQ-9 or GAD-7, possibly because the entire highly stressed sample had low HRV, but did observe lower HRV with specific stressors such as fear of COVID-19 infection (Krieger, Rhein et al. 2024). Measurement setting and confounding factors must therefore be considered.

Relationships Between HRV and Psychological Scales

Carnevali et al. (2018) found longitudinally that people with lower HRV, especially RMSSD, were more prone to rumination and depressive symptoms, and that HRV changes could predict subsequent deterioration in mental health. Autonomic dysfunction may be an important mechanism connecting stress and emotional disorders. Jo et al. (2024), in a four-week longitudinal study, reported significant negative associations between HRV measures, including RMSSD, SDNN, and LF/HF, and PHQ-9 and GAD-7 scores, supporting possible use in mental-health risk detection.

Related Research and Practical Potential

Wearables have increased the feasibility of everyday real-time HRV measurement. However, a large field study found that HRV explained only approximately 1% of daily subjective-stress variation in natural environments, indicating susceptibility to interference and limited explanatory power outside controlled conditions (Martinez, Grover et al. 2022). Effective workplace use requires control of measurement timing, simultaneous psychological-scale assessment, and data-quality management.

In a cross-sectional study of medical students, Xiao et al. (2022) found no clear overall association between sleep quality and HRV, but the sleep-disturbance component was negatively associated with SDNN and LF, suggesting a physiological relationship between interrupted sleep and reduced parasympathetic activity. This supports analysis of sleep subcomponents alongside nighttime HRV to evaluate interactions between sleep and autonomic balance. Barckhan et al. (2024) found that long-term night workers did not have significantly lower HRV than controls, suggesting possible physiological adaptation in some high-pressure populations.

Evidence for clinical and high-stress applications is increasing. Li et al. (2022) found that nursing shifts and ward workload affected HRV and sympathetic-parasympathetic patterns, with high device acceptance and good data quality. Krieger et al. (2024) associated specific pandemic-related stressors, such as infection concerns and work-family conflict, with nurses' HRV, but found weak overall associations with PHQ-9. HRV and subjective experience are not always synchronous, requiring a carefully designed interpretive framework. These findings support field feasibility while emphasizing confounder management and integration of psychological reference measures.

Practical Applications and Potential

Clinical testing of the Leadtek HRV device, such as amor H2 Plus, will strengthen translational potential and product value. Its medical-grade heart-rate and HRV sensing and Taiwan authorization support healthcare use. Field validation in healthcare and high-stress shift-working populations will assess data stability, acceptance, and feasibility of prolonged use, providing evidence for integration into healthcare systems.

Practical Applications and Potential (Continued)

Simultaneous analysis of HRV with PSS, PHQ-9, PSQI, and GAD-7 will establish a quantitative model relating HRV to psychological status. The device could develop from a physiological measuring tool into an intelligent sensing system supporting mental-health evaluation and stress warnings. Future functions may include graded stress advice and sleep-quality risk distributions for personal health management, employee assistance programs (EAPs), and smart health-check centers.

Cloud data management and real-time risk analysis will form an architecture for immediate uploads, cloud processing, and automatic warning notifications. Industry partners could commercialize modules for employee health, remote care, or long-term-care warnings. Expansion from wearable hardware into software-as-a-service health modules may enable multiple business models.

Clinical validation reports and empirical data will provide medical evidence for participation in healthcare projects, procurement, government tenders, and international markets. The project is expected to accelerate development from medical-sensing hardware to integrated clinical and health-management solutions, strengthening competitiveness and long-term industrial growth.

Implementation Strengths

Leadtek and Taipei Medical University Shuang Ho Hospital offer complementary practical expertise. Shuang Ho is a medical-center-level hospital with comprehensive clinical capacity, experience in digital health, telecare, and smart medicine, and established ethics review, cross-specialty collaboration, and research involving shift-working healthcare personnel. Representative participants, such as residents and emergency nurses, will generate realistic and challenging data.

Leadtek has extensive experience with wearable ECG and HRV sensing. Its amor H2 Plus combines medical-grade precision, Taiwan medical-device certification, real-time uploads, cloud analytics, and hospital information-system integration. Combining this technology with Shuang Ho's clinical research will accelerate validation for stress detection, psychological-status estimation, and health warnings.

Shuang Ho's work integrating smart-care modules and clinical information platforms may facilitate incorporation of HRV alerts and mental-health risk flags into care workflows. Clinical evidence and publications can support product credibility and expansion. The collaboration therefore links technical development, clinical validation, commercialization, and deployment, providing a translational model for domestic smart healthcare.

Research Methods and Procedures

The following sections explain the methods selected and their rationale.

Core Methods and Rationale

The project will develop health-risk warning technology combining autonomic monitoring and psychological assessment. Core methods include wearable HRV sensing, concurrent psychological scales, randomized crossover intervention, clinical field validation, and data analysis with cloud integration.

1. Continuous wearable HRV measurement using PPG and ECG. Leadtek devices such as amor H2 Plus provide optical PPG and medical-grade single-lead ECG sensing for continuous real-time heart-rate and HRV monitoring. SDNN, RMSSD, LF, HF, and LF/HF are used to characterize autonomic activity and sympathetic-parasympathetic balance in relation to stress, sleep, and emotion. Wearables reduce the location and timing constraints of conventional instruments and provide continuous ecologically valid data in settings such as shift work. Accuracy, low invasiveness, and immediacy support an integrated physiological-psychological model.

2. Concurrent psychological assessment and HRV correlation analysis. To capture subjective states that physiological signals alone cannot describe, four commonly used scales will be collected: PSS for perceived stress, PHQ-9 for depression, GAD-7 for anxiety, and PSQI for sleep quality. Dynamic correspondence between HRV and psychological variables will support an integrated sensing model and evaluate HRV-based mental-health warnings. Concurrent assessments can improve clinical interpretation and decision support.

3. Randomized crossover intervention and HRV-change detection. Participants receive a nano-curcumin patch and a control patch in different periods with a washout interval. Each person serves as their own control, reducing interindividual interference, increasing statistical power, and reducing sample-size requirements. The patches are low-risk nonpharmacological interventions used to test HRV responsiveness. HRV and psychological changes before and after intervention will assess whether HRV reflects physiological and psychological effects promptly.

4. Field validation in shift-working and high-pressure populations. The target groups are clinical personnel, shift workers, and other high-pressure occupational populations. Continuous data will be obtained during actual work and sleep to assess stability, adherence, and prediction under stress. Collaboration with Shuang Ho will strengthen credibility for smart healthcare and workplace health applications and support translation and policy implementation.

5. HRV algorithms and cloud-data integration. A cloud analysis platform will connect wearable information, questionnaire returns, and warning algorithms.

Core Methods (Continued)

The cloud platform will create a closed loop from real-time sensing to health-risk reminders. It will support time-segment analysis, such as day/night HRV changes, individual baseline construction, visual feedback, and automatic abnormality detection. The architecture will allow comparison and follow-up across individuals and future commercialization, workplace deployment, and remote-care integration.

6. Statistical and model analysis. Linear mixed models (LMMs) and repeated-measures ANOVA will assess temporal HRV and psychological changes and intervention effects. Skewed HRV variables will be log-transformed when appropriate. Crossover data increase power, and random effects control individual differences. Cross-correlation functions (CCFs) or lagged regression will examine delayed associations between psychological variables and HRV to support warning logic. Sample size is based on power analysis for a moderate intervention effect.

Together, these methods integrate engineering sensors, physiological-signal analysis, psychological and behavioral evaluation, and clinical validation. They balance real-world clinical relevance, diverse data, and commercialization to translate wearable HRV systems into stress and health-risk warning applications.

Detailed Methods and Procedures: Data Collection

The engineering-oriented empirical workflow has three components: data collection and preprocessing, development of HRV features and recognition models, and validation of sensitivity and accuracy.

The study will collaborate with Shuang Ho emergency and critical-care units and use a crossover design to collect physiological and subjective information from healthcare workers. Approximately 50 currently employed shift-working clinical nurses or resident physicians will be recruited to provide statistical power. Each participant undergoes two patch periods: a cooling control patch and a nano-curcumin patch. Both are provided by Leadtek. The cooling patch offers cooling relief without active curcumin. The other contains a high concentration of nano-formulated curcumin, intended to reduce stress and improve sleep. One patch is applied to a designated location, such as the trunk, for 8 hours daily and replaced each day. Each period lasts at least 14 consecutive days to cover a complete two-week work cycle.

Participants are randomly assigned to cooling-first or curcumin-first order to reduce sequence bias, with a washout between periods to remove residual effects. Before participation, approximately 50 eligible hospital healthcare workers provide informed consent and complete baseline demographic and questionnaire assessments. Each then receives one two-week nano-curcumin period and one two-week cooling-control period in randomized order.

Data Collection (Continued)

The two intervention periods are separated by a washout of at least two weeks. No patches are used during washout, although participants may continue wearing the device to collect natural-state data. The overall study lasts approximately seven weeks. Before each period, the research team supplies the relevant patches and explains the application site, such as the trunk. Participants apply a fresh patch daily at a fixed time.

Participants wear the H2 Plus ECG device throughout the study, removing it only as necessary for charging or cleaning. It records cardiac signals periodically and uploads HRV data to a cloud database through a mobile application. Researchers check uploads regularly for completeness. HRV recording begins three days before patch intervention. During the approximately seven-week study, except during washout, participants initiate a daily HRV recording while resting quietly for 3 to 5 minutes.

Questionnaires are completed at the beginning and end of each period, giving four assessments of PSS, PSQI, GAD-7, and PHQ-9. Brief daily sleep diaries record sleep duration and subjective quality, while work diaries record shift type, subjective stress, and fatigue. Brief questions, such as a daily stress rating from 0 to 10, provide higher-resolution subjective time series. Information is collected through an application or paper forms.

Participants can notify the team at any time about discomfort, including patch-site skin irritation or device discomfort. Researchers contact participants at least weekly in person or remotely to monitor their status and remind them about assessments. After the second period, participants return the equipment and information and complete a final interview concerning their overall experience and unusual events. Participants may withdraw at any time. Previously collected information is handled according to their wishes, either not used further or retained for analysis with permission.

After completion, each participant's HRV and questionnaire scores are compared between curcumin and control periods. Aggregated data are analyzed for group trends. No additional invasive examinations, such as blood tests or imaging, and no hospitalization are required. Procedures take place during ordinary work and life with minimal disruption.

During each period, participants continue using the Leadtek H2 Plus watch-type ECG/HRV device for regular daily ECG and HRV measurements. R-R intervals and related raw information are synchronized by Bluetooth to a mobile application and cloud database. Participants are asked to wear it as close to 24 hours per day as possible, except when charging or cleaning, especially during work shifts and nighttime sleep, to cover stressful events and sleep cycles.

Subjective questionnaires and records also provide model labels and validation data. PSS assesses perceived stress over the week, PSQI assesses sleep quality, and daily sleep/work diaries record duration, shift type, and fatigue. Questionnaires are collected at the beginning and end of each period, while brief stress questions may be completed daily. For example, participants record the preceding sleep episode's duration and quality and rate that day's stress after each shift. These reports are compared with HRV to train and validate stress and sleep detection models.

Concomitant Treatment, Ethics, and Statistical Analysis

Participants may continue normal daily routines and existing treatment or medication for chronic conditions, if any. They are not required to change diet or exercise or stop medically necessary prescribed drugs. To limit interference, they are encouraged not to introduce new stress-relief or sleep measures, such as unnecessary supplements or calming herbal drinks, or alter work schedules. Necessary treatment or medication changes should be reported so the team can assess whether the data remain analyzable.

Participants must not start interventions that substantially affect autonomic function or sleep during the trial. Examples include new hypnotics, anxiolytics, antidepressants, or other centrally acting drugs. Additional interventional stress-reduction programs, such as mindfulness training, are also discouraged. These restrictions aim to reduce confounding. If urgent medical care requires such treatment, the team will document it and may discontinue participation to protect safety and data validity.

All participants provide informed consent. Only information necessary for the study is collected, and it is anonymized. If extreme stress or abnormal health conditions are detected, the team will promptly inform the relevant supervisory unit or recommend medical assistance to protect participants.

Appropriate statistical methods will test the hypotheses. LMMs and repeated-measures ANOVA will primarily analyze HRV and questionnaire changes across time and intervention conditions. LMMs will include participant-level random effects to account for individual differences and test the fixed effect of the curcumin patch. Repeated-measures ANOVA can evaluate intervention-by-time interactions. Skewed HRV data may be log-transformed or otherwise normalized to meet analysis assumptions. CCFs or lagged regression will examine temporal relationships between HRV and daily or weekly stress and sleep ratings, supporting an initial stress-warning model.

The planned sample of 50 was estimated by an a priori power analysis for a moderate effect size of approximately 0.5, a two-sided alpha of 0.05, and power above 80%, allowing approximately 10% withdrawal, to provide adequate power for the principal intervention effect. Safety assessment will follow an intention-to-treat principle including all randomized participants, while intervention effects will be assessed in a per-protocol set. Occasional missing measurements will be handled as appropriate, for example by maximum-likelihood estimation within mixed models or, if necessary, last-observation-carried-forward imputation to reduce bias.

HRV Algorithm Development

After substantial HRV time-series data have been obtained, stress and sleep recognition models will be developed. Development comprises feature extraction and model training. Multidimensional features will be calculated from R-R interval sequences, including the following categories.

HRV Feature Extraction and Model Development

Time-domain features include mean R-R interval (Mean RR or AVNN), standard deviation of normal-to-normal intervals (SDNN), root mean square of successive differences between normal-to-normal intervals (RMSSD), and the proportion of successive R-R intervals differing by more than 50 milliseconds (pNN50). These reflect overall variation and short-term parasympathetic activity.

Frequency-domain features are derived by spectral analysis of R-R intervals: LF power at 0.04-0.15 Hz, HF power at 0.15-0.4 Hz, and LF/HF. HF mainly reflects vagal activity, LF reflects a mixture of sympathetic and parasympathetic influences, and their ratio is commonly used to estimate relative sympathetic activity.

Nonlinear features include sample entropy, Poincare-plot SD1 and SD2, and detrended fluctuation analysis (DFA), capturing regulatory complexity and long-range correlations to identify subtle autonomic changes.

Features will be calculated in time windows, for example sliding five-minute windows, balancing real-time responsiveness and smoothness. Preprocessing will include abnormal-beat detection and interpolation to remove movement-related R-R artifacts, and smoothing, to ensure reliable inputs. Supervised machine learning will build stress and sleep classifiers, potentially as two submodels.

1. Stress detection. Prelabeled segments, based on high/low PSS scores or work/rest status, will train a classifier to distinguish high stress from low stress or relaxation. Labels may combine subjective ratings and objective conditions, such as shift type, with potentially greater stress on day shifts and less on rest days. Outputs may be a continuous stress index or a binary class. Candidate algorithms include k-nearest neighbors, support vector machines, random forests, XGBoost, and exploratory long short-term memory (LSTM) networks for time-series patterns. Cross-validation will guide selection of the best-performing model with appropriate complexity.

2. Sleep recognition. Nighttime HRV and activity will identify sleep state and quality. Tasks may include binary wake/sleep classification and overall good/poor sleep quality. Model development combines accelerometer data from a ring device, using an actigraphy-like approach, with HRV features such as average variability during sleep and horizontal changes in the HF component to estimate deep/light sleep proportions. Outputs may include 0 for awake, 1 for asleep, and a quality score calibrated against PSQI. Random forests or time-series classifiers will be evaluated for stable performance.

Generalizability will be assessed with cross-validation, preferably leave-one-subject-out: one participant's information is held out for testing and all other participants are used for training, repeated across participants.

Model Validation and Sensitivity Assessment

Leave-one-subject-out validation evaluates performance in previously unseen individuals, which is important for future healthcare users. Metrics include accuracy, sensitivity or recall, specificity, and F1 score. Unsatisfactory performance will prompt iterative changes to features and parameters or evaluation of model ensembles.

Prior research using wearable HRV to identify driving stress reported approximately 80% recall (pubmed.ncbi.nlm.nih.gov). Integrating multiple features and training tailored to healthcare workers is expected to support real-time stress indices and sleep-state information for feedback and intervention.

After model development, comprehensive performance validation and sensitivity analyses will assess practical effectiveness.

1. HRV variation and patch intervention effects. Crossover data will compare HRV between cooling-control and curcumin conditions using paired statistical tests, such as a paired t test or Wilcoxon signed-rank test. Principal HRV parameters, including SDNN, RMSSD, and LF/HF, will be compared across patch conditions. The study will assess whether the curcumin patch produces significant physiological changes. The hypothesis is that stress reduction may be accompanied by lower LF and higher HF power and RMSSD during curcumin use. Corresponding subjective outcomes, such as lower PSS and improved PSQI, will also be compared. Combined physiological and psychological validation will provide an initial assessment of patch effects and a reference for detection validity.

2. Algorithm accuracy. Cross-validation test results will quantify performance in stress classification and sleep recognition. Sensitivity to high stress and specificity for nonstress states will receive particular attention. In healthcare applications, sensitive warnings are favored over missing potential stress-related overwork events. Sleep detection should identify transitions into sleep and wakefulness while minimizing false alarms. Beyond overall accuracy, the model's response to subtle changes will be evaluated through sensitivity analyses.

Short-term stress fluctuations: assess whether the model identifies brief increases during daytime work, such as emergencies within a shift that cause transient HRV changes. Outputs before and after manually labeled high-stress events may be compared to assess responsiveness.

Small physiological changes: determine whether a modest improvement over two weeks, for example a 5-10% HRV change after the second week of patch intervention, is accompanied by a corresponding reduction in the model's stress index.

Sensitivity Assessment (Continued)

Continuous model outputs will be examined using correlation coefficients or analysis of covariance to quantify their linear association with measured HRV changes. A significant relationship would indicate sensitivity to small physiological changes. Otherwise, sensitivity may need adjustment, for example by lowering classification thresholds or adding finer features.

Individual differences: baseline HRV varies across healthcare workers. Performance will therefore be assessed separately for participants, including individual stress-classification accuracy, to identify poorer performance. Marked differences will prompt assessment of data quality or unusual personal HRV stress responses and consideration of individualized calibration.

3. System integration and real-time validation. After offline performance is established, final HRV algorithms will be embedded in a prototype, such as a mobile application or server, to analyze wearable data and provide feedback in real time. Selected participants will connect their devices for real-time calculation of stress and sleep predictions. Outputs will be compared with actual situations, for example a participant reporting that they are handling a stressful event. Engineering measures, including latency and data-loss rate, will assess practicality. Discrepancies will lead to revisions of algorithms or device-interface modules.

Anticipated Difficulties and Solutions

This application-oriented study combines wearable devices with clinical field measurement. Despite its innovation and practical potential, several implementation challenges are anticipated.

1. Limited adherence after enrollment. Long working hours and high stress may reduce adherence to wearing devices, completing scheduled questionnaires, or using patches correctly, producing incomplete data.

Proposed solutions are participant education before the trial to explain HRV's value for health warnings; simple workflows such as application reminders, automatic synchronization, and short forms; appropriate incentives such as personal health feedback or transport support; and regular research-assistant follow-up and encouragement.

Anticipated Difficulties and Solutions (Continued)

2. Numerous confounders affecting heart rate and sleep. Emotional fluctuations, caffeine, physical activity, BMI, sex, age, and other factors can affect HRV and sleep, obscure intervention effects, or cause misinterpretation.

Solutions include collecting potential confounders at enrollment for adjustment in statistical models; using diaries of exercise, diet, and emotional events to interpret unusual HRV changes; using mixed-effects models with participants as random effects to account for baseline differences; and conducting day/night stratified analyses and continuous-trend analyses rather than relying only on isolated observations.

3. Low signal-to-noise ratio and invalid HRV data. Unstable wear, movement during walking or shift changes, and signal loss may introduce noise, spikes, and missed beats, reducing quality and increasing the proportion of unusable segments.

Solutions include medical-grade heart-rate sensing, such as ECG, and instruction to maintain a stable posture during measurements; standardized artifact detection and moving-average filtering; excluding low-quality segments and analyzing only data meeting quality thresholds, such as R-R standard-deviation criteria and a missed-beat rate below a threshold; and adding resting HRV tests if necessary, for example a fixed daily 30-second resting recording, to improve completeness and comparability.

These anticipated measures are expected to improve data quality, adherence, implementation benefits, and research credibility.

Expected Work, Results, and Performance

Within one year, the industry-academia project aims to complete the following work and tangible outputs to establish a practical, clinically feasible, and commercially expandable high-stress occupational-risk warning system.

Expected Work and Tangible Outputs

1. Clinical validation of wearable HRV monitoring.

- Complete field testing of an HRV device, such as amor H2 Plus, in high-pressure populations such as healthcare and shift workers.

- Collect continuous HRV and concurrent PSS, PHQ-9, GAD-7, and PSQI data from at least 30 participants.

- Validate data stability and acceptance in challenging conditions, including night shifts and long fatigued working hours, to support deployment.

2. Integrated physiological-psychological analysis and HRV risk models.

- Build immediate and delayed association models linking HRV with stress, emotion, and sleep quality.

- Design HRV risk-grading logic and explanatory rules for stress estimation using psychological scales as reference standards.

- Evaluate prediction of psychological imbalance and fatigue under heavy workload as a basis for overload warnings.

3. Crossover patch trial and responsiveness validation.

- Conduct the randomized curcumin/control crossover trial and collect HRV and psychological changes during intervention.

- Analyze patch effects on HRV and assess sensitivity for tracking physiological-psychological regulation.

- Establish patterns of HRV response curves to support future validation of relaxation and wellness products.

4. Prototype warning system and demonstration integration.

- Build cloud modules for automatic HRV uploads, computation, and abnormality alerts.

- Design a high-stress warning dashboard for workplace or healthcare settings to support clinical intervention or human-resources decisions.

- Complete a prototype graded stress-risk algorithm adaptable to employee-health platforms and smart-care modules.

5. Translation and expanded applications.

- Prepare at least one representative academic paper on integrated HRV and mental-health risk models for journals or conferences.

- Complete one integrated clinical-application and product-validation report as evidence for industry marketing, healthcare collaboration, and tenders.

- Propose modular integration of the HRV device and risk-analysis logic for commercialization.

Expected Outputs (Continued)

- Develop future service scenarios with the partner hospital for employee-health monitoring or chronic-disease warnings.

The project is expected to advance HRV sensing from single-point physiological monitoring to intelligent warnings in high-pressure workplaces and clinical settings, providing a translational demonstration for remote care, occupational health, and smart medicine.

Expected Contributions to Innovation and National Development

The project aims to generate innovative and translatable outcomes in wearable autonomic sensing, integrated physiological-psychological analysis, and intelligent warning systems.

1. Technical innovation. The project describes a new integration of medically certified HRV wearables, standardized mental-health scales, and real-time data-stream analysis to support clinical and high-pressure workplace warnings. Innovations include multimodal modeling of objective HRV and subjective psychological status; real-time prediction of HRV abnormalities; a randomized crossover evaluation of nonpharmacological effects and tracking potential; and a modular platform supporting cloud applications and remote monitoring. Commercializability, scalability, and adaptability are intended to establish a representative integrated model of physiological sensing, AI warnings, and clinical evidence.

2. National development. In the post-pandemic and aging-society context, stress management, mental healthcare, and chronic-disease warnings are central digital-health priorities. The proposed system may:

- Promote domestic intelligent-health technology and reduce reliance on expensive imported sensors.

- Support workplace health promotion and labor policy for high-pressure groups, including healthcare workers, police, firefighters, and night workers.

- Establish evidence for technology-assisted mental-health monitoring, address delayed screening and care, and facilitate early identification and prompt intervention.

- Upgrade the wearable industry by combining biotechnology, information technology, and care expertise, strengthening international competitiveness in devices and data analytics.

The project anticipates high added value and policy alignment across wearable physiological sensing, smart-medical integration, and mental-health technology.

National and Commercial Benefits

These technical contributions are expected to support upgrading of Taiwan's smart-health industry and strengthening of healthcare.

The combination of certified wearable HRV devices, cloud analysis, and integrated physiological-psychological algorithms offers commercialization and scaling potential. Anticipated benefits include technology transfer, expanded industry-academia collaboration, product sales, new business models, and market applications.

1. Technology transfer and modular licensing. HRV abnormality-detection logic, integrated analytics, and stress-warning systems will provide complete algorithms and cloud APIs that can be licensed to Leadtek or other partners for devices, applications, and management platforms. Other smart-care vendors may use them as B2B health-data analysis engines.

2. Extended collaboration and clinical product validation. A clinically supported monitoring and risk-prediction platform can underpin future projects with hospitals, corporate health-check centers, and insurers. Further indication-specific trials or population deployments may establish a continuing cycle of clinical validation and product improvement.

3. Product upgrades and expanded sales. Field and clinical evidence for use as a stress-warning or physiological-psychological risk-management tool may facilitate entry into hospitals, employee assistance programs, and smart health checks. HRV-response analysis of nonpharmacological products such as curcumin patches may also form a scientific validation platform for wellness products and create cross-selling opportunities.

4. New business models and services. Potential SaaS offerings include employee stress-risk dashboards with warnings (B2B), subscription remote-health-risk monitoring applications (B2C), wellness-product effectiveness analytics (B2B2C), and combined physiological/psychological monitoring for health-check or long-term-care facilities. These could help transform a device manufacturer into an integrated health-technology service provider.

5. Market potential. A 2023 MarketsandMarkets report forecasts a global wearable-health-device market of USD 85.7 billion by 2028, driven especially by heart-rate, stress, and sleep-management applications.

Market Potential (Continued)

Taiwan's smart-care market is also growing with aging and greater workplace-health awareness. The project may strengthen domestic HRV competitiveness, differentiated international positioning, and export capacity. Integrated physiological sensing, mental-health warnings, and clinical validation are expected to support technical expansion from products to platforms and create high-value commercial outcomes.

Dissemination and Exhibitions

After completion, the team will participate in industry-academia promotion, technical exhibitions, and academic exchanges. Near-term plans include submissions to smart-medicine, physiological-sensing, and occupational-health conferences such as IEEE EMBC, APAMI, and Taiwanese smart-medicine meetings. The team will present clinical applications of wearable HRV and stress-warning systems and discuss analytics and mental-health models with international researchers.

In cooperation with Leadtek, the team will also participate in startup-technology and innovative medical-device exhibitions organized by Taiwan's science and technology authorities and the Industrial Technology Research Institute, including the Taiwan Healthcare Expo and the COMPUTEX smart-healthcare pavilion. Demonstrations will combine wearables, cloud platforms, and clinical evidence. These activities will increase understanding, promote further collaboration with companies, healthcare institutions, and long-term-care providers, and strengthen Taiwan's international visibility and competitiveness.

Staff Training

Students and clinical personnel are expected to gain interdisciplinary skills through:

- Practical physiological-signal analytics: acquisition, cleaning, and feature extraction of ECG and HRV; preprocessing, time-series computation, and machine-learning development.

- Clinical-engineering collaboration: joint interpretation and model evaluation by medical and information-technology staff to improve communication and practical problem solving.

- Clinical research and ethics: IRB and ethics training, informed consent, confidentiality, and field implementation procedures for future trials and collaborative projects.

- Technical presentation and writing: journal manuscripts, conference abstracts, and posters to build publication and demonstration experience and support academic or industrial careers.

Implementation and dissemination are intended both to translate the research into practice and to train the next generation of smart-health researchers with clinical-engineering perspectives and practical experience.

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PART II: REGISTRATION AND ANALYSIS SPECIFICATIONS

Registration and Analysis Specifications

Document date: 19 October 2026

These specifications describe the completed patch trial and the analysis definitions documented during retrospective registration. The original protocol is Version 1.1 dated 24 November 2025.

Trial and Device

The trial is a randomized, open-label, placebo-controlled crossover study with two treatment sequences. The active patch contains nano-formulated curcumin. The cooling placebo patch contains no active curcumin. Each patch is applied to the trunk for 8 hours daily and replaced each day for at least 14 days. A washout of at least 14 days separates the periods.

The wearable device used for the registered patch comparison is the Leadtek amor H2 Plus ECG/HRV watch, model 8Z37. The broader protocol also describes development of sleep-recognition algorithms with ring accelerometer data. The registered patch outcomes use the H2 Plus HRV measurements, not ring-derived sleep-stage estimates.

Registered Outcomes and Assessments

The five primary HRV outcomes are SDNN, RMSSD, LF power, HF power, and LF/HF. LF covers 0.04-0.15 Hz and HF covers 0.15-0.4 Hz. LF/HF is dimensionless. Each metric is analyzed separately.

The secondary questionnaire outcomes are PSS, PSQI, GAD-7, and PHQ-9 scores. All four questionnaires are scheduled at the beginning and end of each intervention period, for four assessment occasions. This schedule follows the four-instrument assessment described in the IRB application and the completed questionnaire collection confirmed by the study team.

Participant-Level HRV Comparisons

The unit of analysis is the participant. For SDNN, RMSSD, LF and HF, available numeric wearable records are averaged separately within each intervention period. LF/HF is calculated as the period mean LF divided by the period mean HF; it is not the mean of record-level LF/HF ratios. LF/HF is calculated only when both means are available and mean HF is nonzero. The resulting curcumin-period and placebo-period values are compared within the same participant. Participants contribute one paired set per metric.

The period comparison includes the available records across each intervention period. The daily 3-to-5-minute resting recording describes the acquisition procedure. The period-level outcome is not defined as a single resting measurement or as a night-only measurement. Day/night recording-time comparisons are separate subgroup analyses; a nighttime timestamp alone does not identify sleep state.

Baseline-Normalized Analysis

For each participant, baseline records comprise all available records from the last three recorded baseline dates before the first intervention, pooled with up to the final three available washout records between intervention periods. If no eligible washout records are available, baseline uses the pre-intervention records alone. For SDNN, RMSSD, LF and HF, the baseline value is the mean of the selected records. Baseline LF/HF is the selected records' mean LF divided by their mean HF. The same participant-specific baseline is used for both patch conditions.

The normalized value is 100 multiplied by the intervention-period value divided by that participant's baseline value. Thus, baseline equals 100%, and the curcumin and placebo percentages are compared within participants. A percentage is calculated only when the baseline value is available and nonzero. This normalization is an additional analysis of the same HRV outcomes. The combined baseline rule is documented here as a subsequent analysis specification, dated 19 October 2026.

Statistical Tests and Presentation

The finalized paired comparisons use the two-sided Wilcoxon signed-rank test, designated p2 in the analysis reports. Zero paired differences are excluded, and tied absolute differences receive average ranks. Two-sided p values use exhaustive sign enumeration for up to 20 nonzero pairs and 200,000 Monte Carlo sign assignments to ranks for larger samples, with a fixed reproducible seed. The test is applied separately to raw participant-level period values and baseline-normalized values.

Participant-level period values or normalized values are summarized across participants by the median and first and third quartiles (Q1 and Q3). Box plots display these quantiles, and each dot represents one participant. The median shown in a box plot summarizes participant-level values; it does not replace the within-participant means or the LF/HF ratio-of-means calculation.

The complete paired cohort and the adherence subgroup are analyzed separately. The adherence subgroup requires at least 10 recordings in each of the two intervention periods. Multiple metric and subgroup comparisons are exploratory; reported p values are not adjusted for multiplicity. The original protocol's mixed-effects, repeated-measures, and model-development methods remain part of the broader research plan.

Actual Study Status

Enrollment began on 20 March 2026 and wearable measurements began on 4 April 2026. Of 51 enrolled participants, 50 completed the study and one withdrew. Measurements and questionnaires were completed on 15 October 2026, which is both the primary completion date and study completion date. There were no adverse events requiring further follow-up. Registration was prepared after study completion.