

Prospective Clinical Research Protocol

Validation of Wearable Core Body Temperature Signal–Based Circadian Rhythm Digital Biomarkers

(Korean title: 웨어러블 심부체온 신호 기반 일주기리듬 디지털 바이오마커 검증 연구)

Version No. 1.1

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Note on this translation. This is an English translation of the Korean-language protocol (Version 1.1, dated October 7, 2026), prepared for registration on ClinicalTrials.gov. The structure and section numbering of the original have been preserved. In the event of any discrepancy, the Korean original approved by the Institutional Review Board of Korea University Anam Hospital prevails. Personal names are romanized. Notes marked “Translator’s note” are not part of the original.

[Protocol Revision History]

No.	Version No.	Version Date	Major Changes
1	1.0	2026-08-10	Initial review
2	1.1	2026-10-07	Changes to study design (increase in the number of participants to be enrolled to account for dropout and missing data; addition of Fitbit to the inpatient study; change in the Calera wearing schedule/design for the inpatient study [intermittent wear → continuous wear]; addition of BPRS to the inpatient study assessments; refinement of collected environmental variables and the analysis plan, etc.)

Prospective Clinical Research Protocol

1. Study Title

Korean title: 웨어러블 심부체온 신호 기반 일주기리듬 디지털 바이오마커 검증 연구

English title: Validation of Wearable Core Body Temperature Signal–Based Circadian Rhythm Digital Biomarkers

2. Investigator Information, Study Site, and Study Period

2-1. Names and Titles of the Principal Investigator and Co-Investigators

1) Investigators at this institution

Role	Affiliation	Position	Name
Principal Investigator	Dept. of Psychiatry	Professor	Heon-Jeong Lee
Co-Investigator	Dept. of Psychiatry	Assistant Professor	Ji Won Yeom
Co-Investigator	Dept. of Psychiatry	Clinical Fellow	Jaekwon Jeong
Research Staff	Dept. of Psychiatry	Researcher	Soo-Hyun Park
Research Staff	Dept. of Psychiatry	Researcher	Yerin Oh
Research Staff	Dept. of Psychiatry	Researcher	Hayoung Bae

2) Investigators at other institutions: Not applicable

2-2. Study Site

Institution: Korea University Anam Hospital

Address: Sleep Laboratory, 6th floor, New Building, Korea University Anam Hospital, 73 Goryeodae-ro, Seongbuk-gu, Seoul, Republic of Korea (outpatient study)

Psychiatric inpatient ward, Department of Psychiatry, Korea University Anam Hospital, 73 Goryeodae-ro, Seongbuk-gu, Seoul, Republic of Korea (inpatient study)

※ When a measurement in progress at the time of discharge is extended beyond discharge, device return and the end-of-study assessment at the end of the extended measurement period are conducted in the Sleep Laboratory on the 6th floor of the New Building, as in the outpatient study.

2-3. Expected Study Period: Date of IRB approval to December 31, 2028

2-4. Sponsor (Commissioning Institution): Not applicable

2-5. Name and Address of the Funding Agency

- Funding agency: Ministry of Science and ICT (75 Yulgok-ro, Jongno-gu, Seoul)
- The research team receives funding from the “2024 Challenge-Driven (Han-gye Dojeon) R&D Project” (Project No. RS-2024-00469788), supported by the Ministry of Science and ICT / National Research Foundation of Korea, and conducts this study to achieve the research goals of that R&D project.

3. Background and Rationale

3-1. Limitations of Existing Wearable-Based Circadian Rhythm Measurement

- Recent mood disorder research has actively used wrist-worn wearables (e.g., Fitbit) to collect long-term, real-life data on sleep, activity, and heart rate, and to derive circadian and behavioral rhythm characteristics from these data. The advantage of wrist-worn wearables is that long-term data can be collected continuously and non-invasively in real-life settings.
- However, wrist-worn wearables have limitations: (1) access to raw accelerometer data is restricted, so they rely on summary indices processed by manufacturer algorithms, and (2) they cannot directly measure physiological circadian phase markers such as core body temperature (CBT). Therefore, how accurately these indices reflect actual physiological circadian phase and high-resolution behavioral rhythms has not been sufficiently validated.

3-2. Significance of Rhythm Measurement Based on Core Body Temperature and Raw Acceleration

- The circadian variation of core body temperature, particularly the timing of its minimum (CBT trough), is known to be an established physiological circadian phase marker. Although the wearable core body temperature sensor (Calera) is limited for long-term follow-up, it has the advantage of simultaneously measuring the CBT rhythm and a high-resolution rest-activity rhythm based on raw accelerometry over a short period (approximately 1 week).
- This makes it possible to directly compare, validate, and calibrate circadian and behavioral rhythm indices derived from wrist-worn wearables against physiological CBT phase markers and high-resolution raw-acceleration-based behavioral rhythm markers.

3-3. Circadian Rhythm Disruption as a Pathophysiological Mechanism of Mood Disorders

- In this research team's previous study (Moon et al., *EBioMedicine* 2016), 31 mood episodes in patients with bipolar disorder were repeatedly assessed from early hospitalization to recovery, and changes in biochemical circadian phase were tracked using salivary cortisol and PER1/ARNTL expression. In most manic episodes, a phase advance of approximately 7 hours relative to the recovered state was observed in the acute phase; a phase delay of approximately 6–7 hours was observed in mixed manic episodes and approximately 4–5 hours in depressive episodes; and these phase abnormalities returned to the normal range with treatment and clinical recovery.
- The previous study also showed that changes in sleep–wake and gross activity rhythms were relatively small compared with the large changes in biochemical circadian phase, suggesting that a misalignment between endogenous physiological rhythms and behavioral rhythms may exist while behavioral rhythms are aligned first by the inpatient environment and treatment. Because Calera can continuously measure CBT and raw accelerometry on the same time axis, it is well suited to directly exploring such physiological–behavioral misalignment and recoupling during recovery.

3-4. Basic Direction of the Study and Transdiagnostic Extension of the Inpatient Study

In Study 1, circadian and behavioral rhythm characteristics measured with a wrist-worn wearable (Fitbit) are validated and calibrated against physiological circadian rhythms and accelerometer-based behavioral rhythms collected at high resolution with a core body temperature sensor (Calera). In Study 2, a transdiagnostic longitudinal cohort is constructed that comprehensively enrolls psychiatric inpatients regardless of diagnosis, including those whose final diagnosis has not been established at enrollment. The CBT rhythm, rest-activity rhythm, and the phase relationship between the two rhythms are repeatedly measured from early hospitalization to discharge and linked with dimensional symptom measures such as the MADRS, YMRS, BPRS, and CGI.

4. Study Objectives

The objectives of this study are (1) to validate and calibrate circadian and behavioral rhythm characteristics measured with a wrist-worn wearable (Fitbit) against physiological circadian rhythms and accelerometer-based behavioral rhythms collected at high resolution with a core body temperature sensor (CALERAResearch), and (2) to explore the association of variation in circadian rhythm characteristics measured with the core body temperature sensor with mood symptoms, and with psychopathological symptoms and the course during hospitalization in psychiatric inpatients.

To this end, the study is conducted along two axes.

Study 1 (outpatient study)

1. To evaluate how well Fitbit-derived circadian phase features agree with the Calera-derived CBT trough midpoint.
2. To evaluate how well Fitbit-derived sleep/activity rhythm features agree with rest/sleep and activity rhythm markers based on Calera raw accelerometry.
3. To explore whether a composite phase estimator integrating multiple Fitbit features predicts the CBT trough midpoint better than single features.
4. To compare whether the patient group shows greater physiological–behavioral rhythm discrepancy than healthy controls.
5. To evaluate the test–retest reliability of the Calera-derived CBT trough midpoint and Fitbit-derived circadian phase features by conducting repeated measurements in a subset of participants ($n = 50$).

Study 2 (inpatient study)

1. To explore, in patients admitted to a psychiatric ward regardless of diagnosis, how the CBT rhythm, Calera/Fitbit-derived rest-activity rhythm, and the coupling between the physiological rhythm (CBT) and the behavioral rhythm (Calera/Fitbit-derived rest-activity rhythm) change from immediately after admission to discharge.
2. To evaluate the within-subject association between changes in rhythm indices and changes in depression, mania/activation, overall psychopathology, and overall clinical severity measured with the MADRS, YMRS, BPRS, and CGI.
3. To explore whether the circadian phenotype in early hospitalization and the recovery trajectory differ according to final diagnostic group and psychopathological symptom profile.

5. Risk/Benefit Analysis

This is a minimal-risk study consisting of non-pharmacological, non-invasive procedures such as research interviews, self-report questionnaires, and wearing of wearable devices (a skin-attached core body temperature sensor and a wrist-worn wearable).

- Participants may experience skin irritation or discomfort at the attachment site when the plastic core body temperature sensor is attached to (worn on) the body using medical tape. The device and tape are designed for contact that is harmless to the human body, and participants will be instructed to stop wearing the device immediately if any skin problem occurs.
- Participants may experience fatigue or discomfort during clinical assessments; they may take breaks freely during the assessment and may withdraw from the study at any time without giving a reason.

Participants may receive no direct benefit from participating in this study; however, if this study contributes to identifying circadian and behavioral rhythm biomarkers of mood disorders and mental disorders, it may contribute

to the development of better diagnostic, treatment, and prevention methods in the future. Considering the importance of the knowledge that can be gained from this study, the risks associated with participation are minimal.

6. Target Number of Participants and Rationale

6-1. Target Number of Participants

- Study 1 (outpatient study): 150 (75 outpatients with mood disorders, 75 healthy controls)
 - Repeated-measurement validation substudy of Study 1: 50
- Study 2 (inpatient study): 50 psychiatric inpatients
- Total: 200

6-2. Rationale

Study 1 is a validation study that examines cross-sectional agreement between wrist-worn-wearable-based indices and physiological CBT/raw-acceleration-based indices. Given the nature of validation studies, rather than calculating a sample size for confirmatory hypothesis testing, the target was set at 75 patients and 75 controls (150 in total), considering the size of previous wearable validation studies, the recruitment period and research funding of this institution, and an expected dropout and missing-data rate of approximately 30–35%.

Study 2 is a repeated-measures observational study exploring the trajectory of biological rhythm changes from early hospitalization to discharge; the target is 50 inpatients, considering the recruitment period and research funding of this institution and an expected dropout and missing-data rate of approximately 30–35%. Because a target sample size of 50 may be insufficient for confirmatory comparisons by final diagnostic group and symptom profile, overall within-subject change is set as primary, and analyses by diagnostic group and symptom profile are exploratory.

7. Participant Eligibility Criteria (Inclusion/Exclusion, Withdrawal Criteria, etc.)

7-1. Inclusion/Exclusion Criteria for the Patient Group (Study 1)

Patient group inclusion criteria	Patient group exclusion criteria
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<div>1. Adults aged 19 to 75 years inclusive</div> <div>2. Can be diagnosed with major depressive disorder (MDD), bipolar I disorder (BD-I), or bipolar II disorder (BD-II) based on a diagnostic interview (M.I.N.I.) by a psychiatrist (including residents) or clinical psychologist and on DSM-5 criteria, with a history of visiting a psychiatry department for these symptoms</div> <div>3. Agrees to wear the core body temperature sensor and the wrist-worn wearable for 7 days</div>	<div>1. History of moderate or severe intellectual disability</div> <div>2. Current or past head trauma with loss of consciousness, degenerative neurological disease, or organic brain disease (stroke, epilepsy, traumatic brain injury, multiple sclerosis, Alzheimer’s disease, Parkinson’s disease, etc.)</div> <div>3. Engaged in shift work (including night work) within the past 3 months</div> <div>4. Travel across three or more time zones (e.g., intercontinental travel) within the past 2 weeks</div> <div>5. Fever (body temperature ≥ 37.5 °C) or acute infection at the start of measurement</div> <div>6. Pregnant or breastfeeding</div> <div>7. Unsuitable for sensor attachment, e.g., skin disease at the wearing site or history of allergy to medical adhesive (tape)</div> <div>8. Difficulty reading and understanding Korean</div> <div>9. Judged by the principal investigator to be unsuitable for study participation</div>
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7-2. Inclusion/Exclusion Criteria for the Control Group (Study 1)

Control group inclusion criteria	Control group exclusion criteria
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<ol style="list-style-type: none"> 1. Adults aged 19 to 75 years inclusive 2. No history of psychiatric diagnosis or treatment, and not screened as having a major mood disorder on the diagnostic interview (M.I.N.I.) 3. Agrees to wear the core body temperature sensor and the wrist-worn wearable for 7 days 	<ol style="list-style-type: none"> 1. History of significant mood symptoms, operationally defined as one or more of the following: ① a history of diagnosis of or treatment for a mood disorder in a psychiatry department; ② findings of a past or current major depressive episode or (hypo)manic episode on the diagnostic interview (M.I.N.I.) or a screening interview 2. Currently taking hypnotics or psychotropic medications (antidepressants, mood stabilizers, antipsychotics, benzodiazepines, etc.) 3. History of moderate or severe intellectual disability 4. Current or past head trauma with loss of consciousness, degenerative neurological disease, or organic brain disease 5. Engaged in shift work (including night work) within the past 3 months 6. Travel across three or more time zones within the past 2 weeks 7. Fever (body temperature ≥ 37.5 °C) or acute infection at the start of measurement 8. Pregnant or breastfeeding 9. Unsuitable for sensor attachment, e.g., skin disease at the wearing site or history of allergy to medical adhesive 10. Difficulty reading and understanding Korean
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7-3. Inclusion/Exclusion Criteria for the Inpatient Group (Study 2)

Inpatient group inclusion criteria	Inpatient group exclusion criteria
<ol style="list-style-type: none"> 1. Adults aged 19 to 75 years inclusive 2. Admitted to the psychiatric ward of Korea University Anam Hospital for psychiatric treatment; participation is possible even if the diagnosis has not been established at enrollment 3. Agrees to wear the core body temperature sensor and the Fitbit device continuously during hospitalization 	<ol style="list-style-type: none"> 1. Judged unsuitable for sensor wear and assessments owing to acute safety concerns (risk of harm to self or others, etc.) 2. Judged to lack capacity to consent or to have difficulty giving voluntary consent 3. History of moderate or severe intellectual disability 4. Current or past head trauma with loss of consciousness, degenerative neurological disease, or organic brain disease 5. Fever (body temperature ≥ 37.5 °C) or acute infection at the start of measurement 6. Pregnant or breastfeeding 7. Unsuitable for sensor attachment, e.g., skin disease or history of allergy to medical adhesive 8. Difficulty reading and understanding Korean

7-4. Withdrawal (Dropout) Criteria

Participants who withdraw consent during the study, participants who express a wish to discontinue participation without completing the full study schedule, and participants who have not explicitly reported discontinuation but have no valid measurement days after consent are treated as dropouts.

8. Investigational Devices

8-1. Overview of the Investigational Wrist-Worn Wearable Device (Fitbit Charge 6)

1) Classification

This device is not a medical device but a wellness product intended for everyday health management, not for diagnosing or treating a specific disease or condition, and it uses commercially available contact sensors that are harmless to the human body.

2) Manufacturer / country of manufacture: Fitbit Inc. / China

3) Principle of operation and intended use

When the wearable device is worn on the wrist, photoplethysmogram (PPG) and acceleration signals can be measured. The device collects information on heart rate, activity, distance traveled, calories, active time (Active Zone Minutes), heart rate variability, SpO2, respiratory rate, and sleep.

4) Appearance and structure

[Fitbit Charge 6]

Dimensions	39.7 × 23.1 × 11.2 mm (L × W × H)	
Display	1.4-inch full-color AMOLED	
Weight	37.64 g	
Battery	65 mAh	

* Fitbit is a commercially available product, not a medical device, and has no medical intended use such as diagnosis, treatment, or prevention of disease.

5) Method of use

Wearing on the non-dominant wrist (the left wrist for right-handed individuals) is recommended; however, considering the follow-up period, participants may wear it on whichever wrist they prefer. Participants are advised to wear it every day, at all hours, including during sleep, except while charging. The wearing period for each study is as follows.

- Outpatient study: worn for the 7 days during which the CALERAResearch device is attached, and returned at the final visit.
- Inpatient study: worn continuously from the start of the study until discharge. Participants are instructed to charge the device themselves on the ward, and may suspend wearing temporarily if they wish. In principle, the Fitbit is worn together with the Calera sensor during the periods when the Calera sensor is worn. If the measurement period in progress at discharge is extended beyond discharge, the device is worn until the end of that measurement period and then returned.

6) Device management

The Fitbit is distributed in person after the participant's enrollment and baseline clinical assessment, and the participant is informed of how to use it and precautions.

- Delivery of the Fitbit is recorded in the device accountability log together with the date of delivery. The device identification number is written on the case of each wearable device (Fitbit 001, Fitbit 002, ...), and upon distribution and retrieval of the wearable device, the device identification number, date, and researcher's signature are recorded in the wearable device accountability log.
- The device is returned at the final visit in the outpatient study and at the end of the study (at the last sensor retrieval or at the end of the extended measurement period) in the inpatient study, and the device identification number, date, and researcher's signature are recorded in the wearable device accountability log.

8-2. Overview of the Core Body Temperature Measurement Device (CALERAResearch)

1) Classification

This device is not intended for the diagnosis or treatment of a specific disease; it is a wellness device whose contact parts are harmless to the human body.

2) Manufacturer / country of manufacture: greenTEG / Switzerland

3) Principle of operation and intended use

A wearable device attached to or worn on the body that non-invasively measures skin temperature, core body temperature (CBT), and raw accelerometry signals. Skin temperature is strongly affected by external environmental conditions and is therefore easily misinterpreted; however, greenTEG's core body temperature measurement solution, the gSKIN-XU sensor (heat-flux sensor), compensates for environmental effects so that the actual core body temperature signal can be measured. It uses a non-invasive, skin-attached method and is attached to the chest/arm as a patch or belt. Core temperature is displayed within 4 minutes of the start of measurement, and the battery and storage capacity allow continuous measurement for 7 days.

4) Appearance and structure

[CALERAResearch]

Dimensions	50 × 40 × 8.35 mm (diameter × thickness × height)	
Mass	17 g	
Battery life	7 days of measurement	

5) Method of use

The device is, in principle, attached to the chest. Recording is started by Bluetooth synchronization with a laptop in the Sleep Laboratory of Korea University Anam Hospital, and the device is then attached using medical tape. The attached device has battery and storage capacity for approximately 7 days of continuous measurement.

- Outpatient study: the participant returns for the final visit 7 days after the first visit; the device is removed and the data are downloaded.
- Inpatient study: a researcher visits 5–7 days after attachment and removes the device. Re-attachment follows removal; if the participant wishes, a rest period of the desired length may be taken. If the

measurement period in progress at discharge is extended, the participant visits the site at the end of that measurement period to have the device removed and returned.

6) Device management

The CALERAResearch device is handed over in person after the participant’s enrollment and baseline assessment, and the participant is informed of how to use it and precautions.

- Delivery of the device is recorded in the accountability log together with the device serial number and date of delivery. Upon distribution and retrieval of the device, the device serial number, date and time of delivery/return, participant study number, and researcher’s signature are recorded in the device accountability log.
- Data are downloaded within 1 day of return.
- If a device malfunctions or is lost during participation, the investigators record the information and issue a replacement device. Participants are not required to bear any cost for device malfunction or loss.

9. Study Design (Treatment/Control Groups, Allocation, Blinding, Flow Chart, etc.)

This is a prospective observational study composed of two substudies. The two studies share the same devices and biological-rhythm concepts but differ in research questions and analytic objectives. In both studies, no intervention other than data collection is administered to participants, and no randomization or blinding is performed.

Item	Study 1 (outpatient study)	Study 2 (inpatient study)
Participants	75 outpatients with mood disorders, 75 healthy controls	50 psychiatric inpatients
	Repeated-measurement study in 50 of the outpatient-study participants	
Design	Cross-sectional validation study (single wear period) * For test–retest validation, 50 of these participants are measured twice at an interval of at least 1 month	Prospective observational study (continuous wear during hospitalization; a measurement period in progress at discharge may be extended after discharge)
Key objective	Validation of agreement between Fitbit indices and CBT/raw-acceleration indices	Exploration of changes in biological rhythms from early hospitalization to discharge and of changes in physiological–behavioral rhythm coupling
Key words	validation, calibration, phase estimator, physiological–behavioral rhythm discrepancy	acute psychiatric state, recovery trajectory, CBT rhythm, recoupling

10. Detailed Study Methods

10-1. Basic Study Information

- The basic objectives of the overall study are (1) to validate and calibrate circadian and behavioral rhythm characteristics measured with a wrist-worn wearable (Fitbit) against physiological circadian rhythms and accelerometer-based behavioral rhythms collected at high resolution with a core body temperature sensor (CALERAResearch), and (2) to explore the association of variation in circadian rhythm characteristics measured with the core body temperature sensor with mood symptoms and the clinical course during hospitalization.

10-2. Participant Recruitment Plan

The recruitment plan, including screening procedures, is described in detail in “16. Participant Recruitment Methods and Consent Procedures” of this protocol.

10-3. Study Procedures

Study 1 (outpatient study) — basic study procedures

- The purpose and procedures of the study are explained to the participant, voluntary consent is obtained, and the baseline clinical assessment is conducted.
- The core body temperature sensor (CALERAResearch) and the wrist-worn wearable (Fitbit) are provided, and the participant is instructed to wear them from the first enrollment day until the final visit and then sent home. If the final visit is scheduled later than 7 days after the first visit, the participant removes the devices on the morning of Day 8 after the first visit, once 7 days of wear have been completed.
- The final visit is conducted 7 days after the first enrollment day, and the end-of-study clinical assessment is performed.
- The CALERAResearch and Fitbit devices are retrieved, and it is confirmed that the collected data have been synchronized properly.

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
First visit and sensor attachment						Final visit after Day 7		
							Sensor removal	

Study 1 (outpatient study) — repeated-assessment procedures

- The purpose and procedures of the study are explained to participants who wish to take part in the repeated assessment, and additional voluntary consent is obtained. The repeated assessment may be undertaken at least 1 month after completion of the baseline assessment.
- For the repeated assessment, no separate assessment is conducted when the sensors are provided. The core body temperature sensor (CALERAResearch) and the wrist-worn wearable (Fitbit) are provided, and the participant is instructed to wear them from the first enrollment day until the final visit (or for 7 days if the final visit is scheduled later than 7 days after the first visit) and then sent home.
- The final visit is conducted 7 days after the first enrollment day, and the end-of-study clinical assessment is performed.
- The CALERAResearch and Fitbit devices are retrieved, and it is confirmed that the collected data have been synchronized properly.

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
First visit and sensor attachment							Final visit	
							Sensor removal	

Study 2 (inpatient study) — procedures

1. The purpose and procedures of the study are explained to the participant, voluntary consent is obtained, and the study begins.
2. At the start of the study, the baseline assessment is conducted, after which the core body temperature sensor and the Fitbit are provided.
3. Considering battery depletion of the core body temperature sensor, the sensor is replaced at intervals of approximately 7 days (5–7 days). Sensor retrieval and re-attachment are performed by a researcher visiting the inpatient ward, and a clinical assessment is conducted at each sensor retrieval. Considering participant fatigue, participants may, if they wish, take a sufficient rest period between sensor retrieval and re-attachment. Participants are instructed to charge the Fitbit themselves.
4. At each sensor retrieval, the sensor data are saved and checked on the day of retrieval.
5. If discharge occurs earlier than expected and the measurement period in progress at discharge (5–7 days) has not been completed, device wear may be continued beyond discharge only if the participant agrees. In this case, the same criteria as for in-hospital measurements apply to participation compensation and clinical assessment items, while ward-environment-related information that is difficult to collect owing to the change in environment after discharge is treated as missing. When the extended measurement period ends, the participant visits the Sleep Laboratory to return the devices, the same clinical assessment as at sensor retrieval (MADRS, YMRS, CGI, BPRS, and notable events during measurement) is conducted, and the participant's study participation is thereby completed.

10-4. Clinical Assessment Items

Study 1 (outpatient study)

Assessment item	Time point	Content
Baseline characteristics	First visit	Sex, age, height, weight, socioeconomic status, employment status, highest education level, marital status, medical history, smoking, alcohol use, etc.
History of mood disorder	First visit	Family history, history of mood episodes, history of psychiatric hospitalization, diagnosis, most recent episode
Mood disorder symptoms	Final visit	MADRS, YMRS, CGI, mood-episode recurrence status in the past 3 months
Medication information	Final visit	Type, dose, and adherence of medications taken in the past 3 months
Clinical self-report	Final visit	PSQI, BRIAN, MEQ, SPAQ, MDQ
Notable events during measurement	Final visit	Suicide attempts, overseas travel, presence and timing of fever, times of voluntary device removal and re-attachment, adverse events, menstrual cycle

Study 1 (outpatient study) — repeated assessment

Assessment item	Time point	Content
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Mood symptoms	Final visit	MADRS, YMRS, CGI
Medication information	Final visit	Type, dose, and adherence of medications taken in the past 3 months
Clinical self-report	Final visit	PSQI, BRIAN, MEQ
Notable events during measurement	Final visit	Menstrual cycle, suicide attempts, overseas travel, presence and timing of fever, times of voluntary device removal and re-attachment, adverse events

Study 2 (inpatient study)

Assessment item	Time point	Content
Baseline characteristics	At consent	Sex, age, height, weight, medical history, provisional diagnosis at enrollment
Psychopathological symptoms	Baseline & at each sensor retrieval	MADRS, YMRS, CGI, BPRS
Notable events during measurement	At each sensor retrieval	At each sensor retrieval, events occurring since the previous retrieval are recorded: occurrence of high fever, times of voluntary device removal and re-attachment, times of seclusion/restraint/leave from the ward, menstrual cycle, and adverse events
Sleep environment	At each sensor retrieval	Sleep times by time of day, based on nursing records
Medication administration information	At each sensor retrieval	Drug name, dose, and regimen on the day of sensor retrieval
Final diagnosis	At end of study	Final diagnosis

10-5. Construction of Circadian and Behavioral Rhythm Markers

The circadian/behavioral rhythm markers in this study are constructed along three axes.

(1) CBT-based physiological circadian markers

- Primary: CBT trough midpoint (center of the lowest core-body-temperature segment)

Rationale for selecting the CBT trough midpoint as primary: a single CBT minimum can be sensitive to noise, transient movement, sensor contact, awakenings during sleep, and environmental changes, whereas the trough midpoint reflects the center of the lowest-temperature segment and is therefore likely to be a more stable phase marker than a single time point.

- Secondary: CBT minimum timing, CBT acrophase, CBT amplitude, CBT mesor, CBT rhythm robustness, day-to-day variability of CBT trough midpoint/minimum timing

(2) Raw-accelerometry-based sleep/activity markers

- Sleep/rest: estimated rest/sleep onset, offset, midpoint, and duration; nighttime movement; rest fragmentation; rest bout continuity; day-to-day variability of rest/sleep midpoint
- Activity rhythm: activity acrophase and amplitude, M10 timing, L5 timing, relative amplitude, interdaily stability (IS), intradaily variability (IV), daytime activity level, sedentary/rest duration, activity fragmentation, rhythm robustness

(3) Physiological–behavioral coupling/decoupling markers

- Phase gap between the CBT trough midpoint and rest midpoint / estimated sleep midpoint / L5 timing / activity acrophase
- Phase gap between the CBT trough midpoint and Fitbit sleep midpoint / Fitbit activity acrophase

These indices are intended to evaluate how well physiological circadian phase is aligned with the actual sleep–activity rhythm, whether physiological–behavioral rhythm discrepancy is greater in the patient group than in healthy controls, and whether symptoms, sleep fragmentation, and reduced activity are associated with CBT–activity decoupling.

10-6. Cost of Study Participation

There are no costs arising from the clinical assessments for this study. Participants who take part in the study are paid the following amounts as transportation expenses/participation compensation.

Study 1 (outpatient study)

- Participants who complete 7 days of continuous wear and the assessments receive participation compensation of KRW 120,000. The KRW 120,000 consists of KRW 14,000 in transportation expenses for the first visit, KRW 14,000 in transportation expenses for the final visit, and KRW 13,000 per day of device wear. Payment according to the wear rate is intended to compensate in proportion to the actual burden of participation without forcing completion, thereby reducing pressure to continue wearing the devices despite discomfort.
- If the participant voluntarily removes the devices before completing the 7-day measurement, participation compensation is calculated based on the actual number of valid wear days. Here, one day of wear is defined as one night, and valid wear days are determined by whether the measurement period included the participant's sleep period.
- If both the Fitbit and Calera devices are worn, the full participation compensation for that day (KRW 13,000 per day) is paid. If only one of the two devices is worn, 50% of that day's participation compensation is paid. However, if the participant wore the devices properly but measurement was not performed properly for reasons not attributable to the participant, such as device error or data transmission error, this is recognized as proper wear.
- Participants in the repeated assessment are paid up to KRW 120,000 per session under the same criteria.
- However, if the devices are removed at the discretion of an investigator or clinician because of adverse events such as skin problems or for clinical reasons, or if measurement is interrupted for reasons not attributable to the participant, such as device malfunction or early battery depletion, the full amount for that session is paid regardless of the wear rate.

Study 2 (inpatient study)

- The design is, in principle, continuous wear throughout hospitalization; however, participants who wish to take a break from wearing may choose not to wear the devices. Participation compensation is calculated in proportion to the final number of nights worn (KRW 13,000 per day × valid wear days), and one night is determined by whether the measurement period included the participant's sleep period.
- If both the Fitbit and Calera devices are worn, the full participation compensation for that night is paid; if only one of the two devices is worn, 50% of that night's compensation is paid. However, if the participant wore the devices properly but measurement was not performed properly for reasons not attributable to the participant, such as device malfunction or data transmission error, this is recognized as proper wear.
- If the devices are removed at the discretion of an investigator or clinician because of adverse events such as skin problems or for clinical reasons, the full participation compensation for that night is paid.

11. Study Procedures and Assessments

Study 1 (outpatient study)

Study visit	V1 (Baseline)		V2 (Final visit)
Day	1	7-day measurement	8
Informed consent	X		
Inclusion/exclusion criteria	X		
Baseline characteristics, history of mood disorder	X		
CALERA continuous measurement	X		
Fitbit continuous measurement	X		
Mood symptoms, clinical self-report			X
Medication information for the past 3 months			X
Notable events during measurement			X

- The repeated assessment follows the same procedure, except that the “baseline characteristics, history of mood disorder” assessment is omitted.

Study 2 (inpatient study)

Time point	V1	Continuous measurement		End of study
	First device attachment	Device attachment	Device removal	Last device removal
Informed consent	X			
Inclusion/exclusion criteria	X			
Baseline characteristics	X			
CALERA continuous measurement	X			
Fitbit continuous measurement	X			
Psychopathological symptoms	X		X	X
Notable events during measurement			X	
Sleep environment			X	
Medication administration information			X	
Final diagnosis				X

* If the measurement period in progress at discharge is extended beyond discharge, psychopathological symptoms, notable events during measurement, medication administration information, and the final diagnosis are assessed and recorded together with the last device removal at the end of the extended measurement period, and ward-environment items (sleep environment, etc.) are treated as missing.

12. Criteria for Study Completion and Early Termination

All participants may withdraw consent or discontinue participation at any time during the study, and this will be clearly specified and explained at the time of consent. Discontinuation is also possible when the study staff judge that discontinuation is in the best interest of the participant. Participants who withdraw or discontinue will be informed that discontinuation of the study and withdrawal of consent will not affect their treatment at the institution. In addition, participation will be discontinued in the event of a serious adverse event (SAE), when the clinician judges that discontinuation is necessary because of worsening of the medical condition or other reasons, or when the study staff judge that continuation would interfere with the study.

13. Criteria, Methods, and Reporting of Safety Assessment Including Adverse Events

- This study will be conducted in accordance with the principles of the Declaration of Helsinki (2013) and relevant local laws and regulations.
- Because no direct intervention is administered, the expected risk is minimal; however, if an adverse event such as a skin problem at the wearing site occurs, wearing is stopped immediately, the event is recorded, and appropriate measures are taken as necessary.
- All SAEs are reported to the principal investigator and the IRB within 24 hours of awareness, and serious protocol non-compliance and unanticipated problems are reported to the IRB within 15 working days of the date the investigator becomes aware of them.

14. Data Analysis and Statistical Considerations

14-1. Study 1 Analysis Plan

Data alignment

- Fitbit data for the same period as Calera wear are extracted, and day-level features are derived according to the analysis criteria.
- The trough segment is defined in the Calera CBT rhythm, and the trough midpoint is calculated.
- Sleep/rest, activity, M10, L5, relative amplitude, IS, and IV are derived from Calera raw accelerometry.

Primary analysis

- Evaluation of agreement between Fitbit-derived phase features and the Calera-derived CBT trough midpoint
- In participants with repeated measurements, evaluation of the test–retest reliability and agreement of the Calera-derived CBT trough midpoint and of Fitbit-derived circadian phase features between the two time points
- Metrics: circular correlation, signed phase difference, absolute phase difference, mean absolute phase error, Bland–Altman bias and limits of agreement

Secondary analysis

- Comparison of Fitbit-derived sleep markers with Calera raw-acceleration-based rest/sleep markers
- Comparison of Fitbit-derived activity markers with Calera raw-acceleration-based activity markers

- Comparison of patients vs. healthy controls; exploratory subgroup analysis of MDD vs. BD-I vs. BD-II
- Analysis of associations of symptom severity, sleep fragmentation, reduced activity, and medication with phase discrepancy
- Coupling/decoupling analysis between Calera CBT markers and Calera accelerometry markers
- Development of a composite Fitbit-derived phase estimator

14-2. Study 2 Analysis Plan

Descriptive statistics and definition of clinical phenotypes

- Final diagnosis, MADRS, YMRS, BPRS, and CGI scores, clinical severity at admission, and length of hospitalization are summarized together. The final diagnosis is not an inclusion criterion for enrollment but is used for post hoc phenotype analysis.
- For each measurement period (sensor cycle) defined by Calera sensor replacement during hospitalization, valid wear time, number of valid measurement days, and missing rate for Calera and Fitbit are calculated, and the total measurement period and number of valid measurement periods per participant are reported.
- Major events identified in each measurement period, including sleep- and ward-environment-related events, fever/infection, seclusion/restraint/leave, and medication information, are described.
- From Fitbit data, sleep timing, sleep duration/continuity, activity volume and timing, resting/sleeping heart rate, and circadian phase-related features are derived using data temporally aligned with each Calera measurement period.

Primary longitudinal analysis (transdiagnostic)

- Primary outcomes are defined as CBT phase markers centered on the CBT trough midpoint, CBT amplitude and rhythm robustness, Calera-accelerometry-based rest/activity rhythm features, and physiological–behavioral phase misalignment between the CBT trough midpoint and rest/sleep midpoint, L5 timing, and activity acrophase. Longitudinal changes in Fitbit-derived sleep/activity timing and phase-related markers are also evaluated.
- The main time variables are defined as measurement time point and actual days since admission (days from admission). Time-varying symptom severity, such as MADRS, YMRS, BPRS, and CGI at each time point, is considered together, and when clinical stabilization or recovery can be clearly defined, it is used as an auxiliary time variable.
- Mixed-effects models or circular mixed-effects models with a subject-level random intercept are used for the basic analysis of repeated-measures data. If necessary, random slopes are added exploratorily, considering the number of repeated measurements and the data structure.
- Clock-time outcomes are treated as circular variables. To prevent phase shifts in opposite directions from cancelling out in simple arithmetic means, circular distance or absolute phase deviation is evaluated together with signed phase change.
- Where possible, using the distance from a reference phase or phase-angle distribution derived from the Study 1 healthy controls, the study explores whether misalignment in early hospitalization moves toward the reference range with clinical course.
- Fitbit-derived markers are analyzed in temporal alignment with Calera-derived markers for the same period, and whether CBT-derived physiological phase and Fitbit-derived sleep/activity rhythms change in the same direction over the hospital course is evaluated. If a Fitbit-derived phase estimator with sufficient agreement is identified in Study 1, it is used as an auxiliary longitudinal phase marker.

Symptom–rhythm association

- Associations between within-subject changes in the MADRS, YMRS, BPRS, and CGI and changes in CBT trough midpoint shift, CBT amplitude/robustness, rest/activity rhythm, and physiological–behavioral phase misalignment are evaluated.
- Associations between changes in Fitbit-derived sleep timing, sleep continuity, activity level/timing, and phase-related features and changes in clinical symptoms are evaluated.
- Whether the discrepancy between CBT-derived physiological phase and Fitbit- or Calera-accelerometry-derived behavioral rhythm decreases with clinical improvement is explored.

Cross-device and physiological–behavioral coupling analysis

- The phase relationship and coupling/decoupling between Calera CBT markers and Calera accelerometry markers are evaluated.
- Phase angle and phase misalignment between the Calera CBT trough midpoint and Fitbit-derived sleep midpoint, activity timing, or activity acrophase are calculated, and whether physiological–behavioral coupling changes over the hospital course is evaluated.
- The levels and directions of longitudinal change of rest/sleep and activity markers that can be derived from both Calera accelerometry and Fitbit are compared.
- When discrepancies between devices are observed, the effects of wear time, missingness, sleep fragmentation, activity level, fever/infection, and ward-environment-related events are evaluated exploratorily.

14-3. Missing Data and Validity Criteria

- In Study 1, a session is included in the primary agreement analysis if at least 3 common valid days are available on which both the Calera CBT trough midpoint and the corresponding Fitbit-derived marker can be derived.
- A valid CBT measurement day is defined as a day with sufficient wear data, including the sleep period, on which the CBT trough or CBT minimum can be derived.
- Fitbit- and Calera-accelerometry-derived markers include only days that meet the minimum wear time or valid-data criteria required to derive each marker.
- In Study 2, each Calera sensor attachment–replacement interval is defined as one measurement period (sensor cycle), and the number and proportion of valid CBT, accelerometry, and Fitbit data per measurement period are examined. The primary longitudinal analysis includes measurement periods with sufficient valid data to derive the target markers.
- Because the number of repeated measurements in Study 2 may vary with each participant’s length of hospitalization and sensor wear period, mixed-effects models are used to analyze data from participants with different numbers of measurements together.
- For periods in which fever, acute infection, voluntary device removal, or other events likely to substantially confound measurements occurred, the timing and duration of the event are confirmed, and the period is excluded from the analysis of the relevant marker or evaluated separately in sensitivity analyses.
- The same validity criteria apply when a measurement in progress at discharge is extended beyond discharge because discharge occurred earlier than expected. However, items of ward-environment information that cannot be collected after discharge are treated as missing.
- The amount and pattern of missing data are described, and device non-wear, device error, clinical discontinuation, and other reasons are reported separately to the extent possible. Longitudinal analyses using mixed-effects models use all available repeated-measures data, and sensitivity analyses are performed if systematic missingness that could affect the main results is suspected.

15. Measures for Protection of Personal Information and Confidentiality of Research Data

15-1. Recording and Collection of Research Data

- Collected data will be recorded on the REDCap server, an electronic case report form system. Data recorded on the REDCap server, a secured server, can be accessed only through authorized accounts. This is to protect and process participants' personal information and to ensure the confidentiality of research data and records. The research staff authorized to access the REDCap server are as follows:

Research Staff	Dept. of Psychiatry	Researcher	Soo-Hyun Park
Research Staff	Dept. of Psychiatry	Researcher	Yerin Oh

15-2. Access to Research Data and Provision of Information to Third Parties

(1) Provision for payment of transportation expenses

For payment of participants' transportation expenses, the resident registration number (through submission of a copy of the resident registration card) and the bank account number (through submission of a copy of the bankbook) are provided to Korea University Medicine. The purpose of provision is reporting of other income for tax purposes. The resident registration number and bank account number provided to Korea University Medicine for payment of transportation expenses are retained semi-permanently in the computer system and are not separately destroyed; however, they are encrypted and cannot be accessed by ordinary means.

(2) HEROES cohort data sharing

A total of four research teams were selected for this R&D program, and all four teams conduct research toward the common goal of discovering digital phenotypes of mental disorders. Although the studies are not necessarily conducted simultaneously, the collected data may later be combined and analyzed based on common data items (MCD). Participants will be informed of this in advance and their consent will be obtained. When data are shared, they will be pseudonymized with study numbers to minimize the possibility of personal identification.

(3) Use for secondary research purposes

If participants consent to secondary research use, the wearable and clinical data collected in the study may be used; in this case, the data are pseudonymized with study numbers and used without personal identifiers.

(4) Use for linkage with medical records and public data sources

If a participant consents to the provision of personal identifiers for linkage with medical records and public data sources, the principal investigator separately maintains, in encrypted form, a file linking study numbers with personal identifiers. In this case, personal identifiers are used only for data linkage based on those identifiers, and clinical information collected in the study is not provided to the linked institutions.

(5) Presentation of results

Study results will be presented in a form in which individuals cannot be identified, and this will be explained to participants and their consent obtained.

15-3. Storage of Research Data

- The participant enrollment log file is encrypted and stored on a computer with restricted access within Korea University Anam Hospital, retained for 3 years from the end of the study in accordance with the Bioethics and Safety Act, and then destroyed.

- Research data recorded in REDCap are anonymized after the end of the study and retained semi-permanently by the principal investigator.
- Access to the original research files recorded in REDCap is limited to the principal investigator and authorized researchers, whose affiliations and names are as follows. When a researcher leaves, previously granted authority is revoked and another responsible researcher is designated.
 1. Soo-Hyun Park, Researcher, Department of Psychiatry, Korea University Anam Hospital
 2. Yerin Oh, Researcher, Department of Psychiatry, Korea University Anam Hospital

15-4. Disposal of Study-Related Data

- In accordance with Article 15 of the Enforcement Rule of the Bioethics and Safety Act, study-related records containing personal information are retained for 3 years from the end of the study and then destroyed.
- After the end of the study, research data collected during the study are pseudonymized and retained semi-permanently by the principal investigator only for participants who consented, in the informed consent form, to use for secondary research purposes. For participants who consented to linkage with medical records and public data sources, the information needed for matching is separated, encrypted, and stored. Personal identification data unrelated to the content of the research are destroyed 3 years after the end of the study.
- In the case of withdrawal of consent or discontinuation: if a participant wishes to discontinue during participation or to withdraw consent after completion of participation, no new research information is collected. If consent is withdrawn, all of the participant's research data are deleted at the time of withdrawal; however, if a participant drops out without expressing an intention to withdraw consent, the research information collected up to the time of dropout will, by default, be used in the study unless the participant separately requests destruction of the research information. If a participant requests destruction of research data, all research information will be destroyed (deletion from the electronic case report form server and deletion of collected sensor information). However, the originally obtained informed consent form is retained separately, and the fact of withdrawal is recorded separately together with the reason.
- Study results will be presented in a form in which individuals cannot be identified.

16. Participant Recruitment Methods and Consent Procedures

Recruitment of outpatients

- Patients visiting the psychiatry outpatient clinic of Korea University Anam Hospital who meet the inclusion criteria are invited to participate by the principal investigator or co-investigators (physicians) during outpatient visits, and patients who express willingness to participate are enrolled.
- They sign the informed consent form after receiving a sufficient oral explanation of the study and understanding it, and the inclusion/exclusion criteria are confirmed.
- Explanation of the study to individuals who express willingness to participate → signing of the informed consent form → confirmation of inclusion/exclusion criteria and assignment of a study number (CBT-PT-01) → start of assessment

Recruitment of healthy controls

- Individuals who see recruitment notices posted inside and outside the hospital and contact a researcher to express willingness to participate will receive a brief explanation of the study by telephone, and if they wish to participate, a visit will be scheduled.
- They sign the informed consent form after receiving a sufficient oral explanation of the study and understanding it, and the inclusion/exclusion criteria are confirmed.

- Explanation of the study to individuals who express willingness to participate → signing of the informed consent form → confirmation of inclusion/exclusion criteria and assignment of a study number (CBT-HC-01) → start of assessment

Recruitment of outpatients and controls for the repeated assessment

- Willingness to take part in the repeated assessment is confirmed when consent is obtained for the first visit.
- Only for those who wish to participate, willingness is reconfirmed at least 1 month after the final visit, and a visit is scheduled.
- Inclusion/exclusion criteria are based on those reviewed at the baseline assessment; however, characteristics that change over time (e.g., jet lag, fever, shift work, pregnancy/breastfeeding/menstruation, medication use) are additionally checked at the repeated assessment.
- They sign the informed consent form for the repeated assessment after receiving a sufficient oral explanation of the study and understanding it.
- No separate study number is assigned for the repeated assessment, and the assessment begins after the consent form is signed.

Recruitment of inpatients

- Patients admitted to a ward of Korea University Anam Hospital are invited to participate by the principal investigator or co-investigators (physicians).
- Patients who show willingness to participate sign the informed consent form after receiving a sufficient explanation of the study and understanding it, and the inclusion/exclusion criteria are confirmed.
- Explanation of the study to individuals who express willingness to participate → signing of the informed consent form → confirmation of inclusion/exclusion criteria and assignment of a study number (CBT-AD-01) → start of assessment

[Common]

- Employees of this hospital may be enrolled as controls if they meet the inclusion/exclusion criteria; voluntary participation is ensured, and individuals or students in a hierarchical relationship with the principal investigator will not be enrolled.
- Because this study is conducted under the Bioethics and Safety Act and is not a clinical trial of a pharmaceutical product, a researcher who has been delegated consent authority by the principal investigator and recorded in the delegation log may directly explain the study to participants and obtain consent.

17. Protection Measures for the Recruitment of Vulnerable Participants

- Employees working at this hospital who meet the inclusion/exclusion criteria may be enrolled as participants if they voluntarily express willingness to participate through recruitment notices posted at the institution. However, voluntary participation is ensured, and individuals or students in any direct or indirect hierarchical relationship with the principal investigator or the head of the institution will not be enrolled. If such a case is found or suspected, that participant's study participation will be discontinued immediately.

18. Quality Control and Quality Assurance Plan (Data and Safety Monitoring Plan)

1) Monitoring personnel

- **Responsible for monitoring:** Jaekwon Jeong / Department of Psychiatry, Korea University Anam Hospital / Clinical Fellow
- **Monitoring staff:** Soo-Hyun Park / Department of Psychiatry, Korea University Anam Hospital / Researcher

- **Monitoring staff:** Yerin Oh / Department of Psychiatry, Korea University Anam Hospital / Researcher

2) Data and safety monitoring methods and frequency

- At every assessment, side effects and discomfort (adverse events) are checked, and any identified cases are recorded separately.
- Once every 6 months, the monitoring staff will monitor overall data and safety. Monitoring includes review of obtained consent forms and data cleansing of collected eCRF responses.

3) Reporting of adverse events, protocol non-compliance, and unanticipated problems

- All SAEs will be reported to the principal investigator and the IRB within 24 hours of becoming aware of their occurrence, and information on all SAEs will be collected and recorded on the adverse event report form. Serious adverse drug reactions, serious protocol non-compliance, and unanticipated problems will be reported to the IRB within 15 working days of the date the investigator becomes aware of them.

19. Study Timeline

Activity	Detailed schedule (IRB approval to December 2028; approximately 30 months)											
	2026				2027				2028			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Study planning and IRB approval												
Investigator training												
Participant recruitment and assessment												
Data analysis												
Writing of study outputs (papers)												

Translator's note: the original labels the sub-columns 1–4 within each year; these are shown here as quarters.

20. References

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