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Identifying and validating cognitive profiles in schizophrenia and bipolar disorder

Submission date 01/04/2026	**Recruitment status** Not yet recruiting	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [X] Record updated in last year
Registration date 30/04/2026	**Overall study status** Ongoing	
Last Edited 30/04/2026	**Condition category** Mental and Behavioural Disorders	

Plain English summary of protocol
Not provided at time of registration

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Instituto de Salud Carlos III, AES 2026, funding application number
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Study information

Scientific Title
PerfilesMICEmiEZ-TB: protocol for a four-year ambispective multicenter study to identify and validate neurocognitive endophenotype profiles in schizophrenia and bipolar disorder using the MICEmi model

Acronym
PerfilesMICEmiEZ-TB

Study objectives
General Objective:

To identify, select, validate, compare, and differentiate cognitive deficits in schizophrenia and bipolar disorder that are suitable for inclusion in specific neurocognitive endophenotypic profiles, using the MICEmi model with a transdiagnostic approach of mechanistic and clinical relevance.

Specific Objectives:

1. To identify deficits that are candidates for neurocognitive endophenotypes through a scope review and retrospective analysis of existing cohorts.

2. To prospectively evaluate the identified deficits in a de novo longitudinal cohort, including neurocognitive modulating mechanisms.

3. To validate the candidate deficits by applying the MICEmi protocol to integrate retrospective and prospective results.

4. To define specific endophenotypic profiles for each disorder, exploring their impact on diagnostic stratification and the design of personalized interventions.

Ethics approval required
Ethics approval required

Ethics approval(s)
Not yet submitted

Primary study design
Observational

Secondary study design
Cohort study

Study type(s)

Health condition(s) or problem(s) studied
Schizophrenia; Bipolar Disorder

Interventions
This is a four-year ambispective, observational, longitudinal multicenter cohort study structured in three sequential phases, conducted across nine CIBERSAM research groups in eight Spanish National Health System centres in four autonomous communities.
Phase 1 — Retrospective (Months 1–11). Two parallel scoping reviews (SZ and BD) are conducted following PRISMA-ScR guidelines across PubMed, PsycINFO, Embase and Web of Science. Preexisting neurocognitive cohorts from all participating CIBERSAM groups are harmonised into a centralised database (BDGC, hosted on REDCap). Individual participant data (IPD) meta-analyses estimate effect sizes per cognitive domain using mixed-effects multilevel models. A first MICEmi analysis scores five endophenotypic criteria (MICEmiC1–C5) for each candidate deficit. A two-round Delphi process constructs the Unified Neurocognitive Evaluation Battery (BUEN) for the prospective phase. Assessors are trained and certified prior to recruitment (Cohen's κ ≥0.80; ICC ≥0.85).
Phase 2 — Prospective (Months 12–45). A novel multicenter cohort of 900 participants (180 per group: schizophrenia, bipolar disorder, first-degree relatives of schizophrenia patients, first-degree relatives of bipolar disorder patients, and healthy controls) is recruited across the nine participating groups. Each group contributes 100 participants (20 per group type). Participants are assessed at baseline (T0), 12 months (T1) and 24 months (T2). A 70% retention rate is anticipated at T1 and T2. Each assessment includes: (a) the full BUEN protocol (verbal learning and memory, cognitive flexibility, verbal fluency, working memory, attention, processing speed and visual memory); (b) fasting peripheral blood sampling for quantification of inflammatory cytokines (IL-6, IL-10, TNF-α) by multiplex xMAP/Luminex technology, neurotrophins (BDNF, NT-3) by ELISA, leukocyte-endothelial interaction, mitochondrial function and oxidative stress markers, and metabolic profile; (c) physical frailty assessment using the Fried phenotype (unintentional weight loss, fatigue, physical activity, gait speed and handgrip strength), classified as robust, pre-frail or frail; (d) psychosocial functioning (FAST, GAF), quality of life (WHOQoL-Bref), symptom severity (PANSS for SZ; YMRS/HDRS for BD), multimorbidity (Charlson index) and lifestyle (SMILE-C). A second MICEmi analysis integrates retrospective and prospective findings for definitive endophenotype validation.
Phase 3 — Consolidation and transfer (Months 46–48). Expert consensus panels (ExC) in SZ and BD integrate MICEmi findings to define definitive neurocognitive endophenotype profiles for each disorder. Consensus workshops following GRIPP2 methodology, with participation of patient researchers and patient and family association representatives, co-create personalised clinical intervention guidelines and diagnostic update proposals for DSM-5-TR, ICD-11 and RDoC. Patient researchers receive fair economic compensation (€15/hour) and initial training in study design and guideline writing. Selection of patient researchers ensures diversity across diagnosis, sex, age, socioeconomic status, ethnicity and geographic origin.
All data are registered in the BDGC with individual credentials, full audit trail and pseudonymisation at source. A Participant Retention Protocol (automated alerts, reminders, flexible scheduling and travel compensation) is implemented across all centres.

Intervention Type
Other

Primary outcome(s)
1. Identification of the neurocognitive endophenotypes of schizophrenia and bipolar disorder, separately measured using PRISMA-ScR scope reviews; harmonization of CIBERSAM cohorts; IPD meta-analysis; first MICEmi analysis at months 1 to 9

2. Prospective evaluation of the identified deficits measured using an evaluation of a de novo cohort with BUEN (Unified Neurocognitive Evaluation Battery, constructed ad hoc by Delphi consensus); recording of biological mechanisms modulating cognition (blood analysis and measurement of physical frailty); and recording of sociodemographic and clinical variables and evaluation with clinical scales, social functioning and quality of life at baseline, 12 and 24 months

3. Validation of the neurocognitive endophenotypes of SZ and BD, separately, measured using a second IPD meta-analysis; and second MICEmi analysis (integrating retrospective and prospective results) at months 43 to 45

4. Definition of the specific endophenotypic profiles for each disorder measured using Hierarchical models and technical consensus protocols, panels of experts in EZ and TB (including the patient as an expert) will integrate and harmonize the findings of the MICEmi analyses to define the definitive profiles of each disorder, describing its specific components, the associated modulating mechanisms, and its mechanistic and clinical relevance. at Month 46

5. Development of Clinical Guidelines and Diagnostic Proposals measured using hierarchical models and technical consensus protocols, panels of experts in EZ and TB (including the patient as an expert) and consensus-building sessions with citizen participation will develop clinical guidelines and diagnostic proposals at months 47 and 48

Key secondary outcome(s)

Completion date
31/12/2029

Eligibility

Key inclusion criteria
1. Adults aged ≥18 years
2. Confirmed diagnosis of schizophrenia or bipolar disorder according to DSM-5-TR/ICD-11 (patient groups)
3. Unaffected first-degree relatives (parents, siblings or offspring) of individuals with schizophrenia or bipolar disorder (relative groups)
4. No personal or first-degree family history of mental disorder (healthy control group)
5. Written informed consent provided.

Healthy volunteers allowed
Yes

Age group
Mixed

Lower age limit
18 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Major neurocognitive disorder or intellectual disability
2. Sensory or language barriers precluding cognitive assessment
3. For relative and healthy control groups: any lifetime diagnosis of a psychotic or major affective disorder.

Date of first enrolment
01/01/2027

Date of final enrolment
30/06/2029

Locations

Countries of recruitment
Spain

Sponsor information

Organisation
Centro de Investigación Biomédica en Red de Salud Mental

ROR
https://ror.org/009byq155

Funder(s)

Funder type

Funder Name
Centro de Investigación Biomédica en Red de Salud Mental

Alternative Name(s)

Biomedical Research Centre for Mental Health Network, Center for Biomedical Research Network, CIBER of Mental Health, Mental Health CIBER, CIBERSAM

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
Spain

Results and Publications

Individual participant data (IPD) sharing plan
Anonymised data and associated metadata will be deposited in an open-access repository (ISCIII institutional repository or Zenodo/OSF) following FAIR principles upon study completion. Access to restricted data will be granted upon motivated request and evaluation by the Steering Committee.

IPD sharing plan summary
Stored in publicly available repository